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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, CABI, Index Copernicus, Embase, Scopus, ProQuest, J-Gate, IdealOnline, TÜBİTAK/ULAKBİM, Hinari, GOALI, ARDI, OARE, AGORA, Türk Medline, Türkiye Atıf Dizini** 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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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 requirements 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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4) Bilimsel Mektuplar:
Bu yazılar orijinal araştırma yapısında olmayan bilimsel ilgi uyandırabilen yeni fikir, buluş ve verilerin sunulduğu ön bildirilerdir. Bu konuyla ilgili gelecekteki yayınlara merak uyandırmayı amaçlar. Metnin bölümleri yoktur.
5) Eğitim Yazıları:
Bu kategoride otörler osteoporoz, metabolik kemik hastalıkları ve rehabilitasyon konularındaki güncel bilgileri özetlerler.

Yazışma
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Türk Osteoporoz Dergisi

TURKISH JOURNAL OF OSTEOPOROSIS

INSTRUCTIONS TO AUTHORS

The 'Turkish Journal of Osteoporosis' is an official journal of the Turkish Society of Osteoporosis. An additional supplement is also published on the occasion of the National Osteoporosis Congress.
The Journal publishes papers on all aspects of osteoporosis, metabolic bone diseases and its rehabilitation. In addition to original articles, review articles, original case reports, letters to the editor, scientific letters, educational articles, abstracts from new literature and announcements of future congresses and meetings are also published.
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Türk Osteoporoz Dergisi
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Türk Osteoporoz Dergisi
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Editörden / Editorial

Sevgili Meslektaşlarımız,

Türkiye Osteoporoz Derneği tarafından ana teması "OSTEOAKADEMİ 2022 Sorularınızı Yanıtlıyor" olan **OSTEOAKADEMİ 2022** Sempozyumu 13-15 Mayıs 2022 tarihlerinde Ilıca Otel Çeşme, İzmir'de gerçekleşmiştir. Koronavirüs hastalığı-2019 (COVİD-19) pandemisi nedeniyle bu süreçte online olarak gerçekleştirilmiş derneğimiz aktivitelerinden sonra fiziki katılımla meslektaşlarımızla birlikte olmanın mutluluğunu yaşadık. İki kurs, iki uydu ile bilimsel konferans ve panellerle organize edilmiş olan bu sempozyumda osteoporoz, osteoartrit ve kas iskelet sistemi ağrıları konularındaki bilgilerimiz güncellenmiştir. Bilimsel program değerli meslektaşlarımızın katılım ve katkıları ile zenginleşmiştir.

Ayrıca ülkemizi ve tüm dünyayı etkisi altına alan COVİD-19 pandemisi nedeniyle Osteoporoz, Osteoartrit ve Kas İskelet Sistemi Hastalıkları Dünya Kongresi (WCO-IOF-ESCEO) Berlin 2022 tümüyle online kongreye dönüştürülerek, 24-26 Mart 2022 tarihlerinde gerçekleştirilmiştir. Bu kongrede Türkiye Osteoporoz Derneği aktiviteleri Ulusal Dernekler Köyünde poster sunumu olarak yerini almıştır. Aynı zamanda derneğimiz adına "COVID-19 ve Kas-İskelet Sistemi" başlıklı bir sempozyum düzenlenmiş olup, konuyla ilgili üç konferans sunumu yapılmıştır.

Pandemi sırasında bile değerli meslektaşlarımızın akademik çalışmaları devam ederek, bu çalışmaların meyvesi olan araştırma makalesi ve olgu sunumları yayınlanmak üzere Emerging Sources Citation Index (ESCI) tarafından indekslenen dergimize düzenli olarak iletildiğinden değerli meslektaşlarımıza çok teşekkür ederiz.

Siz değerli meslektaşlarımıza çalışmalarınızda kolaylıklar dileyerek, sevgi ve saygılarımı sunarım.

Editör
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Contribution of Lumbar Vertebral Magnetic Resonance Imaging to Diagnosis in Women with Osteoporosis

Osteoporozlu Kadınlarda Lomber Spinal Manyetik Rezonans Görüntülemenin Tanıya Katkısının Değerlendirilmesi

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Abstract

Objective: The aims of this study are to compare bone mineral densitometry and magnetic resonance imaging (MRI) findings in postmenopausal women diagnosed with osteoporosis and the investigation of the effectiveness of MRI in the diagnosis of osteoporosis.
Materials and Methods: Forty female patients, 50 years of age or older who underwent lumbar MRI examination and were diagnosed with dual-energy X-ray absorptiometry (DEXA) osteoporosis were included in our study. Forty healthy women aged 20-29 years with lumbar MRI examinations were included in the control group. On sagittal T1-weighted (T1W) images of individuals in the patient and control groups signal-to-noise ratio (SNR) was measured from L1-L4 vertebrae. To facilitate the diagnosis of osteoporosis, a quantitative score called the M-score was obtained using SNR values. The relationship between DEXA and the obtained SNR and M-score values were investigated.
Results: In the patient group, median SNR values of L1, L2, L3, L4 vertebrae obtained from T1-weighted sequence was 57.49 (25.18-182.48), and they were 24.90 (7.40-41.70) in the control group. Receiver operating characteristics analysis was performed for L1, L2, L3, L4 vertebrae. The area under the curve for the mean value of L1-L4 vertebra was found to be 0.966 ($p<0.001$), and the 95% confidence interval was found 0.933-1.000. The mean SNR predictive value of L1-L4 was calculated as 33.45, and sensitivity for this value was found to be 90%, and specificity was found to be 90%. There was a negative correlation between lumbar MRI SNR-DEXA ($p>0.05$) and M score-DEXA ($p>0.05$).
Conclusion: It has been concluded that L1-L4 vertebral SNR measurement in T1-weighted sequence in lumbar MRI can be used to distinguish osteoporosis patients from normal individuals. Thus, osteoporosis can be diagnosed without X-ray exposure.
Keywords: Magnetic resonance imaging, osteoporosis, M-score

Öz

Amaç: Bu çalışmanın amacı osteoporoz tanılı postmenopozal kadınlarda kemik mineral dansitometri ve manyetik rezonans görüntüleme (MRG) bulgularının karşılaştırılması ve osteoporoz tanısında MRG'nin etkinliğinin araştırılmasıdır.
Gereç ve Yöntem: Çalışmamıza 6 ay içerisinde lomber MRG incelemesi yapılan ve dual-enerji X-ışını absorbsiyometri (DEXA) ile osteoporoz tanısı almış 50 yaş ve üstü 40 kadın hasta dahil edildi. Kontrol grubunda lomber MRG incelemesi bulunan 20-29 yaşlarında 40 sağlıklı kadın incelendi. Hasta ve kontrol grubundaki bireylerin sagittal T1 ağırlıklı görüntülerinde L1-L4 vertebralardan sinyal gürültü oranı (SNR) ölçümü yapıldı. Osteoporoz tanısında kolaylık sağlaması için SNR değerleri kullanılarak M-skoru adında kantitatif bir skor elde edildi. Elde edilen SNR ve M-skoru değerleri ile DEXA arasındaki ilişki araştırıldı.
Bulgular: L1, L2, L3, L4 vertebralarının T1 ağırlıklı sekanstan elde edilen SNR ortanca değerleri hasta grubunda 57,49 (25,18-182,48), kontrol grubunda 24,90 (7,40-41,70) idi. L1, L2, L3, L4 vertebralarının alıcı işletim karakteristiği analizi yapıldı. L1-L4 vertebra ortalama değeri için eğri altında kalan alan 0,966 ($p<0,001$), %95 güven aralığı 0,933-1,000 bulundu. L1-L4 ortalama SNR kestirim değeri 33,45 olarak hesaplanmış olup bu değer için duyarlılık %90, özgünlük %90 olarak bulundu. Lomber MRG SNR-DEXA ($p>0,05$) ile M-skoru-DEXA arasında negatif yönlü bir ilişki saptandı ($p>0,05$).
Sonuç: Lomber MRG'de T1 ağırlıklı sekansta L1-L4 vertebra SNR ölçümünün osteoporozlu hastaları normal bireylerden ayırt etmede kullanılabileceği sonucuna varılmıştır. Böylece osteoporoz, röntgen ışınlarına maruz kalmadan teşhis edilebilir.
Anahtar kelimeler: Manyetik rezonans görüntüleme, osteoporoz, M-skoru

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Introduction

Osteoporosis (OP) is a chronic, degenerative, systemic skeletal disease that, as a result of a decrease in bone mass and deterioration in its microarchitecture, predisposes to fracture (1). Bone fractures caused by OP are an important cause of morbidity and mortality. The disease is characterized by low mineral density without fractures in the preclinical period (2).

Dual-energy X-ray absorptiometry (DEXA) and quantitative computed tomography are used routinely and widely in the diagnosis of OP and evaluation of fracture risk. Thanks to these methods, bone mass and density can be determined. However, with the studies conducted, it has been shown that bone mass and density alone are not important in determining bone strength, but also bone structural changes should be evaluated (2).

Since OP is an asymptomatic disease, although bone mineral density testing is required, many patients do not receive DEXA and cannot be diagnosed. However, many magnetic resonance imagings (MRIs) are performed due to the complications that are caused by low back pain and OP (3).

As the bone density decreases, the fat content in the vertebral bone marrow is observed to increase in osteoporotic patients (4). With studies, it has been shown that bone marrow adipose tissue is significantly higher in osteoporotic patients and there is an inverse relationship between bone mineral density and adipose tissue in the vertebral bone marrow (5,6). In addition, the risk of fracture was higher in patients with high bone marrow fat content (7).

With MR standard T1W images, the measurement of adipose tissue volume is quantitatively confirmed. In the determination of cellularity and adipose tissue in bone marrow, MR standard T1W images are the most sensitive sequence (8,9). There is an inverse relationship observed between bone marrow adipose tissue and bone mineral density in T1W images in healthy middle-aged men and women (10). T1W images cannot be used for scanning in OP patients due to the lack of quantitative score, even though there is a correlation between fat tissue that can be evaluated in T1W images in MRI and bone mineral density measured by the DEXA method (3). L1-L4 vertebra signal-to-noise ratio (SNR) measurement and M-score can be calculated from the MRI T1A sequence, and thus a new quantitative method can be applied to detect OP (11).

The objective of this study is to compare DEXA and no exposure to X-ray to perform quantitative MRI findings in postmenopausal women diagnosed with OP and to study the effectiveness of MRI in the OP diagnosis.

Materials and Methods

Study Group

The present study is retrospective and its permission was obtained from Sivas Cumhuriyet University Non-Invasive Clinical Research Ethics Committee on 11.09.2019 (decision no: 2019-09/03).

In our study, postmenopausal female patients over the age of 50 who underwent lumbar MRI between November 2013 and September 2019 in our hospital with a T-score of -2.5 and below in DEXA were included. The patients who have oncologic pathologies, demyelinating diseases, metal prosthesis, traumas, inadequate quality sagittal T1W images and those with a duration of more than 6 months between DEXA and Lumbar spinal MRI examinations were excluded from the study. The study group consisted of 40 postmenopausal women who met the criteria.

In order to calculate the M-score similar to the T-score measured in DEXA, 40 healthy women aged 20-29 years, who underwent lumbar spinal MRI between August 2018 and February 2019 due to low back pain, were included in the study as a control group. The exclusion criteria are the same as those for the study group.

Analysis of MR Images

All MR images were obtained with a 1.5T MRI device (Siemens, Magnetom Aera, Germany). All views include sagittal T1 fast spine echo (TR: 540, TE: 9.7, averages 2, slice thickness 4 mm, slice range 0.8 mm, FOV: 260x100, matrix: 320x72 mm).

Signal measurement was performed by placing it in the largest region of interest (ROI) from the sagittal T1W images from the L1-L4 vertebral corpuses, cortical bone, subchondral anomaly, to the area other than the posterior venous plexus (3,11). Each vertebral body was measured in 3 separate sections and with the same ROI width, and the mean value was used in our study. The noise value was measured from the outside of the image area with the same ROI size (Figure 1). SNR calculations were done by the averaged signal measured from 3 different sections for each vertebra and divided into noise.

DEXA Analysis

Results were obtained by automatically using the DEXA device (QDR 4500 W) in the supine position. Lumbar bone mineral densities were measured from L1-L4 vertebrae. T-score was calculated by using bone mineral densitometry (BMD). According to the criteria of the World Health Organization, if the T-score is ≥-1, it means there is no OP. T-score between -1 and -2.5 was evaluated as osteopenia, and T-scores as ≤-2.5 was evaluated as OP. Our study group consisted of only those with a T-score of -2.5 and below (12).

Statistical Analysis

In our study, SPSS 22.0 software was used for statistical analysis. Comparison of SNR values obtained from L1, L2, L3, L4 vertebral bodies in Lumbar MRI of individuals in patient and control groups was made and analysis was performed with graphics. To find a predictive value in distinguishing individuals with OP from normal individuals in the control group, receiver operating characteristics (ROC) analysis was performed. The best predictive values for L1, L2, L3, L4, L1-L4 mean SNR levels, and diagnostic performance indicators were calculated.

For the diagnosis of OP, there is a score obtained from MR images called the M-score. It is similar to the T-score in DEXA. T-score for a patient is found by the ratio of BMD to the average BMD in the reference population. Similarly, the M-score is calculated by the following formula using the SNR L1-L4 and SNR ref values of the patient and control group and the standard deviation (SD ref) value of the control group (3,11).

$$\bullet\ \text{M-score} = \frac{SNR_{(L1\text{-}L4)} - SNR_{(Ref)}}{SD_{(Ref)}}$$

Spearman correlation test was performed to investigate the relationship between the SNR and the T-score and between the M-score and the T-score.

Results

Characteristics of the Patient and Control Groups

Forty postmenopausal women over 50 years of age who underwent lumbar MRI due to suspicious X-ray, laboratory and clinical findings and were also diagnosed with OP by DEXA (T-score -2.5) were included in the study. The youngest in the patient group was 53 years old, and the oldest was 81 years old and the patient's mean age was 64.97±6.30. Forty women aged 20-29 years who underwent lumbar spinal MRI for low back pain were included in the study as the control group. The youngest in the control group was 21 years old, and the oldest was 29 years old and their mean age was 25.32±2.28 (Table 1).

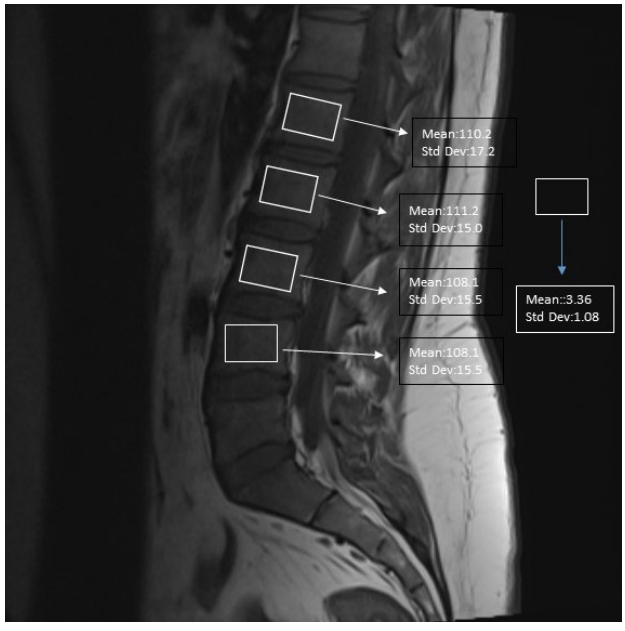

Figure 1. In T1W sagittal measurements, signal measurement by placing the ROI on the L1-L4 vertebral corpuses, and noise measurement by placing it outside the image

ROI: Region of interest, Std Dev: Standard deviation

SNR Analysis

The median SNR values for each vertebra are as follows respectively; in vertebra L1, 57.2 (26.31-187.50) in the patient group, 26.76 (8.88-45.9) in the control group; in vertebra L2, 57.74 (24.03-194.61) in the patient group, 24.36 (7.16-41.81) in the control group; in vertebra L3, 56.27 (23.26-193.70) in the patient group, 23.44 (6.54-41.81) in the control group; in vertebra L4, 56.48 (23.65-182.67) in the patient group, 23.06 (7.03-37.72) in the control group; and L1-L4 mean SNR was 57.49 (25.43-182.48) in the patient group and 24.90 (7.40-41.70) in the control group.

Individuals in the patient and control groups were compared in terms of L1, L2, L3, L4 and L1-L4 mean SNR values, and the difference between the groups was found to be significant ($p<0.05$) (Figure 2).

In order to find a predictive value in distinguishing individuals with OP from normal individuals in the control group, ROC analysis was performed (Figure 3).

The best predictive values, as a result of the ROC analysis, were found to be 36.35 for L1, 34.96 for L2, 32.20 for L3, 32.67 for L4, and 33.45 for L1-L4 mean. Table 2 shows the sensitivity and descriptive ratios of the predictive values.

Analysis of SNR and M-score with DEXA

Between L1-L4 mean SNR value and M-score and DEXA value, Spearman correlation test was performed in the patient group

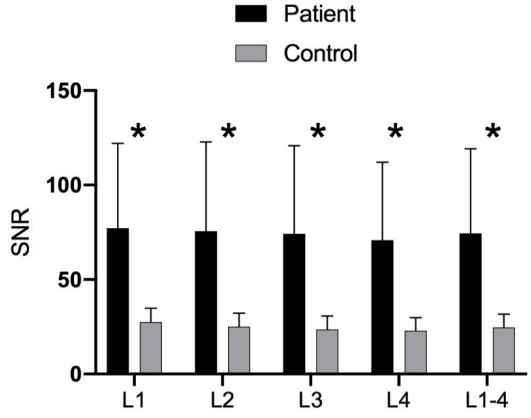

Figure 2. SNR values of L1, L2, L3, L4, and L1-4 means. Data were expressed as mean with standard deviation (*p<0.05)

SNR: Signal-to-noise ratio

Table 1. The mean age of groups

	Groups	n	Mean
Age	Patient	40	64.97±6.30
	Control	40	25.32±2.28

and as a result, a negative correlation of -0.067 was found. This relationship is statistically insignificant (Figure 4).

Discussion

DEXA is quantitative imaging with standardization in the diagnosis of OP (13), however many patients cannot be properly evaluated and diagnosed because it is not used frequently (1,14). Today, lumbar MR imaging is performed very frequently. In routine MRI images, a new quantitative measurement method based on SNR and M-score may help diagnose patients at risk of OP, and enable early diagnosis of many patients incidentally (11). MR T1A images are used to show bone marrow cell content due to their good detection of fat content. The hyperintensity in T1-weighted images indicates a decrease in cells in the bone marrow and an increase in fat content. This increase is associated with OP (8). One claim is that the increase in the amount of fat in the bone marrow is a mechanism to compensate for cellular content associated with OP in trabecular microarchitecture. Fat cells may fill areas with trabecular thinning and volume loss (15). All women in the patient group had postmenopausal OP. In the literature using T1W images, postmenopausal women were selected in 2 publications in which SNR and M-score were used as the patient group. In our study, women diagnosed with OP were included. However, unlike our study, in the other two studies mentioned, postmenopausal women were grouped as OP, osteopenia and normal, and all of them were included (3,11). The aim is to be able to distinguish between patients with definite OP.

SNR and M-score are device-dependent and there are not enough studies on this subject in the literature. In addition to these, L1, L2, L3, L4, and L1-4 mean SNR values were found

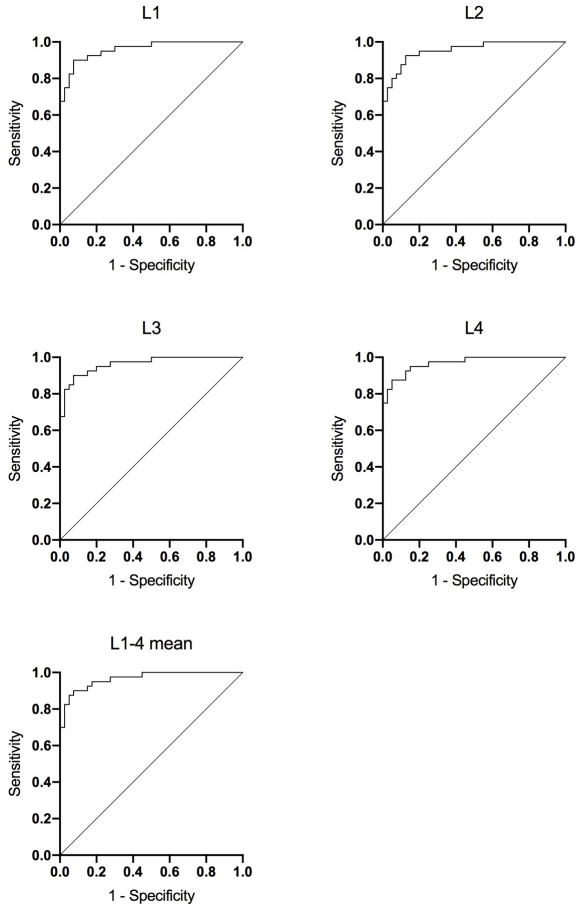

Figure 3. ROC curves for L1, L2, L3, L4, and L1-4 mean SNR measurements in distinguishing the patient group with OP from the control group

ROC: Receiver operating characteristics, SNR: Signal-to-noise ratio, OP: Osteoporosis

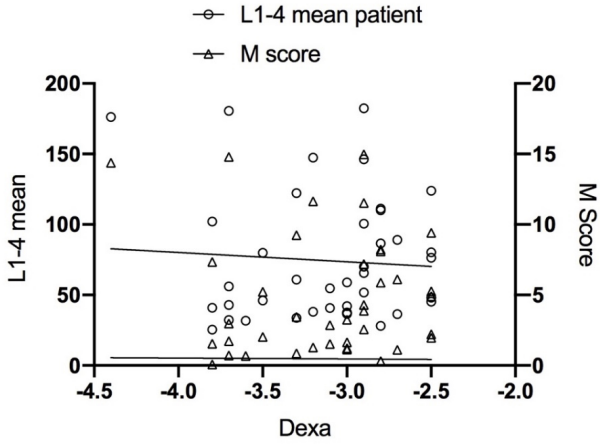

Figure 4. Relationship between patient group DEXA, L1-4 mean and M-score

DEXA: Dual-energy X-ray absorptiometry

Table 2. Best predictive values and diagnostic performance indicators for L1, L2, L3, L4, L1-L4 mean SNR levels to distinguish osteoporotic individuals from normal individuals

Indicators	L1 SNR	L2 SNR	L3 SNR	L4 SNR	L1-L4 mean SNR
Predictive value	36.35	34.96	32.20	32.67	33.45
Case (n)	80	80	80	80	80
Sensitivity	36/40 (90%)	35/40 (87.5%)	36/40 (90%)	35/40 (87.5%)	36/40 (90%)
Specificity	36/40 (90%)	36/40 (90%)	36/40 (90%)	36/40 (90%)	36/40 (90%)
p-value	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01

SNR: Signal-to-noise ratio

to investigate the situation in our country. In the light of these values, the M-score was calculated and the relationship between T and M scores was investigated.

In the measurement of SNR, there was a significant difference between the patient group and the control group ($p<0.001$). ROC analysis was performed on the SNR values and the predictive values were calculated in our study and it was investigated which values can be used in the diagnosis of OP in daily MRI use. The predictive values were found 36.35 for L1, 34.96 for L2, 32.20 for L3, 32.67 for L4, and 33.45 for L1-L4 mean. According to these values, the sensitivity of the predictive value was found 90%, and its specificity was found 90%. For the early diagnosis of patients with suspected OP, quantitative values can be determined in routine lumbar MRI examinations with predictive values. Shayganfar et al. (3) and Bandirali et al. (11) found a significant difference in SNR measurement between the patient group and the control group in their studies ($p<0.001$). Also, the sensitivity and specificity for the predictive values they found were found to be 90%, which are similar to our results.

L1, L2, L3, L4, L1-L4 mean SNR values obtained with lumbar vertebra T1W images were measured separately for the patient and control group and the M-score was calculated similarly to the T-score in the DEXA. In this direction, the aim is to obtain a quantitative score, facilitate the diagnosis of OP and reveal a general validity value.

There was a negative correlation found between the M-score and T-score obtained in our study, and the result is not statistically significant ($r=-0.067$, $p>0.005$). In the study conducted by Shayganfar et al. (3) on this matter, similar to our study, a negative correlation ($r=0.564$) was found, and the result was statistically significant ($p=0.0001$). Similarly, a negative correlation ($r=-0.682$) was found in the study performed by Bandirali et al. (11), and the result was statistically significant ($p<0.001$). The fact that we had a small number of patients and that only patients with OP were included in the case group and postmenopausal women with osteopenia and normal T-scores were not included in the case group may be the reason why the correlation between SNR and T-score and between M-score and T-score was not significant in our study. Also, although DEXA is the gold standard in the diagnosis of OP, we believe that its low sensitivity may also affect the results.

The reliability of our study increases due to the fact that all cases in our study consisted of postmenopausal female patients and all of them were proven by DEXA. To ensure the homogeneity of the case group, postmenopausal patients with normal bone mineral density and compatibility with osteopenia were not included in the study. Additionally, male patients with OP were not included in our study, and structural differences were avoided. Patients were not classified only according to DEXA results, lumbar MR images and files of 80 cases were examined and those with other diseases affecting the bone structure were not included in the study. In the study we conducted by excluding other factors, the aim is to increase reliability.

The reliability of our study increases due to the fact that all cases in our study consisted of postmenopausal female patients and all of them were proven by DEXA. To ensure the homogeneity of the case group, postmenopausal patients with normal bone mineral density and compatibility with osteopenia were not included in the study. Additionally, male patients with OP were not included in our study, and structural differences were avoided. Patients were not classified only according to DEXA results, lumbar MR images and files of 80 cases were examined and those with other diseases affecting the bone structure were not included in the study. In the study we conducted by excluding other factors, the aim is to increase reliability.

Despite the limitations stated in our study, it has been shown that T1W sequences in lumbar MR images taken for another reason can be used to predict OP. We believe that in the patient group who undergo lumbar MRI for low back pain every day, it may be possible to expand OP scanning without additional cost and radiation exposure. Studies conducted with large case groups prospectively are needed for the diagnostic value of MRI.

Conclusion

In this study, it has been shown that lumbar MRI T1W sequences can be used to predict OP. It may be possible to expand the screening for OP without the additional cost and radiation exposure of multiple lumbar MRIs for low back pain. We think that prospective studies with larger groups are needed on this subject.

Ethics

Ethics Committee Approval: The present study is retrospective and its permission was obtained from Sivas Cumhuriyet University Non-Invasive Clinical Research Ethics Committee on 11.09.2019 (decision no: 2019-09/03).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.A., E.G., S.A., Concept: S.A., S.B., Design: S.B., S.A., Data Collection or Processing: İ.A., E.G., Analysis or Interpretation: İ.A., E.G., Literature Search: İ.A., S.A., E.G., Writing: İ.A.

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

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Effectiveness Comparison of Extracorporeal Shock Wave Therapy and Conventional Physical Therapy Modalities in Primary Knee Osteoarthritis

Primer Diz Osteoartritinde Konvansiyonel Fizik Tedavi Modaliteleri ve Ekstrakorporeal Şok Dalga Tedavisinin Etkinliklerinin Karşılaştırılması

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Abstract

Objective: In this study, it was aimed to compare the effects of radial-extracorporeal shockwave treatment (r-ESWT) and conventional physical therapy (PT) modalities treatments on pain, joint range of motion (ROM), functional status and walking speed in patients with primary knee osteoarthritis (KOA).

Materials and Methods: A total of 51 patients (26 patients in the ESWT group and 25 patients in the combined PT group) diagnosed with stage 2 or stage 3 primary KOA according to the Kellgren-Lawrence staging were included in the study. ESWT protocol of 2.0 bar, 0.25 mJ/mm^2 , and ten beats/sec frequency was used once a week for a total of three sessions. In the PT group, hot-pack 30 min/day, transcutaneous electrical nerve stimulation 30 min/day, and ultrasound 10 min/day were performed as a combination therapy for five sessions a week and in a total of three weeks. Besides, a therapeutic home exercise program was administered to both groups. The groups were assessed on days 0, 10, and 21 using the parameters of visual analog scale (VAS), Western Ontario McMaster Universities Osteoarthritis index (WOMAC), joint ROM measurements, and the Timed "Up & Go" (TUG) test.

Results: No statistically significant differences were determined between the groups regarding the pretreatment and 10-day and 21-day posttreatment scores, VAS, WOMAC, joint ROM, and TUG parameters ($p>0.05$). In intra-group evaluations, statistically significant improvements were determined when the 10-day and 21-day values of VAS, WOMAC, joint ROM, and TUG parameters were compared to the pretreatment values ($p<0.05$).

Conclusion: r-ESWT and conventional PT were determined to have similar effects on primary KOA treatment. However, further and comprehensive studies are needed to reach more precise and accurate results.

Keywords: Extracorporeal shockwave therapy, conventional physical therapy modalities, primary knee osteoarthritis

Öz

Amaç: Bu çalışmada, primer diz osteoartriti (DOA) tanılı hastalarda, radyal-ekstrakorporeal şok dalga tedavisi (r-ESWT) ve konvansiyonel fizik tedavi (FT) modaliteleri tedavilerinin ağrı, eklem hareket açıklığı (EHA), fonksiyonel durum ve yürüme hızı üzerindeki etkilerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya, Kellgren-Lawrence evrelendirmesine göre evre 2 ve 3 primer DOA tanılı 51 hasta (26 hasta ESWT grubu, 25 hasta kombine FT grubu) dahil edildi. ESWT protokolü, 2,0 bar, 0,25 mJ/mm^2 ve 10 atım/sn frekansında, haftada bir seans olmak üzere toplam 3 seans uygulandı. FT grubuna ise haftada 5 seans toplam 3 hafta 20 dk/gün hot-pack, 30 dk/gün transkutanöz elektriksel sinir stimülasyonu, 10 dk/gün ultrason kombine tedavisi uygulandı. Her iki gruba terapötik ev egzersiz programı verildi. Gruplar 0., 10. ve 21. günlerde vizüel analog skalası (VAS), Western Ontario ve McMaster Üniversitesi Osteoartrit indeksi (WOMAC), EHA ölçümü ve the Timed "Up & Go" (TUG) testi parametreleri ile değerlendirildi.

Bulgular: Gruplar arasında tedavi öncesi ile tedavi sonrası 10. ve 21. gün skorlarında VAS, WOMAC, EHA ve TUG parametrelerinde istatistiksel olarak anlamlı bir fark saptanmadı ($p>0,05$). Grup içi değerlendirmede ise; her iki grupta da tedavi öncesi değerlerine göre 10. ve 21. günlerde VAS, WOMAC, EHA ve TUG parametrelerinde istatistiksel olarak anlamlı bir iyileşme gözlendi ($p<0,05$).

Sonuç: Primer DOA tedavisinde r-ESWT, konvansiyonel FT ile benzer etkinlik göstermiştir. Ancak, daha kesin ve doğru sonuçlara ulaşmak için daha ileri ve geniş kapsamlı çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Ekstrakorporeal şok dalga tedavisi, konvansiyonel fizik tedavi modaliteleri, primer diz osteoartriti

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Introduction

Osteoarthritis is the most prevalent joint disorder in the developed world. The knee is the most commonly involved joint, and knee osteoarthritis (KOA) is the leading cause of physical functional loss and chronic disability, particularly in the elderly population (1). Due to the prolongation of populations' life expectancies, its increased incidence and prevalence have made KOA a significant public health problem (2).

Today, even though KOA's definitive treatment is not yet possible, patients' quality of life can be improved by measures such as reducing pain, increasing mobility, and decreasing disabilities. The pain-relieving effects of pharmacological agents used in KOA treatment are generally limited (3), and they are frequently associated with severe side effects, including bleeding and gastrointestinal ulcers (4). Besides, complementary treatments such as local injections, acupuncture, transdermal patches, cupping therapy, exercise, and laser therapy are used for treating KOA. However, they are not sufficient to take chronic, severe KOA pain under control (5). Even though surgical treatment is usually effective in treating patients with advanced KOA, some elderly patients with limiting comorbidities might not be suitable for such a treatment approach (6). Besides its use in many orthopedic disorders with chronic pain (5,7,8), extracorporeal shockwave treatment (ESWT), which is a non-invasive method performed by administering shock waves from outside the body, can be used as an alternative treatment with a low number of complications in KOA patients (5,9). Various animal studies on KOA treatment have reported that ESWT delayed osteoarthritis progression, improved motor dysfunction, reduced pain, provided regression of osteoarthritis, and manifested chondroprotective effects (9-12). Besides a limited number of recently conducted human studies reporting improvements in pain relief and knee functions with ESWT (7,13,14), there are other studies reporting that it was ineffective (15). The number of studies comparing ESWT therapy with conventional physical therapy (PT) is not enough (16).

In this study, we aimed to compare ESWT with conventional modalities [hot-pack (HP), ultrasound (US), and transcutaneous electrical nerve stimulation (TENS)] regarding their effectiveness on pain, function and joint range of motion (ROM) in patients diagnosed with primary KOA [Kellgren-Lawrence (K-L), stages 2 and 3].

Materials and Methods

The study was designed as a prospective, randomized study. A total of 54 patients who had presented to the Physical Medicine and Rehabilitation Outpatient Clinic in Atatürk University Medical Faculty Research Hospital with the complaint of knee pain and were diagnosed with primary KOA according to the American College of Rheumatology's (ACR) clinical/radiological diagnostic criteria and were at K-L 2-3 stages were included in the study (17). This study was approved by the Ethical Committee of the Atatürk University Medical Faculty (22.04.2019/03; 24). All patients were informed following the Declaration of Helsinki about the study's purpose and procedures to be performed. With computer-assisted simple randomization, patients were divided into two equal groups as group 1 (n=27, radial-ESWT group) and group 2 (n=27, conventional PT modalities group). Written informed consent was obtained from all patients before participating in the study. One patient in the ESWT group and two patients in the PT group quit participating in the study due to personal reasons. As a result, 51 patients were included, consisting of 26 patients in group 1 and 25 in group 2.

The study's inclusion criteria were being diagnosed with primary KOA following the ACR's clinical/diagnostic criteria, being within the age range of 40-70 years, and having radiological signs of knee degeneration (stages 2 or 3 according to the K-L staging).

The study's exclusion criteria were to have a pathology that prevented ambulation, a history of spinal stenosis, evidence of a neurological disorder in history or physical examination, a disorder (inflammatory or metabolic) that could cause secondary osteoarthritis, intra-articular knee injections within the last one year, non-steroidal anti-inflammatory drugs (NSAIDs) within the last one week, and a history of surgery for the knee joint.

Interventions

In group 1, a total of three ESWT sessions, one per week, with 3000 beats, 10 Hz, 2.0 bar, 0.125 mJ/mm^{2,} were performed as the ESWT protocol. In group 1, the first treatment session was on the first day of the study, the second treatment session was on the 8th day of the study, and the third treatment session was on the 15th day of the study. The first 1000 beats were applied at the knee joint capsule (trigger points) at the supine position and the knee joint at 90° flexion (Figure 1). The successive 2000

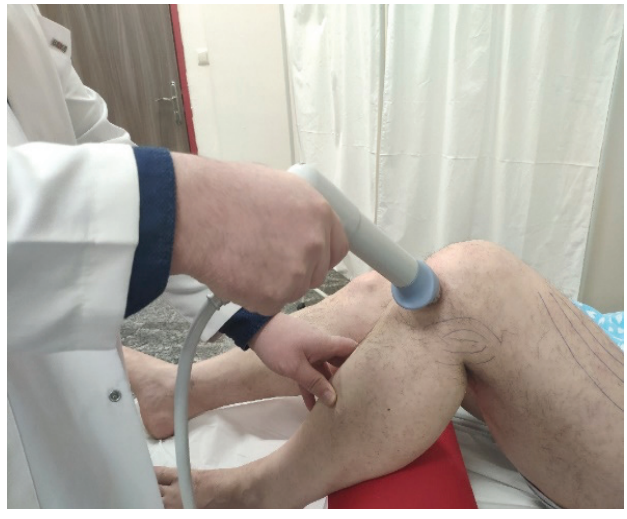

Figure 1. Application of ESWT to trigger points in knee osteoarthritis
ESWT: Extracorporeal shockwave treatment

beats were applied at the quadriceps muscle region and the peri-articular area outside the popliteal region while the patient was lying at the supine position and the knee joint at 30° flexion (Figure 2).

In group 2, a combined protocol, involving 20 minutes of HP, 30 minutes of TENS (with 20-60 microseconds pulse duration, 95 Hz stimulus frequency, and the intensity adjusted according to the patient, and not to cause contractions), and 10 minutes of US (with a dose of 1 watt/cm^2) was applied five sessions a week and 15 sessions in total. Besides, therapeutic home exercise programs for the knee, such as joint ROM, stretching, isometric strengthening, and isotonic strengthening exercises, were practically taught and practiced after presenting an exercise form-sheet with pictures and explanations in both groups. This home exercise program is suggested as 30 minutes every day.

Clinical Evaluation

Visual analog scale (VAS) of for pain, knee joint ROM, Western Ontario and McMaster Universities Osteoarthritis index (WOMAC), and the Timed "Up & Go" (TUG) tests were used for assessment of patients' pain and functional status. All patients were evaluated using these parameters before treatment (0-day), the 10th day, and the 21st day after the treatment initiation. VAS pain evaluated the patients' mean resting, activity, and nocturnal pain levels (18). ROM measurements were made actively and passively by a goniometer according to the neutral position 0° method. The WOMAC index and the TUG test were used for the assessment of patients' functional status. WOMAC consists of three subscales and 24 items as Pain (5 items), Stiffness (2 items), and Physical Function (17 items). In its Likert-scale version, the scores are summed up for each subscale's items within the following probable ranges: Pain: 0-20 points, Stiffness: 0-8 points, and Physical Function: 0-68 points (19). For the TUG test, the individuals were asked to stand up from a fixed-arm chair while sitting with feet contacting the floor, walk three meters, turn back from the marked site at the end of three meters, walk back to the chair, and sit on the chair. The duration, recorded as seconds by a stopwatch, was started as soon as the individual's hips lost contact with the chair and stopped when they contacted the chair after turning back (20).

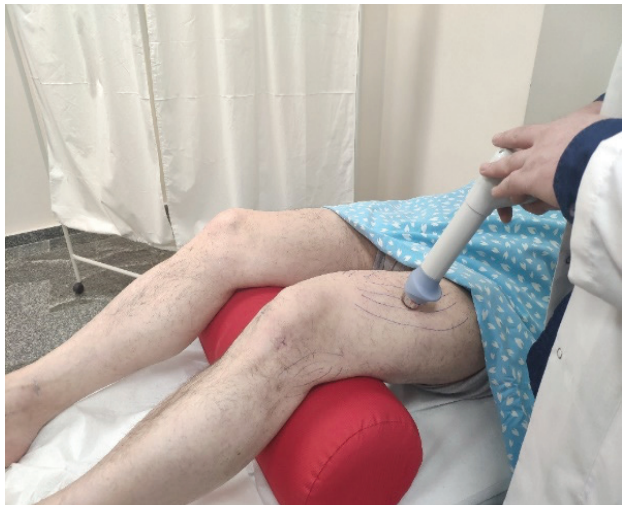

Figure 2. Application of ESWT to quadriceps muscle region in knee osteoarthritis

ESWT: Extracorporeal shockwave treatment

Statistical Analysis

The study's data were evaluated for statistical analysis using the Statistical Package for Social Sciences for Windows, version 22 software. The normality of numerical data distribution was assessed by the Shapiro-Wilk and Kolmogorov-Smirnov tests. The general descriptive statistics of continuous variables such as mean, median, and standard deviation were obtained. The inter-group discrete distribution analyses were made using either chi-square or Fisher's Exact test analysis. For continuous variables' analysis of inter-group differences, the t-test for independent two groups was used for normally distributed data and the Mann-Whitney U test for data that did not have a normal distribution. Variables such as VAS pain, WOMAC, and TUG were intragroup compared using the Analysis of Variance for data showing a normal distribution and the Freadman test for data that were not normally distributed. The group differences were determined using post-hoc and Wilcoxon tests. The results' confidence interval was 95%, and $p<0.05$ was considered statistically significant.

Results

No significant differences were present between the ESWT and PT groups regarding the demographic characteristics (Table 1). The patients' mean 0-day, 10th day, and 21st day ROM, VAS pain, WOMAC, and TUG values were evaluated in both groups.

Regarding intra-group comparisons, in both groups, significant differences were present between the 0-day and 10th-day values of all parameters ($p<0.05$). In the ESWT group, significant differences were present between the 10th-day and 21st-day values of WOMAC-PF, WOMAC-total, and TUG ($p<0.05$), whereas no significant differences were determined regarding other parameters. In the PT group, significant differences were present between the 10th-day and 21st-day values of VAS pain, WOMAC-pain, WOMAC-PF, WOMAC-total, right knee active flexion, left knee passive flexion, and TUG ($p<0.05$), whereas no differences were determined regarding other parameters (Table 2).

Regarding inter-group comparisons, no statistically significant differences were determined among the 0-day, 10th-day, and 21st-day values of all parameters except for the 0-day WOMAC-Stiffness value ($p<0.05$) (Table 3). The changing trends of 0-day, 10th-day, and 21st-day VAS pain and WOMAC values in both groups were shown in Figure 3.

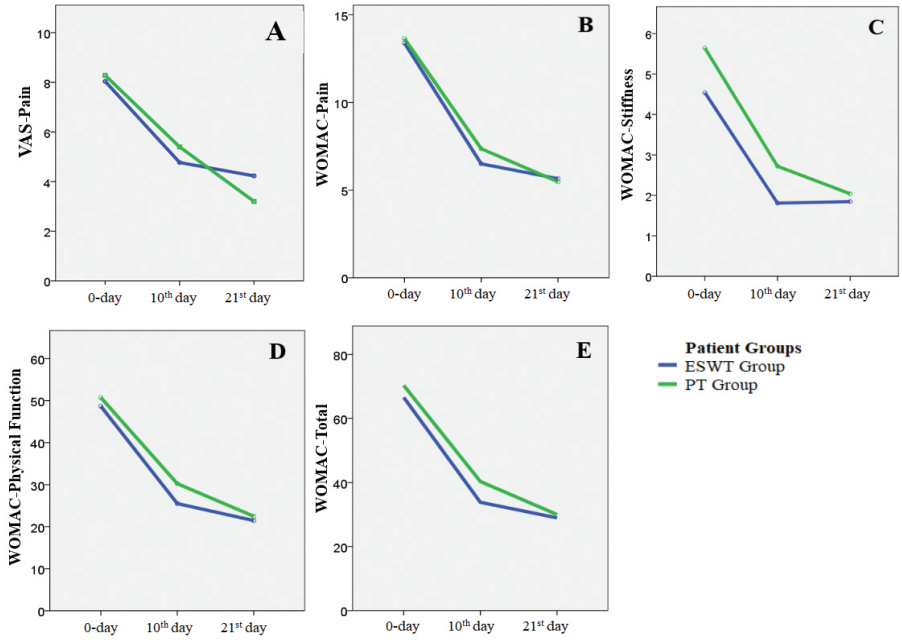

Figure 3. Change graph of VAS pain (A), WOMAC-Pain (B), WOMAC-Stiffness (C), WOMAC-Physical Function (D), WOMAC-Total (E) scores of the groups on 0-day, 10th day and 21st day

VAS: Visual analog scale, WOMAC: Western Ontario McMaster Universities Osteoarthritis index, ESWT: Extracorporeal shockwave treatment, PT: Physical therapy

Table 1. Comparison of the demographic characteristics of the groups

Variables	ESWT (n=26)	PT (n=25)	p-value
Age (mean ± SD; min-max)	57.35±8.3 (42-70)	58.2±6.2 (48-67)	>0.05[a]
Gender			
Male	4 (15.4%)	2 (8%)	>0.05[b]
Female	22 (84.6%)	23 (92%)	>0.05[b]
BMI (kg/m²); (mean ± SD; min-max)	34.07±5 (25.59-44.44)	33.04±5.2 (22.23-45.79)	>0.05[a]
KOA involvement			
Unilateral	6 (23.1%)	1 (4%)	>0.05[b]
Bilateral	20 (76.9%)	24 (96%)	
Right KOA diagnosis			
Medial OA	14 (66.7%)	16 (66.7%)	>0.05[b]
Medial+PF OA	7 (33.3%)	8 (33.3%)	
Right KOA stage			
Stage II	13 (50%)	17 (68%)	>0.05[b]
Stage III	13 (50%)	8 (32%)	
Left KOA diagnosis			
Medial OA	18 (72%)	18 (72%)	>0.05[b]
Medial+PF OA	7 (28%)	7 (28%)	
Left KOA stage			
Evre II	15 (57.7%)	16 (64%)	>0.05[b]
Evre III	11 (42.3%)	9 (36%)	

n: Number of patients, ESWT: Extracorporeal shock wave therapy, PT: Physical therapy, BMI: Body mass index, KOA: Knee osteoarthritis, PF: Patello-Femoral, OA: Osteoarthritis, SD: Standard deviation, min-max: Minimum-maximum, *p<0.05: Statistically significant difference between groups [a]Independent samples t-test, [b]chi-square (2x2) independency test

Table 2. Intra-group comparisons of 0-day, 10th day and the 21st day mean values of the parameters for both groups

	Groups	0-day	10th day	21st day	p-value
VAS	ESWT	8±1.8	4.8±3.1	4.2±3	<0.05^{y,a,b}
	PT	8.3±1.7	5.4±2	3.2±1.9	<0.05^{y,a,b,c}
WOMAC-pain	ESWT	13.4±2.5	6.5±3	5.7±3.4	<0.05^{x,a,b}
	PT	13.6±3.3	7.4±3.9	5.5±3.4	<0.05^{y,a,b,c}
WOMAC-stiffness	ESWT	4.5±2.1	1.8±1.6	1.8±1.3	<0.05^{y,a,b}
	PT	5.6±1.3	2.7±1.6	2±1.4	<0.05^{y,a,b}
WOMAC-PF	ESWT	48.7±9.5	25.5±9.6	21.5±10.3	<0.05^{y,a,b,c}
	PT	50.7±9.4	30.2±13.2	22.5±11.1	<0.05^{y,a,b,c}
WOMAC-total	ESWT	66.6±12.3	33.8±13.3	29±13.9	<0.05^{x,a,b,c}
	PT	70.3±13.2	40.3±18.2	30±15.4	<0.05^{y,a,b,c}
Right knee Flexion-active	ESWT	111±13	115±12	115±14	<0.05^{y,a,b}
	PT	108±16	112±14	116±12	<0.05^{y,a,b,c}
Right knee Flexion-passive	ESWT	125±1	129±12	130±11	<0.05^{y,a,b}
	PT	123±12	124±12	130±9	<0.05^{y,b,c}
Left knee Flexion-active	ESWT	107±11	113±10	116±10	<0.05^{y,a,b}
	PT	108±13	110±16	117±13	<0.05^{x,b,c}
Left knee Flexion-passive	ESWT	122±8	129±7	131±6	<0.05^{y,a,b}
	PT	121±13	125±11	130±11	<0.05^{y,a,b,c}
TUG (sec)	ESWT	12.5±3.4	10.1±2.5	9.6±2.2	<0.05^{y,a,b,c}
	PT	13.7±5	10.9±2.3	10.1±2.1	<0.05^{y,a,b,c}

VAS: Visual analog scale, WOMAC: Western Ontario McMaster Universities Osteoarthritis index, PF: Physical function, sec: second, [x]Repeated Measures ANOVA, [y]Freadman test. Values are given as mean ± standard deviation.
[a]Difference between 0-day and 10th day, [b]Difference between 0-day and 21st day, [c]Difference between 10th day and 21st day, p<0.05: Statistically significant difference

Discussion

KOA is the leading cause of disability and joint pain in adults and is mainly characterized by exacerbating chronic pain due to aggravated central sensitization and decreased physical function (1,21). Even though the exact treatment mechanism of ESWT in KOA has not been fully revealed in the literature, several hypotheses have been proposed on this subject. ESWT has been suggested to create an analgesic effect through a reflex mechanism by inducing axon excitability and inhibiting the non-myelinated sensory nerve fibers (22). Besides, it has been suggested in several animal studies that the analgesic effect might have occurred due to the reduction of calcitonin gene-related peptide and substance P, which are significant neuropeptides of nociceptive pathways in the target tissues and dorsal root ganglions. On the other hand, it was stated that ESWT might have contributed to healing by reducing KOA progression, cartilage disruption, and chondrocyte apoptosis through reduction of nitric oxide levels, leading to local endorphin release and reformation of subchondral bone (16). ESWT has been reported to be superior to placebo-ESWT in pain reduction and improvements in knee functions and TUG values (16,23-25). Kim et al. (13) in their study on K-L grade 2 and 3 KOA patients, reported that ESWT at a moderate-level energy intensity (0.093 mJ/mm^2) had led to more improved results regarding pain relief and functional restoration when compared to ESWT at a low-level energy intensity (0.040 mJ/mm^2). They suggested that the higher energy intensity had significantly inhibited the non-myelinated nerve fibers and had produced a more significant analgesic effect. In a meta-analysis review study, Wang et al. (26) reported that ESWT had a positive impact up to 12 months on the analgesic effect evaluated with VAS pain and the physical function evaluated with WOMAC. Besides, even though they reported that ESWT was more effective when used with moderate-level intensities over 0.093 mJ/mm^2, they stated that the ESWT frequency and the dose levels required for achieving maximal improvement were not clear. On the other hand, Imamura et al. (15) in their study on primary KOA patients with K-L grades 2-4, reported that ESWT with 2000 beats, 0.10-0.16 mJ/mm^2 energy intensity, 2.5-4.0 bar pressure, and 8 Hz frequency in patients with severe KOA was effective on WOMAC-Pain values, but ineffective on VAS pain scores, and that higher energy intensities would have been required for treatment success.

Our study determined that both treatments significantly improved KOA patients' ROM, pain, and function values on the 10th and 21st days after the treatment. In the ESWT group, improvements of function and TUG values were determined

Table 3. Comparisions of the parameters of both groups at 0-day, 10th day and the 21st day

	ESWT	PT	
	Mean ± SD	Mean ± SD	p-value
VAS (0-day)	8±1.8	8.3±1.7	>0.05[b]
VAS (10th day)	4.8±3.1	5.4±2	>0.05[b]
VAS (21st day)	4.2±3	3.2±1.9	>0.05[b]
WOMAC-pain (0-day)	13.4±2.5	13.6±3.3	>0.05[b]
WOMAC-pain (10th day)	6.5±3	7.4±3.9	>0.05[a]
WOMAC-pain (21st day)	5.7±3.4	5.5±3.4	>0.05[a]
WOMAC-stiffness (0-day)	4.5±2.1	5.6±1.3	<0.05*[b]
WOMAC-stiffness (10th day)	1.8±1.6	2.7±1.6	>0.05[b]
WOMAC-stiffness (21st day)	1.8±1.3	2±1.4	>0.05[b]
WOMAC-PF (0-day)	48.7±9.5	50.7±9.4	>0.05[b]
WOMAC-PF (10th day)	25.5±9.6	30.2±13.2	>0.05[a]
WOMAC-PF (21st day)	21.5±10.3	22.5±11.1	>0.05[a]
WOMAC-total (0-day)	66.6±12.3	70.3±13.2	>0.05[b]
WOMAC-total (10th day)	33.8±13.3	40.3±18.2	>0.05[a]
WOMAC-total (21st day)	29±13.9	30±15.4	>0.05[a]
Right knee Flexion-active (0-day)	111±13	108±16	>0.05[b]
Right knee Flexion-passive (0-day)	125±11	123±12	>0.05[b]
Left knee Flexion-active (0-day)	107±11	108±13	>0.05[a]
Left knee Flexion-passive (0-day)	122±8	121±13	>0.05[b]
Right knee Flexion-active (10th day)	115±12	112±14	>0.05[b]
Right knee Flexion-passive (10th day)	129±12	124±12	>0.05[b]
Left knee Flexion-active (10th day)	113±10	110±16	>0.05[b]
Left knee Flexion-passive (10th day)	129±7	125±11	>0.05[b]
Right knee Flexion-active (21st day)	115±14	116±12	>0.05[b]
Right knee Flexion-passive (21st day)	130±11	130±9	>0.05[b]
Left knee Flexion-active (21st day)	116±10	117±13	>0.05[b]
Left knee Flexion-passive (21st day)	131±6	130±11	>0.05[b]
TUG (sec) (0-day)	12.5±3.4	13.7±5	>0.05[b]
TUG (sec) (10th day)	10.1±2.5	10.9±2.3	>0.05[b]
TUG (sec) (21st day)	9.6±2.2	10.1±2.1	>0.05[a]

SD: Standard deviation, VAS: Visual analog scale, WOMAC: Western Ontario McMaster Universities Osteoarthritis index, PF: Physical function, TUG: The Timed "Up & Go", sec: second, *p<0.05: Statistically significant difference between groups [a]Independent samples t-test [b]Mann-Whitney U test

to continue between 10-21 days. Thus, we determined that the significant improvement effect of ESWT on the ROM and pain values started faster than those of the PT. Besides, ESWT's effect on function continued increasingly until the 21st day. In their study, Chen et al. (27) reported that ESWT ameliorated the knee pain and improved the joint ROM, and following every ESWT session, they observed that the improvement in ROM occurred rapidly, consistent with the pain and ROM values in our study. Our study determined that all parameters progressively improved until the 21st day in the PT Group, and no significant differences were present between the treatment groups on both the 10th and 21st days.

In our study, ESWT was performed with 3000 beats and moderate-level (0.125 mJ/mm^2) energy intensity once a week in KOA patients with K-L grades of 2-3. The significant improvements observed in both the VAS pain scores and function values were consistent with the literature (24,25). On the other hand, since the number of beats was less (2000 beats) and KOA patients with a K-L grade of 4 were included in Imamura et al.'s (15) study, their results might not have been similar to our study. Therefore, we suggest that a sufficient energy intensity dosing, number of beats, and application frequency should be set up to achieve maximal-level effectiveness in ESWT.

In the meta-analysis study performed by Wang et al. (26), in the four articles considering ESWT's reliability, pain and discomfort were reported to occur due to minor complications such as mild bruising, temporary soft tissue swelling, or temporary flushing after ESWT. In the same study, five articles reported no clinical neuromuscular, equipment-related, or systemic side effects after ESWT. On the other hand, degenerative hyaline cartilage changes were reported to be associated with energy intensity levels over 0.50 mJ/mm^2 in rats (28). We determined no significant local or systemic side effects of ESWT in our study. However, some patients in the ESWT group expressed slightly increased pain in the application area at the onset of treatment, decreasing afterward during and after the session. Therefore, ESWT can be used as an alternative treatment method in patients, particularly the elderly, who can not use NSAIDs because of their gastrointestinal and cardiovascular side effects due to its relative reliability and low-degree side effects. Besides, ESWT might be a non-invasive, effective, low complication rate, and reliable treatment option with lower cost and not necessitating hospitalization when compared to other conservative treatment methods and surgery (29).

Our study's limitations were the lack of a control group and absence of study groups without exercise therapy, receiving only-ESWT and sham-ESWT treatments. Moreover, because our study covered 21 days only, we could not evaluate the long-term efficacy of ESWT in KOA.

Conclusion

In conclusion, we determined that both ESWT and conventional PT applications on pain, ROM and function were similarly effective in KOA treatment. When its faster starting effects on pain and joint ROM and other potential advantages are considered, ESWT can be an effective, safe, and promising alternative treatment option. However, placebo-controlled studies with more extensive participation involving long-term follow-up periods are required to determine the optimal energy dose, number of beats, and application frequency.

Ethics

Ethics Committee Approval: This study is approved by the Atatürk University Ethics Committee with the date 22.04.2019 and decision number 24.

Informed Consent: All patients were informed following the Declaration of Helsinki about the study's purpose and procedures to be performed.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Yeni Tanı Alan Akromegali Hastalarında Kemik Mineral Dansitometri Ölçümlerinin Değerlendirilmesi

Evaluation of Bone Mineral Densitometry Measurements in Newly Diagnosed Acromegaly Patients

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Öz

Amaç: Akromegali artmış büyüme hormonu (BH) ve insülin benzeri büyüme faktörü-1 (IGF-1) konsantrasyonlarına neden olan kronik bir hastalıktır. BH ve IGF-1 düzeyinin kemik homeostazı, kemik döngüsü ve kemik "remodeling"i üzerinde önemli etkileri vardır. Akromegali ve kemik mineral yoğunluğu (KMY) arasındaki ilişkiyi inceleyen çalışmaların sonuçları tartışmalıdır. Bu çalışmanın amacı yeni tanı alan akromegali hastalarında KMY'yi değerlendirmek ve BH ile IGF-1 düzeyinin KMY ile ilişkisini belirlemektir.
Gereç ve Yöntem: Bu kesitsel çalışma Sağlık Bilimleri Üniversitesi, Dışkapı Yıldırım Beyazıt Eğitim Araştırma Hastanesi kayıtlarından kemik mineral yoğunluğu değerlerine ulaşılabilen ve hipogonadizm öyküsü olmayan yeni tanı almış 36 akromegali hastası üzerinde yürütüldü. BH ile IGF-1 düzeylerinin femur ve lomber bölgelerden ölçülen KMY ile olan ilişkileri ayrı ayrı incelendi.
Bulgular: Hastaların ortalama yaşı 46,2±12,5 yıl olarak saptandı. Medyan IGF-1 ve BH düzeyleri sırasıyla 551 ng/mL ve 8,2 ng/mL idi. Hastaların %58,3'ünde osteopeni mevcutken hiçbir hastada osteoporoz saptanmadı. Femur boynundan ölçülen KMY değeri ile IGF-1 (r=0,484, p=0,036) ve BH (r=0,595, p=0,007) düzeyleri arasında pozitif korelasyon saptandı. Lomber vertebralardan değerlendirilen KMY ölçümleri ile BH ve IGF-1 düzeyleri arasında anlamlı bir korelasyon yoktu.
Sonuç: Yeni tanı alan ögonodal akromegali hastalarında BH ve IGF-1 düzeylerindeki artışın femurdan ölçülen KMY'yi artırdığı bulundu. Lomber bölgeden ölçülen KMY ile BH ve IGF-1 düzeyleri arasında anlamlı bir ilişki saptanmadı.
Anahtar kelimeler: Akromegali, kemik mineral yoğunluğu, büyüme hormonu, insülin benzeri büyüme faktörü-1

Abstract

Objective: Acromegaly is a chronic disease that causes high concentrations of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). GH and IGF-1 levels have important effects on bone homeostasis, bone turnover, and bone remodeling. The results of studies investigating the relationship between acromegaly and bone mineral density (BMD) are controversial. The aim of the current study was to evaluate BMD in newly diagnosed acromegaly patients and to determine the relationship between GH and IGF-1 levels with BMD.
Materials and Methods: This cross-sectional study was conducted on 36 newly diagnosed acromegaly patients without a history of hypogonadism, whose BMD values can be obtained from the records of University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital. The relationship between GH and IGF-1 levels and BMD measured from the femur and lumbar regions was examined separately.
Results: The mean age of the patients was 46.2±12.5 years. Median IGF-1 and BH levels were 551 ng/mL and 8.2 ng/mL, respectively. While 58.3% of the patients had osteopenia, no osteoporosis was found in any patient. A positive correlation was found between the BMD value measured from the femoral neck and IGF-1 (r=0.484, p=0.036) and GH (r=0.595, p=0.007) levels. There was no significant correlation between BMD measurements evaluated from lumbar vertebrae and GH and IGF-1 levels.
Conclusion: It was found that the increase in GH and IGF-1 levels in newly diagnosed eugonadal acromegaly patients increased BMD measured from the femur. There was no significant relationship between BMD measured from the lumbar region and GH and IGF-1 levels.
Keywords: Acromegaly, bone mineral density, growth hormone, insulin-like growth factor-1

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Giriş

Akromegali genellikle hipofiz adenomuna bağlı aşırı büyüme hormonu (BH) üretimi sebebiyle artmış insülin benzeri büyüme faktörü-1 (IGF-1) ile karakterize, iskelet sisteminde şekil bozukluğu ile birlikte sistemik etkilere neden olan bir hastalıktır. Genellikle 4. veya 5. dekadda tanı alır (1,2). Sinsi bir hastalık olup semptom başlangıcı ile tanı konulması arasındaki süre ortalama 5 yıldır (3). BH ve IGF-1 kemik büyümesi, modellemesi ve yeniden şekillenmesinin önemli düzenleyicileridir (4). BH'nin kemik üzerine direkt etkisi olmasına rağmen etkilerinin büyük çoğunluğu IGF-1 aracılığı ile gerçekleşir. Osteoblastların proliferasyonu ile mezenkimal prekürsör hücrelerin kondrogenez veya osteoblastogenez yönünde farklılaşmasını uyarırken adipogenezin yavaşlamasını sağlar (5).

BH fazlalığı, çocukluklarda uzun kemiklerin epifiz plakları kapanmadan önce ortaya çıkarsa lineer büyümeye neden olur ve hipofizer gigantizm tablosu ile sonuçlanır (6). Erişkin yaşlardaki fazlalığının ise lineer büyümeye etkisi yoktur. Yumuşak dokularla birlikte el, ayak ve yüz kemiklerinde genişlemeye neden olur. BH'nin arttığı durumlarda kemik döngüsü hızlanır (7). Aktif akromegali hastalarında osteokalsin gibi kemik yapım belirteçleri ile idrar hidroksiprolin, serum C-terminal kollajen tip 1 çapraz bağları ve idrar tip 1 kollajen N-telopeptid gibi kemik rezorpsiyon belirteçleri artar (5). Buna ek olarak çalışmalarda serum kalsiyum ve fosfat düzeyleri ile birlikte günlük idrar kalsiyum ekskresyonunun da arttığı gösterilmiştir (8-10). Aktif akromegali hastalarına eşlik eden hiperkalsemi, hiperfosfatemi ve hiperkalsiüri osteoporoz gelişimine katkıda bulunabilir.

Akromegali ve kemik mineral yoğunluğu (KMY) arasındaki ilişkiyi inceleyen çalışmaların sonuçları tartışmalıdır. Literatür incelendiği zaman KMY'de artışın saptandığı veya değişmediği çalışmaların yanı sıra KMY'de azalmanın saptandığı çalışmalar da bildirilmiştir (11-14). Çalışma popülasyonlarının çeşitliliği, çalışma protokolündeki farklılıklar, akromegali hastalığının süresi, hastalığın aktivitesi, KMY'nin ölçüldüğü bölgelerin farklı olması, hastalıkla beraber hipogonadizmin var olup olmaması gibi nedenler bu farklı sonuçlara neden olabilir. Biz bu çalışmada hipogonadizmi olmayan yeni tanı almış akromegali hastalarında KMY'yi değerlendirmeyi ve BH ile IGF-1 düzeyinin KMY üzerine etkilerini incelemeyi amaçladık.

Gereç ve Yöntem

Bu çalışma için Sağlık Bilimleri Üniversitesi, Dışkapı Yıldırım Beyazıt Eğitim Araştırma Hastanesi Endokrinoloji ve Metabolizma Kliniği'nde Eylül 2015-Aralık 2020 yılları arasında akromegali tanısı alıp takip edilen 66 hastanın dosyası geriye yönelik olarak incelendi. Postmenapozal 11 kadın hasta, hipogonadizmi olan 5 erkek hasta, sigara kullanımı olan 2 hasta, alkol kullanımı olan 1 hasta, primer hiperparatiroidisi olan 1 hasta ve dosyadaki verileri eksik olan 10 hasta çalışma dışında bırakıldı. Sonuç olarak çalışmaya yeni tanı alan ve KMY ölçümleri bulunan 36 akromegali hastası dahil edildi. Elli yaş üzeri erkeklerde T-skoru -2,5 ve altı olanlar, premenapozal kadın ve 50 yaşından küçük erkeklerde ise Z-skoru -2 ve altı olan hastalar osteoporoz olarak kabul edildi. T-skoru -1 ile -2,5 arasında olan hastalar osteopeni olarak kabul edildi. Akromegali tanısı, karakteristik klinik özellikler, yaş ve cinsiyet için normal değerlerin üzerinde IGF-1 seviyelerinin olması ve oral glukoz yüklemesinden sonra BH düzeyinin ≥1 ng/mL olması ile konuldu. Tüm hastaların hipofize yönelik yapılan manyetik rezonans görüntülemesinde hipofiz adenomu mevcuttu.

Hasta verileri bir anket formu aracılığıyla antropometrik ölçümler ve hastane kayıtlarındaki bilgiler kullanılarak toplandı. Hastaların yaşı, cinsiyeti, antropometrik ölçümleri, D vitamini düzeyleri, kalsiyum-fosfor magnezyum gibi elektrolit düzeyleri, ön hipofiz hormon paneli ve çift enerjili X-ışını absorbsiyometri (DXA) ölçümleri değerlendirme kapsamına alındı. Vücut kitle indeksi (VKİ) vücut ağırlığının metre kare cinsinden vücut boyuna bölünmesiyle (kg/m^2) hesaplandı. Venöz kan örnekleri en az 8-12 saatlik açlığı takiben sabah saat 8:00 ile 09:00 arasında alındı. BH ve IGF-1 düzeyleri, IMMULITE 2000 Xpi'de (Siemens Healthcare Diagnostics Inc.) kemilüminesans yöntemi ile analiz edildi. BH için normal aralık 0-0,8 ng/mL idi. IGF-1 için normal aralık 64-188 ng/mL idi. Hastaların KMY'leri DXA ölçümü ile belirlendi. Lomber vertebra ve proksimal femurdan DXA cihazı ile yapılan KMY sonuçları gr/cm^2 olarak ve pik genç erişkin kemik yoğunluk değerine göre belirlenen Z ve T-skorları ile değerlendirildi.

Bu çalışma için Sağlık Bilimleri Üniversitesi, Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu'ndan (karar no: 77/05, tarih: 09.12.2019) onay alındı ve çalışma Helsinki Bildirgesi'ne uygun olarak yürütüldü.

İstatistiksel Analiz

Tüm veriler bilgisayar ortamına aktarıldı ve istatistiksel analizler için SPSS for Windows, versiyon 21 (IBM Corporation, Armonk, New York, United States) uygulama istatistiksel analiz programı kullanılarak analiz edildi. Ölçümlerin normal dağılıma uyup uymadığı Kolmogorov-Smirnov testi ile analiz edildi. Kategorik değişkenler sıklık ve yüzde (%) ile ifade edildi. Normal dağılıma uyan devamlı değişkenler ortalama ± standart sapma olarak, normal dağılıma uygun olmayan değişkenler ise medyan (minimum-maksimum) değerler olarak özetlendi. Değişkenler arasındaki ilişkiler normal dağılıma uygun olup olmamasına göre Spearman veya Pearson korelasyon analizi ile incelendi. Tüm analizlerde istatistiksel olarak $p<0,05$ düzeyi anlamlı olarak kabul edildi.

Bulgular

Çalışmaya %55,6'sı (n=20) kadın ve %44,4'ü (n=16) erkek olan, ortalama yaşı 46,2±12,5 yıl olan 36 yeni tanı akromegali hastası dahil edildi. Hastaların %33,3'ünde (n=12) hipertansiyon ve %19,4'ünde diyabet öyküsü mevcuttu. Çalışmaya alınan hastaların antropometrik ve laboratuvar verileri Tablo 1'de verilmiştir. Hastaların ortalama adenom boyutu 12,7 mm (5-43) olup %16,6'sında (n=6) çevre yapılara invazyon mevcuttu.

Medyan IGF-1 ve BH düzeyleri sırasıyla 551 ng/mL ve 8,2 ng/mL saptandı. Adenom boyutu büyük olan hastalarda BH sekresyonunun daha fazla olduğu gözlendi (r=0,443, p=0,014). Adenom boyutu ile IGF-1 düzeyi arasında korelasyon izlenmedi (r=0,096, p=0,602). Alkalen fosfataz düzeyi ile BH düzeyi arasında pozitif korelasyon saptandı (r=0,437, p=0,033). Kalsiyum, fosfor, vitamin D düzeyi ile BH ve IGF-1 düzeyi arasında istatistiksel açıdan anlamlı bir korelasyon saptanmadı (p>0,05).

DXA sonuçları değerlendirildiği zaman hastaların %58,3'ünde (n=21) osteopeni saptandı. Hastaların hiçbirinde osteoporoz saptanmadı. Hastaların femur boynundan değerlendirilen KMY düzeyi 1,15±0,13 g/cm^2 saptandı. Erkek ve kadın hastalar karşılaştırıldığında lomber bölge ve femurdan ölçülen KMY değerleri arasında fark saptanmadı. VKİ ile KMY ölçümleri arasında istatistiksel açıdan anlamlı bir korelasyon saptanmadı. Femur boynundan ölçülen KMY değeri ile IGF-1 (r=0,484, p=0,036) ve BH (r=0,595, p=0,007) düzeyleri arasında pozitif korelasyon saptandı. Femur T-skoru ile BH arasında pozitif korelasyon saptandı (r=0,507, p=0,027). Lomber bölge KMY ölçümleri ile BH ve IGF-1 düzeyleri arasında istatistiksel açıdan anlamlı bir korelasyon bulunmadı. Hastaların KMY ölçümleri ve bu ölçümlerin IGF-1/BH düzeyleri ile korelasyon analizi Tablo 2'de verilmiştir.

Tartışma

Bu çalışma, yeni tanı alan akromegali hastalarında artmış BH ve IGF-1 düzeylerinin proksimal femur KMY'si ile pozitif korele olduğunu gösterirken lomber bölge KMY ölçümleriyle ilişkilerinin olmadığını göstermektedir. Ayrıca artmış BH sekresyonuyla proksimal femur T-skoru arasında pozitif korelasyon saptanmıştır. BH fazlalığının KMY üzerindeki etkisi ile ilgili bilgiler literatürde değişiklik göstermektedir. Bazı çalışmalarda KMY'nin arttığı veya referans aralıklar içinde olduğu bildirilirken, bazı çalışmalarda azaldığı bildirilmiştir (7,15-17).

Padova ve ark. (18) 20 (12 aktif, 8 remisyon) akromegali hastasını değerlendirdikleri bir çalışmada LI-L4 DXA sonucuna göre hastaların %32'sinde osteopeni ve %26'sında osteoporoz olduğunu bildirmişlerdir. Femur boynu DXA sonucuna göre hastaların %42'sinde osteopeni ve %32'sinde osteoporoz

Tablo 1. Hastaların klinik ve laboratuvar verileri

	Sonuçlar	**Referans aralıkları**
Boy (cm)	166,5±8	-
Kilo (kg)	85,1±17,5	-
Vücut kitle indeksi (kg/m^2)	30,8±6,9	-
Kreatinin (mg/dL)	0,74±0,17	0,7-1,2
Açlık kan glukozu (mg/dL)	108,2±26,7	74-106
HbA1c (%)	6,1±0,9	-
IGF-1 (ng/mL)	551 (329-1581)	64-188
Büyüme hormonu (ng/mL)	8,2 (1,6-55,7)	0-10
TSH (mIU/L)	1,05 (0,27-3,8)	0,27-4,2
Serbest T4 (ng/dL)	0,9 (0,6-1,6)	0,93-1,7
ACTH (pg/mL)	33,6 (7-117)	0-46
Kortizol (mg/dL)	11,9±4,3	6,7-22,6
FSH (IU/L)	4,76 (2,7-15,3)	1,27-19,26
LH (IU/L)	2,79 (1,28-8,53)	1,24-8,62
Total testosteron* (ng/dL)	317 (249-479)	175-781
Östradiol** (ng/L)	28 (5-237)	-
Prolaktin (ng/mL)	12,7 (0,2-77)	2,64-13,13
Kalsiyum (mg/dL)	9,6±0,43	8,6-10,2
Fosfor (mg/dL)	4,1±0,65	2,5-4,5
Magnezyum (mg/dL)	1,94±0,18	1,6-2,6
Parathormon (pg/mL)	44,3±16,7	19,8-74,9
25(OH)D (ng/mL)	12 (5,4-44,3)	-
Alkalen fosfataz (U/L)	87,9±28,8	40-129

IGF-1: İnsülin benzeri büyüme faktörü-1, TSH: Tiroid stimülan hormon, ACTH: Adrenokortikotrop hormon FSH: Follikül uyaran hormon, LH: Luteinizan hormon, HbA1c: Hemoglobin A1c, 25(OH)D: 25-hydroksivitamin D
*Erkek hasta grubunda değerlendirilmiştir.
**Kadın hasta grubunda değerlendirilmiştir.

olduğunu raporlamışlardır. Aynı çalışmada L1-L4 düzeyinden ölçülen KMY 0,95±0,15 g/cm^2, femur bölgesinde ölçülen KMY 0,79±0,12 g/cm^2 olarak saptanmıştır. Bizim çalışmamızdan farklı olarak bu çalışmada 7 kadın hastanın postmenapozal olması ve 4 hastanın hipogonadizm öyküsünün olması osteoporoz gelişimine zemin hazırlamış olabilir. Son yayınlar özellikle aktif hastalığı olan ve hipogonadizmin eşlik ettiği akromegali hastalarında kemik döngüsünün arttığını ve vertebral kırıkların daha sık olduğunu göstermektedir. Hipogonadizmin eşlik ettiği akromegali olgularında vertebral KMY'nin gonadal fonksiyonları normal olan olgulardan daha düşük bulunması, vertebral KMY'nin BH etkisinden çok gonadal fonksiyonlar ile ilişkili olduğu görüşünü desteklemektedir. Sadece birkaç çalışma akromegali hastalarında düşük KMY bildirmiştir ve bu durumun tedavi edilmemiş hipogonadizm varlığıyla ilişkili olduğu gösterilmiştir (19). Hipogonadizm öyküsü olmayan hastalarda ön kol ve kalçada KMY'nin korunduğu, hatta arttığı saptanmış olup hipogonadal akromegali hastaları ve kontrol grubu ile kıyaslandığında KMY'nin daha yüksek olduğu gösterilmiştir (12,15,20).

Akromegali hastalarında cinsiyetin, VKİ'nin ve hastalık süresinin KMY üzerindeki etkisi tartışmalıdır (7,16,20,21). Scillitani ve ark. (16) akromegali hastalarında BH fazlalığının kemik üzerindeki anabolik etkisinin cinsiyetten bağımsız olduğunu raporlamışlardır. Buna ek olarak femurdan ölçülen KMY'nin hastalık süresi ile ilişkili olmadığını, lomber bölgenin KMY'sinin hastalık süresi ile pozitif kolerasyon gösterdiğini saptamışlardır. Ueland ve ark. (7) akromegali hastalarında femur ve lomber KMY ölçümlerinin her iki cinsiyette farklılık göstermediğini ama akromegalik kadınlarda total vücut KMY'sinin azaldığını bildirmişlerdir. Hastalık süresi ile total Z-skoru arasında negatif ilişki bulmuşlar ve yaşı, VKİ'yi ve cinsiyeti total KMY'nin bağımsız belirleyicileri olarak bildirmişlerdir. Qin ve ark. (21) lomber bölge ve kalçadan ölçülen Z-skorları ile hastalık süresi arasında negatif bir korelasyon olduğunu raporlamışlar ama VKİ ile Z-skoru arasında bir ilişki bulamamışlardır. Bolanowski ve ark. (20) ise akromegali hastalarında KMY'nin cinsiyete ve kemik yapısından bağımsız olarak ölçüm yapılan bölgeye göre değiştiğini bildirmişlerdir. Bu çalışmaların hepsinde hipogonodal ve aktif hastalığı olmayan akromegali hastaları analize dahil edilmiştir. Bizim çalışmamızda cinsiyetin ve VKİ'nin KMY ölçümleri ile ilişkisi saptanmamıştır. Bu çalışma önceki çalışmalardan farklı olarak yeni tanı alan akromegali hastaları ile yapılmıştır. Çalışmaya alınan hasta popülasyonun önceki çalışmalardan farklı seçilmesinin nedeni ise IGF/BH düzeylerindeki artışın KMY üzerindeki etkisini hastalık süresinden ve tedavi etkisinden bağımsız olarak değerlendirmektir.

Aksiyel iskeletin %70'i trabeküler kemikten oluşurken, appendiküler iskeletin %90'ı kortikal kemikten oluşmaktadır. BH'nin kortikal ve trabeküler kemik üzerine etkileri farklıdır. Trabeküler kemikler kortikal kemiklere kıyasla rezorpsiyona daha duyarlıdır (7). Akromegali hastalarında kortikal kemik kitlesi genellikle artarken, trabeküler kemik kitlesi değişkenlik gösterir (12,22). Akromegali daha çok trabeküler kemik mikromimarisini olumsuz yönde etkilemektedir. Kotzmann ve ark. (13) seksen iki akromegali hastasını içeren çalışmalarında, KMY'yi

Tablo 2. İnsülin benzeri büyüme faktörü-1 ve büyüme hormonu düzeylerinin kemik mineral yoğunlukları ile korelasyon analizleri

	Sonuçlar	IGF-1 ile kolerasyon	BH ile kolerasyon
Femur KMY (g/cm^2)	1,15±0,13	r=0,484 , p=0,036	r=0,595, p=0,007
Femur T-skoru	0,6 (-1,2-2)	r=0,429, p=0,067	r=0,507, p=0,027
Femur Z-skoru	0,9 (-0,7-2,8)	r=0,391, p=0,098	r=0,281, p=0,244
Lomber (L1-L4) KMY (g/cm^2)	1,05±0,12	r=0,228, p=0,363	r=0,294, p=0,236
Lomber (L1-L4) T-skoru	-0,3 (-2,3-2,2)	r=0,274, p=0,271	r=0,287, p=0,247
Lomber (L1-L4) Z-skoru	0,5 (-1,5-3,2)	r=0,039, p=0,877	r=0,123, p=0,627
L1 KMY (g/cm^2)	0,96±0,15	r=0,189, p=0,453	r=0,439, p=0,069
L1 T-skoru	-0,75 (-2,4-3)	r=0,167, p=0,507	r=0,393, p=0,107
L1 Z-skoru	0,5 (-1,9-4)	r=-0,011, p=0,964	r=0,244, p=0,329
L2 KMY (g/cm^2)	1,02±0,15	r=0,191, p=0,448	r=0,321, p=0,194
L2 T-skoru	-0,75 (-2,8-2,6)	r=0,223, p=0,374	r=0,322, p=0,192
L2 Z-skoru	-0,2 (-1,6-3,2)	r=0,118, p=0,641	r=0,293, p=0,238
L3 KMY (g/cm^2)	1,08±0,13	r=0,255, p=0,307	r=0,290, p=0,243
L3 T-skoru	-0,2 (-2,5-2,3)	r=0,278, p=0,265	r=0,265, p=0,287
L3 Z-skoru	0,85 (-1,4-2,9)	r=0,053, p=0,835	r=0,193, p=0,442
L4 KMY (g/cm^2)	1,11±0,12	r=0,407, p=0,094	r=0,064, p=0,801
L4 T-skoru	0,1 (-2,2-2,1)	r=0,412, p=0,090	r=0,057, p=0,823
L4 Z-skoru	0,7 (-2,1-3)	r=0,141, p=0,578	r=0,019, p=0,942

IGF-1: İnsülin benzeri büyüme faktörü-1, BH: Büyüme hormonu, KMY: Kemik mineral yoğunluğu

DXA ile, kemik mikromimarisini ise yüksek rezolüsyonlu periferal kantitatif bilgisayarlı tomografi (HR-pQCT) ile değerlendirmişler ve hipogonadizmin KMY ile mikromimariyi etkileyen en önemli belirleyici faktör olduğunu raporlamışlardır. Gonadal fonksiyonu normal olan akromegalik hastaları kontrol grubu ile karşılaştırdıklarında; distal tibiada DXA ile KMY'yi normal bulmalarına rağmen trabeküler mikromimarinin daha düşük olduğu sonucuna varmışlardır (13). İtalya'da yapılan bir meta-analizde akromegali hastalarında kortikal kemikten zengin olan femur boynunda daha yüksek KMY olduğu raporlanmıştır. Aynı meta-analizde hipogonadizmi olan hastaların normal gonadal fonksiyonu olan hastalara kıyasla lomber omurga ve femur boynunda daha düşük KMY'ye sahip olduğu gösterilmiştir (19). Bu çalışmalar incelendiğinde BH'nin anabolik etkilerinin daha çok kortikal kemik üzerinde meydana geldiği, aksine trabeküler mikromimarinin BH fazlalığından olumsuz etkilendiği düşünülebilir. Scillitani ve ark. (16) akromegali hastalarında BH artışının kemikteki etkisinin ögonadal hastalarda hastalık aktivitesinden bağımsız olarak sadece omurgada belirgin olduğunu ve aktif hastalarda gonadal durumdan bağımsız olarak sadece femur boynunda mevcut olduğunu bildirmişlerdir. Bu çalışmada da hipogonadal hastalar çalışma dışında bırakılarak BH'nin KMY üzerindeki etkisi daha iyi anlaşılmaya çalışılmıştır. Literatür ile uyumlu olarak BH ve IGF-1 düzeyinin kortikal kemikten zengin olan proksimal femur KMY'si ile pozitif korele olduğu, lomber vertebra bölgesinden ölçülen KMY ile ilişkisi olmadığı saptanmıştır.

Bu çalışmanın bazı sınırlayıcı faktörleri mevcuttur. Bunlardan ilki çalışmanın retrospektif olarak tek merkezden yapılması nedeniyle örneklem sayısının az olması ve egzersiz alışkanlıkları gibi KMY ölçümünü etkileyecek bilgilerin tam olarak değerlendirilememesidir. BH ve IGF-1 düzeyleri normal olan kontrol grubunun olmaması çalışmanın gücünü sınırlamaktadır. Akromegalide normal ya da artmış KMY'ye rağmen kırık riski artmıştır (15,17-19,23). Çalışmamızda kırık riskinin değerlendirilmemiş olması BH'nin kemik üzerine etkisini açıklamakta sınırlı kalmaktadır. BH fazlalığı nedeni ile kemik yapılarda ortaya çıkan değişiklikler akromegali hastalarında DXA ölçümlerinin yanıltıcı olmasına neden olabilir. Bu durumu ekarte etmek için yapılan ve kemik kalitesini daha iyi yansıtan HR-pQCT ve kantitatif ultrasonometri gibi tanı araçlarının kullanılmaması çalışmanın bir diğer sınırlayıcı faktörü olarak kabul edilebilir. Son olarak kemik yapım ve yıkım belirteçlerinin ölçümünün yapılamaması BH düzeyinin kemik döngüsü üzerindeki etkisini açıklamakta yetersiz kalmaktadır.

Sonuç

Yeni tanı alan akromegali hastalarında BH ve IGF-1 düzeyi ile proksimal femurdan ölçülen KMY arasında pozitif korelasyon saptanırken, lomber bölgeden ölçülen KMY arasında ilişki saptanmamıştır. Bugün için klinik pratiğimizde akromegali hastalarında osteoporoz açısından hangi tarama metodunu kullanmamız gerektiğini belirleyen bir kılavuz yoktur. Bu çalışma yeni tanı almış akromegali hastalarında yapılmış ve hastaların hiçbirinde osteoporoz gözlenmemiştir. Bu nedenle akromegali hastalarında osteoporoz değerlendirmesini yetersiz kalsiyum alımı, hiperparatiroidi, hipogonadizmin ve steroid tedavisi gibi ek risk faktörleri varlığında önermekteyiz.

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Osteoporosis and Related Factors in Patient with Type 2 Diabetes and Prediabetes

Tip 2 Diabetes Mellituslu ve Prediyabetli Hastalarda Osteoporoz ve İlişkili Faktörler

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Abstract

Objective: Osteoporosis is a disease leading to increased morbidity and mortality. Untreated patients are prone to fracture. In consequence, early diagnosis of osteopenia and osteoporosis is important. Diabetes mellitus (DM) is among the leading causes and is associated with an increased risk of skeletal fractures. The high prevalence of osteoporosis and associated fractures is an important health problem. Although many studies have been conducted to evaluate the frequency of osteoporosis in DM, there are only limited data for prediabetes.
Materials and Methods: Prediabetes patients and type 2 patients with DM applying to our internal medicine and endocrinology and metabolic diseases outpatient clinics were included in this cross-sectional study. Twenty-nine women and 6 men with prediabetes, and 53 women and 8 men with DM were evaluated. Lumbar spine and femur bone mineral densities were investigated using dual-energy X-ray absorptiometry. The study was conducted in accordance with the Declaration of Helsinki.
Results: Lumbar spine T-scores were lower in patients with diabetes. Also, FRAX value for major fracture risk was higher. Prediabetes patients bone mineral density measurements revealed osteopenia. In our study, a major risk factor for osteoporosis was advanced age.
Conclusion: Prediabetic patients are at risk of osteopenia and osteoporosis. Therefore, the necessity of preventive measures starting from the prediabetic period is underlined.
Keywords: Osteopenia, osteoporosis, prediabetes, type 2 diabetes mellitus, bone mineral density, fracture risk

Öz

Amaç: Osteoporoz, morbidite ve mortalitenin artmasına neden olan bir hastalıktır. Tedavi edilmemiş hastalarda artmış kırık riski ile ilişkilidir. Osteopeni ve osteoporozun erken teşhisi bu nedenle önemlidir. Diabetes mellitus (DM) artmış iskelet kırıkları ile ilişkilidir. Osteoporoz ve ilişkili kırıklar önemli bir sağlık sorunudur. DM'de osteoporoz sıklığını değerlendirmek için birçok çalışma yapılmış olsa da prediyabet için yalnızca sınırlı veri vardır.
Gereç ve Yöntem: Kesitsel tipteki bu çalışmaya dahiliye ve endokrinoloji ve metabolizma hastalıkları polikliniğimize başvuran prediyabet hastaları ve tip 2 DM hastaları dahil edildi. Yirmi dokuz kadın ve 6 erkek prediyabet, 53 kadın ve 8 erkek diyabet hastası olarak değerlendirildi. Lomber omurga ve femur kemik mineral yoğunlukları dual-enerji X-ışını absorbsiyometri ile araştırıldı.
Bulgular: Diyabetik hastaların lomber omurga T-skorları daha düşüktü. Ayrıca majör kırık riski için FRAX değeri daha yüksekti. Prediyabet hastalarının kemik mineral yoğunluğu ölçümleri osteopeni olduğunu gösterdi. Çalışmamızda osteoporoz için majör risk faktörü ileri yaştı.
Sonuç: Prediyabetik hastalar osteopeni ve osteoporoz açısından risk altındadır.
Anahtar kelimeler: Osteopeni, osteoporoz, prediyabet, tip 2 diabetes mellitus, kemik mineral yoğunluğu, kırık riski

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Introduction

Diabetes and osteoporosis are increasing and important health issues worldwide (1,2). Poorly controlled diabetes may lead to nephropathy, retinopathy, neuropathy, and cardiovascular diseases. Although diabetes has been included as a secondary cause for osteoporosis, in clinical practice osteoporosis is not screened usually as the other complications (3,4). Osteoporosis may lead to impaired quality of life, and disability due to hip and vertebral fractures. As a natural course of longer life expectancy, the number of fractures increases throughout the world (3-6). Hip fracture especially was found to be related with increased mortality and morbidity (3,4). All types of fractures will also increase the economic expenditure (3,4). There are inconsistent reports for osteoporosis in type 2 diabetes mellitus (T2DM) (3-6). Janghorbani et al. (6) evaluated this risk and concluded in their meta-analysis that diabetes and hip fracture are correlated.

Evaluating a patient with T2DM for osteoporosis only with bone mineral density (BMD) is not adequate, and may lead to underestimation of fracture risk (7). Bone turnover was low in diabetes because markers of bone resorption and formation has been found to be lower than in controls (8). The Women's Health Initiative stated that women with T2DM at baseline had a 20% increased risk of fracture at any part of the body (9). Strotmeyer et al. (10) proposed that patients with impaired fasting glucose (IFG) may be releated with an intermediate risk of fractures. Poor glycaemic control was interreleated with increased likelihood of osteoporosis and osteopenia (11).

Another problem in diabetes may be accompanying obesity, because increased fat may lead to under or over estimation of BMD calculated using dual energy X-ray absorptiometry (DEXA). Quantitative computer-assisted tomography should be an alternative in these patients, by giving more accurate measurements in severe obese patients (12). Bone turnover is decreased in T2DM and the microstructure of bone is altered, especially in patients presenting microvascular complications. The pathophysiological mechanisms underlying bone fragility may be correlated with hyperglycaemia and oxidative stress. Also accumulation of advanced glycation end products (AGEs) may compromise collagen properties and the function of osteocytes (13). Patients with T2DM generally tend to develop sarcopenia with time and they are prone to falls. Alteration in cortical bone structure and bone pattern may also contribute to the risk of fragility. Another problem is that medications used to treat diabetes may interfere with bone health (14).

Bone turnover has been reported to be low both in diabetic and prediabetic patients. The pathophysiologic mechanism of bone changes in diabetes have not yet been explained in details (15,16).

There are many studies about BMD in diabetes, while studies about prediabetes are limited. The purpose of our study was to appraise osteoporosis and related factors such as total calcium intake, D vitamin status, and fracture risk in diabetes as well as in prediabetes patients.

Materials and Methods

A hospital-based cross-sectional study was conducted and all patient were chosen consecutively from our endocrinology and internal medicine department outpatient policlinics between January 2019 and January 2020. All selected participants were patients presenting T2DM or prediabetes and older than 18 years. T2DM was diagnosed based on the standards of medical care in diabetes by the American Diabetes Association as follows: (a) hemoglobin A1c (HbA1c) ≥6.5%; or (b) fasting blood glucose (FBG) ≥126 mg/dL (no caloric intake for 8 hours at least); or (c) 2-h blood glucose ≥200 mg/dL by oral glucose tolerance test (using glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water); or (d) random blood glucose ≥200 mg/dL in patients with typical hyperglycaemia symptoms or hyperglycaemia crisis, which occurs in the absence of unequivocal hyperglycaemia. The results were confirmed by repeating tests (17). Prediabetic patients were defined as patient with IFG, impaired glucose tolerance and/or HbA1c values between 5.7 and 6.4. The exclusion criteria inclusive (a) diagnosis of malignant tumour and severe organ failure; (b) diagnosis of endocrinologic diseases; (c) long-term bedridden patients.

Written informed consent was taken from each patient. The patients were asked for eventual smoking, alcohol consumption and exercising. Also previous histories of fractures and lactose intolerance were queried. Daily calcium intake from each patient was calculated using iofbonehealth-calcium-calculator.

BMD measurement: DEXA (Hologic-Discovery, USA) was used to detect the BMD of each patient at three sites: total lumbar, femur neck, and total hip.

FRAX score was calculated for each patient. Vitamin D levels were measured using a Beckman coulter DxI 800 immunoassay system. Laboratory analyses were performed with a Beckman Coulter AU5800.

This study was approved by the Kütahya Health Sciences University Non-Invasive Clinical Research Ethics Committee (decision no: 2019/2, date: 30.01.2019).

Statistical Analysis

Analyses in prediabetes and diabetes patients were performed separately. Results were expressed as mean value ± standard deviation to describe continuous variables and with n values or percentages to describe categorical variables. Chi-square tests were used for categorical variables, One-Way ANOVA for normally distributed continuous variables, and the Kruskal-Wallis test for skewed continuous variables. Also logistic regression analysis was used to assess the relationship between BMD measurements and affecting factors. A univariate model was used first. Then a multivariate analysis was performed. A two-sided p-value of <0.05 was considered to be statistically significant.

Results

Table 1 shows a comparison between diabetic and prediabetic patients. Twenty-nine women (30%), and 6 men (0.06%)

with prediabetes and 53 women (0.55%) and 8 men (0.08%) with T2DM were included in the study. The mean body mass index was higher in diabetic patients. Other variables such as age, weight, height, and smoking and alcohol consumption were similar between the groups. Calcium intake and lactose intolerance were also similar. Forty-seven women in the diabetic group and 26 women in the prediabetic group did not have any complaint for lactose intolerance. Three women with prediabetes and 6 women with diabetes described lactose intolerance. This numbers were 2 in prediabetic group and 1 in diabetic group for men, respectively (Table 1). Properties and related complications of diabetic patients are given in Table 2. Biochemical values of the patients were similar, but creatinine levels were slightly higher and hemoglobin levels were slightly lower in the diabetic group (Table 3). BMD measurements for hip and lumbar spine, and T-score results for both groups were similar, but FRAX major osteoporosis risk was higher in the diabetic group (Table 4). Among the prediabetics, 8 patients did already know that they had osteoporosis and 1 of them had experienced a fracture, while they were 22 and 3 respectively among the diabetic patients (22 patients presented osteoporosis history; 3 had fractures) (Table 5). Although not all patients with insufficient daily calcium intake had lactose intolerance, all lactose intolerant patients were not ingesting enough calcium daily. Also, none of the patients with sufficient calcium intake had lactose intolerance (Table 6). The frequencies of osteopenia published by World Health Organization (WHO) are given in Table 7. Prediabetes group did not differ from the diabetes group at the hip and lumbar spine for frequency of osteopenia. The osteoporosis frequencies published by WHO are given in Table 8. The frequency of osteoporosis was not different in the prediabetes group at the femoral neck, but it was more frequent at lumbar spine in the diabetic patients.

In order to evaluate factors that may affect osteopenia and/or osteoporosis, a logistic regression analysis was performed. In multivariate analysis, the most important factor was age (Table 9).

In the prediabetes group, there were 2 patients using acarbose and 7 patients using metformin. In the T2DM group, 55 patients were using metformin, 10 patients were using acarbose, 6 patients were using glinides, 21 patients were using sulphonylurea, 10 patients were using pioglitazone. Thirty-seven patients were on DPP-4 inhibitor therapy. Eleven patients were using SGLT-2 inhibitors, 8 patients were using GLP-1 analog therapy and 30 patients were using insulin.

Table 1. Characteristics of the study sample

	DM	Prediabetes	p
Gender (female) (n; %)	53 (64.6%)	29 (82.9%)	NS
Age (year)	59.9±1.2	57.7±2.3	0.202
Height (cm)	1.57±0.01	1.59±0.01	0.239
Body weight (kg)	78.3±1.9	73.9±1.9	0.137
BMI (cm/kg^2)	31.6±0.8	29.1±0.8	0.028*
Menopause (n)	46	21	0.144
Smoker (n)	8	9	0.152
Alcohol consumption (n)	2	0	0.159
Daily Ca intake (mg)	780±41	752±27	0.586
Lactose intolerance	6 female,1 male	3 female, 2 male	0.692

*Although the p-value was <0.05, it was not considered clinically significant.
BMI: Body mass index, DM: Diabetes mellitus, Ca: Calcium

Table 2. Characteristics of and frequency of related complications among the diabetic patients (n=61)

Diabetes variable	
Diabetes duration	12.3±0.9/year
HbA1c level (%, mean ± SD)	7.6±0.1%
Peripheral neuropathy (%)	33.8%
Retinopathy (%)	9.6%
Micro albuminuria (%)	32.2%
Hypertension (%)	44.8%
CAD (%)	19%
Cerebrovascular event (%)	1.6%
Peripheral vascular disease (%)	3.2%

CAD: Cardiovascular disease, SD: Standard deviation

Table 3. Biochemical properties of the study group

	DM	Prediabetes	p
25-(OH)D (ng/mL)	35.7±2.0	32.8±1.2	0.319
Ca levels (mg/dL)	9.4±0.1	9.6±0.07	0.201
Phosphorus (mg/dL)	3.5±0.08	3.5±0.06	0.918
Magnesium (mg/dL)	1.8±0.04	1.9±0.01	0.077
Hemoglobin (g/dL)	13.1±0.1	13.7±0.1	0.013*
Creatinine	0.89±0.02	0.83±0.01	0.035*
ALT (U/L)	21.6±1.8	20.0±1.6	0.565
AST (U/L)	20.2±0.8	21.6±1.3	0.381
HDL (mg/dL)	49.4±1.5	51.3±2.6	0.595
LDL (mg/dL)	116.0±4.5	122.3±4.0	0.202
Triglyceride (mg/dL)	162.5±11.5	145.6±11.1	0.239

*Although the p-value was <0.05, it was not considered clinically significant.
DM: Diabetes mellitus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Ca: Calcium, 25(OH) D: 25-hydroxyvitamin D

Table 4. DEXA results and FRAX risk of the patients

	DM	Prediabetes	p
Femur neck T-score	-0.91±0.17	-0.76±0.19	>0.05
Femur neck BMD (gr/cm^2)	0.747±0.018	0.781±0.025	>0.05
L1-L4 T-score	-1.00±0.19	-0.73±0.19	>0.05
L1-L4 BMD (gr/cm^2)	0.944±0.021	0.972±0.024	>0.05
FRAX major osteoporosis risk (%)	6.7±0.5	5.3±0.7	<0.05*
FRAX femur fracture risk (%)	1.3±0.1	1.1±0.3	>0.05

*There was no significant difference in the risk of femoral fracture between the diabetes and prediabetes groups.
BMD: Bone mineral density, DM: Diabetes mellitus, DEXA: Dual energy X-ray absorptiometry

Table 5. Fracture and history for old osteoporosis diagnosis distribution

				Prediabetes	Diabetes
Old osteoporosis diagnosis	No	Fracture	No	25	34
			Yes	2	5
	Yes	Fracture	No	7	19
			Yes	1	3

Table 6. Distribution of lactose intolerance according to groups, gender and daily calcium intake

					Prediabetes	DM
Male	Lactose intolerance	No	Calcium consumption	Low	4	7
				Enough	0	0
		Yes	Calcium consumption	Low	2	1
				Enough	0	0
Female	Lactose intolerance	No	Calcium consumption	Low	25	36
				Enough	1	11
		Yes	Calcium consumption	Low	3	6
				Enough	0	0

DM: Diabetes mellitus

Table 7. Frequency of osteopenia according to T-scores			
	Prediabetes	**DM**	**p**
Femur neck	37	31	NS
Lumbar spine (L1-L4)	31	29	NS

Data are expressed as percentages. NS: Not significant osteopenia were similar among diabetics and prediabetics for femur neck and lumbar spine, DM: Diabetes mellitus

Table 8. Frequency of osteoporosis according to T-scores			
	Prediabetes	**DM**	**p**
Femur neck	8.6	8.2	NS
Lumbar spine (L1-L4)	8.6	21.3	0.001

Data are expressed as percentages. NS: Not significant osteopenia were similar among diabetics and prediabetics for femur neck and lumbar spine, DM: Diabetes mellitus

Table 9. Logistic regression analysis for osteoporosis and affecting factors								
	Univariate model				**Multivariate model**			
	OR	**95% CI**		**p**	**OR**	**95% CI**		**p**
Age	1.840	1.370	1.133	0.000	1.068	1.021	1.118	0.004
Height	0.000	0.000	0.016	0.001	1.084	1.037	1.133	0.000
Weight	0.957	0.925	0.913	0.546	-	-	-	-
BMI	0.980	0.913	1.051	0.562	-	-	-	-
Smoking	0.950	0.324	2.786	0.926	-	-	-	-
Exercise	0.478	0.147	1.553	0.220	-	-	-	-
DM year	0.995	0.947	1.045	0.838	-	-	-	-
FBG	1.006	0997	1.015	0.201	-	-	-	-
HbA1c	0.932	0.681	1.275	0.657	-	-	-	-
25-(OH)D	0.954	0.901	1.010	0.108	-	-	-	-
Corrected Ca	0.662	0.304	1.442	0.299	-	-	-	-
Phosphorus	0.787	0.384	1.614	0.514	-	-	-	-
Magnesium	0.111	0.010	1.258	0.076	-	-	-	-
Ca intake	1.001	0.999	1.002	0.403	-	-	-	-
Lactose intolerance	2.100	0.586	7.522	0.254	-	-	-	-
Retinopathy	1.467	0.234	9.206	0.683	-	-	-	-
Neuropathy	0.946	0.364	2.458	0.909	-	-	-	-
Micro albuminuria	1.583	0.580	4.321	0.370	-	-	-	-

DM: Diabetes mellitus, BMI: Body mass index, 25(OH)D: 25-hydroxyvitamin D, Ca: Calcium, OR: Odds ratio, CI: Confidence interval, FBG: Fasting blood glucose

Discussion

T2DM population is growing in Turkey and in the world (18). T2DM is correlated with increased risk of skeletal fractures, despite of increased BMD (9,19). Women's Health Initiative study confirmed that women with T2DM at baseline had a 20% increased risk of fracture at any site (9,20). Valderrábano and Linares (9) mentioned that high BMD in T2DM is not enough to be protective, and bone strength could indeed be lower than what is predicted for BMD. They also stated that the microvascular damages of diabetes may be releated with microarchitectural bone defects, which may lie behind bone fragility. Increased risk of fracture in patients with T2DM despite increased BMD may be explained with high propensity for falls, poor blood glucose control, and AGEs. AGEs like pentosidine and carboximethyl lysine may be produced in collagen fibers and may thus deteriorate bone strength. Hyperglycaemia can also inhibit osteoclastogenesis.

The study Health in Aging and Body Composition confirmed that older people with T2DM had increased risk of fractures, while patients with IFG did not have a significantly increased risk (9,10). The pathophysiology of increased risk of fracture in these patients has been described, but there are only few studies about fracture risk in prediabetes patients and studies about

the prevalence of osteopenia and osteoporosis in prediabetes are also very limited. Chen et al. (21) examined the trends of osteoporosis and osteopenia in prediabetes. U.S. adults over 40 years tended to have lower BMD and high number of case of bone patology at the femoral neck and lumbar spine between 2005 and 2014. They also reported that prediabetes patients were associated with a higher prevalence of fracture than healthy people. Natour et al. (22) investigated the forearm bone density in inuit women with IFG and diabetes. They found that the forearm bone density and T-score was lower in diabetics in comparison to patients with IFG levels.

Dietary calcium is a basic nutrient, which is important for bone health, and its insufficiency constitutes a risk factor for osteoporosis (23). Our study revealed that daily calcium consumption is unfortunately low in our region. Mean daily calcium consumption was 780±41 mg for diabetics and 752±27 mg for prediabetics. This is lower than the recommended level. Another restrictive factor for sufficient calcium consumption is lactose intolerance (24). Calcium intake was also insufficient in all lactose intolerant patients. Education may be proposed and other foods rich in calcium may be recommended to these persons presenting risk for osteopenia and osteoporosis.

In the present study, BMD and T-score measurements at the lumbar spine and femur were compared between T2 diabetic and prediabetic patients. Furthermore, the frequencies of osteopenia and osteoporosis in these two groups and possible confounding factors were investigated. BMD measurements were generally similar for prediabetes and diabetes, but the frequency of osteoporosis at the lumbar spine is higher in diabetics compared to prediabetics.

It has been suggested that hyperglycaemia may lead to osteoblast dysfunction (25). Decreased osteoblast function may induce accelerated bone loss, osteopenia and osteoporosis. Hyperglycaemia stimulates production of macrophage colony stimulating factor, tumour necrosis factor-α and receptor activator of nuclear factor-κB ligand. These are osteoblast-derived activators of osteoclast proliferation and differentiation (26). FBG and HbA1c levels were not correlated in our study population. The HbA1c value of our diabetic patients was not very high and this may have influenced the results.

Diabetic complications were not correlated with osteoporosis/osteopenia in our study. Patients with macroalbuminuria or renal failure were not included in our study. Including patients with more complicated renal failure may affect the results of the study. One study from our country revealed that among the chronic diabetic complications only microalbuminuria had a negative impact on femoral neck BMD (27).

There are contradictory studies for lipid levels and BMD measurements (28). In a study from Asia, a significantly negative correlation was proposed between serum cholesterol levels and BMD in both men and women with T2DM (29). In our study, lipid levels were not correlated with BMD measurements.

Another important factor for osteoporosis is aging. Fracture risk has been defined to be greater with advancing age (30). Afshinnia et al. (31) reported that in patients with diabetes, older age, low body weight, low serum calcium, and low-density lipoprotein cholesterol levels were independently associated with lumbar spine osteoporosis. In our study, the most important confounding factor was age.

Lactose intolerance history was only asked in patients, no lactose intolerance test was performed, which constitutes a limitation of our study. Another limitation is the number of male patients. Further evaluation with a larger study group may be more informative.

Conclusion

In conclusion, T2DM patients have more frequent lumbar osteoporosis than prediabetic patients. Candidates for diabetes (prediabetes) and diabetic patients should be evaluated for osteopenia/osteoporosis. Aging is an important risk factor and early screening may prevent any fractures is this population at risk.

Ethics

Ethics Committee Approval: This study was approved by the Kütahya Health Sciences University Non-Invasive Clinical Research Ethics Committee (decision no: 2019/2, date: 30.01.2019).

Informed Consent: Written informed consent was taken from each patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.Ü., K.O., T.P.K., Concept: D.Ü., K.O., T.P.K., Design: D.Ü., K.O., T.P.K., Data Collection or Processing: D.Ü., K.O., T.P.K., Analysis or Interpretation: D.Ü., K.O., T.P.K., Literature Search: D.Ü., T.P.K., Writing: D.Ü.

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The Association Between Chest CT Severity Scores, CO-RADS, Vitamin D Levels and Other Laboratory Parameters of COVID-19 Patients

COVID-19 Hastalarında Toraks BT Şiddet Skorları, CO-RADS, D Vitamini Düzeyleri ve Diğer Laboratuvar Parametreleri Arasındaki İlişki

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Abstract

Objective: This study determined the correlation between several laboratory variables, chest computed tomography severity score (CTSS), and coronavirus disease-2019 (COVID-19) Reporting and Data System (CO-RADS) in COVID-19 patients.

Materials and Methods: Ninety-one patients with COVID-19 infection verified by polymerase chain reaction test, presented to the emergency department with COVID-19 symptoms, and had a thoracic computed tomography (CT) scan at the time of admission were included in this retrospective study. 25-hydroxyvitamin D [25(OH)D] levels, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimer, glucose, ferritin, creatinine, alanine aminotransferase, aspartate aminotransferase, phosphorous, and calcium levels recorded and CO-RADS and CTSS data. The correlation of laboratory parameters with radiological findings was analyzed.

Results: A positive correlation was found between CTSS and age, ESR, CRP, D-dimer while a negative correlation was found between CTSS and lymphocyte count. Patients with high CTSS levels had higher ESR, CRP, D-dimer, ferritin values and lower lymphocyte count, and lower calcium levels. Patients with typical CO-RADS involvement had higher sedimentation, CRP, glucose, and ferritin levels and lower lymphocyte count. No significant correlation was determined between the 25(OH)D level, CO-RADS, and CTSS.

Conclusion: The results of this study highlight that the reduced lymphocyte count, high D-dimer, sedimentation, ferritin, and CRP levels are predictors of severe lung involvement in COVID-19 patients. Hypocalcemia can also be considered a marker of severe lung involvement evaluated by CT in COVID-19 patients. the association between vitamin D deficiency and COVID-19 pneumonia should be investigated in future studies.

Keywords: COVID-19, CO-RADS, CTSS, real-time reverse transcription-polymerase chain reaction, vitamin D deficiency, hypocalcemia

Öz

Amaç: Bu çalışma, koronavirüs hastalığı-2019 (COVID-19) hastalarında laboratuvar parametreleri, toraks bilgisayarlı tomografisi (BT) şiddet skoru (CTSS) ve COVID-19 Raporlama ve Veri Sistemi (CO-RADS) arasındaki ilişkiyi belirlemeyi amaçlamaktadır.

Gereç ve Yöntem: COVID-19 semptomları ile acil servise başvuran ve başvuru anında toraks BT çekilmiş olan, polimeraz zincir reaksiyon testi ile COVID-19 olduğu doğrulanan 91 hasta çalışmaya dahil edildi. Hastaların 25-hydroksivitamin D [25(OH)D] seviyeleri, eritrosit sedimantasyon hızı (ESR), C-reaktif protein (CRP), D-dimer, glikoz, ferritin, kreatinin, alanin aminotransferaz, aspartat aminotransferaz, fosfor ve kalsiyum seviyeleri ile birlikte CO-RADS ve CTSS verileri retrospektif olarak kaydedildi. Laboratuvar parametrelerinin radyolojik bulgularla korelasyonu incelendi.

Bulgular: CTSS ile yaş, ESR, CRP, D-dimer arasında pozitif korelasyon bulunurken, CTSS ile lenfosit sayısı arasında negatif korelasyon bulundu. Yüksek CTSS seviyeleri olan hastalarda daha yüksek ESR, CRP, D-dimer, ferritin değerleri ve daha düşük lenfosit sayısı ile kalsiyum seviyeleri vardı. Tipik CO-RADS tutulumu olan hastalar daha yüksek sedimantasyon, CRP, glikoz ve ferritin seviyelerine ve daha düşük lenfosit sayısına sahipti. 25(OH)D düzeyi ile CO-RADS ve CTSS arasında anlamlı bir ilişki saptanmadı.

Sonuç: Bu çalışmanın sonuçları, düşük lenfosit sayısı, yüksek D-dimer, sedimantasyon, ferritin ve CRP düzeylerinin COVID-19 hastalarında şiddetli akciğer tutulumunun belirleyicileri olduğunu düşündürmektedir. Hipokalsemi, BT ile değerlendirilen COVID-19 hastalarında ciddi akciğer tutulumunun bir belirteci olarak da düşünülebilir. D vitamini eksikliği ve COVID-19 pnömonisinin ilişkisi ileri çalışmalarda araştırılmalıdır.

Anahtar kelimeler: COVID-19, CO-RADS, CTSS, gerçek zamanlı polimeraz zincir reaksiyonu, vitamin D eksikliği, hipokalsemi

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Introduction

In December 2019, several patients with pneumonia and no recognized etiology were reported in Wuhan, China. Molecular analysis of the lower respiratory system samples taken from the patients showed that the disease-causing organism is a virus from the coronavirus family. On February 11, 2020, this virus was identified as a coronavirus disease-2019 (COVID-19) by the World Health Organization (1). Worldwide, more than 2.5 million fatalities and more than 116.3 million confirmed cases had been reported as of March 5, 2021 (2).

Previously, a decrease in leukocyte count and an increase in C-reactive protein (CRP) levels are observed in COVID-19 with several other abnormalities in some of the laboratory tests (3). Furthermore, a number of risk factors for COVID-19 disease have been discovered, including advanced age, ethnicity, type 2 diabetes, hypertension, obesity, renal dysfunction, and cardiovascular disorders (4). It is well recognized that each of these factors has some connection to vitamin D insufficiency. This has led to the question of whether low vitamin D levels can alter the development or even prognosis of COVID-19 disease (5). On the other hand, hypocalcemia is a frequent in-hospital consequence that happens in tandem with other clinical problems including an imbalance in the secretion of parathyroid hormone (PTH) and vitamin D (6).

The most accurate method for determining if a person has COVID-19 infection is real-time reverse transcriptase-polymerase chain reaction (RT-PCR) and chest computed tomography (CT) has been reported to be predictive in case of false-negative results of RT-PCR. CT is not only a diagnostic tool but also has great importance in monitoring the progression of the disease and evaluating the treatment outcomes (7). In COVID-19, pneumonia is the most frequent cause of morbidity and death. PCR test is not found to be a predictive factor for the severity of pulmonary involvement (8,9). On the other hand, chest imaging plays an important role in both diagnosis and classification of disease severity in COVID-19 triage (10,11). Conventional chest radiography is the first step of imaging in emergency services due to its easy accessibility and cheapness. However, the sensitivity of chest radiography is quite low in the diagnosis of COVID-19 pneumonia. The sensitivity of chest CT in the diagnosis of COVID-19 pneumonia is quite high compared to the PCR tests (12,13).

We aimed to determine the correlation between various laboratory parameters including vitamin D, chest CT severity scores (CTSS), and COVID-19 Reporting and Data System (CO-RADS) in COVID-19 patients in this study.

Materials and Methods

Study Protocol and Design

This study was approved by the Ethics Committee of Erzurum Regional Training and Research Hospital (decision no: 2021/02-21, date: 18.01.2021). This study was conducted in January-February 2021 after ethical approval, using patient recorded data of 2020. Ninety-one patients who were admitted to the emergency department with suspected COVID-19 infection, screened with chest CT and had positive COVID-19 RT-PCR results, were included in this retrospective study. Age, gender, laboratory data, chest CT images and RT-PCR results of the patients were retrospectively scanned from the hospital database. The laboratory data and chest CT images at the first admission to the emergency department were recorded. Laboratory investigations included erythrocyte sedimentation rate (ESR), white blood cell, lymphocyte and platelet counts, 25-hydroxyvitamin D [25(OH)D] levels evaluated in the last three months, CRP, D-dimer, glucose, ferritin, creatinine, alanine aminotransferase, aspartate aminotransferase, phosphorus and calcium levels.

CO-RADS and CTSS

The CO-RADS, a procedure mostly based on the suggestions of the North American Radiology Association, was published by the Netherlands Radiology Association (NVvR) in 2020. From the lowest degree of suspicion (CO-RADS 1) to the highest level of suspicion (CO-RADS 5), this method employs a scoring system from 0 to 5 to classify COVID-19 pulmonary involvement on CT (14). Two additional categories denote a technically deficient review (CO-RADS 0) and COVID-19 infection that was verified at the time of the research by RT-PCR (CO-RADS 6). In the diagnosis of COVID-19 pneumonia, CO-RADS 2 corresponds to "Atypical", CO-RADS 3 "Low Probability, Suspicious", CO-RADS 4 "High Probability, Suspicious" (Table 1). The inter-observer variation of CO-RADS 2, 3, and 4 classifications can be high. Since a

Table 1. CO-RADS, COVID-19 infection suspicion level, CT findings

CO-RADS	COVID-19 infection suspect level	CT findings
CO-RADS 0	-	Technically inadequate
CO-RADS 1	Highly unlikely	Normal or non-infectious anomalies
CO-RADS 2	Unlikely	Abnormalities consistent with infections other than COVID-19
CO-RADS 3	Equivocal	Unclear whether COVID-19 is present
CO-RADS 4	Probable	Abnormalities suspicious for COVID-19
CO-RADS 5	Highly likely	Typical COVID-19
CO-RADS 6	PCR proven	

CO-RADS: COVID-19 reporting and data system, CT: Computed tomography, COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction

mild infection may have a negative CT scan in the first few days, CT findings should be interpreted together with clinical symptoms and duration of symptoms (15). The CTSS, which was determined using a semi-quantitative scoring approach, has been shown to be related to the severity of the disease and can be used as a prognostic indicator (16-21). With CTSS, each of the five lobes of the lung is evaluated. Involvement in each lobe is scored between 0 and 5. Each lobe's overall scores might vary from 0 (without involvement) to 25 (maximum involvement) (Table 2).

CO-RADS classification and CTSS data were recorded by a six-year experienced radiologist according to chest CT of the patients. CO-RADS was classified from 1 to 5. The CTSS was scored between 0 and 5 for each five lobes of the lung. The chest CT was evaluated by a radiologist who was blinded to the other features of the patients.

Statistical Analysis

SPSS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) program was used for data analysis. Results of evaluations are documented using descriptive statistics, including mean and standard deviation for numerical variables and number and percentage for categorical variables. The one-sample Kolmogorov-Smirnov test was used to examine if the groups' distributions were normal. Comparison of numerical variables between two independent groups; the Mann-Whitney U test was used to assess it because the normal distribution requirement was not satisfied. Since the normal distribution requirement was not satisfied, Spearman test was utilized in correlation analysis. The statistical significance level of alpha was accepted as $p<0.05$.

Results

The research involved 91 patients in total. Among the patients, 71 (78.0%) were men and 20 (22.0%) were women 71. The average age of the patients is 57.8±16.4. Table 3 provides an overview of the patients' demographics and laboratory results. The CTSS score was recorded as the lowest 0 and the highest 24. Correlation analyses were performed by evaluating CTSS scores into two groups as below 10 and above 10 and also CO-RADS scores into two groups as 1-3 and 4-5.

Table 2. CTSS in each lung lobe

Score	Pulmonary lobe involvement rate
0	No involvement
1	<5% involvement
2	5%-25% involvement
3	26%-49% involvement
4	50%-75% involvement
5	>75% involvement

CTSS: Computed tomography severity score

The correlation of age, gender, and laboratory parameters with CTSS and CO-RADS classification is shown in Table 4. CTSS was correlated with age, sedimentation, CRP, D-dimer, and CO-RADS classification positively while it was and correlated with lymphocyte, platelet counts, and calcium levels negatively. The CO-RADS classification was correlated with age, sedimentation, CRP, D-dimer, glucose, ferritin levels, and CTSS positively and was correlated with lymphocyte count negatively. Comparison of the laboratory parameters, CTSS, and CO-RADS classification are summarized in Table 5. While sedimentation, CRP, D-dimer, and ferritin levels were higher in CTSS 10-24 group than CTSS 0-9 group, lymphocyte count and calcium levels were significantly lower ($p<0.05$). Compared to the CO-RADS 1-3 group, the CO-RADS 4-5 group had considerably greater sedimentation, CRP, glucose, and ferritin levels, but the lymphocyte count was much lower ($p<0.05$).

Discussion

COVID-19 is still a cause of significant viral disease and death around the world and continues to spread rapidly. In this study, we hypothesized that the severity of lung involvement on chest CT may be correlated with laboratory findings. CTSS and CO-RADS classification based on chest CT findings obtained at the first admission to the hospital can be predictive for COVID-19 prognosis disease and this can guide physicians to

Table 3. Demographics and clinical characteristics of patients with COVID-19 on admission

	All patients (n=91) mean ± SD
Age (years)	57.8±16.4
Gender, male (n, %)	71 (78.0)
25(OH)D (ng/mL)	17.3±10.5
Lymphocyte (10^9/L)	1645.7±1033.0
WBC (10^9/L)	9003.8±4356.0
Platelet (10^9/L)	243736.5±79500.9
ESR	20.5±18.4
CRP (mg/L)	33.3±48.7
D-dimer (ng/mL FEU)	15407±4431.3
Glucose (mg/dL)	127.3±61.7
Ferritin (ng/mL)	446.3±444.4
Creatinine (mg/dL)	1.0±0.4
ALT (IU/L)	33.1±22.7
AST (IU/L)	31.4±21.5
Phosphorus (mg/dL)	3.3±0.8
Calcium (mg/dL)	8.9±0.7

WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, COVID-19: Coronavirus disease-2019, 25(OH)D: 25-hydroxyvitamin D, SD: Standard deviation

Table 4. Summary of the relationship between chest CT scores. CO-RADS classification and clinical characteristics in COVID-19

	Chest CT scores		CO-RADS
	Correlation coefficient	p-value	Correlation coefficient
Age (years)	0.485	<0.001	0.211
25(OH)D (ng/mL)	-0.058	0.585	-0.082
Lymphocyte (10^9/L)	-0.725	<0.001	-0.437
WBC (10^9/L)	0.080	0.451	-0.095
Platelet (10^9/L)	-0.217	0.038	0.053
ESR	0.460	<0.001	0.347
CRP (mg/L)	0.601	<0.001	0.463
D-dimer (ng/mL FEU)	0.552	<0.001	0.253
Glucose (mg/dL)	0.333	0.001	0.335
Ferritin (ng/mL)	0.395	<0.001	0.441
Creatinine (mg/dL)	0.253	0.016	0.066
ALT (IU/L)	-0.055	0.605	0.155
AST (IU/L)	-0.007	0.951	0.078
Phosphorus (mg/dL)	-0.052	0.622	-0.035
Calcium (mg/dL)	-0.236	0.024	-0.197
CO-RADS classification	0.510	<0.001	-
Chest CT scores	-	-	0.510

WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CO-RADS: COVID-19 reporting and data system, 25(OH)D: 25-hydroxyvitamin D, CT: Computed tomography, COVID-19: Coronavirus disease-2019

establish proper treatment promptly. We compared laboratory parameters with CTSS to determine the poor prognosis risk factors [Decrease in calcium and 25(OH)D levels, lymphocyte, white blood cell and platelet count and increase in liver-kidney function tests, glucose, D-dimer, CRP, ferritin levels, ESR] for COVID-19 disease. Additionally, we investigated the relationship between these laboratory variables and CO-RADS to define the difference between patients with typical lung involvement and those who did not present with typical lung involvement.

Vitamin D levels are frequently measured using serum total 25(OH)D, which is the active form of vitamin D3 and a key regulator of innate and adaptive immunity. Low vitamin D levels have been linked to a number of clinical disorders, including a higher risk of contracting infectious diseases, although its underlying cause is still debatable (22). Retrospective research have shown how vitamin D works to prevent the spread of viruses, lower the incidence of pneumonia and acute viral respiratory tract infections, and reduce inflammation (23). Low vitamin D levels have been linked to an increased risk of developing severe pneumonia through increasing the production of inflammatory cytokines. It has been discovered that thrombotic attacks, which are frequent in COVID-19, are also linked to vitamin D insufficiency (24).

A meta-analysis of 25 randomized controlled trials (RCT) found that vitamin D supplementation helps individuals with very low vitamin D status [25(OH)D:<10 ng/mL] from developing acute respiratory tract infections. Recently, this finding has attracted considerable interest regarding the potential effects of vitamin D status on severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection mortality and vitamin D supplementation as a potential COVID-19 treatment strategy (25). However, data on vitamin D status in relation to the clinical results of SARS-CoV-2 infection are few. Only a few research on vitamin D levels in COVID-19 patients have been reported. Patients having positive PCR results for SARS-CoV-2 had decreased 25(OH)D concentrations, according to research by D'Avolio et al. (26). The supplementation of vitamin D is suggested as a helpful approach to lower the risk of infection. A prognostic influence of vitamin D insufficiency was shown in a newly published meta-analysis by Munshi et al. (27) in determining the likelihood of developing severe COVID-19. The fact that our study was done in the winter, when sun exposure is at a minimum, and in a region where vitamin D insufficiency is endemic can be used to explain why we were unable to discover a correlation between vitamin D deficit and the severity of COVID-19 pneumonia in our study. RCTs and cohort studies on this topic should be conducted as there is insufficient data to demonstrate a relationship between vitamin D levels and the severity of lung involvement and mortality.

Hypocalcemia is a common condition observed in viral infections and pneumonia (28). It was identified as a poor prognostic factor related with the clinical severity of COVID-19 in earlier research

Table 5. Comparison of between CTSS and CO-RADS groups and laboratory findings

	Chest CT scores		p-value	CO-RADS		p-value
	0-9	10-24		1-3	4-5	
25(OH)D (ng/mL)	17.9±11.0	15.4±8.6	0.476	17.3±8.8	17.2±12.0	0.497
Lymphocyte (10^9/L)	1973.8±972.0	675.6±414.0	<0.001	2018.7±1028.1	1264.4±898.6	<0.001
WBC (10^9/L)	8820.5±4229±0	9545.7±4769.4	0.361	9265.5±3179.4	8736.2±5322.6	0.145
Platelet (10^9/L)	249602.9±86536.2	226391.3±51277.1	0.473	236217.4±58707±9	251422.2±96351.5	0.487
ESR	17.2±16.2	30.2±21.3	0.005	14.0±11.5	27.1±21.6	0.002
CRP (mg/L)	24.3±42.3	60.0±57.0	<0.001	23.2±41.1	43.6±54.0	0.001
D-dimer (ng/mL FEU)	778.7±1243.1	3793.3±8278.1	<0.001	1831.6±6083.1	1243.2±1463.9	0.086
Glucose (mg/dL)	124.7±65.2	135.1±50.6	0.087	117.7±58.1	137.1±64.3	0.012
Ferritin (ng/mL)	352.9±395.7	722.3±473.7	0.001	286.3±385.4	609.7±444.9	<0.001
Creatinine (mg/dL)	1.0±0.3	1.2±0.5	0.114	1.0±0.5	1.0±0.4	0.576
ALT (IU/L)	33.4±24.2	32.1±18.2	0.891	29.1±14.8	37.2±28.3	0.221
AST (IU/L)	30.7±22.1	33.4±20.2	0.508	28.7±15.3	34.1±26.3	0.905
Phosphorus (mg/dL)	3.3±0.8	3.1±0.7	0.272	3.2±0.6	3.3±0.9	0.911
Calcium (mg/dL)	9.0±0.6	8.7±0.8	0.049	9.1±0.6	8.8±0.7	0.054

WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CO-RADS: COVID-19 reporting and data system, CT: Computed tomography, COVID-19: Coronavirus disease-2019, 25(OH)D: 25-hydroxyvitamin D, CTSS: Computed tomography severity score

(29). There are a number of potential processes that might explain why people with severe COVID-19 experience hypocalcemia. One of them is the possibility that poor diet and advanced age might result in hypocalcemia and vitamin D insufficiency (30). Cell membrane disruption brought on by tissue and organ hypoxia allows calcium to enter the cell. Proinflammatory cytokines interfere with the response to PTH by preventing its release, which may result in an imbalance of calcium (31). Neuromuscular excitability, shown as muscle twitching, spasms, tingling, and numbness, is one of the most well-known signs of hypocalcemia. Severe hypocalcemia will raise mortality by resulting in major neuroendocrine and cardiovascular consequences if it is not treated over time. It should be kept in mind that individuals with more severe lung involvement may have lower calcium levels at the time of hospital admission. Similarly, our study revealed that CTSS was negatively correlated with calcium levels indicating the relationship between lung disease severity and hypocalcemia.

Inflammatory activation and coagulopathy have been reported to often raise serum CRP and D-dimer levels in COVID-19 patients, and these elevated levels are closely related with the disease's more severe manifestations (32,33). Additionally, it has been shown that the levels of CRP, ESR, ferritin, and procalcitonin increase in response to inflammation, particularly in patients receiving intensive care. These parameters may have increased as a result of both a secondary bacterial infection and an intensifying inflammatory response, which is frequently referred to as a cytokine storm brought on by COVID-19 infection (34).

Previous studies have reported that as the severity of COVID-19 disease increased, CRP, PCT, IL-6, and ESR increased proportionally (35,36). High fasting blood sugar levels may independently predict mortality in non-diabetic people, according to certain studies (37). In our investigation, there was a positive association between age, sedimentation, CRP, D-dimer, glucose, ferritin, and creatinine as well as the CTSS. Similarly, it was discovered that the CO-RADS 4-5 group had statistically substantially higher ESR, CRP, hyperglycemia, and ferritin levels. Accordingly, typical lung involvement may not be visible on a CT scan in individuals whose sedimentation, CRP, glucose, and ferritin levels are not high as well as lymphocyte count is not low for those who applied to the emergency room with the suspicion of COVID-19. According to earlier research, lymphopenia is a common symptom in COVID-19 patients and is a crucial and accurate

sign of the severity of the disease (1,38,39). Lymphopenia may result from the virus suppressing lymphocyte production directly (such as cells with ACE2 receptors being the target of the virus) or indirectly, or shortening the half-life of lymphocytes (40,41). In our study, as the blood lymphocyte count of the patients decreased, more typical and severe CT findings were observed. For COVID-19 patients, thrombocytopenia has been linked to an elevated risk of severe disease and mortality (42). A possible cause of thrombocytopenia may be that damaged lung tissue and pulmonary endothelial cells increase platelet consumption by activating platelets in the lungs, causing microthrombin aggregation and formation (43). Hypocalcemia, thrombocytopenia, and lymphopenia during admission to the hospital may lead to the conclusion that the lung involvement may be more severe.

In the scientific community, there is still debate concerning the diagnostic value of chest CT. Despite some research opposing the use of CT as a first-line diagnostic test (7), our study's findings suggest that combining a highly sensitive imaging technique like CT with laboratory measurements may aid in quick diagnosis and therapy. According to Orsi et al. (44), CT can be utilized to discharge patients without waiting for the results of the swab test who have clinical stability and are not at risk based on laboratory parameters, especially in the presence of negative radiographic findings.

This study has some limitations. First, we conducted a retrospective and single-center study among a limited sample of patients. We assessed the relationship between the severity of lung involvement and laboratory parameters, however we could not demonstrate this relationship including patients' clinical condition, hospitalization status, survival, or death. The direct effect of CT on the clinical decision has not been evaluated.

Conclusion

To date, several clinical laboratory variables were found to be related with COVID-19 severity across various studies without consistency. Lymphocyte count and calcium D-dimer, sedimentation, ferritin, and CRP levels may serve as markers of severe or critical COVID-19. Although vitamin D deficiency is thought to be a risk factor for COVID-19 pneumonia, the degree of lung involvement may not be reflected by this risk factor. To clarify the probable link between vitamin D deficiency and COVID-19 pneumonia, more research should be performed.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Erzurum Regional Training and Research Hospital (decision no: 2021/02-21, date: 18.01.2021).
Informed Consent: Retrospective study.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.A., Concept: K.A., Design: K.A., G.S., Data Collection or Processing: D.Ç.A., Analysis or Interpretation: D.Ç.A., S.K., Literature Search: G.S., Writing: K.A., G.S.

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The Evaluation of Individuals with Low Back Pain in Terms of Social Adaptation

Bel Ağrısı Olan Bireylerin Sosyal Uyum Yönünden Değerlendirilmesi

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Abstract

Objective: The aim of the present study is to assess individuals with low back pain in terms of social adaptation.
Materials and Methods: The population of this descriptive study included individuals with low back pain who were older than 18 years old. 372 individuals suffering from this pain were reached between 02.20.2021 and 03.18.2021 by using the snowball sampling method, one of the non-probabilistic sampling methods. A Personal Information Form, the Oswestry Disability index, and the Social Adaptation Self-Evaluation Scale were used to collect data. Data were gathered through a web-based survey.
Results: It was found that 32.5% of the participants suffering from low back pain were aged between 18-29 years and 60.9% of them were female. The Social Adaptation Self-Evaluation scale mean score of all participants was 40.81±8.86 and their Oswestry Disability index mean score was 15.81±9.43. There was a moderate negative correlation between the Social Adaptation Self-Evaluation scale and the Oswestry Disability index scores of the participants (r=-0.528, p=0.000).
Conclusion: Consequently, as low back pain increased, the level of social adaptation decreased, and this in turn affected the daily lives of people with low back pain. Knowing the risk factors for low back pain and social maladaptation is important for taking the associated measures, and it is thought that it would be beneficial to repeat the related studies in a more comprehensive and multi-centered manner.
Keywords: Low back pain, pain, social adaptation, social adaptation self-evaluation scale

Öz

Amaç: Bu araştırma, bel ağrısı olan bireylerin sosyal uyum yönünden değerlendirilmesi amacıyla yapılmıştır.
Gereç ve Yöntem: Tanımlayıcı tipte yürütülen bu araştırmanın evreni 18 yaş üzeri bel ağrısı olan bireylerden oluşmuştur. Olasılıklı olmayan örnekleme yöntemlerinden kartopu örnekleme yöntemi kullanılarak 20.02.2021-18.03.2021 tarihleri arasında 372 bel ağrısı olan bireye ulaşılmıştır. Verilerin toplanmasında Kişisel Bilgi Formu, Oswestry Bel Ağrısı ölçeği ve Sosyal Uyum Kendini Değerlendirme ölçeği kullanılmıştır. Veriler web tabanlı anket ile toplanmıştır.
Bulgular: Bel ağrısı yaşayan bireylerin %32,5'i 18-29 yaş aralığında ve %60,9'u kadındı. Tüm katılımcıların, Sosyal Uyum Kendini Değerlendirme Ölçeği puan ortalaması 40,81±8,86, Oswestry Bel Ağrısı ölçeği puan ortalaması 15,81±9,43 olarak bulundu. Bel ağrısı olan bireylerin Sosyal Uyum Kendini Değerlendirme ölçeği ile Oswestry Bel Ağrısı ölçeği arasında negatif yönde orta şiddette bir ilişki saptandı (r=-0,528, p=0,000).
Sonuç: Çalışmamızda, bel ağrısı arttıkça sosyal uyum düzeyinin azaldığı görülmüş ve bel ağrısı yaşayan kişilerin günlük hayatlarını etkilediği sonucuna ulaşılmıştır. Bel ağrısı ve sosyal uyumsuzluk için risk faktörlerinin bilinmesi, bu gibi durumlara yönelik tedbirlerin alınması açısından önemli olup, bu tür çalışmaların daha kapsamlı ve çok merkezli olarak tekrarlanmasının faydalı olacağı düşünülmüştür.
Anahtar kelimeler: Bel ağrısı, ağrı, sosyal uyum, sosyal uyum kendini değerlendirme ölçeği

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Introduction

Although low back pain is a common health problem worldwide, it causes significant economic and social burdens (1,2). Low back pain problems directly or indirectly affect the job performance of employees, the families of individuals, industry and the governments (2,3). In addition, low back pain can seriously affect the participation in daily life activities. The estimated frequency of recurrence of low back pain in many individuals with activity limitations is in the range of 24-80% (4). Many people suffer from low back pain in some periods of their lives. One study conducted in Afyon, Turkey reported that the lifetime prevalence of low back pain was 51% and the prevalence of chronic low back pain was 13.1% (5). Low back pain is highly recurrent and causes patients to feel sadness and despair, thus frequently resulting in impairing their quality of life and possibly developing depression and anxiety disorders (6).

Social functionality refers to a person's ability to function -motivation, behavior, self-perception, and activities included- at work, home, and in their social life. This also pertains to how they interact with their spouse, parents, friends, and interests, plus the satisfaction they gain from them (7). People who suffer from physical disorders and chronic pain (incl. low back) also tend to suffer from depression, because their pain has a negative impact on their psychology (8). Accordingly, the study was conducted to identify the social adaptation levels of individuals with low back pain by comprehensively evaluating their social functioning ability, which is one of common health problems in the society.

Materials and Methods

The Population and Sample

The population of this descriptive study consisted of people who had low back pain and were older than 18 years old in Turkey. In the study, the sample size was determined as 330 at α=0.05, 1-β=0.98, and effect size of 0.2 using G Power 3.1.9.7 program. Using the snowball sampling method, one of the non-probabilistic sampling methods, 372 individuals with low back pain were reached between 02.20.2021 and 03.18.2021.

A web-based survey was created to minimize face-to-face interaction due to the coronavirus disease-2019 pandemic. This survey form was shared on social media platforms (Facebook, Instagram, WhatsApp and Twitter etc.), and respondents were asked to share it with other people. At the beginning of the web-based questionnaire, the participants were asked whether or not they wished to participate in the study or not, hence allowing the researcher to obtain their consent.

Data Collection

The study was conducted with 372 individuals, who had low back pain and agreed to participate, between 02.20.2021 and 03.18.2021. The participants completed the survey form within 15-20 minutes. 24 forms were not included in the study because the individuals under the age of 18 and without low back pain responded to them.

Inclusion criteria;

- Having low back pain,
- Being over the age of 18,
- Using social media,
- Volunteering to participate in the study.

Data Collection Tools

The data collection tools used in this study were a Personal Information Form, the Oswestry Disability index (ODI), and the Social Adaptation Self-Evaluation scale (SASS).

The Personal Information Form: This form, which was developed by the researchers upon the literature review, has a total of 16 questions regarding the socio-demographic characteristics of the participants, as well as their low back pain complaints.

SASS: Bosc et al. (9) developed SASS in order to assess the areas of social functioning in ordering leisure time, family and environment, and the ability to cope positively. Its Turkish validity and reliability study was conducted by Akkaya et al. (10). All of the questions supplemented one another. They assess the respondents' sense of motivation, their behavior, their sense of self-perception, how interested they are in their various roles in life, and how much satisfaction they receive from them. The items 1 and 2 of the 21-item scale are answered according to the occupation status and is rated between 0-3 points. Minimum and maximum scores of the scale 0 and 60, respectively. A score of at least 35 on the scale indicates that the individual has normal social functionality and a score below 25 indicates that there is a problem with his/her social functionality. The Cronbach's alpha coefficient was 0.90 in overall scale (10). In this study, the Cronbach's alpha coefficient for SASS was calculated as 0.86.

ODI: The scale was developed by Fairbanks et al. (11) in order to evaluate the function disability. Its Turkish validity and reliability study was carried out by Yakut et al. (12). It measures daily life activities from 10 dimensions. The scale has 10 items and each item is rated between 0-5 points. The minimum and maximum scores of the scale are 0 and 50 points, respectively. 0 point means = No functional impairment, 1-10 points mean = Mild functional impairment, 11-30 points mean = Moderate functional impairment, and 31-50 points mean = Severe functional impairment. Its Cronbach's alpha coefficient was 0.91 (12). In this study, the Cronbach's alpha coefficient for the ODI was calculated as 0.90.

Statistical Analysis

The SPSS 24.0 (Statistical Packet for Social Sciences for Windows) software was employed to analyze the data. Whether or not the data were normally distributed was determined via Skewness and Kurtosis (±1) distribution test. In addition to descriptive statistics (percentage, frequency, average, standard deviation, minimum and maximum values) used in the data analysis, ANOVA was used to compare the normally distributed

independent variables. Kruskal-Wallis and Mann-Whitney U tests were used to compare the independent variables that did not show a normal distribution. The Pearson correlation analysis was employed to measure the correlation between SASS and ODI scores. Pearson's correlation coefficients were expressed <0.2 as very poor, 0.2-0.39 as poor, 0.4-0.59 as medium, 0.6-0.79 as high, and ≥0.8 as very high correlation. The Cronbach's alpha coefficient was calculated.

Ethical Considerations

The approval of the Kilis 7 Aralık University Ethics Committee (decision no: 6, date: 13.01.2021) was obtained to conduct the study. The web-based survey mentioned about purpose of the study. The participants were informed about participation on a volunteer basis and then their consents were obtained. This study was conducted in accordance with the Principles of Declaration of Helsinki.

Results

It was found that 32.5% of the participants were between the ages of 18-29, 60.9% were female, 68.4% were ≥university graduates, 83.6% had a moderate economic status, 38.8% were civil servants, and 31.3% had a chronic disease. The chronic disease was an endocrine system disease in 10.1% of them (Table 1).

Also, 43.4% of the participants had a body mass index of 18.5-24.9 kg/m^2, 20.4% were smokers, 60.9% were affected by a serious event in their life, 46.0% of them had no sleep pattern and their sleep time changed every day, 17.8% had limitations in daily life activities due to low back pain, 49.4% had low back pain for 1-5 years, 60.9% of them consulted a doctor for low back pain, 48.3% of them received medical help for low back pain, 63.2% of them had an examination for his/her pain. A statistically significant difference was determined between the SASS and the ODI mean scores of the subjects included in the

Table 1. The distribution of socio-demographic characteristics of the participants (n=348)

		n	%
The average age (years) 36.41±12.07			
Age	Age range of 18-29 years	113	32.5
	Age range of 30-39 years	97	27.9
	Age range of 40-49 years	89	25.5
	Age range of ≥50 years	49	14.1
Gender	Female	212	60.9
	Male	136	39.1
Educational level	≤Primary education	61	17.5
	High school	49	14.1
	≥University	238	68.4
Economic status	High	26	7.5
	Medium	291	83.6
	Low	31	8.9
Occupation	Civil servant	135	38.8
	Worker	95	27.3
	Retired	21	6.0
	Housewife	53	15.2
	Student	44	12.6
The presence of chronic illness	Yes	109	31.3
	No	239	68.7
Which system disease*	Respiratory system diseases	17	4.9
	Musculoskeletal system diseases	12	3.3
	Endocrine system diseases	35	10.1
	Digestive system diseases	12	3.4
	Cardiovascular system diseases	15	4.3
	Neurological system diseases	18	5.3
Total		438	100.0

*Those with chronic illnesses were calculated

study according to the status of being affected by a serious event in their lives, experiencing limitations in daily life activities due to sleeping habits, duration of experiencing low back pain, consulting a physician for low back pain and getting medical help, and having an examination. The SASS mean score for all participants was 40.81±8.86, and the ODI mean score was 15.81±9.43 (Table 2).

Out of the participants, 91.4% had a SASS score of ≤25 points (Figure 1).

Moreover, 59.5% of the participants experienced moderate functional impairment due to low back pain (Figure 2).

A moderate negative correlation was found between the SASS and the ODI scores of the participants (r=-0.528, p=0.000). In other words, as low back pain increased, the level of social functionality decreased. The level of education, occupation and the presence of chronic disease were negatively correlated with the SASS. A positive correlation was determined between the age and economic status and the SASS. The participants' age and economic status were negatively correlated with the ODI.

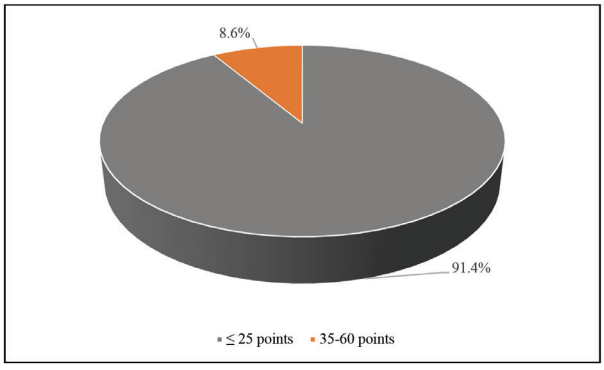

Figure 1. The distribution of SASS categorical values of the participants

SASS: The Social Adaptation Self-Evaluation scale

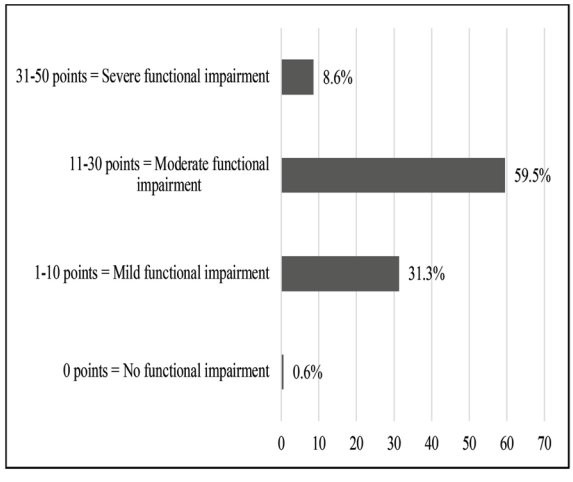

Figure 2. The distribution of ODI categorical values of the participants

ODI: The Oswestry Disability index

The educational level and presence of chronic disease were positively correlated with the ODI (Table 3).

Discussion

Low back pain is the most common musculoskeletal pain (13). It is a common and complex health problem that is difficult to manage with many important consequences such as job loss, disability and social adaptation disorder.

In the present study, which aimed to evaluate persons suffering from low back pain in terms of social adaptation, 32.5% of the participants were in the age range of 18-29 years. Chronic low back pain generally affects the middle age group (14,15). It was determined that 83.6% of the participants had a medium economic status and 60.9% of them were female. Considering the gender factor in patients with chronic low back pain, it was shown that women were more affected (16-18). Given that low back pain is a bio-psychosocial pathological disorder, this rate would be higher in women. In their case-control study, Marty et al. (19), evaluated the sleep quality in patients with low back pain and the female gender ratio was more common. In the study by Oksuz (20), female patients with low back pain were more common in all age groups than men. The present study revealed that female gender was more common, too.

In the current paper, 43.4% of the participants had a body mass index of 18.5-24.9 kg/m^2, 20.4% of them were smokers, 60.9% were affected by a serious event in their life, and 46.0% had no sleep pattern. Numerous studies have revealed the correlation between people with low back pain and sleep disorders (19,21,22). In their study with 268 patients, Marin et al. (23), reported that chronic low back pain adversely affected the sleep quality. A study involving 56 patients with chronic low back pain from Brazil, reported that chronic low back pain adversely affected the sleep quality (24).

It was determined in the present study that 49.4% of the participants had low back pain for 1-5 years, 60.9% consulted a doctor for low back pain, 48.3% received medical help for low back pain, 63.2% had an examination for low back pain and 17.8% of them experienced limitations in daily life activities due to low back pain. In the patients with low back pain, the physical endurance decreased, and functional capacity was lost due to pain, spasm, decrease in muscle strength and posture. The daily and social lives of patients experiencing these problems were restricted (25,26).

A statistically significant difference was determined between the SASS and ODI mean scores in terms of the status of being affected by a serious event, having limitations in daily life activities due to sleeping habits, the duration of experiencing low back pain, consulting a physician for low back pain and getting medical help, and having an examination. It was found that the SASS mean score for all participants was 40.81±8.86, and their ODI mean score was 15.81±9.43. 91.4% of individuals with low back pain had a SASS score of ≤25 points. In addition, a moderate negative correlation was determined between SASS and ODI in individuals with low back pain (r=-0.528, p=0.000).

Table 2. The comparison of some characteristics of individuals related to low back pain and risk factors for low back pain with the SASS and ODI mean scores

			SASS	ODI
		n (%)	$\bar{x}$ ± SD	$\bar{x}$ ± SD
Body mass index	<18.5 kg/m^2	9 (2.6)	37.00±9.09	13.88±10.67
	18.5-24.9 kg/m^2	151 (43.4)	41.50±8.18	15.94±9.48
	25-29.9 kg/m^2	117 (33.6)	40.82±9.42	15.23±9.28
	≥30 kg/m^2	71 (20.4)	39.84±9.23	16.73±9.51
	Significance[a]		p=0.331	p=0.682
Smoking status	Never smoked	175 (50.3)	41.86±8.47	15.34±9.26
	Sometimes	102 (29.3)	39.47±9.44	16.91±9.41
	Addicted	71 (20.4)	40.18±8.73	15.39±9.87
	Significance[b]		p=0.120	p=0.288
The status of being affected by a serious event*	Financial difficulties	60 (17.2)	38.03±10.17	18.10±10.88
	Disease	64 (18.4)	39.45±9.68	18.73±10.63
	Accident	37 (10.6)	38.02±9.38	16.43±10.90
	Death	51 (14.7)	42.68±7.93	13.11±7.62
	Significance[b]		p=0.004	p=0.014
Sleeping habit	I make sure to regularly go to bed at the same time and sleep in the same amount of time every day	100 (28.7)	43.67±6.37	13.25±7.34
	Some nights I only sleep a few hours, otherwise I sleep regularly	88 (25.3)	35.76±10.02	20.51±10.54
	I don't have a sleep pattern, my sleep time changes every day	160 (46.0)	41.81±8.41	14.83±9.08
	Significance[a]		p=0.001	p=0.001
The status of having disability in daily life activities due to pain	Yes	62 (17.8)	38.18±10.13	23.08±9.98
	No	70 (20.1)	43.16±6.27	7.46±5.00
	Partially	216 (62.1)	41.00±8.87	15.85±8.19
	Significance[b]		p=0.021	p=0.001
The duration of experiencing low back pain	<1 year	29 (8.4)	42.51±6.38	12.89±7.60
	1-5 years	172 (49.4)	41.53±8.85	14.33±8.53
	6-10 years	69 (19.8)	38.50±9.15	18.72±10.63
	≥11 years	78 (22.4)	40.65±9.14	17.57±9.96
	Significance[b]		p=0.042	p=0.005
The status of consulting a physician due to low back pain	Yes	212 (60.9)	39.51±9.53	19.13±9.55
	No	136 (39.1)	42.85±7.26	10.63±6.44
	Significance[c]		p=0.001	p=0.001
The status of seeking medical assistance for low back pain	Yes	168 (48.3)	39.01±9.73	20.35±9.70
	No	180 (51.7)	42.50±7.61	11.57±6.86
	Significance[c]		p=0.001	p=0.001
The status of having an examination for low back pain***	Plain graphy	30 (8.6)	43.40±8.53	13.66±9.13
	Computed tomography	64 (18.4)	38.21±10.14	20.42±11.59
	Magnetic resonance	126 (36.2)	39.73±9.31	18.45±8.55
	Significance[b]	15.81±9.43	p=0.017	p=0.001
	Total		40.81±8.86	

SASS: The Social Adaptation Self-Evaluation scale, ODI: The Oswestry Disability index, SD: Standard deviation
*Only those who were affected by a serious event in their life were calculated.
**Only those who had an examination were calculated.
[a]ANOVA test. [b]KW=Kruskal-Wallis H test. [c]Z=Mann-Whitney U test. p<0.05

Table 3. The correlation distribution of SASS and ODI scores

		1	2	3	4	5	6
1. SASS	r p	1					
2. ODI	r p*	-0.528 0.000	1				
3. Age	r p*	0.414 0.000	-0.317 0.000	1			
4. Educational level	r p*	-0.483 0.000	0.482 0.000	-0.483 0.000	1		
5. Economic status	r p*	0.132 0.014	-0.257 0.000	0.054 0.317	-0.225 0.000	1	
6. Occupation	r p*	-0.122 0.022	0.076 0.156	-0.247 0.000	0.277 0.000	-0.030 0.580	1
7. The presence of chronic illness	r p*	-0.334 0.000	0.255 0.000	-0.324 0.000	0.323 0.000	-0.083 0.121	0.244 0.000

SASS: The Social Adaptation Self-Evaluation scale, ODI: The Oswestry Disability index
r=Correlation coefficient, *p<0.001

The age and economic status of the participants were negatively correlated with the ODI. Their educational level and presence of chronic disease were positively correlated with the ODI. In the literature, age, female gender, low socioeconomic status, and chronic disease were positively correlated with presence of low back pain (27-30).

In the present study, we aimed to determine the social adaptation levels of individuals with low back pain and to investigate the effect of low back pain severity on their social functioning. There is no study in the literature that examines the social adaptation of individuals with low back pain using the social adaptation scale.

The current study has some limitations. Firstly, the study does not have a control group. Secondly, the survey measured social adaptation and social functioning levels of the patients. However, the patient form did not contain data regarding a previous diagnosis of depression or similar mood disorders. The survey did not include any additional indexes assessing the mood either.

Conclusion

Low back pain negatively influences the social adaptation levels of individuals. In this study, it was concluded that as the severity of low back pain increased, social adjustment levels were also negatively affected. The individuals suffering from low back pain were affected in terms of their level of social adaptation, which negatively disturbed their daily life routines.

Finally, the present study has some limitations. Although the number of patients was sufficient, there was no control group. In addition, the present study, to the best of our current knowledge, is the only study that examined the social adaptation levels of individuals with low back pain in Turkey. Some studies have evaluated anxiety, depression, and quality of life in the individuals with low back pain. Knowing the risk factors for low back pain and social maladaptation is important for taking the measures for these conditions, and it was thought that it would be beneficial to repeat related studies in a more comprehensive and multi-centered manner.

Ethics

Ethics Committee Approval: The approval of the Kilis 7 Aralık University Ethics Committee (decision no: 6, date: 13.01.2021) was obtained to conduct the study.

Informed Consent: At the beginning of the web-based questionnaire, the participants were asked whether or not they wished to participate in the study or not, hence allowing the researcher to obtain their consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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What Information is Provided in Turkish Videos About Osteoporosis and Does YouTube Provide Reliable and High-quality Information: A Systematic Analysis of YouTube Videos

Osteoporoz Hakkındaki Türkçe Videolarda Hangi Bilgiler Verilmektedir ve YouTube Güvenilir ve Kaliteli Bilgiler Sağlıyor mu: YouTube Videolarının Sistematik Bir Analizi

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Abstract

Objective: This study aims to evaluate what information is given in Turkish videos about osteoporosis on YouTube and to determine the quality and reliability of the videos.

Materials and Methods: The first 50 Turkish videos about osteoporosis on YouTube were evaluated in terms of quality, reliability, and information level. Two searches were conducted for related content on YouTube and two orthopedics surgeons evaluated the videos simultaneously. The Global Quality score (GQS) (1-5) and DISCERN (15-75) scoring systems were used to assess the quality of the video content. With the Osteoporosis Specific scale (1-29), it was questioned what information specifically about osteoporosis was given in the videos while the accuracy of the video source information was evaluated with the Journal of American Medical Association (JAMA) score (1-4). Descriptive data regarding the number of views, comments, likes, dislikes were recorded, as well as the upload date to YouTube and the duration of the videos. The popularity of videos was evaluated with the video power index.

Results: Considering the messages given in the videos, the most frequent information was "decrease in bone mass" with 41 videos. This was followed by "osteoporosis is a risk of fracture" and "there are risk factors for osteoporosis." The Osteoporosis Specific score was low 8.92. The mean DISCERN score was 25.020 (15-75) and the mean GQS was 1.98 (0-5), indicating low quality. The JAMA score (1-4) for which the video source was questioned showed a low level of reliability of 1.66. Videos about osteoporosis prepared by people other than healthcare professionals were more popular (82.25 vs. 56.80) (cc=0.296, p=0.037).

Conclusion: The content of the videos on YouTube osteoporosis is generally inadequate or inaccurate. Higher quality and informative videos based on international guidelines can contribute to patient compliance and increase public awareness of osteoporosis.

Keywords: Osteoporosis, bone loss, YouTube, reliability, quality, video

Öz

Amaç: Bu çalışmanın amacı YouTube'da yer alan osteoporoz hakkındaki Türkçe videolarda hangi bilgilerin verildiğini değerlendirmek ve video kalitesi ile güvenilirliğini belirlemektir.

Gereç ve Yöntem: YouTube'da osteoporoz ile ilgili ilk 50 Türkçe video kalite, güvenilirlik ve bilgi düzeyi açısından değerlendirildi. YouTube'da ilgili içerik için iki arama yapıldı ve iki ortopedi cerrahı videoları eş zamanlı olarak değerlendirdi. Video içeriğinin kalitesini değerlendirmek için Global Kalite skoru (GKS) (0-5) ve DISCERN (15-75) puanlama sistemleri kullanıldı. Osteoporoza Spesifik ölçek (1-29) ile videolarda osteoporoza özgü hangi bilgilerin verildiği sorgulanırken, video kaynak bilgilerinin doğruluğu Amerikan Tabipler Birliği Dergisi (JAMA) skoru (1-4) ile değerlendirildi. İzlenme, yorum, beğeni, beğenmeme sayıları ile YouTube'a yüklenme tarihleri ve videoların süreleri ile ilgili açıklayıcı veriler kaydedildi. Videoların popüleritesi video güç endeksi ile değerlendirildi.

Bulgular: Videolarda verilen mesajlar göz önüne alındığında en sık verilen bilgi 41 video ile "kemik kitlesinde azalma" idi. Bunu "osteoporozun kırık riski oluşturması" ve "osteoporoz için risk faktörlerinin olduğu" izlemekteydi. Osteoporoza spesifik skor 8,92 ile düşüktü. Ortalama DISCERN skoru 25,020 (15-75) ve ortalama GKS 1,98 (0-5) ile düşük kaliteyi göstermekteydi. Video kaynağının sorgulandığı JAMA skoru (1-4) 1,66 ile düşük güvenilirlik seviyesi göstermekteydi. Sağlık profesyonelleri dışındaki kişiler tarafından hazırlanan osteoporoz hakkındaki videoların popüleritesi daha fazlaydı (82,25 vs 56,80) (cc=0,296, p=0,037).

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Öz

Sonuç: YouTube üzerinde osteoporoz hakkında yer alan videoların içeriği genel olarak yetersiz veya hatalıdır. Uluslararası kılavuzları baz alan daha yüksek kalitede ve bilgi seviyesinde videolar hazırlanması, hasta uyumu ve osteoporoza yönelik kamu farkındalığının artırılmasına katkı sağlayabilir.
Anahtar kelimeler: Osteoporoz, kemik erimesi, YouTube, güvenilirlik, kalite, video

Introduction

Osteoporosis is a progressive bone disease characterized by decreased bone density and deterioration in the microarchitecture of bone structure. It is usually asymptomatic and presents with fractures. The prevalence of osteoporosis increases with age and although it is known as a disease of the elderly, it can also occur in younger patients (1-3).

The presence of osteoporosis is known in 200 million women worldwide (4). According to the National Health and Nutrition Examination Survey conducted by the National Center for Disease Control and Prevention Health Statistics, it is estimated that more than 9.9 million Americans have osteoporosis and 43.1 million Americans have low bone mass (3,5). Women are affected by osteoporosis at a rate of 4/1 compared to men (3). In 2009, the prevalence of osteoporosis over the age of 50 in Turkey was 7.5% in men and 12.9% in women (6). In the Thrace Region, the prevalence of osteoporosis is 15.1% in women over 40 years old and 10.7% in men, while it reaches 25.7% over 55 years of age (7).

12% of patients with a history of fractures due to osteoporosis break another bone within one year, and 25% within five years. Bone resorption has a negative impact on the quality of life of patients in general. In addition, fractures caused by osteoporosis also create an economic burden for patients' relatives and the health system (8). Osteoporotic fractures cost more in women over 55 years of age than myocardial infarction, stroke, or breast cancer (1,3). One out of every three patients with hip fractures who lived independently before need care within at least one year after the fracture (9). And one-fifth of these patients die within a year (5). For this reason, it is necessary to provide the necessary information and inform the patients in order to prevent osteoporosis and reduce the risk of falling.

It has been reported that 75% of people at risk for osteoporosis do research on their health on the internet (10). Based on information obtained from YouTube, the site is visited by more than one billion internet users every month and YouTube has become one of the most popular video-sharing websites (11). This rich content makes YouTube a huge online video library. Although easy access to information on YouTube seems to make life easier, the lack of verified sources and an expert-peer review process are important problems. This means that it is necessary to review the reliability quality and of the videos on YouTube.

The aim of this study is to determine the level of information about osteoporosis in Turkish videos on YouTube and to determine the quality or reliability of these videos.

Materials and Methods

In this cross-sectional study, Turkish YouTube videos about osteoporosis were evaluated. Google trends (https://trends.google.com/trends/?geo=TR) search terms were used to select the videos. A search was made for the word "osteoporosis", and it was listed in the filters by setting "Turkey" as the region, "2008-Today" as the date, and "YouTube search" section. Turkish terms in the results were -in order of frequency- as follows: "kemik erimesi" (bone loss), "kemik erimesi belirtileri" (signs of bone loss), "kemik erimesine ne iyi gelir" (what is good for bone loss), "osteoporoz" (osteoporosis) and "kemik erimesi neden olur" (what causes bone loss). The resulting key terms were used when searching on YouTube.

Two searches were made on YouTube on May 8, 2021, in Tekirdağ, Turkey. Searches were made using a web browser with cleared history and cookies. Without logging in on YouTube and searches were made with the "sort by relevance" option selected. The first 50 URLs obtained were saved for each search term. The resulting videos were evaluated simultaneously by two orthopedic surgeons. The inclusion criterion was: Turkish videos with osteoporosis-related content. The exclusion criteria were: Videos that did not address the primary topic or had no audio or subtitles. Repeated videos were not evaluated. Data on the number of views of the videos, the number of comments, the number of "likes", "dislikes", the date of upload to YouTube, and the total duration of the video were recorded.

Global Quality score (GQS) (1-5) and DISCERN (15-75) scoring systems were used to determine the quality of video content (12,13). The accuracy of the video source information was evaluated with the Journal of American Medical Association (JAMA) score (1-4) (14).

DISCERN scale is a scoring system developed in Oxford, United Kingdom, which aims to measure written health information consisting of 15 questions in total and one additional question for overall evaluation (13). In the DISCERN scoring system, each question is scored between 1 and 5 points and the total score is between 16-75. Scores are evaluated as very poor between 16-26 points, poor between 27-38 points, fair between 39-50 points, good between 51-62 points and, excellent between 63-75 points (13). The JAMA scoring system consists of 4 criteria (authorship, attribution, clarity, currency), with 1 point for each and a maximum of 4 points. 1 point indicates the lowest quality information and 4 points the highest quality information (14). The GQS consists of 5 questions for evaluating the general quality and educational level of the content. In the scoring

system, 1 point indicates poor quality and 5 points indicates excellent quality (12).

What information was provided in the videos was checked using a checklist based on international control guidelines called Osteoporosis Specific scale (3,8). If the information was mentioned in the video, a score was given for the presence of each message, ranging from 0 points to 29 points.

The popularity of videos was evaluated by view rate and video power index (VPI). View ratio was calculated using (number of views/time since upload) formula. The formula [number of likes×100/ (like+dislike)] was used to calculate the like ratio. VPI was calculated using the (like ratio×view ratio/100) formula (12). In particular, VPI was preferred to evaluate viewer-video interaction and to avoid YouTube's ranking algorithm parameters that may contain commercial concerns.

This article does not contain any studies with human participants or animals performed by any of the authors and no ethical approvement is required for this study.

Statistical Analysis

IBM SPSS Statistics Version 25 (IBM Corp. Armonk, NY, USA) was used for statistical analysis. Descriptive statistical methods were used to evaluate study data. Whether the data were normally distributed or not was evaluated using the Shapiro-Wilk test and graphical examinations. The Mann-Whitney U test was used to compare two groups of quantitative variables that did not show normal distribution. Spearman correlation test was used to determine the correlation between variables. Chi-square test was conducted for each messages counting over the number of 5 to evaluate association between the groups and Fisher's Exact test for the rest. Inter-observer agreement was determined by Interclass Correlation Coefficient (ICC). P-value of <0.05 was considered statistically significant.

Results

ICC was found to be high with a value of 0.922 and no significant difference was observed between observers.

There was a moderate correlation between DISCERN, JAMA (cc=0.437, p=0.002). There was also a very strong correlation between DISCERN, GQS (cc=0.843, p<0.001), and a weak correlation between GQS, JAMA (cc=0.379, p=0.007). In addition, strong, strong, and moderate correlations were observed with the Osteoporosis Specific score and DISCERN, GQS and JAMA scores, respectively (cc=0.742, 0.752, 0.385, p<0.05, respectively) (Table 1).

No correlation was found between DISCERN, JAMA, GQS, and VPI. In addition, there was a weak negative correlation between the Osteoporosis Specific score and VPI (cc=-0.323, p=0.022). It is concluded that the popularity of the video decreases as the information content of the video increases.

Videos prepared by healthcare professionals and non-healthcare professionals were compared with the Mann-Whitney U test in terms of scoring systems, VPI, and number of views. Although there was no significant difference between DISCERN, GQS and JAMA values, it was high in favor of healthcare professionals. The Osteoporosis Specific score was significantly higher in videos prepared by healthcare professionals (p=0.004, 10.58 vs 5.72). However, the number of views (16.425 vs 116.919, p=0.016) and mean VPI (56.80 vs 82.25) (cc=0.296, p=0.037) values in terms of popularity were higher in the other group. Significant and weak correlation was observed between VPI and video sources. The average VPI value of videos of non-healthcare professionals (n=14) was significantly higher than that of healthcare professionals (n=36). It was observed that the popularity of non-healthcare professionals in osteoporosis videos was higher (Figure 1).

No significant relationship was found between the like ratio and the video source (p=0.514). A weak correlation was observed between the view ratio and the video source, and the view ratio of healthcare professionals was low (p=0.035, cc=0.299).

In order of frequency, the messages given in the videos are "Decrease in bone mass" in 41 videos (82%), "Osteoporosis is a risk for fracture" in 37 videos (74%), "There are risk factors for

Table 1. P-values and correlation coefficients presented with p and Spearman's rho values

	DISCERN (rho/p)	JAMA (rho/p)	GQS (rho/p)	VPI (rho/p)	OSS (rho/p)
DISCERN	1.000	0.437	0.843	-0.011	0.742
	-	0.002	0.000	0.938	0.000
JAMA	0.437	1.000	0.379	0.128	0.385
	0.002	-	0.007	0.374	0.006
GQS	0.843	0.379	1.000	-0.008	0.752
	0.000	0.007	-	0.955	0.000
VPI	-0.011	0.128	-0.008	1.000	-0.323
	0.938	0.374	0.955	-	0.022
OSS	0.742	0.385	0.752	-0.323	1.000
	0.000	0.006	0.000	0.022	-

JAMA: Journal of the american medical association, GQS: Global Quality score, VPI: Video power index, OSS: Osteoporosis Specific score

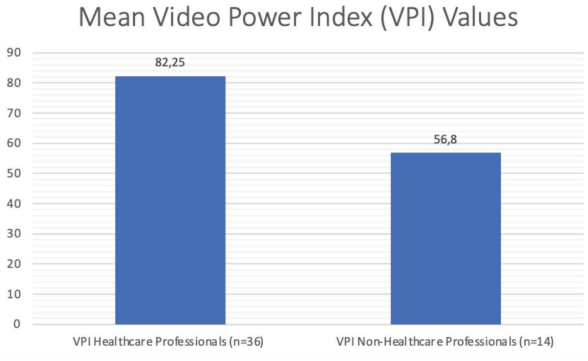

Figure 1. Distributional graphic of video power index between healthcare professionals and non-healthcare professionals

osteoporosis (family history, age, sex, etc.)" in 36 videos (72%), "Sufficient calcium intake" in 32 (64%) videos and "Sufficient intake of vitamin D" in 31 (62%) videos (Table 2).

The least given messages were from low to high with 0 videos "Self medicating should be avoided", 1 video with "Prolonged treatment", 2 videos with "The importance of continuation of treatment even if there are difficulties", 3 videos with "Vertebral images" and "Rule out fragility fractures" and "Specific bone disease". Messages about the definition and diagnosis of osteoporosis and recommendations were found most frequently, while messages for treatment and follow-up were found to be less. The number of information given in Recommendations (133) and Definition categories (130) were more frequent than

Table 2. Numbers and proportional distribution of information in Osteoporosis Specific scale content by groups. Each of the 29 messages on the Osteoporosis Specific scale is recorded if mentioned in the videos, and the total number is presented separately between healthcare professionals and non-health professionals

	Information	HP		NHP	
		n	%	n	%
1. Definition	Asymptomatic-silent	18	48.6	4	30.8
	Progressive	10	27.0	5	38.5
	Specific to bone	3	8.1	0	0.0
	Decrease in bone mass	32	86.5	9	69.2
	Fracture risk	30	81.1	7	53.8
	Treatment required	9	24.3	3	23.1
2. Diagnosis	Risk factors (family history, age, sex)	28	75.7	6	46.2
	Vertebral images	3	8.1	0	0.0
	Search for physician	7	18.9	0	0.0
	Decrease in hight	11	29.7	0	0.0
	DEXA, bone dansitometry	15	40.5	6	46.2
	Asymtomatic vertebral fructures	3	8.1	1	7.7
	Secondary, other causes (corticosteroid etc.)	14	37.8	1	7.7
3. Recommendations	Alcohol intake should be limited	14	37.8	4	30.8
	Smoking should be avoided/quitted	15	40.5	4	30.8
	Self-medication should be avoided	0	0.0	0	0.0
	Confirmation of absence of fragility fracture	3	8.1	0	0.0
	Sufficient vitamin D intake	23	62.2	8	61.5
	Sufficient calcium intake	22	59.5	13	100.0
	Physical activity	22	59.5	5	38.5
4. Treatment	Medications that reduce bone loss	12	32.4	3	23.1
	Supplement of calcium	15	40.5	2	15.4
	Supplement of vitamin D	17	45.9	4	30.8
	Reduce the risk of fracture	4	10.8	1	7.7
	Prolonged treatment	1	2.7	0	0.0
	Medications that increase bone formation	10	27.0	1	7.7
	Reduce falling risk	8	21.6	2	15.4
	The importance of continuation of treatment even if difficulties are experienced	2	5.4	0	0.0
5. Recommendations	Bone densitometry should be repeated within 2 years	5	13.5	1	7.7

HP: Health professionals, NHP: Non-health professionals

Diagnosis (95), Treatment (82), and Follow-up (6) categories (Figure 2).

For the messages over number of 5 chi-square test was conducted and significant difference was observed between the groups ($p<0.001$). Also Fisher's Exact test was conducted for messages under number of 5 and significant difference was observed ($p<0.001$). While the number of messages was more than 5 in the health professionals group, it was the opposite in the other group. To exclude that non-homogenity, percantages were used and weighted as frequencies and chi-square test was conducted for all. The results were similar and consistent with the previous tests ($p<0.001$). Also for most common messages (Decrease in bone mass and Osteoporosis is a risk for fractures), 2x2 contingency table was used and chi-square test were conducted. There was no significant difference between the groups ($p=0.741$).

The mean DISCERN score was low with 25.020±6.625 (16-46), while the JAMA score was 1.66±0.658 (1-3) and the GQS was 1.98±1.097 (1-5). The Osteoporosis Specific score was found to be 8.920±5.91 (1-29). Descriptive statistics are presented in Table 3.

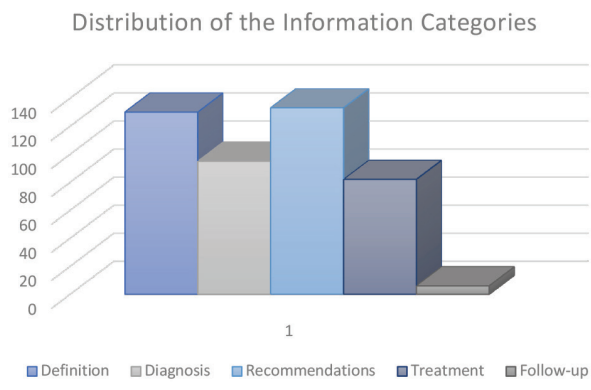

Figure 2. Distibution of messages mentioned in the videos according to categories of Osteoporosis Spesific scale

Discussion

The main finding of our study was that the Turkish videos about osteoporosis were of insufficient quality and did not provide sufficient information according to the scoring systems used.

Rozenfeld et al. (15) conducted a survey-based study involving 3,000 women aged 50-85 years and investigated what information about osteoporosis was searched on the internet and what surveyors wanted to found. They found that middle-aged women were more interested in the management of the disease on internet-based information. In line with this interest, more messages were given in the recommendations part of the videos and our results are consistent with the study.

While there are various scoring systems to evaluate the content of YouTube videos, there is no standard approach (16). The information about healthcare videos on YouTube is generally inaccurate and a patient is highly likely to find such misleading information (17). In a study, Gutlapally et al. (18) found that only 11 of 45 sites had reliable information about osteoporosis. This can be dangerous as it may affect public opinion and primary perception of the disease and the management. In addition, people trying to learn about osteoporosis on the Internet may also be affected when they receive false feedback from comments, which can lead to the adoption of behaviors that may affect treatment, such as lack of compliance (19).

In our study, it was questioned which of the 29 important messages (Table 1) were given in Turkish videos with the Osteoporosis Specific score, and it was seen that messages were given at a low rate with an average of 8.92. This is similar to the results of other studies and shows that the messages given are incomplete (8,18). But also Tejada-Llacsa et.al (8) found that most mentioned information in Spanish videos about

Table 3. Descriptive data for evaluated YouTube videos

	Minimum	Maximum	Mean	Standard deviation
DISCERN	16.0	46.0	25.02	6.63
JAMA	1.0	3.0	1.66	0.66
GQS	1.0	5.0	1.99	1.10
Like ratio	1.00	100.00	91.98	16.45
View ratio	0.04	889.76	67.30	195.69
VPI	0.01	868.06	63.93	187.36
OSS	1.00	25.00	8.92	5.92
Number of likes	0	9100	570.44	1622.35
Number of dislikes	0	931	33.30	133.73
Number of comments	0	248	18.22	41.45
Number of views	58	1095814	44563.54	159261.19
Duration	1.090	35.58	8.11	7.79

JAMA: Journal of the American Medical Association, GQS: Global Quality score, VPI: video power index, OSS: Osteporosis Specific score

osteoporosis was "Osteoporosis is a risk factor for fractures". In contrast with that "Decrease in bone mass" was the most common information given in the videos in our study, and this was the most common search criterion with "kemik erimesi" (bone loss), which was accepted as a similar term in the Turkish society and indicates a decrease in the bone mass.

There are numerous studies investigating the quality of medical information videos on YouTube (11,12,16,17,20,21). In these studies, medical information videos on YouTube were of low quality.

In 2014, Brooks et al. (20) reviewed lumbar discectomy videos-which are an informative resource for patients on YouTube. Recently, Celik et al. (21) examined the information about rotator cuff injury on YouTube and found that it was of poor quality.

In our study, the DISCERN score was 25.020±6.625 (16-46), while the JAMA score was 1.66±0.658 (1-4) and the GQS was 1.98±1.097 (1-5). These results are consistent with the results of other studies in the literature and show that Turkish videos about osteoporosis are of low quality. In terms of messages separately presented in Table 2, there were significant differences between health-care prefesional and non-healthcare professionals ($p<0.001$). But in terms of the most common two messages (Decrease in bone mass and osteoporosis is a risk for fractures) there was no significant differences ($p=0.741$). It can be assumed that although the total number of messages were mentioned more in videos prepared by health-care professionals, the most common messages were given almost in the same manner between the two groups. In addition, there was a weak negative correlation between the Osteoporosis Specific score and VPI (cc=-0.323, $p=0.022$). The average VPI value of videos of non-healthcare professionals was significantly higher than that of healthcare professionals (82.25 vs 56.80) (cc=0.296, $p=0.037$) and also the view ratio of healthcare professionals was low ($p=0.035$, cc=0.299). Also mean Osteoporosis Specific score was significantly higher in healthcare professionals compared to other group ($p=0.004$, 10.58 vs 5.72). Although the video is more informative, it has been concluded that this situation does not increase the popularity of the video in the first place. Welbourne and Grant (22) analyzed 390 videos from 39 YouTube channels to explore factors affecting video popularity and found that user-created videos were more popular than those uploaded by professionals. It is mentioned that popularity is related to more interaction in user-sourced videos. It can be thought that the low popularity may be related to a proposition that health professionals are less interactive in videos. However, our study specifically examined videos in the field of health and the trust of the viewers towards the healthcare professional can be effective in their video selection. Viewers' video choices in the field of health can be multifactorial, and this could be the subject of another study.

In conclusion, our study shows that the number of information in Turkish videos about osteoporosis and the video quality is low, which may cause people at risk to have incomplete information about osteoporosis and create a challenging environment for the patient-doctor relationship. Because it is easy and inexpensive to access the Internet, patients tend to obtain medical information from the Internet (19). For this reason, videos shared on a platform such as YouTube may be beneficial to be verified by an expert in order to ensure the optimum patient-doctor relationship, especially if the video is about health care or better quality videos may be recorded by healthcare professionals.

Our study has several strengths. First of all, our study is the first study to examine Turkish videos on osteoporosis, and to our knowledge, there are only three studies in the literature examining Turkish videos overall (23-25). YouTube searches are restricted to Turkey, which also provides information specific to the Turkish society's approach to osteoporosis-related videos. The examined videos were in the native language of the surgeons without language a barrier and the interrater agreement was quite high. In addition, when compared with other studies in this field, multiple scoring systems evaluating quality and also a scale assessing what information specific to osteoporosis were used together and analyzed (8,11,12,16,17,20,21).

There are also some limitations of this study. Firstly, YouTube is a growing platform and the search results can change over time. Secondly, the first 50 videos that appeared after searching for the keywords were examined. However, we think that the videos that appeared at the top were watched more. Thirdly, we only examined Turkish videos. Although this is a limitation, it can also provide a cross-sectional benefit in terms of examining videos for Turkish Society, which we see as an important aspect. Fourth, only YouTube videos were evaluated in this study, and the quality and reliability of osteoporosis-related videos on other sites were not covered. Despite the limitations, we believe that our study shows beneficial information about the educational quality of videos and YouTube should be considered as a platform to improve public information and perception of osteoporosis.

Conclusion

Turkish YouTube videos about osteoporosis contain incomplete or incorrect information about osteoporosis and the quality of the videos is low. Especially, the videos prepared by healthcare professionals based on international guidelines and scoring systems can increase the quality of these videos. Considering that osteoporosis is a progressive and silent disease, as well as other platforms, it is important to provide preventive and informative videos on YouTube.

Ethics

Ethics Committee Approval: No ethical approvement is required for this study.

Informed Consent: This article does not contain any studies with human participants or animals performed by any of the authors.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: The authors confirm that there are no known conflicts of interest associated with this publication.

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The Effect of Type 2 Diabetes Mellitus on Osteopenia and Vertebral Fractures in Elderly Women

Tip 2 Diabetes Mellitusun İleri Yaş Kadınlarda Osteopeni ve Vertebral Kırıklar Üzerine Etkisi

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Abstract

Objective: In our study, we examined the effects of type 2 diabetes mellitus (DM) on the thoracic and lumbar vertebrae in patients with osteopenia.

Materials and Methods: Ninety patients had type 2 DM while 64 patients did not have any chronic disease. We analyzed the patients' total lumbar T-score with dual energy X-ray absorptiometry. We included patients with a T-score between -1 and -2.4 and evaluated the thoracic and lumbar vertebrae of the patients with dorsal and ventral X-ray imaging.

Results: In the results of the study in which we examined 154 osteopenic female patients, we found the mean osteopenia depth to be -1.52 in individuals with type 2 DM and -1.74 in the control group. We found the lumbar T value to be statistically significantly higher than the control group cases (p=0.001; p<0.01). However, the fracture rate was 21.9% in the control group, while it was 36.7% in type 2 DM. We found the fracture rate in patients with type 2 DM to be statistically significantly higher than that in the control group (p=0.049; p<0.05). In the control group, 64.3% of the fractures were grade 1, and 35.7% were grade 2, and there was no collapse fracture, while in the group with diabetes, we found grade 1 fractures 24.2%, grade 2 27.3%, and grade 3 collapse fractures 48.5%. Notably the incidence and severity of fractures was significantly higher than the control group, however, the lumbar T-score in the presence of type 2 DM was not as low as the control group in our study.

Conclusion: Although the lumbar T-score in the presence of the type 2 DM was not as low as the control group in our study, it is noteworthy that the incidence and severity of fractures was significantly higher than the control group.

Keywords: Osteopenia, elderly women, diabetes mellitus, vertebrael fracture

Öz

Amaç: Çalışmamızda osteopenili hastalarda tip 2 diabetes mellitusun (DM) torasik ve lomber vertebra üzerindeki etkilerini incelemeyi amaçladık.

Gereç ve Yöntem: Doksan hastada tip 2 DM varken 64 hastada herhangi bir kronik hastalık bulunmamaktaydı. Hastaların total lomber T-skoru dual-enerji X-ışını absorbsiyometri ile analiz edildi. Çalışmaya T-skoru -1 ile -2,4 arasında olan hastaları dahil edildi ve dorsal ve ventral X-ışını görüntüleme ile hastaların torasik ve lomber vertebraları değerlendirildi.

Bulgular: Osteopenik 154 kadın hastayı incelediğimiz çalışmanın sonuçlarında ortalama osteopeni derinliği tip 2 DM olan bireylerde -1,52, kontrol grubunda ise -1,74 olarak bulundu. Lomber T değeri kontrol grubu olgulara göre istatistiksel olarak anlamlı derecede yüksek bulundu (p=0,001; p<0,01). Ancak fraktür oranı kontrol grubunda %21,9 iken tip 2 DM'de %36,7 idi. Tip 2 DM'li hastalarda fraktür oranı kontrol grubuna göre istatistiksel olarak anlamlı derecede yüksek bulundu (p=0,049; p<0,05). Kontrol grubunda kırıkların %64,3'ü 1. derece, %35,7'si 2. derece olup kollaps kırığı yoktu, diyabetik grupta ise 1. derece fraktür %24,2, 2. derece fraktür %27,3 ve 3. derece fraktür %48,5 tespit edildi. Çalışmamızda fraktür insidans ve şiddetinin kontrol grubuna göre anlamlı derecede yüksek olması ancak tip 2 DM varlığında lomber T-skorunun kontrol grubu kadar düşük olmaması dikkat çekicidir.

Sonuç: Çalışmamızda tip 2 DM varlığında lomber T-skoru kontrol grubu kadar düşük olmasa da kırık insidansı ve şiddetinin kontrol grubuna göre anlamlı derecede yüksek olması dikkat çekicidir.

Anahtar kelimeler: Osteopeni, ileri yaş kadın, diabetes mellitus, vertebral fraktür

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Introduction

The World Health Organization (WHO) defines a T-score between -1 and -2.5 as osteopenia. With the aging of the population and the prolongation of life expectancy, osteoporosis and osteopenia are emerging as more critical health problems. In the FRACTURK (1) study, the prevalence of osteoporosis in Turkey was 25% over the age of 50, while the prevalence of osteopenia was 50%. The United States expects the cost of care for direct and indirect fragility fractures to exceed $25 billion by 2025 (2). Osteopenia was shown to increase the risk of high fractures in many studies (3,4), just like in osteoporosis, and the risk of osteopenic and osteoporotic fractures is high, especially in elderly women (3). Fragility fractures are fractures that occur as a result of mechanical force, known as trauma with energy too low to normally cause a fracture. This mechanical power is the force equivalent to falling from standing height according to WHO (5). In the TURDEP 2 (6) study, the prevalence of diabetes in our population was 16.5%. Osteopenia isalso associated with type 2 diabetes mellitus (DM); however, the pathogenesis of diabetic osteopenia is unclear. In an experimental study evaluating bone mineral density (BMD) by dual energy X-ray absorptiometry (DEXA), bone metabolism in rats was evaluated 120 days later. In the study, the femoral trabecular distance increased approximately 3 times in rats with plasma glucose above 250 mg/dL compared to the non-diabetic control group, and the trabecular thickness decreased by 2 times and the bone trabecular volume by 77% (7). Type 2 DM increases the risk of fracture, and risk assessment is challenging in these individuals because BMD is often underestimated. Low bone turnover, accumulation of advanced glycation end products, and changes in bone micro and macro architecture impair bone strength and mass. Diabetic patients with impaired glycemic regulation, length of disease duration, -cell damage, and insulin therapy are at highest risk of fracture. Diabetes-induced complications such as sarcopenia, neuropathy, oculomotor problems, and frequent hypoglycemic episodes increase the risk of falling and the incidence of fractures (8). It was shown that white women with type 2 DM lose more BMD per year on average compared to acontrol group (9); however, post-fracture recovery is also impaired in these patients (10). Type 2 DM, metabolic bone diseases, including low BMD, fractures and falls in geriatric patients were associated with other bone-related events (11). Diabetes not only exacerbates low BMD but also causes osteopenia and osteoporosis (12). Mathen et al. (13) showed that BMD was significantly lower in both the lumbar vertebra and femoral neck in indians with type 2 DM compared to the control group and concluded that diabetes is an "overlooked complication" for osteopenia and osteoporosis.

Purpose of the Study

Fracture presence and degrees were compared by evaluating the lumbar T-score and thoracic and lumbar vertebrae in elderly osteopenic diabetic patients and patients with osteopenia who do not have any chronic disease. We evaluated whether the severity of osteopenia, frequency of fracture, and degree of fracture were higher in type 2 DM compared to the control group. In our study, the plan was to investigate how much attention should be paid to osteopenia in individuals with diabetes and how much antiresorptive therapy is required in the diabetic osteopenic population.

Materials and Methods

A total of 154 female patients aged between 48 and 74 years treated in the internal medicine outpatient clinic of a secondary health care institution were included. Cases were reviewed retrospectively. A total of 90 patients had type 2 DM, while 64 patients did not have any chronic disease. We analyzed the patients' total lumbar T-score with lunar DPX-L DEXA. The entire study was performed on patients evaluated with the same device. Patients with a T-score between -1 and -2.4 were included and the thoracic and lumbar vertebrae of the patients were evaluated with dorsal and lateral X-ray imaging. The presence of vertebral fractures in patients was examined and if present, fracture level was determined. The criterion by which Genant et al. (14) categorized vertebral fractures by fracture level was used. Mild fracture wascharacterized by the concavity of the vertebra and evaluated as stage 1 fracture, moderate fracture wascharacterized by wedging of the vertebra and evaluated as a stage 2 fracture, and severe fracture wascharacterized by vertebral crushing and collapse and evaluated as stage 3 fracture. The presence of vertebral osteophytes was excluded. Patients who exceeded the osteoporosis threshold and had a T-score of -2.5 and above were excluded from the study. Patients with diagnosis of osteoporosis and those receiving osteoporosis treatment were excluded from the study. The cases without major or minor trauma and the presence of fracture due to osteopenia were evaluated during outpatient follow-up. Medications used by patients were reviewed retrospectively. Patients who used antiepileptics, pioglitazone, anticoagulants, furosemide, glucocorticoids, and levothyroxine were excluded from the study because adequate standardization could not be achieved. Patients with hyperthyroidism, primary hypothyroidism, diagnosed with type 1 DM, malignancy disease, with rheumatic disease and using chronic steroids were excluded. We examined the fracture frequency, severity, and osteopenia severity in type 2 diabetic patients and the group without any chronic disease. Patients who were followed up due to the presence of metabolic bone diseases such as osteopetrosis and osteomalacia were excluded from the study. Patients with diabetic nephropathy were excluded because the presence of low glomerular filtration rate may affect bone metabolism at various levels.

Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee approval was obtained (decision no: 2021/514/200/2, date: 28.04.2021).

Statistical Analysis

Number cruncher statistical system 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive

statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used when evaluating study data. Conformity of quantitative data to normal distribution was examined with the Shapiro-Wilk test and graphical examinations. The Mann-Whitney U test was used for comparisons between two groups of normally distributed and non-normally distributed quantitative variables. The Pearson chi-square test and Fisher-Freeman-Halton exact test were used to compare qualitative data. Statistical significance was accepted as $p<0.05$.

Results

Diabetes was observed in 58.4% (n=90) of the cases (Table 1).
Lumbar T measurements forthe cases ranged from -2.4 to -1.5, and the mean was -1.62±0.55.

Fractures were present in 30.5% of the cases (n=47). The fracture severity was grade 1 in 36.2% (n=17), grade 2 in 29.8% (n=14), and grade 3 in 34% (n=16) of the cases with fracture. When the fracture frequencies of the cases with fractures were examined, 36.2% (n=17) of the cases had concave, 29.8% (n=14) had wedge, and 34% (n=16) had crush fractures (Table 2).
The lumbar T value of patients with diabetes was statistically significantly higher than those in the control group. (p=0.001; p<0.01) (Figure 1).
The rate of fracture in patients with diabetes was statistically significantly higher than in the control group (p=0.049; p<0.05) (Figure 2).
No statistically significant difference was found between the diagnoses of the cases according to sex (p=0.004; p>0.01). Fracture frequencies of the cases in the DM group were

Table 1. Distribution of findings

n (%)		
Group	Control group	64 (41.6)
	DM's	90 (58.4)
Lumbar T	Mean ± SD	-1.62±0.55
	Median (min-max)	-1.6 (-2.4-1.5)
Fracture	No	107 (69.5)
	Exist	47 (30.5)
Fracture severity	Grade 1	17 (36.2)
	Grade 2	14 (29.8)
	Grade 3	16 (34)
Fracture frequency	Concave	17 (36.2)
	Wedge	14 (29.8)
	Crush	16 (34)

DM: Diabetes mellitus, SD: Standard deviation, min: Minimum, max: Maximum

Table 2. Comparisons by group

		Group		**p**
		DM's control group	**Control group**	
Lumbar T	Mean ± SD	-1.53±0.54	-1.74±0.54	[a]0.001**
	Median (min-max)	-1.4 (-2.4-1.4)	-1.8 (-2.4-1.4)	
Fracture	No	57 (63.3)	50 (78.1)	[b]0.049*
	Exist	33 (36.7)	14 (21.9)	
Fracture severity	Grade 1	8 (24.2)	9 (64.3)	[c]0.004**
	Grade 2	9 (27.3)	5 (35.7)	
	Grade 3	16 (48.5)	0 (0)	
Fracture frequency	Concave	8 (24.2)	9 (64.3)	[c]0.004**
	Wedge	9 (27.3)	5 (35.7)	
	Crush	16 (48.5)	0 (0)	

DM: Diabetes mellitus, SD: Standard deviation, min: Minimum, max: Maximum. [a]Mann-Whitney U test , [b]Pearson chi-square test, [c]Fisher Freeman Halton test, *p<0.05, **p<0.01

significantly lower than those in the control group. The incidence of grade 2 and grade 3 fractures was significantly higher in the type 2 DM group (Figure 3).

Discussion

Fractures can occur in osteopenic patients, just like osteoporotic patients (15). While the rate of vertebral fractures in women over 50 in the general population is between 20-30%, this rate is 40% over the age of 80. In our study, vertebral fractures were identified in 30.5% of all patients, and this result is consistent with literature data.

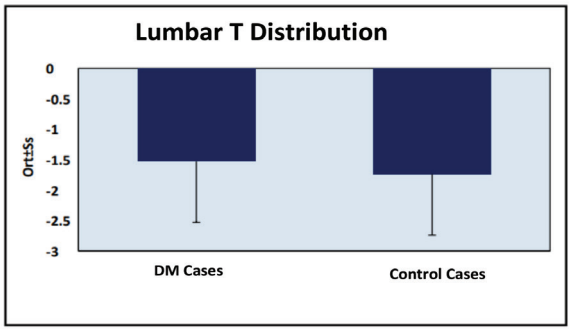

Figure 1. Lumbar T distribution by group
DM: Diabetes mellitus

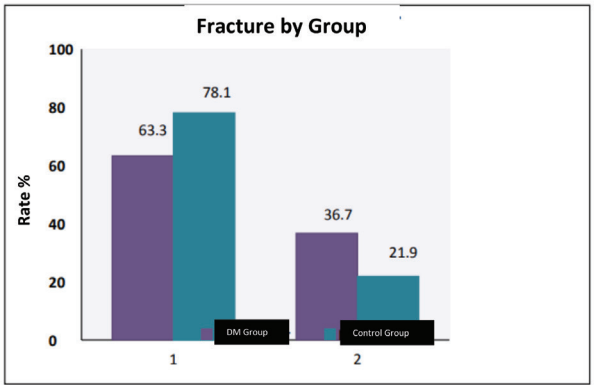

Figure 2. Fracture distribution by group
DM: Diabetes mellitus

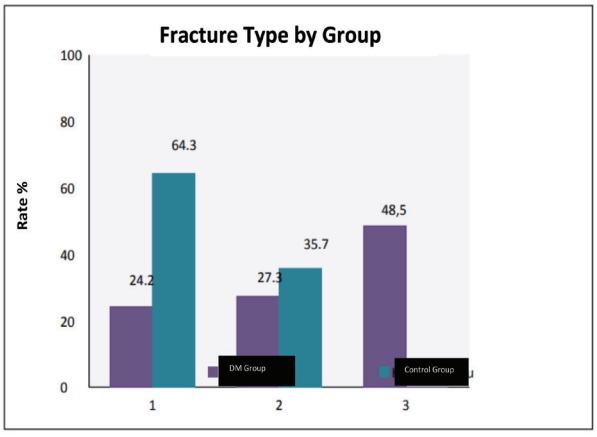

Figure 3. Distribution of fracture type by group
DM: Diabetes mellitus

There are studies showing that BMD is severely decreased in patients with uncontrolled type 2 DM (16,17). Yaturu et al. (18) found significantly deeper BMD in type 2 DM when they compared 2 groups in the same age group. Asokan et al. (19) showed an inverse correlation between the duration of diabetes and glycemic control with BMD. At the same time, the incidence of osteopenia was higher in the control group in this study and in 3 different studies conducted by Sosa et al. (20) and Wakasugi et al. (21). Petit et al. (22) reported better BMD values in elderly patients with type 2 DM compared to the same age group without chronic disease. In our study, when the patients with type 2 DM and the control group were compared forseverity of osteopenia, the severity of osteopenia was higher in the control group. While the mean T-score was -1.53 in the diabetic group, it was -1.74 in the control group. Contrary to the general literature and our initial expectations, BMD was better in individuals with type 2 DM. Our result, like the result by Petit et al. (22), gave a positive result for the T-score in favor of the group with diabetes. While there are studies reporting a lower incidence of fractures in patients with type 2 DM (23,24), there are also studies that correlate it with a high fracture risk (25). Jain et al. (26) also showed that the development of lumbar vertebral fracture increases if the T-score in diabetic osteoporosis and osteopenia falls below -1.5. Vestergaard (27) reported an increased risk of fracture in many regions, including the vertebrae and the femur. In our study, the incidence of fracture in the control group was 21.9%, while it was 36.7% in the diabetic group. While grade 1 fractures were more common in the control group, grade 2 and grade 3 fractures were significantly higher in the diabetic group. While the lumbar T-score gave a more positive result in the diabetic group, it is surprising that the incidence and overall severity of fractures were significantly higher in this group. While the incidence and severity of fractures are expected to be higher in the group with a lower T-score, the result is outside of expectations. This result leads to the consideration that there may be other factors that affect the development of fracture in diabetics besides BMD. However, the literature data aboutthis condition is limited and the pathogenesis of diabetic osteopenia is not clear. While osteoporosis is better known and treatable in the general population, osteopenic patients cannot benefit from antiresorptive treatments unless fracture assessment is performed. The FRACTURK study (1) showed the prevalence of osteopenia was twice that of osteoporosis in our population. In our study, in which patients with type 2 DM a type of chronic disease were evaluated, in the osteopenic groupthe results show that silent fractures can accompany type 2 DM more frequently compared to the control group, even with more positive T-score results. It was shown that when type 2 DM and osteopenia are comorbid, osteopenia progresses more catastrophically and fractures heal later.

Patients using pioglitazone, one of the thiazolidinedione group oral antidiabetic agents known to cause osteoporosis and osteopenia in type 2 DM cases, were excluded because adequate standardization could not be achieved. Other oral antidiabetic agents have no osteopenic effect.

When compared with the decrease in the treatment response with the progression of osteopenia accompanying fractures to osteoporosis and the cost of fractures due to the decrease in BMD, taking the necessary precautions and providing antiresorptive treatment for osteopenic fractures are cost-effective. Our study showed that diabetic osteopenics should be evaluated further in terms of fractures. If fractures are detected by X-ray evaluation of thoracic and lumbar vertebrae, antiresorptive treatment should be arranged immediately.

Since our study is retrospective, the inability to evaluate body mass index and the inability to make inquiries about smoking, alcohol use and caffeine consumption are limitations of our study.

Conclusion

Type 2 DM and osteopenia often accompany each other. Osteopenia is thought to be an "overlooked complication" of type 2 DM, but the underlying mechanism has not been elucidated. Studies show that diabetic patients with BMD values of -1 and below should be screened for fractures. In our study, although the severity of osteopenia was not as bad as the control group, it seems that the frequency of fractures is unexpectedly higher in diabetic individuals with higher T-scores. The presence of fracture should be investigated considering that the vertebrae of these patients are evaluated with X-rays and the healing of osteopenic fracture is impaired and delayed in type 2 DM. If we take into account the progression to osteoporosis and various mortality and morbidities if left untreated, detecting fractures in the osteopenic group and arranging antiresorptive treatment will be cost-effective. The aging population, long life expectancies, and increasing frequency of these problems are becoming increasingly crucial. The presence of diabetes should be an alarming finding especially in the osteopenic group in terms of the presence of vertebral fractures and fractures that can be detected in these patients should not be missed.

Ethics

Ethics Committee Approval: Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee approval was obtained (decision no: 2021/514/200/2, date: 28.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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Awareness and Knowledge Levels of Osteoporosis in Patients with Multiple Sclerosis

Multipl Sklerozlu Hastalarda Osteoporoz Farkındalık ve Bilgi Düzeyleri

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Abstract

Objective: This study examines the awareness and knowledge levels of osteoporosis in patients with multiple sclerosis (MS).
Materials and Methods: A total of 88 adult patients with MS (22 male, 66 female) were included in the study. The demographic and socioeconomic status of all patients were recorded. First, a question was asked the participants: "Have you ever heard of osteoporosis before?". After that, a survey was conducted on the participants. The survey consisted of a questionnaire assessing their knowledge using a 30-item instrument reflecting 9 knowledge domains (eg, risk factors, diagnosis, prognosis).
Results: The mean age of the patients was 39.85±9.67 years. The duration of the disease was median [interquartile range (IQR) (Q1-Q3) 4 (1-10)] years. Expanded disability status scale score of the patients was median [IQR (Q1-Q3) 2 (1-4.5)]. Most of the participants (81.8%) were aware of osteoporosis. Awareness of osteoporosis was higher in those who received corticosteroid treatment and had comorbid diseases (respectively p=0.011 and p=0.009). On average, the knowledge questions score was 13 (0-23). Mean knowledge scores were not associated with education status or gender. The knowledge score levels were higher in those who had heard of osteoporosis than in those who had not heard, respectively 14 (10-18) to 4 (0-13,75) (p<0.001).
Conclusion: Although awareness of osteoporosis was high in MS patients, the level of knowledge on osteoporosis was insufficient. Awareness and knowledge levels of osteoporosis were higher in those who received corticosteroid treatment. Additionally, osteoporosis awareness was higher in those who had comorbid diseases. Increasing knowledge about osteoporosis may be important for preventing osteoporosis and reducing its complications in MS patients.
Keywords: Multiple sclerosis, osteoporosis, bone mineral density, awareness

Öz

Amaç: Bu çalışmanın amacı multipl sklerozlu (MS) hastalarda osteoporoz farkındalık ve osteoporoz bilgi düzeylerini incelemektir.
Gereç ve Yöntem: MS (22 E, 66 K) toplam 88 erişkin hasta çalışmaya dahil edildi. Tüm hastaların demografik ve sosyoekonomik durumları kaydedildi. Katılımcılara ilk olarak "Osteoporozu daha önce duydunuz mu?" sorusu soruldu. Ardından katılımcılara osteoporoz ile ilgili dokuz bilgi alanını yansıtan (örneğin, risk faktörleri, tanı, prognoz) 30 maddelik bir anket uygulandı.
Bulgular: Hastaların yaş ortalaması 39,85±9,67 yıl idi. Hastalık süresi medyan [IQR(Q1-Q3)] 4 (1-10) yıldı. Hastaların genişletilmiş özürlülük durum ölçeği skoru ortanca [IQR(Q1-Q3)] 2 (1-4,5) idi. Katılımcıların çoğu (%81,8) osteoporozu daha önce duyduklarını belirtti. Komorbid hastalığı olanlarda ve daha önce kortikosteroid kullanımı olanlarda osteoporoz farkındalığı daha yüksekti (sırasıyla p=0,009, p=0,011). Osteoporoz bilgi puanı medyan 13 (0-23) idi. Ortalama bilgi puanları eğitim durumu ve cinsiyet ile ilişkili değildi. Osteoporozu duyanlarda duymayanlara göre osteoporoz bilgi puanı daha yüksekti [sırasıyla 14 (10-18) ile 4 (0-13,75) (p<0.001)].
Sonuç: MS hastalarında osteoporoz farkındalığı yüksek olmakla birlikte, osteoporoz bilgi düzeyi yetersizdi. Kortikosteroid tedavisi alanlarda osteoporoz farkındalık ve bilgi düzeyleri daha yüksekti. Yine komorbid hastalıkları olanlarda osteoporoz farkındalığı daha yüksekti. MS hastalarında osteoporoz hakkında bilgi birikiminin artması, osteoporozun önlenmesi ve komplikasyonlarının azaltılması açısından önemli olabilir.
Anahtar kelimeler: Multipl skleroz, osteoporoz, kemik mineral yoğunluğu, farkındalık

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Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease affecting the brain and spinal cord, which usually has a relapsing-remitting course (1,2). It is one of the most common causes of neurological disability in young adults and affects approximately 1.3 million people worldwide (3). Osteoporosis is a disease characterized by low bone mineral density (BMD) and deterioration of bone tissue predisposing to fragility fractures (4-6). Several current studies have suggested that patients with MS have lower BMD and higher rates of osteoporosis than healthy adults (7-9). Causes of osteoporosis in MS include immobility, vitamin D deficiency, chronic inflammatory process, use of glucocorticoids (10-12). Patients with MS have an increased risk of falling due to impaired gait, balance, coordination, cognition, and cerebellar, sensory, and pyramidal functions (3). Therefore, there is an increased risk of osteoporotic fractures in patients with MS compared to the general population (3,9). Furthermore, since MS patients have a higher risk of fracture, the awareness of osteoporosis is crucial among them. If the awareness of osteoporosis is determined and information about the disease can be increased in MS patients, the negative consequences such as fractures and physical disabilities will also be reduced to that extent (11,13). There was not any study found during our literature search on the awareness of osteoporosis in patients with MS and the factors affecting it. The study examined the awareness and knowledge levels of osteoporosis and the factors affecting them in adult patients with MS.

Materials and Methods

Study Design and Population

We conducted a cross-sectional survey study. The approval of the local Ethics Committee at Dokuz Eylül University was obtained prior to the start of the study (decision no: 2016/26-31, date: 06.10.2016). Since MS is a rare disease, all MS patients who applied to the outpatient clinic during the study period (between May 2016 and May 2018) and met the inclusion criteria were included in the study, without a specific sample size. One hundred thirteen patients were interviewed. Nineteen patients did not want to participate in the study. One patient had been illiterated and one patient had severe cognitive dysfunction and four patients had a diagnosis of osteoporosis, they were not included. A total of 88 patients were included. All subjects gave written informed consent before participating in the study. The inclusion criteria of the study; being an adult patient with MS and volunteer to participate in the study. The exclusion criteria were not agreeing to voluntarily participate in the study, the presence of severe cognitive dysfunction, and the presence of a diagnosis of osteoporosis.

Data Collection

The demographic characteristics of the patients were recorded. The presence of additional disease, previous osteoporosis diagnosis, glucocorticoid medication, how the subjects reached information sources about osteoporosis, menopausal status, and a history of osteoporotic fracture were questioned. To consider a participant as being aware of osteoporosis, we asked if they have heard about osteoporosis before, and the ones who had heard about it previously were considered aware. A questionnaire developed from a previous study (14), with a content reliability of 0.89, was performed on participants. The 30-item questionnaire comprises questions that cause, signs/symptoms, risk factors, prognosis, diagnosis, treatment, complications, and prevention of osteoporosis. Patients responded to the questions as "agree," "disagree," or "unsure." Knowledge scores were created assigning 1 point to every correct answer and 0 points to every incorrect or "unsure" answer. The items were summed for a possible range of 0 to 30, with higher scores reflecting greater knowledge.

Statistical Analysis

The SPSS software version 24.0 (SPSS IBM Corp.; Armonk, NY, USA) was used for statistical analyses. The Kolmogorov-Smirnov test was used to determine the normality of data distribution. Demographics and descriptive data are presented as median (interquartile range Q1-Q3) or mean standard deviation. Pearson's chi-squared and Fisher's Exact tests were used to compare between categorical variables. Group comparisons of baseline characteristics were performed with independent samples t-test, as appropriate. Statistical significance was defined as $p<0.05$. The factors on osteoporosis awareness were assessed univariate and multivariate logistic regression. Covariates [age, gender (F), education (high school and above), presence of comorbid disease, corticosteroid administration] were tested. The correlation between the age and knowledge level of patients was evaluated using Spearman's correlation analysis.

Results

A total of 88 adult patients with MS (22 male, 66 female) were included in the study. The median age of the patients was 39.85±9.67 (range, 20-64) years. Baseline characteristics are shown in Table 1. The awareness of osteoporosis in patients with MS was 81.8% (n=72). Thirty-seven patients (42.04%) had known that MS disease was a risk factor for developing osteoporosis. Awareness of osteoporosis was higher in those who received corticosteroid treatment and had comorbid diseases (respectively p=0.011 and p=0.009). The median knowledge score of all subjects was 13 (8,25-17). The knowledge score levels were higher in those who had heard of osteoporosis than those who had not heard, respectively 14 (10-18) to 4 (0-13,75) ($p<0.001$). There was a significant difference between the osteoporosis knowledge scores of patients with received corticosteroid treatment before (p=0.003). The factors related to osteoporosis knowledge score levels are shown in Table 2. When the sources of osteoporosis information were questioned in patients, the results were as follows: doctors (34.1%), television-

internet (25%) and relatives (23.9%) and were in the first place, followed by friends (9.1%) newspapers and magazines (4.5%) and others (3.4%). When education levels were divided as primary school and high school and above, no significant relationship was found between educational levels and the level of knowledge of osteoporosis (p=0.154). However, the effect of education level was shown in the multiple regression analysis. Univariate and multivariate regression analyses of osteoporosis awareness are shown in Table 3. It was observed that as the age of the patients increased, their level of knowledge also increased (p=0.008, Spearman's rho=0.281). Table 4 presents descriptive data for the knowledge items.

Discussion

In this study, we determined that although there was high awareness of osteoporosis in patients with MS, the knowledge level of osteoporosis was poor in most of this population.

In our study, the awareness of osteoporosis in patients with MS was 81.8%. Osteoporosis awareness varies in different studies. In a study conducted in a Greek female population, it was reported that 96% of the participants knew the definition of osteoporosis (15). Nguyen et al. (14) reported that awareness of osteoporosis in the Vietnamese women population is 81.6%. Gemalmaz and Oge (16) found awareness of osteoporosis in the Turkish women population as 60.8% in their study. In another study evaluating osteoporosis awareness and osteoporosis knowledge level in Turkish patients with neuromuscular disease, osteoporosis awareness was 97.9% (17). Our study results were comparable to these studies in terms of osteoporosis awareness. The fact that our patients with MS were regularly followed up in a particular unit may also have contributed to the high awareness of osteoporosis in these patients.

Osteoporosis awareness was higher in those who received corticosteroid treatment and had comorbid diseases. This may be related to increased health literacy in patients to understand other diseases and corticosteroid side effects. It may also be related to informing the patients by other physicians.

Table 2. Osteoporosis knowledge score level-related factors

Osteoporosis knowledge score level-related factors	p-value*
Have heard of osteoporosis before	<0.001
Gender	0.23
Education status	0.13
Received corticosteroid treatment	0.003
Comorbid disease	0.164
Menopausal status	0.403
History of fracture	0.571

*The Mann-Whitney U test and independent sample t-tests were used to compare the knowledge levels of patients and related factors, as appropriate

Table 1. Demographic and descriptive data of patients

Item	Awareness of osteoporosis[a]			
	All patients (n=88)	Yes (n=72)	No (n=16)	p-value
Age, years (mean ± SD)	39.85±9.67	40.7±9.8	36.2±8.1	0.094
Female, n (%)	66 (75)	53 (73.6)	13 (81.3)	0.751
Symptom duration, years [median, IQR (Q1-Q3)]	8 (4-13)	8.5 (4-13.5)	8 (4-12)	0.545
Disease duration, years [median, IQR (Q1-Q3)]	4 (1-10)	4.5 (1-9.75)	4 (1-10)	0.484
EDSS score, [median, IQR (Q1-Q3)]	2 (1-4.5)	2 (1-4.62)	2 (0-3.5)	0.470
Body mass index (kg/m²)	24.37±4.45	24.7±4.6	22.9±3.2	0.141
Education status				
Primary school n (%)	20 (22.7)	14 (19.4)	6 (37.5)	0.183
High school and above n (%)	68 (77.3)	58 (80.6)	10 (62.5)	
Comorbid disease, n (%)	30 (34.1)	29 (40.3)	1 (6.3)	0.009*
Menopausal status				
Pre, n (%)	48 (72.7)	37 (69.8)	11 (84.6)	0.488
Post, n (%)	18 (27.3)	16 (30.2)	2 (15.4)	
Corticosteroid administration, n (%)	70 (79.5)	61 (84.7)	9 (56.3)	0.011*
History of fracture, n (%)	14 (15)	12 (16.7)	2 (12.5)	0.680
Osteoporosis knowledge score [median, IQR (Q1-Q3)]	13 (8.25-17)	14 (10-18)	4 (0-13.75)	0.002*

SD: Standard deviation, IQR: Interquartile range, EDSS: Expanded disability status scale. Group comparisons of baseline characteristics were performed with independent samples t-test or χ^2 test, as appropriate (p<0.05). [a]For the question, "have you ever heard of osteoporosis disease?", patients who answered yes were considered aware of osteoporosis. They were included in the awareness group.
*p<0.05 statistically significant

Table 3. Univariate and multivariate regression analysis of osteoporosis awareness

	Results from univariate analysis			Results from multiple analysis		
Parameters	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age	1.053	0.991-1.119	0.098	1.081	0.993-1.176	0.071
Gender (female)	1.553	0.399-6.055	0.526	1.104	0.207-5.902	0.907
Disease duration	1.040	0.934-1.158	0.480	-	-	-
EDSS score	1.100	0.851-1.424	0.466	-	-	-
Education (high school and above)	2.486	0.773-7.996	0.127	7.812	1.548-39.423	0.013*
Presence of comorbid disease	10.116	1.266-80.838	0.029*	21.953	2.026-237.895	0.011*
Corticosteroid administration	0.232	0.071-0.753	0.015*	9.660	1.984-47.029	0.005*
History of fracture	1.400	0.281-6.976	0.681	-	-	-

EDSS: Expanded disability status scale, OR: Odds ratio, CI: Confidence interval, *p<0.05 statistically significant

Table 4. Percentage correct for osteoporosis knowledge items, by domain

Domain	**(Correct response: T= True, F= False)**	**Correct, n (%)**
Definition of osteoporosis	1) Osteoporosis is a condition of an easy joint (F)	53 (60)
	2) Osteoporosis is a condition of low bone mineral density (T)	63 (71)
	3) Osteoporosis is a condition of high bone mineral density (F)	50 (56)
Common causes of Osteoporosis	4) Overweight is a common cause of osteoporosis (F)	17 (19)
	5) Lack of estrogen is a common cause of osteoporosis (T)	32 (36)
	6) High protein diet is a common cause of osteoporosis (T)	21 (23)
Common signs of osteoporosis	7) A headache is a common sign/symptom of osteoporosis (F)	27 (30)
	8) Frequent fractures are a common sign/symptom of osteoporosis (T)	50 (56)
	9) Mood change is a common sign/symptom of osteoporosis (F)	27 (30)
Risk factors for osteoporosis	10) Low rice intake is a risk factor for osteoporosis (F)	27 (30)
	11) Post menopause is a risk factor for osteoporosis in women (T)	58 (65)
	12) Smoking is a risk factor for osteoporosis (T)	40 (45)
	13) Having MS disease is a risk factor for osteoporosis (T)	37 (42)
Risk of osteoporosis over a lifetime	14) Men are at the highest risk of osteoporosis during their childhood (F)	17 (19)
	15) Women are at the highest risk of osteoporosis after menopause (T)	59 (67)
Diagnosis of osteoporosis	16) Osteoporosis is diagnosed using the X-ray of the bone (T)	33 (37)
	17) Osteoporosis is diagnosed with a physical exam (F)	22 (25)
	18) Osteoporosis is diagnosed with blood tests (F)	16 (18)
Treatment of osteoporosis	19) Osteoporosis can be treated with calcium and vitamin D (T)	59 (67)
	20) Osteoporosis can be treated with surgical correction (F)	30 (34)
	21) Osteoporosis can be treated with hormone replacement (T)	16 (18)
Complications of osteoporosis	22) Diabetes is a complication of osteoporosis (F)	15 (17)
	23) Hypertension is a complication of osteoporosis (F)	20 (22)
	24) Hip fracture is a complication of osteoporosis (T)	64 (72)
Prognosis	25) Osteoporosis can lead to joint swelling and morning stiffness (F)	3 (3,4)
	26) Osteoporosis can lead to hip fractures and subsequent complications (T)	57 (64)
Prevention of osteoporosis	27) Moderate physical exercise can reduce the risk of osteoporosis (T)	47 (53)
	28) Increased rice consumption can reduce the risk of developing osteoporosis (F)	19 (21)
	29) A diet rich in calcium and vitamin D can reduce the risk of developing osteoporosis (T)	53 (60)
	30) Cigarette smoking cessation can reduce the risk of developing osteoporosis (T)	45 (51)

MS: Multiple sclerosis

We found that osteoporosis knowledge scores were lower in MS patients who had not heard of osteoporosis disease before. Similar to our result, it has been shown that hearing of osteoporosis disease increases the level of osteoporosis knowledge in different osteoporosis awareness studies (18,19). Although there was a high rate of awareness in our study group, this was not accompanied by actual knowledge. While osteoporosis awareness of the patients was 81.8%, osteoporosis knowledge levels of patients were inadequate. The knowledge level was especially low in terms of two critical aspects of the disease: causes and signs of osteoporosis. The low-level knowledge about osteoporosis may be related to not being informed by the physician following the patient. This situation indicates that information should also be given frequently by physicians. Also, although the definition of osteoporosis was unknown well enough, the subjects answered questions about the complications of osteoporosis at a high rate. This may be related to the difficulty of understanding some medical terms, and because of the emphasized fracture risk of osteoporosis by the information sources.

In our study, patients with awareness of osteoporosis were older, but it was not statistically significant. Contrary to our study, several studies have shown a significant inverse relationship between age and osteoporosis knowledge level (20-22). The fact that our study included only MS patients and the relatively lower mean age in our study group compared to these studies may have led to this result.

Some studies showed that when the education level of patients increased the level of knowledge about osteoporosis increased (15,16). In another study involving 1,114 osteoporotic patients, there was no significant difference between education level and awareness of osteoporosis (5). In our study, awareness of osteoporosis and knowledge scores did not differ by education. However, the effect of education level was shown in the multiple regression analysis. When the patients are compared according to their education level, the lack of difference between the levels of knowledge score may be related to the small number of patients with low education levels in the study.

Different results were reported in the literature when access to information sources regarding osteoporosis was examined. Radio-television, newspapers, friends-relatives, and doctors were reported as information resources (14,16,23). In our study, when the sources of information about osteoporosis were examined, doctors ranked first and television ranked second in MS patients. In addition, it has also been found that having a relative with osteoporosis disease leads to higher awareness of osteoporosis. The fact that our patients with MS are regularly followed up in a unit may have contributed to the fact that the most frequent source of information is doctors.

Fourteen patients had a history of fractures, and 72% predicted that hip fracture might occur because of osteoporosis. However, there was no effect of fracture history on osteoporosis awareness and osteoporosis knowledge level in patients with MS. Fractures are the most important complications that may lead to morbidity and mortality in patients with MS (3,24). The assessment of risk factors for osteoporosis is essential for preventing fractures in patients with MS (12,13,25). Education may play an important role in determining and preventing risk factors.

Our study had some limitations. First, there was no control group to compare patients with MS in our study. In addition, we enrolled patients who were admitted to the outpatient clinic who were monitored regularly. We could not standardize and exclude the effect of regular follow-up on awareness and knowledge levels because our study had a cross-sectional design. Future studies evaluating the awareness and knowledge levels of this population with a larger sample size are needed.

Conclusion

In this study, although awareness of osteoporosis was high in MS patients, the level of osteoporosis knowledge was insufficient. Awareness and knowledge levels of osteoporosis were higher in those who received corticosteroid treatment. In addition, osteoporosis awareness was higher in those who had comorbid diseases. Increasing knowledge about osteoporosis may be important for preventing osteoporosis and reducing its complications in MS patients.

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Ethics

Ethics Committee Approval: The approval of the local Ethics Committee at Dokuz Eylül University was obtained prior to the start of the study (decision no: 2016/26-31, date: 06.10.2016).

Informed Consent: All subjects gave written informed consent before participating in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.K., B.D., S.G., Se.Ö., M.Ö.P., Design: A.K., B.D., S.G., Se.Ö., M.Ö.P., Data Collection or Processing: A.K., N.E.G., S.Ö., H.L., Analysis or Interpretation: A.K., B.D., S.G., Se.Ö., M.Ö.P., Literature Search: A.K., N.E.G., S.Ö., H.L., B.D., S.G., Se.Ö., M.Ö.P., Writing: A.K., N.E.G., S.Ö., H.L., B.D., S.G., Se.Ö., M.Ö.P.

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Evaluation of Vertebral Deformations in Women with Osteopenia

Osteopenili Kadınlarda Vertebra Deformasyonlarının Değerlendirilmesi

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Abstract

Objective: The extent to which vertebral integrity is affected in patients with osteopenia was investigated in this study.
Materials and Methods: We included 304 female patients aged between 40 and 74 and treated in the internal medicine outpatient clinic of a secondary healthcare institution. Total lumbar T and Z-scores and femoral neck T and Z-scores were analyzed by dual-energy X-ray absorptiometry. We included patients with a T-score between -1 and -2.4 and evaluated the thoracic and lumbar vertebrae of the patients with dorsal and ventral X-ray imaging. We examined whether the patients had vertebral fractures and if so, we determined the fracture level.
Results: The vertebral fracture was found in 30.6% of the patients, and the frequency of scoliosis in these patients was found to be higher than those without fractures ($p<0.001$). There was a significant correlation between the frequency of vertebral fractures and the number of years that passed after menopause ($p<0.001$). When the premenopausal and postmenopausal periods were compared, a significant increase was observed in the menopausal threshold and the frequency of fractures ($p=0.036$). Body mass index (BMI) levels were found to be significantly higher in patients with fractures ($p=0.001$). No significant correlation between the lumbar T-score and the frequency of vertebral fractures ($p=0.469$) and the frequency of scoliosis ($p=0.116$) was found.
Conclusion: The time elapsed after menopause increases the frequency of fractures. Contrary to the general literature, our study showed an increase in the frequency of fractures with obesity and increased BMI. When we scanned 304 osteopenic patients with X-rays, we found a significant frequency of fractures, but the fractures of most patients were 'silent.' Although osteopenia is common in the community, as in the literature, our study also shows that these patients should be examined in terms of vertebral fracture even if they do not have any symptoms.
Keywords: Osteopenia, elderly women, vertebrael deformation, scoliosis

Öz

Amaç: Bu çalışmada osteopenili hastalarda vertebra bütünlüğünün ne ölçüde etkilendiği araştırıldı.
Gereç ve Yöntem: Çalışmaya ikinci basamak bir sağlık kuruluşunun iç hastalıkları polikliniğinde tedavi gören 40-74 yaş arası 304 kadın hasta dahil edildi. Total lomber T ve Z-skorları ile femur boyun T ve Z-skorları çift enerjili X-ışını absorbsiyometri ile analiz edildi. T-skoru -1 ile -2,4 arasında olan hastaları dahil edildi ve dorsal ve ventral X-ışını görüntüleme ile hastaların torasik ve lomber vertebraları değerlendirildi. Hastalarda vertebra kırığı olup olmadığı incelendi ve varsa kırık şiddeti belirlendi.
Bulgular: Hastaların %30,6'sında vertebra kırığı saptandı ve bu hastalarda skolyoz sıklığı kırık olmayanlara göre daha yüksek bulundu ($p<0,001$). Omurga kırıklarının sıklığı ile menopozdan sonra geçen yıl sayısı arasında anlamlı bir ilişki vardı ($p<0,001$). Premenopozal ve postmenopozal dönemler karşılaştırıldığında menopoz eşiğinde ve kırık sıklığında anlamlı artış görüldü ($p=0,036$). Vücut kitle indeksi (VKİ) düzeyleri kırıklı hastalarda anlamlı olarak yüksek bulundu ($p=0,001$). Lomber T-skoru ile vertebral kırık sıklığı ($p=0,469$) ve skolyoz sıklığı ($p=0,116$) arasında anlamlı bir ilişki bulunmadı.
Sonuç: Menopoz sonrası geçen süre kırık sıklığını artırmaktadır. Genel literatürün aksine, çalışmamız obezite ve artmış VKİ ile kırık sıklığında artış göstermiştir. Üç yüz dört osteopenik hastayı direkt radyografi ile taradığımızda, önemli bir kırık sıklığı bulduk, ancak çoğu hastanın kırıkları "sessiz" idi. Toplumda osteopeni sık görülmekle birlikte literatürde olduğu gibi çalışmamız da bu hastaların herhangi bir semptomu olmasa bile vertebra kırığı açısından incelenmesi gerektiğini göstermektedir.
Anahtar kelimeler: Osteopeni, ileri yaş kadın hasta, vertebral deformasyon, skolyoz

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Introduction

Osteopenia defines the decrease of T-score level and bone mineral density (BMD) in dual-energy X-ray absorptiometry (DXA). The World Health Organization (WHO) defines a T-score between -1 and -2.5 as osteopenia, values less than -2.5 as osteoporosis. Osteopenia is a "pre-diagnosis" for osteoporosis. With the aging of the population and the prolongation in life expectancy worldwide, osteoporosis and osteopenia are considered as a more serious health problem. In the FRACTURK (1) study, the prevalence of osteoporosis in our society was 25% over the age of 50, while the prevalence of osteopenia was 50%. While the prevalence of osteoporosis was evaluated as 14.9% in patients undergoing lumbar fusion surgery, it was shown in a study that the prevalence of osteopenia was 43.6% (2). If necessary precautions are not taken in patients with osteopenia, progression to osteoporosis is inevitable and decreased bone density is a major risk factor for fragility fracture (3,4). Osteopenia and osteoporosis are "silent" until a fracture occurs, they are mostly asymptomatic in this period, and in case of fracture, they create an economic burden in terms of both the cost of the fracture and the complications (5,6). While the cost of fragility fractures was $19 billion in 2005 in the United States, direct and indirect care activities are expected to exceed $25 billion in 2025 (7).

Fragility fractures are fractures that occur as a result of mechanical force, known as a trauma with too low energy to normally cause a fracture. The mentioned mechanical power is the force equivalent to falling at a standing distance according to the WHO (8). Some of the fractures that develop due to these conditions such as osteopenia and osteoporosis are "silent" and could be detected incidentally on imaging. Just like in osteoporosis, osteopenia has been shown to increase the risk of high fracture in many studies. Especially in elderly women, the risk of osteoporotic fracture is high, as well as the risk of osteopenic fracture. Vertebral fractures can cause kyphosis, thoracic deformities and scoliosis. Asymptomatic vertebral fractures are also a well-known risk factor for subsequent fractures which may develop (9-11).

Menopausal (hormonal) component of loss of bone mass and early menopausal age are the main factors causing vertebral osteopenia (12). Early menopause is characterized by low bone density in later years and is associated with a higher fracture rate. These women should be evaluated with DXA within 10 years after menopause for early diagnosis of osteoporosis and osteopenia (13). Although it has been shown that the risk of idiopathic osteoporotic fracture increases significantly at the T-score of -2.5 threshold (14), the OFELY study showed that the risk of fracture is higher when the T-score is -2 and above (15).

The prevalence of scoliosis in adults varies between 1% and 10% (16,17). Deformity that develops later in adults is seen in more than 30% of elderly patients without spinal anomaly. Adult degenerative scoliosis is typically diagnosed in patients older than 40 years of age and without a history of adolescent scoliosis (18). There are studies in which osteopenia is thought to play a role in increasing the scoliosis slope (18,19).

Purpose of the Study

In some of the patients with osteopenia, degeneration develops in the thoracic and lumbar vertebrae, in our study, we planned to investigate how many fractures were detected in the patients and the degree of these fractures and we also planned to evaluate whether thoracic, lumbar, or thoracolumbar scoliosis accompanies vertebral degeneration and fractures and to observe the frequency of kyphosis and scoliosis in cases of osteopenia. This study plans to evaluate how much awareness should be taken about BMD examination and fracture risk in patients with scoliosis and kyphosis. We planned to assess the correlation of vertebral deformities with the lumbar T-score evaluated in DXA and at the same time, it will be evaluated whether there is a relationship between patient age, time passed after post-menopause, patient height and fracture risk, and whether there is a significant relationship on the effect of body mass index (BMI) on fractures. Some of the patients in the study are in the pre-menopausal period and crossing the menopausal threshold will also investigate whether there is an increase in the incidence of fracture. As a result of all these findings, the need for antiresorptive treatment in osteopenic patients will be evaluated indirectly as a result of our study.

Materials and Methods

We included 304 female patients aged between 40 and 74 treated in the internal medicine outpatient clinic of a secondary health care institution. Total lumbar T and Z-scores and femoral neck T and Z-scores were analyzed by DXA. We included patients with a T-score between -1 and -2.4 and evaluated the thoracic and lumbar vertebrae of the patients with dorsal and ventral X-ray imaging. We examined whether the patients had vertebral fractures and if so, we determined the fracture level. We used the criterion by which Genant et al. (20) categorized vertebral fractures by fracture level. The mild fracture is characterized by the concavity of the vertebra and evaluated as stage 1 fracture, the moderate fracture is characterized by wedging of the vertebra and evaluated as a stage 2 fracture, and the severe fracture is characterized by vertebral crushing and collapse and is evaluated as a stage 3 fracture (20). It was planned to evaluate the patients in terms of scoliosis and kyphosis, as well as vertebral fractures, to determine whether deformations accompany each other in their fractures. The patients were evaluated in terms of thoracic and thoracolumbar scoliosis, and the presence of scoliosis of 5 or more degrees was evaluated as scoliosis. The presence of compensatory curvature was excluded from the study. Case with a history of childhood and adolescent were excluded from the study. We excluded patients who exceeded the osteoporosis threshold and had a T-score of -2.5 and above. Patients with hyperthyroidism, type 1 diabetes mellitus, rheumatic disease, Celiac disease and patients using chronic steroids were excluded from the study. The height,

weight and BMI of the patients were also included in the study, and how height-weight and BMI increases and decreases affected the osteopenia status was examined. The incidence of vertebral fractures in postmenopausal women and women who have not yet developed menopause was investigated. In our study, we examined whether the number of years passed in the postmenopausal period in women in the postmenopausal period caused an increase in the level of fractures and in the level of scoliosis and kyphosis. Vertebral morphological evaluation was made by the primary investigator and only vertebral fractures were evaluated within the scope of the study, and the presence of non-vertebral fractures was not included in the study.

In our study, informed consent was obtained from the patients. Ethics committee approval with decision number 2021/514/200/2 was obtained from Kartal Dr. Lütfi Kırdar City Hospital (date: 28.04.2021).

Statistical Analysis

Statistical analyses used the Number Cruncher Statistical System (NCSS) program. Descriptive statistics of the data obtained were calculated as arithmetic mean, standard deviation, median value, first (25^{th}) and third quartile (75^{th}) (interquartile range =75^{th}-25^{th}), absolute and relative frequencies, depending on the type and distribution of the characteristics and were summarized in tables. The suitability of the numerical type characteristics to the normal distribution was examined using the Shapiro-Wilks test. Non-parametric tests were used for non-normally distributed characteristics. Relationships between categorical characteristics were compared with Pearson chi-square or Fisher-Freeman-Halton test. Mann-Whitney U test, Independent samples t-test, Kruskal-Wallis test or One-Way ANOVA model were used in the comparison of groups in terms of numerical characteristics by considering the distribution of numerical characteristics and the number of groups. Information about which test is used for which purpose is written under the tables. In addition, correlations between numerical type characteristics were examined by Spearman's rank correlation analysis. Statistical significance level was accepted as $p<0.05$ and SPSS (ver. 25) program was used for calculations.

Results

A total of 304 patients were included in our study. The mean age of the patients was 57 years. Of all the patients, only 28 were in pre-menopausal period and 276 were in postmenopausal period. A total of 93 (30.6%) patients had vertebral fractures, 32 patients had 1^{st} degree fracture (concavity) (34.4%), 25 patients had 2^{nd} degree fracture (wedging) (26.9%), 36 patients had 3^{rd} degree fracture (collapse fracture) (38.7%). Scoliosis was observed in 122 (40%) patients and thoracic kyphosis was observed in 40 (13.2%) patients.

Descriptive statistics of numerical type measurements performed on patients are presented in Table 1.

The distributions of the categorical characteristics of the patients are presented in Table 2. When Table 2 is examined, it is seen that the rate of postmenopausal patients is 90.8%, the frequency of fractures is 30.6%, the frequency of scoliosis is 40.1% and the frequency of kyphosis is 13.2%.

As a result of vertebral morphology, the frequency of scoliosis was found to be significantly higher in patients with first, second and third degree fractures than those with normal vertebral morphology (Table 3, $p<0.001$). However, no significant difference was found between grades ($p=0.254$).

The frequency of scoliosis obtained when the patients were divided into two groups as with and without fracture according to their vertebral morphology by disregarding the degree of fracture is presenting in Table 4. When the table was examined, it was seen that the frequency of scoliosis was significantly higher in patients with fractures (62.4%) than in patients without fractures (30.3%) ($p<0.001$).

No significant correlation was found between the degree of fracture and the degree of scoliosis ($r=-0.47$, $p=0.726$). According to this result, it can be said that there will be no significant change in the direction of increase or decrease in the degree of scoliosis as the degree of fracture increases.

When the patients with and without fractures were compared in terms of the degree of scoliosis, the results presented in Table 5 were obtained. When the table is examined, the rate of those with a scoliosis grade of "5" was significantly higher in those without fractures, while the rate of those with a scoliosis grade of "20" and "30" in those with fractures was significantly higher

Table 1. Descriptive statistics of numerical characteristics

	n	Mean	SD	Percentiles		
				25^{th}	Median	75^{th}
Age	304	56.97	6.822	52.00	56.00	61.00
Menopause age	276	46.36	5.238	44.00	47.00	50.00
Menopause duration	276	11.45	8.030	5.25	10.00	16.00
Lumbar T osteopenia	304	-1.390	0.6580	-1.900	-1.400	-1.000
Height (cm)	304	154.67	5.570	151.00	155.00	158.00
Weight (kg)	304	76.03	12.140	67.00	75.00	83.00
BMI	304	31.41	5.366	28.00	31.00	34.00

BMI: Body mass index, SD: Standard deviation

(p<0.001). On the other hand, the rate of those with scoliosis grade "10" and "15" was similar in those with and without fractures.

The relationship between lumbar T-score and vertebral fracture is summarized in Table 6. When the table was evaluated, it was seen that there was no significant difference between vertebral fracture results in terms of lumbar T-score (p=0.469).

When the relationship between the presence of vertebral fracture and the number of years after menopause was examined, it was observed that the duration of menopause was significantly longer in those with fractures (Table 7, p<0.001). However, no significant relationship was found between duration of menopause and the degree of fracture (r=-0.053, p=0.619).

Fracture was observed in only 4 (14.3%) of 28 pre-menopausal patients. When 28 pre-menopausal patients and 276 menopausal patients were compared in terms of fracture frequency, it was determined that the frequency of fracture was significantly higher in the postmenopausal period (p=0.036, Table 8).

When the degree of fracture was compared in people with pre-menopausal and postmenopausal fractures, it was determined that the frequency of first-degree fractures was significantly higher in the premenopausal group, and the frequency of third-

Table 2. Descriptive values for the categorical characteristics of the patients

		n	%
Menopause status	Pre-menopause	28	9.2
	Menopause	276	90.8
Vertebral morphology	Normal	211	69.4
	1st degree, concave	32	10.5
	2nd degree, cuneiform	25	8.2
	3rd degree, crush	36	11.8
Fracture	None	211	69.4
	Present	93	30.6
Degree of fracture	1st degree	32	34.4
	2nd degree	25	26.9
	3rd degree	36	38.7
Scoliosis	None	182	59.9
	Present	122	40.1
Degree of scoliosis	5	38	31.1
	10	54	44.3
	15	12	9.8
	20	14	11.5
	30	4	3.3
Kyphosis	None	264	86.8
	Present	40	13.2
Obesity	Normal	22	7.2
	Overweight	88	28.9
	Obese	194	63.8

Table 3. The relationship between the degree of vertebral fracture and the presence of scoliosis

		Vertebral morphology*, **								Total
		Normal		1st degree, concave		2nd degree, cuneiform		3rd degree, crush		
		n	%	n	%	n	%	n	%	n
Scoliosis	None	147	69.7	14	43.8	6	24.0	15	41.7	182
	Present	64	30.3	18	56.3	19	76.0	21	58.3	122
Total		211		32		25		36		304

*Pearson chi-square test. **Each subscript letter denotes a subset of vertebra morphology categories whose column proportions do not differ significantly from each other at the 0.5 level

degree fractures was significantly higher in the postmenopausal group (p=0.050, Table 9).

There was no significant difference in fracture frequency between patients shorter and taller than 160 cm (p=0.125, Table 10).

Of the 93 people with fractures, 82 (88.17%) were shorter than 160 cm, while the rest were 160 cm or taller. The frequency of second-degree fractures in patients shorter than 160 cm and third-degree fractures in patients with a height of 160 cm and above was found to be significantly higher (p=0.050, Table 11).

Mean height was found to be significantly shorter in patients with fractures (p=0.030, Table 12).

The mean BMI was found to be significantly higher in patients with fractures (p=0.001, Table 13).

In addition, no statistically significant relationship was found between the degree of fracture and BMI (r=-0.158, p=0.131).

When the obesity groups were compared in terms of fracture frequency, it was determined that the fracture frequency was significantly higher in the obese than the other two groups (normal and overweight) (p=0.004, Table 14).

Table 4. The relationship between the presence of fracture and the frequency of scoliosis

		Fracture*				
		None		Present		
		n	%	n	%	n
Scoliosis	None	147	69.7	35	37.6	182
	Present	64	30.3	58	62.4	122
Total		211		93		304

*Pearson chi-square test.

Table 5. The relationship between the presence of fracture and the degree of scoliosis (thoracic, thoracolumbar)

		Fracture*, **				Total
		None		Present		
		n	%	n	%	n
Degree of scoliosis	5	26	40.6	12	20.7	38
	10	33	51.6	21	36.2	54
	15	5	7.8	7	12.1	12
	20	0	0.0	14	24.1	14
	30	0	0.0	4	6.9	4
Total		64		58		122

*Pearson chi-square test. **Each subscript letter denotes a subset of vertebra morphology categories whose column proportions do not differ significantly from each other at the 0.5 level

Table 6. Descriptive values of lumbar T-score according to vertebral fracture results

Vertebral morphology	n	Mean	SD	Percentiles		
				25th	Median	75th
Normal	211	-1.382	0.6564	-1.900	-1.400	-1.000
1st degree, concave	32	-1.450	0.6525	-1.875	-1.500	-1.125
2nd degree, cuneiform	25	-1.468	0.8112	-2.100	-1.600	-1.100
3rd degree, crush	36	-1.328	0.5675	-1.775	-1.300	-.850

*Kruskal-Wallis test, SD: Standard deviation

Table 7. Descriptive values of duration of menopause according to the presence of vertebral fracture

Fracture	n	Mean	SD	Percentiles		
				25th	Median	75th
None	187	10.15	7.367	5.00	9.00	14.00
Present	89	14.19	8.697	7.50	12.00	17.00

*Mann-Whitney U test

Table 8. The relationship between the development of menopause and the frequency of fractures

		Menopause status*, **				Total
		Pre-menopause		Menopause		
		n	%	n	%	n
Fracture	None	24	85.7	187	67.8	211
	Present	4	14.3	89	32.2	93
Total		28	100.0	276	100.0	304

*Pearson chi-square test
**Each subscript letter denotes a subset of vertebra morphology categories whose column proportions do not differ significantly from each other at the 0.5 level.

Table 9. The relationship between menopausal status and degree of fracture

		Menopause status*, **				Total
		Pre-menopause		Post-menopause		
		n	%	n	%	n
Degree of fracture	1st degree	1	25.0	31	34.8	32
	2nd degree	3	75.0	22	24.7	25
	3rd degree	0	0.0	36	40.4	36
Total		4	100.0	89	100.0	93

*Pearson chi-square test. **Each subscript letter denotes a subset of vertebra morphology categories whose column proportions do not differ significantly from each other at the 0.5 level

Table 10. The relationship between height and frequency of fracture

		Height groups*				Total
		<160 cm		≥160 cm		
		n	%	n	%	n
Fracture	None	171	67.6	40	78.4	211
	Present	82	32.4	11	21.6	93
Total		253	100.0	51	100.0	304

*Pearson chi-square test

Table 11. The relationship between height and degree of fracture

		Height groups*, **				
		<160 cm		≥160 cm		
		n	%	n	%	n
Degree of fracture	1st degree	30	36.6	2	18.2	32
	2nd degree	19	23.2	6	54.5	25
	3rd degree	33	40.2	3	27.3	36
Total		82		11		93

*Fisher-Freeman-Halton test. **Each subscript letter denotes a subset of vertebra morphology categories whose column proportions do not differ significantly from each other at the 0.5 level

Table 12. Descriptive values for height in patients with and without fractures

	Fracture	n	Mean	SD	p*
Height (cm)	None	211	155.13	5.545	0.030
	Present	93	153.62	5.515	

*Independent samples t-test. SD: Standard deviation

Table 13. BMI averages in people with and without fractures

Fracture	n	Mean	SD	Percentiles			p
				25th	Median	75th	
None	211	30.69	5.022	27.00	30.00	33.00	0.001
Present	93	33.05	5.774	29.50	32.00	36.00	

Independent samples t-test. SD: Standard deviation

Table 14. Fracture frequency of obesity groups

		Obesity						Total
		Normal		Overweight		Obese		
		n	%	n	%	n	%	n
Fracture	None	19	86.4	70	79.5	122	62.9	211
	Present	3	13.6	18	20.5	72	37.1	93
Total		22		88		194		304

Pearson chi-square test, each subscript letter denotes a subset of vertebra morphology categories whose column proportions do not differ significantly from each other at the 0.5 level

Discussion

Osteoporotic fractures may also occur in osteopenic patients (21), and while the rate of vertebral fractures in women over 50 years of age is between 20-30% in the general population, this rate is 40% over the age of 80 (22,23). Vertebral fracture rate was detected as 26.5% in osteopenic asymptomatic elderly men and postmenopausal women in Vietnam (24), 9.5% in osteopenic old men and postmenopausal women in Japan (25), and 29% in Thai postmenopausal healthy osteopenic women and 62% of these fractures were graded as grade 1, 19.3% as grade 2, and 18.7% as grade 3. It was observed that 4.9% of patients with fractures were under the age of 50, and the remaining patients were over the age of 50 (26). In our study, fractures were detected in the thoracic or lumbar vertebrae in 30% of the patients, and a similar vertebral fracture rate was found in the study conducted in Thailand. First degree fracture (concavity) was observed in 30% of the patients, 2nd degree fracture (wedge) in 26%, and 3rd degree fracture (collapse fracture) in 38% of the patients. In the International Society for Clinical Densitometry 2019, it was stated that it should be questioned and evaluated whether there is a history of vertebral fracture in patients with a shortening of 4 cm or more in length in those with a T-score of -1 and below (27).

Urritia et al. (28) found a 12.9% lumbar scoliosis prevalence in postmenopausal women over 50 years of age and showed a positive correlation between BMI and age and scoliosis prevalence, but showed that BMD was not indicative for scoliosis. Rozenberg et al. (29) showed a 30% correlation between lumbar BMD and vertebral deformities and degenerative lesions; Spencer et al. (30) showed 11% , and Sahota et al. (31) showed this rate as 81%. In our study, no correlation was found between the degree of lumbar T-score and the presence of vertebral fracture (Table 6, p=0.469). Scoliosis was detected in 40% of our cases, and kyphosis in 13% of our cases, and the scoliosis slope was 10 degrees or less in 75% of patients with scoliosis. Severe scoliosis slope of 20 degrees or more was observed in 14.8% of them. As seen in Table 3, no significant correlation could be found between the lumbar T-score and the presence of scoliosis (p=0.925). As seen in Table 4, there was no significant relationship between BMD and scoliosis, as in the study of Urritia et al. (28) between the lumbar T-score and the degree of scoliosis slope (p=0.116).

The frequency of scoliosis was found to be significantly higher in patients with vertebral fractures compared to patients without fractures (Table 3, p<0.001), but no correlation could be detected between the degree of fracture and the degree of scoliosis (Table 4, p<0.001). In patients with no vertebral fracture, scoliosis slope of 5 degrees, which is not clinically significant, was more common in the presence of scoliosis, while the degree of slope was more pronounced in the group with vertebral fracture, and high slopes such as 20-30 degrees were found to be higher in this group (Table 5, p<0.001).

Only 22 of the cases had a normal BMI, while 88 of the remaining patients were overweight and 194 were obese. In the literature, it has been shown that low BMI is associated with an increase in fragility fracture (32), on the contrary, in our study, 20% of the patients with a BMI below 30% had a vertebral fracture, while this rate was 36% in patients with a BMI of 30% and above. While the BMI values were found to be higher in patients with fractures (Table 13, p=0.131), the frequency of fractures was also higher in obese individuals (Table 14, p=0.004).

While 14% of osteopenic patients had vertebral fractures in the pre-menopausal period, this rate was 32% in post-menopausal women, and a significant difference was observed. (Table 8, p=0.036) While the most commonly 1st degree fracture is detected in patients with pre-menopausal vertebral fractures, this rate is in favor of 3rd degree fractures in postmenopausal

women. In one study (33), increase of the incidence of fractures was shown as the number of years passed after menopause increased. In our study, the rate of vertebral fracture was 32.6% in the group with less than 10 years of postmenopausal years, 63.8% in patients with a postmenopausal year between 10-19 years, and this rate was 83.3% in patients with a postmenopausal year of 20 years or more. While a significant relationship was shown between the number of years passed after menopause and the frequency of vertebral fractures, there was no relationship between the degree of fracture and the number of years after menopause (Table 7, p<0.001).

In our study, the average height was 154 cm, and although no correlation could be shown between height and the frequency of vertebral fractures (Table 10, p=0.125), when 93 people with vertebral fractures were examined, it was observed that 88% were below 160 cm and 12% were 160 cm and above (Table 11, p=0.050). Vertebral fracture rate is 21.5% in patients with a height of 160 cm and above, and the fracture rate is 32.4% in individuals under 160 cm. When the 2 groups with and without vertebral fracture were compared, we found that the mean height was shorter in the group with vertebral fracture (Table 12, p=0.030). In patients with vertebral fractures, short stature may be the first complaint due to unrecognized vertebral fractures. In case of multiple fractures, kyphosis may develop. Although kyphosis is not diagonal for osteoporosis (there also may be kyphosis with normal bone density), kyphosis may develop in case of excessive vertebral fractures (34). In the Spanish guidelines, radiological imaging of the vertebrae of osteopenic patients with shortening is recommended (35), and in Canadian guidelines, it is recommended to evaluate the number of falls annually in addition to vertebral imaging in the presence of shortened height (36).

Also in the OFELY study (159, 8% of 116 women with fractures were normal, 44% were osteoporotic, while 48% of the patients were found to be osteopenic, and it was shown in the study that the incidence of fracture in the osteopenic group was as high as the osteoporotic group. Fifty of a total of 158 fractures were shown only in the vertebrae, and it was determined that the incidence of fractures in the osteopenic group increased gradually over the next 10 years. There are also studies (5) showing micro-damages in osteopenia apart from visible fractures in the vertebrae. Advanced examinations such as peripheral quantitative computed tomography, quantitative ultrasonography are able to examine the trabecular structure of bones in low bone mineral densitometry (37) and detect microfractures (38). In the OSTEOXPRESS study, in which vertebral deformities were evaluated using MorphoXpressSR software, postmenopausal osteopenic defined lumbar vertebral fracture rate of 7% (by X-ray) was found to be 50% (39). Although vertebral fractures are often overlooked in asymptomatic patients (40,41). X-ray is still a very useful imaging method in asymptomatic or symptomatic osteopenic patients (11). The IMPACT study, a multicenter study, evaluated the radiographic diagnosis of vertebral fractures in 2,451 postmenopausal women with osteoporosis. Comparisons between local and central readings showed a false-negative rate of 34% (42). In another study, 28% silent fractures were detected with X-ray in asymptomatic postmenopausal women with X-ray imaging. Although we did not have the opportunity to reach further examinations in which we could evaluate the lumbar and thoracic vertebral integrity, except for X-ray, in the 2nd stage working conditions, we still detected vertebral fractures at varying levels in 30% of 304 osteopenic patients with X-ray, at similar rates to this study (43). We think that the true fracture rate is much higher in micro-fractures that cannot be detected. Considering that a single vertebral fracture increases the risk of subsequent hip fracture by 5 times and the risk of fractures in other bones by 2-3 times (44), the importance of imaging becomes evident in osteopenic patients, even if it is clinically silent. These patients need anti-resorptive treatment and if they are treated, comorbidity is prevented and the rate of progression to osteoporosis slows down. In a study conducted in Australia, it was shown that detecting and treating osteopenicpatients provides an annual cost-effectiveness of $4,992 per patient and $6,135 per year whenbased on quality of life (45). Although osteopenia, osteoporosis, which is a step forward, fractures that develop in various parts of the body, such as the vertebral and femoral head, and various morbidity and mortality caused by these fractures create a financial burden both individually and socially, in case of osteopenia is detected at an early stage, evaluated for the presence of fracture, and if the presence of fracture is detected, initiation of antiresorptive therapy and oral calcium replacement is incomparably more cost-effective considering the aging of the population and the increase in comorbidities from year to year. When all these come together, X-ray imaging of the patient group in whom we have detected osteopenia is still very valuable, and we think that thoracic and lumbar vertebral graphs should be evaluated in order to detect silent fractures and in case of the presence of fracture, that X-ray imaging is important for the regulation of antiresorptive treatment and stabilization of the fracture.

Conclusion

Patients with a diagnosis of osteoporosis need anti-resorptive therapy, as well as patients with a diagnosis of osteopenia need antiresorptive therapy in case of fractures. The axial skeleton is more vulnerable to external influences than the extremity bone tissue due to its smaller size, irregular bone structure and semi-mobile structure compared to other bone structures. While fractures in cortical bone tissue are more easily evaluated, it is almost impossible to evaluate micro-fractures in trabecular bone tissue via direct graphs. The fractures that we could detect in our study data were cortical bone fractures, and we think that they may be in trabecular fractures that we could not detect. Although we expect an increase in this number in case of the presence of fractures is investigated with further investigations, we think that it is necessary to examine the thoracic and lumbar

vertebrae at least by X-ray imaging of patients with osteopenia that detected by DXA and to initiate treatment if fractures are detected. In case of the patient had osteopenia and we detected a fracture, the cost of treatment of patients who are not treated and progressed to osteoporosis, the cost-effectiveness of complications secondary to osteoporosis and even the loss of labor are too high to accept when compared to the cost of treatment of patients we apply anti-resorptive treatment. If the patients with the current clinic are treated appropriately, we avoid the mortality and morbidity of osteoporosis and its complications.

Ethics

Ethics Committee Approval: This study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (decision no: 2021/514/200/2, date: 28.04.2021).

Informed Consent: In our study, informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

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Osteoporoz Olan Hastalarda Laboratuvar Bulguları ile Kemik Mineral Yoğunluğu Arasındaki İlişki

The Relationship Between Laboratory Findings and Bone Mineral Density in Patients with Osteoporosis

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Öz

Amaç: Bu çalışma, Postmenopozal kadınlarda trombosit sayısı, ortalama trombosit hacmi (MPV), trombosit dağılım genişliği (PDW), C-reaktif protein (CRP), trombosit/lenfosit oranı (TLO), nötrofil/lenfosit oranı (NLO) ve sistemik immün-enflamasyon indeksi (SII) ile osteoporoz (OP) arasındaki ilişkiyi araştırmak amacıyla yapılmıştır.

Gereç ve Yöntem: Çalışmamıza en az 2 yıldır menopoza girmiş 482 hasta dahil edildi. Tüm hastaların hemogram, CRP, tiroid stimülan hormon (TSH), paratiroid hormon, 25-hydroksivitamin D_3 vitamini ve dual enerji X-ışını absorbsiyometri sonuçları kaydedildi. L2-L4 ve/veya Femur boynu T-skoru ≤-2,5 olan 295 hasta OP grubu olarak, L2-L4 ve/veya Femur boynu T-skoru ≥-1,0 olan 192 hasta ise kontrol grubu olarak belirlendi. Hemogram sonucundan NLO, TLO ve SII hesaplanarak kaydedildi.

Bulgular: OP grubunun yaş ortalaması 64,2±8,3, kontrol grubunun yaş ortalaması 56,6±8,7 idi. Yaş ve vitamin D3 seviyeleri OP grubunda kontrol grubuna göre anlamlı düzeyde yüksek bulundu (p<0,001). OP olan grupta lökosit, nötrofil ve MPV düzeyleri kontrol grubuna göre anlamlı şekilde düşük saptandı (p<0,005). Diğer laboratuvar parametrelerinde gruplar arasında anlamlı farklılık yoktu. Yapılan korelasyon analizine göre, L2-L4 T-skoru ile yaş ve vitamin D3 negatif korele iken; lökosit, MPV, PDW, TSH ve CRP pozitif korele idi. Femur boynu T-skoru ile yaş ve vitamin D3 negatif korelasyon gösterirken; MPV, PDW, TSH ve CRP pozitif korelasyon gösterdi.

Sonuç: Postmenopozal OP hastalarında trombosit fonksiyonları ve immün sistem belirteçleri kemik mineralizasyonunda etkilidir.

Anahtar kelimeler: Osteoporoz, hematolojik bulgular, kemik mineral yoğunluğu

Abstract

Objective: This study was conducted to investigate the relationship between platelet count, mean platelet volume (MPV), platelet distribution width (PDW), C-reactive protein (CRP), platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR), systemic immune-inflammation index (SII) and osteoporosis (OP) in postmenopausal women.

Materials and Methods: Four hundred eighty two patients who had been in menopause for at least 2 years were included in our study. Hemogram, CRP, thyroid-stimulating hormone (TSH), parathyroid hormone, 25-hydroxyvitamin D_3 vitamin and dual-energy X-ray absorptiometry results of all patients were recorded. Two hundred ninety five patients with L2-L4 and/or femoral neck T-scores ≤-2.5 were determined as the OP group, and 192 patients with L2-L4 and/or Femoral neck T-scores ≥-1.0 were determined as the control group. NLR, PLR and SII were calculated and recorded from the hemogram results.

Results: The mean age of the OP group was 64.2±8.3 years, and the mean age of the control group was 56.6±8.7. Age and vitamin D3 levels were higher in the OP group than in the control group (p<0.001). Leukocytes, neutrophil and MPV levels were found to be lower in the OP group than in the control group (p<0.005). While the L2-L4 T-score was negatively correlated with age and vitamin D3; leukocytes, MPV, PDW, TSH and CRP were positively correlated. The femoral neck T-score was negatively correlated with age and vitamin D3, whereas it was positively correlated with MPV, PDW, TSH and CRP.

Conclusion: Platelet functions and immune system markers are effective in bone mineralization in postmenopausal OP patients.

Keywords: Osteoporosis, hematological findings, bone mineral density

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Giriş

Osteoporoz (OP), kemik kütlesinde azalma, mikromimarisinde bozulma ve kırılmaya yatkınlık ile karekterize karmaşık bir iskelet hastalığıdır (1). Bu hastalığın başlangıcı net değildir, belirgin hastalık karakteristiklerinden yoksundur ve bu yüzden erken dönemde teşhis edilmesi zordur. OP klinik verdiğinde, hastalık zaten hızlanmış bir aşamaya girmiş demektir (2). OP için tanı genellikle dual enerji X-ışını absorbsiyometre (DEXA) ile kemik mineral yoğunluğu (KMY) ölçümüne dayanmaktadır (3). Ancak çoğu kadının postmenopozal OP (PMOP) ile ilgili farkındalığı düşüktür ve ancak kırık ya da boy kısalması gibi klinik bir durum yaşayana kadar DEXA ölçümü yaptırmamaktadır (4). Bu yüzden erken dönemde PMOP'yi belirlemek için ucuz, kolay ulaşılabilir biyobelirteçlerin bulunması gereği doğmuştur.

OP sırasında meydana gelen hematolojik değişiklikler henüz tam olarak aydınlatılabilmiş değildir. Geçen son 10 yıl içerisinde bazı çalışmalar, kemik iliğinin megakaryositlerinden farklılaşan trombositlerin iskelet homeostazisinde, kemik yapım ve yıkımını modüle etmede kritik bir role sahip olduğunu bildirmiştir (5-7). Megakaryosit yüksekliği osteoklast ve osteoblast fonksiyonunda değişikliğe yol açar. Ayrıca, megakaryositlerdeki değişiklikler trombosit sayı ve boyutuyla da ilişkilidir. Trombositlerde bulunan adenozin difosfat reseptörleri ile vitamin D reseptörleri kemik remodelinginde majör rol oynar (8,9). Ortalama trombosit hacmi (MPV), trombositlerin boyutunu ve fonksiyonlarını gösteren bir belirteçtir (10). Bir diğer trombosit fonksiyon belirteci olarak trombosit dağılım genişliği (PDW) kullanılmaktadır. PDW, trombosit fonksiyon ve aktivasyonunu göstermesi bakımından MPV'ye benzer (11,12). Literatürde MPV ve PDW ile KMY arasındaki ilişkiyi inceleyen sınırlı sayıda ve farklı sonuçların sunulduğu çalışmalar bulunmaktadır (13-16).

Enflamatuvar belirteçler, kemik oluşumu ve yıkımında sitokinleri çevreleyerek osteoklast aktivasyonu yoluyla modüle edici bir rol oynar (17,18). Epidemiyolojik çalışmalarda PMOP ile kronik enflamasyon arasında ilişki olduğu gösterilmiştir (19-22). C-reaktif protein (CRP), sistemik immün-enflamasyon indeksi (SII), trombosit/lenfosit (TLO) ve nötrofil/lenfosit oranları (NLO) basit, kolay ulaşılabilir ve ucuz enflamasyon parametreleridir. Bu belirteçlerle çeşitli enflamatuvar, onkolojik ve kardiyovasküler hastalıklar arasında ilişki gösterilmiş olmasına rağmen PMOP ile olan ilişki tam olarak anlaşılamamıştır (22-24).

Biz bu çalışma ile postmenopozal kadınlarda, trombosit sayısı, MPV, PDW, CRP, TLO, NLO ve SII ile OP arasındaki ilişkiyi incelemeyi amaçladık.

Gereç ve Yöntem

Çalışmamıza başlamadan önce Adıyaman Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan etik onay alındı (karar no: 2020/11-1, tarih: 22.12.2020). Tüm katılımcılara çalışma ile ilgili bilgi verilerek aydınlatılmış onamları alındı. Çalışma Helsinki Deklarasyonu'na uygun olarak yapıldı.

Bu çalışmamıza, hastanemiz fiziksel tıp ve rehabilitasyon polikliniğine ayaktan başvuran 40-75 yaş arası, en az 2 yıldır menopoza girmiş ve polikliniğe KMY ölçümü yaptırmak için gelmiş 1000 hasta alındı. Tüm katılımcıların KMY ölçümü DEXA cihazı (Lunar BTX) ile yapıldı. L2-L4 vertebra ile femur boynu T-skorları kaydedildi. Hastaların ayrıca hemogram, CRP, tiroid stimülan hormon (TSH), D vitamini, paratiroid hormon (PTH) ölçümleri yapıldı. Hemogram sayımı için kan örneği 30 dakika içinde ve EDTA'sız tüpe alındı. Hemogram, Abbott Cell Dyn Ruby Analyzer (Abbott, Abbott Park, IL, USA) cihazı kullanılarak hücre sayımı yöntemi (MAPPS optik teknolojisi) ile; CRP, Architect c16000 Automated Analyzer (Abbott Diagnostics Inc, Park City, IL, USA) cihazı kullanılarak spektrofotometrik yöntem ile; TSH, PTH ve vitamin D, Beckman Coulter Dxl-800 Analyzer (Beckman Coulter Inc., Brea, CA, USA) cihazı kullanılarak immunoassay (chemiluminescence immunoassay) yöntemi ile hastanemiz biyokimya laboratuvarında çalışıldı. Menopoz süresi 2 yılın altında olanlar, 40 yaş altı ya da 75 yaş üstü hastalar, herhangi bir enflamatuvar hastalığı olanlar, diabetes mellitusu olanlar, hipertansiyonu olanlar, kalp hastalığı olanlar, hiperlipidemisi olanlar, tiroid fonksiyon bozukluğu olanlar, hiperparatirodi olanlar, anemi, lökopeni ve/veya trombositopenisi olanlar, herhangi bir enfeksiyon öyküsü olanlar, herhangi bir onkolojik hastalık öyküsü olanlar ve herhangi bir hematolojik hastalık öyküsü olanlar ile OP ilaçları dışında herhangi bir ilaç kullanmakta olan hastalar çalışma dışı bırakıldı. Dünya Sağlık Örgütü'nün belirlediği kriterlere uygun olarak; DEXA sonucuna göre femur boynu ve/veya L2-L4 T-skoru -2,5'in altında olan 295 hasta OP çalışma grubu olarak seçildi. Yine DEXA sonucuna göre femur boynu ve L2-L4 T skoru -1,0'den büyük olan 192 hasta ise kontrol grubu olarak belirlendi. Beş yüz on üç hasta çalışmaya dahil edilme kriterlerini karşılamadığı için dışlandı. Tüm katılımcıların yaş, menopoz süresi, kullandığı ilaçlar, sistemik hastalıkları sorgulandı. Tam kan sayımı ölçümlerinden hemoglobin, eritrosit dağılım genişliği, MPV, PDW, trombosit sayısı, lenfosit sayısı, nötrofil sayısı kaydedildi. Yine tüm katılımcıların CRP değerleri, D vitamini düzeyleri, PTH ve TSH değerleri kaydedildi. NLO ve TLO değerleri hesaplanarak kaydedildi. SII; (trombosit sayısı × nötrofil sayısı)/lenfosit sayısı) formülü kullanılarak hesaplandı.

İstatistiksel Analiz

Tüm veriler Statistical Package for Social Science (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA.) kullanılarak analiz edildi. Sürekli veriler ortalama ± standart sapma olarak ifade edildi. Çalışmaya alınacak olgu sayısını belirlemek amacıyla analizlerde kullanılacak olan bağımsız örneklemler t-testi için örneklem hesaplaması yapılmıştır. Buna göre, grupların beklenen ortalamalarından ve standart sapmalarından hareketle etki büyüklüğü (Cohen's d) 0,50 (orta düzey) tutularak örneklem genişliği hesaplaması yapılmıştır. Hesaplamada G*Power 3.1.9.4 yazılımı (Faul, Erdfelder, Lang& Buchner, 2007) kullanılmıştır. Örneklem büyüklüğünün hesaplanmasında gerekli olan diğer parametreler tip 1 hata ve tip 2 hata miktarıdır. Tip 1 hata için %95 ve tip 2 hata için %80 güvenle karar vermek amacıyla yazılıma hatası 0,05 ve 1- hatası 0,80 olarak girilmiştir. Deney ve kontrol grubunun eşit büyüklükte olması varsayıldığından bu

araştırma için beklenen toplam örneklem büyüklüğü deney ve kontrol grubu için 64'er kişi olarak hesaplanmıştır.

Normal dağılım gösteren verileri karşılaştırmak için bağımsız örneklemler için t-testi, normal dağılıma uymayan veriler için Mann-Whitney U testi kullanıldı. Korelasyon analizi Pearson korelasyon ve çok değişkenli doğrusal regresyon analizi kullanılarak yapıldı. P<0,05 istatistiksel olarak anlamlı kabul edildi.

Bulgular

Tüm katılımcıların yaş, DEXA sonuçları ve laboratuvar bulguları Tablo 1'de gösterilmiştir. Yaş ve vitamin D3 seviyeleri OP olan grupta OP olmayan gruba göre anlamlı düzeyde yüksek bulundu (p<0,001). Lökosit, nötrofil ve MPV, OP olan grupta OP olmayan gruba göre istatistiksel olarak anlamlı şekilde düşük saptandı (p<0,005). Diğer laboratuvar parametrelerinde gruplar arasında anlamlı farklılık yoktu (Tablo 1).

Ayrıca, tüm postmenopozal kadınların laboratuvar bulguları ile hem femur boynu T-skoru hem de L2-L4 T-skorları arasında korelasyon analizi yapıldı. Femur boynu ve L2-L4 T-skorları ile korelasyon gösteren laboratuvar bulguları Tablo 2 ve Tablo 3'te gösterilmiştir.

Postmenopozal kadınların femur boynu ve L2-L4 T-skorlarını etkileyen ve OP için risk faktörleri olarak belirlenebilecek laboratuvar bulgularını belirlemek için lineer regresyon analizi yapıldı. Tablo 4'te L2-L4 ve femur boynu için lineer regresyon analiz sonuçları özetlenmiştir.

Tartışma

Çalışmamızda PMOP olan hastalarda OP olmayanlara göre anlamlı düzeyde MPV, nötrofil ve lökosit düşüklüğü saptadık. PMOP olanlarda yaş ve vitamin D3 düzeyleri ise anlamlı düzeyde yüksekti. Ayrıca PMOP hastalarında MPV ile hem Femur boynu hem de L2-L4 T-skorları arasında pozitif korelasyon, PDW ile femur boynu T-skoru arasında pozitif korelasyon tespit ettik. Ek olarak PMOP'de yaş, lökosit, MPV, vitamin D3 ve CRP bağımsız olarak kemik mineralizasyonu ile ilişkili bulundu.

Kadınlar menopoza girdiğinde; yaşlanma, kalsiyum kaybı ve östrojenin düşmesi nedeniyle bir dizi karmaşık biyolojik değişiklik meydana gelir, bunlara enflamatuvar mikro ortam aktivasyonu ve bağışıklık sisteminin hipofonksiyonu da dahildir (25). Çalışmamızda PMOP hastalarındaki lökosit ve nötrofil sayısındaki düşüklüğün nedeni bağışıklık sistemindeki hipofonksiyonla ilişkili olabilir. Modern biyokimya, moleküler biyoloji, immünoloji ve radyografinin hızla gelişmesiyle birlikte, son yıllarda başta OP olmak üzere metabolik kemik hastalıklarının teşhisinde büyük ilerleme sağlanmıştır (2). Erken teşhis çok önemlidir fakat mevcut inceleme yöntemlerinin hiçbiri ile erken aşamada OP tanısı konulamamaktadır (26). DEXA taramasının nispeten pahalı ve radyoaktif bir inceleme olduğu düşünüldüğünde, son yıllarda daha ucuz ve rutin kan incelemesinden kolayca elde edilen belirteçlerle OP'yi belirleme gündeme gelmiştir (27).

Enflamasyonla PMOP arasındaki ilişkiyi araştıran az sayıda çalışma bulunmaktadır (28,29). Enflamatuvar hastalıkları belirlemede

Tablo 1. Hasta ve kontrol gruplarının DEXA ve laboratuvar bulguları

	Hasta (n=295)	Kontrol (n=192)	p
Yaş	64,29±8,34	56,62±8,79	<0,001
L2-L4 T-skor	-3,11±0,57	0,04±0,91	<0,001
Femur boynu T-skor	-1,28±0,94	0,55±0,94	<0,001
Lökosit	7,17±1,65	7,60±1,75	0,006
Nötrofil	4,09±1,2	4,36±1,45	0,029
Lenfosit	2,34±0,78	2,45±0,63	0,103
NLO	1,91±0,91	1,91±0,91	0,989
Hgb	13,28±1,19	13,19±1,17	0,419
RDW	12,54±1,38	12,72±1,48	0,152
Trombosit	251,86±56,89	257,90±53,33	0,241
MPV	10,72±4,64	26,27±13,48	0,001
PDW	17,90±2,46	18,29±2,37	0,090
TLO	117,22±45,61	113,20±44,59	0,338
SII	479,65±241,85	497,09±273,57	0,461
TSH	1,52±1,45	1,76±1,10	0,052
PTH	55,34±27,83	55,90±22,86	0,815
Vitamin D3	21,17±12,23	16,74±7,52	<0,001
CRP	0,41±0,30	0,58±0,70	<0,001

p<0,05 istatistiksel olarak anlamlı. NLO: Nötrofil/lenfosit oranı, Hgb: Hemoglobin, RDW: Eritrosit dağılım genişliği, MPV: Ortalama trombosit hacmi, PDW: Trombosit dağılım genişliği, TLO: Trombosit/lenfosit oranı, SII: Sistemik immün-enflamasyon indeksi, TSH: Tiroid stimülan hormon, PTH: Paratiroid hormon, CRP: C-reaktif protein

yaygın olarak lökosit subgrupları kullanılmakla birlikte son yıllarda yapılan çalışmalarda NLO, monosit/lenfosit oranı (MLO) ve TLO'nun enflamasyonu göstermede daha uygun belirteçler olduğu gündeme gelmiştir. Tüm bu belirteçler çeşitli fizyolojik durumlarda da az miktarda etkilenebilen, sistemik enflamatuvar hastalıkların prognozunu belirlemede kullanılabilen ucuz, basit ve faydalı belirteçlerdir. PMOP ile enflamatuvar belirteçler arasındaki ilişkiyi araştıran artan sayıda çalışma olmasına rağmen NLO, TLO seviyeleri ile KMY arasındaki ilişkiyi inceleyen çalışma sayısı yetersizdir. Öztürk ve ark. (22) çalışmalarında OP'si olan hastaların NLO düzeylerinin osteopeni ve kontrol gruplarına göre artmış olduğunu belirtmişlerdir. NLO, 2 farklı bağışıklık yollarının oranını temsil eder; yüksek nötrofil, aktif non-spesifik enflamasyondan sorumludur ve düşük lenfosit, zayıf fizyolojik stresten sorumludur. Huang ve Li (30) NLO ile PMOP arasında pozitif korelasyon olduğunu, Fisher ve ark. (31) yüksek NLO seviyesinin kırık oluşmasında potansiyel bir belirleyici olduğunu bildirmişlerdir. Yine yakın zamanda Fang ve ark. (32) tarafından yapılan prospektif bir çalışmada; postmenopozal kadınlarda NLO, TLO, MLO oranlarının OP'si bulunan hastalarda normal olanlara göre daha yüksek olduğu bildirilmiştir. Eroğlu ve Karatas (33) TLO'nun OP olan hastalarda olmayanlara göre anlamlı ölçüde yüksek olduğunu, fakat NLO seviyelerinde anlamlı düzeye ulaşmadığını ve menopoz sonrası OP belirlemede TLO'nun yararlı bir belirteç olduğunu savunmuşlardır. Bizim çalışmamızda, OP hastalarında lökosit ve nötrofil sayısında anlamlı düşüklük olması bu hastalarda bozulmuş immün yanıtın göstergesi olabilir. Ayrıca çalışmamızda iki grup arasında NLO, TLO seviyeleri arasında anlamlı bir farklılık yoktu.

Son on yılda SII; çeşitli viral enfeksiyonlar, onkolojik hastalıklar ve otoimmün hastalıklar için bir gösterge olarak keşfedilmiştir (34). Bununla birlikte, bugüne kadar, SII'nın menopoz sonrası kadınlarda PMOP riskinin belirlenmesinde yardımcı olup olamayacağı büyük ölçüde belirsizliğini korumaktadır. Literatürde SII ile PMOP arasındaki ilişkiyi gösteren sadece bir çalışmaya rastladık. Bu çalışmada, SII'nın PMOP riskinin belirlenmesine yardımcı olmak için yararlı bir biyobelirteç olabileceği ve ileride postmenopozal kadınlarda yüksek riskli popülasyonu taramada başvurulan bir belirteç olarak klinisyenler tarafından kullanılabileceği bildirilmiştir (32). Bizim çalışmamız bu konudaki ikinci çalışmadır ve biz çalışmamızda PMOP olan hastalarla olmayan hastalar arasında farklılık olmadığını saptadık. Bizim çalışmaya aldığımız hasta sayısının daha fazla olması, 30

Tablo 2. L2-L4 T-skorları ile laboratuvar bulguları arasındaki korelasyon

n=486	r	p
Yaş	-0,39	0,000
Lökosit	0,09	0,05
MPV	0,16	0,000
PDW	0,10	0,05
TSH	0,11	0,01
Vitamin D3	-0,21	0,000
CRP	0,13	0,005

Pearson korelasyon testi, p<0,05 istatistiksel olarak anlamlı. MPV: Ortalama trombosit hacmi, PDW: Trombosit dağılım genişliği, TSH: Tiroid stimülan hormon, CRP: C-reaktif protein

Tablo 3. Femur boynu T-skorları ile laboratuvar bulguları arasındaki korelasyon

n=486	r	p
Yaş	-0,40	0,000
MPV	0,13	0,005
PDW	0,08	0,05
TSH	0,14	0,001
Vitamin D3	-0,16	0,000
CRP	0,14	0,001

Pearson korelasyon testi, p<0,05 istatistiksel olarak anlamlı. MPV: Ortalama trombosit hacmi, PDW: Trombosit dağılım genişliği, TSH: Tiroid stimülan hormon, CRP: C-reaktif protein

Tablo 4. L2-L4 ve femur boynu T-skorları için lineer regresyon modeli

Bağımsız değişken		Beta	p	Güven aralığı, %95
L2-L4 T-skoru				
	Yaş	-0,34	<0,001	-0,078 - -0,048
	Lökosit	0,41	0,05	0,000 - 0,822
	MPV	0,11	0,01	0,000 - 0,000
	Vitamin D3	-0,15	<0,001	-0,037 - -0,011
	CRP	0,09	0,05	0,017 - 0,577
Femur boynu T-skoru				
	Yaş	-0,36	<0,001	-0,063 - -0,039
	MPV	0,09	0,05	0,000 - 0,000
	Vitamin D3	-0,10	0,05	-0,022 - -0,002
	CRP	0,10	0,05	0,040 - 0,470

p<0,05 istatistiksel olarak anlamlı. MPV: Ortalama trombosit hacmi, CRP: C-reaktif protein

dakika gibi kısa bir sürede kanın çalışılmış olması dolayısıyla sonuçlarımızın daha gerçekçi olduğunu düşünüyoruz.

Bazı çalışmalar, yüksek serum CRP seviyeleri ile PMOP arasında pozitif bir ilişki olduğunu göstermiştir (13,35). Biz çalışmamızda, postmenopozal kadınlarda serum CRP seviyesi ile hem femur boynu hem de L2-L4 T-skorları arasında pozitif korelasyon olduğunu bulduk. Ayrıca bağımsız değişken olarak femur boynu ve L2-L4 T-skorları ile CRP arasında ilişki olduğunu belirledik. Buna karşın Oei ve ark. (36) 6.338 hastayı içeren incelemelerinde serum CRP seviyeleri ile kırık arasında zayıf ilişki olduğunu, serum CRP seviyelerinin OP'de çok az yükseldiğini belirtmişlerdir. Yapılan araştırmalardan elde edilen kanıtlara göre hematopoezle kemik remodelingi arasında yakın ilişki bulunmaktadır (37). Deneysel çalışmalarda megakaryositlerin osteoklast ve osteoblast işlevlerini değiştirdiği gösterilmiştir (38). Trombosit sayısı ile OP arasındaki ilişkiyi inceleyen çalışma sayısı oldukça azdır. Kim ve ark. (39) trombosit sayısı ile ostepeni ve OP arasında pozitif ilişki olduğunu bildirmişlerdir. Biz çalışmamızda farklı olarak OP olan grupla OP olmayan grup arasında anlamlı farklılık olmadığını tespit ettik. Herhangi bir antiagregan ve/veya antitrombotik ilaç tedavisi alan hastaları çalışma dışı bıraktığımızdan sonuçlarımızın daha gerçekçi olduğunu düşünüyoruz.

MPV ve PDW, hematolojik değişiklikleri tespit etmek için kullanılan yeni ve pratik yöntemlerdir. MPV ve PDW seviyeleri kemik mineralizasyonunu yansıtabilir (40). Literatürde, OP ile MPV ve PDW arasındaki ilişkiyi inceleyen sınırlı sayıda ve çelişkili sonuçlar bildiren çalışmalar mevcuttur. Li ve ark. (13) PMOP'de yüksek MPV değerleri olduğunu, MPV ile KMY arasında güçlü ilişki olduğunu ve MPV artıkça KMY'nin azaldığını bildirmişlerdir. Tersine Akbal ve ark. (16) çalışmalarında OP olan hastalarda MPV ve PDW'nin anlamlı düzeyde düşük olduğunu, PDW ile KMY arasında pozitif korelasyon olduğunu fakat MPV ile KMY arasında korelasyon olmadığını bildirmişlerdir. Bizim çalışmamızda, MPV PMOP olan grupta anlamlı düzeyde düşük bulundu. PDW açısından ise gruplar arasında anlamlı fark yoktu. MPV değerindeki bu düşüşün, artan homeostatik talebin bir sonucu olarak daha büyük trombositlerin seçici tüketiminden kaynaklanabileceği, proenflamatuvar sitokinler ile akut faz reaktanlarının aşırı üretiminin megakaryopoezi etkileyebileceği ve küçük boyutlu trombositlerin kemik iliğinden erken salınması yoluyla, trombositlerin boyutunun baskılanabileceği düşünülmektedir (41). Ayrıca trombosit aktivasyonu ile MPV ve PDW değerleri arasındaki ilişkiyi açıklamak bazı faktörlerden dolayı zor olabilir ve çalışmalarda farklı sonuçlar elde edilebilir. Kan alındıktan sonra çalışılana kadar geçen süre, çalışılan tüpteki antikoagülan ajanın farklılığı gibi çeşitli nedenler ölçüm sonuçlarını etkileyebilir (42).

Bizim çalışmamızın, 487 gibi yüksek sayıda hasta içermesi, prospektif bir çalışma olması, OP dışında bilinen ilaç kullanımı ve OP dışında bilinen bir hastalık öyküsü olanların çalışmaya dahil edilmemiş olması, kanın 30 dakika gibi kısa bir sürede çalışılmış olması ve çalışma tüpünde antikoagülan ajan kullanılmamış olması açısından önemi bulunmaktadır. Tek merkezli ve kesitsel bir çalışma olması, hastaların etik nedenlerden dolayı kullandığı OP ilaçlarının kesilmeden çalışmaya alınmış olmaları çalışmamızın limitasyonları idi.

Sonuç

Sonuç olarak, hematolojik bulgularla OP arasında kesin bir ilişki olduğunu söylemek şimdiye kadar yapılan çalışmalarla mümkün görünmemektedir. DEXA, risk faktörleri olan kişilerde OP tanısı koymada önemini korumaktadır. Hematolojik ve laboratuvar bulgularıyla tanı koymak için ileri çalışmalara ihtiyaç duyulmaktadır.

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Zoledronik Asit Maruziyetinin Sinir Hücresi Üzerine Etkisinin SH-SY5Y Nöroblastoma Hücrelerinde Değerlendirilmesi

Evaluation of the Effect of Zoledronic Acid Exposure on Nerve Cell in SH-SY5Y Neuroblastoma Cells

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Öz

Amaç: Bifosfonatlar osteoporoz tedavisinde etkin olarak kullanılan ilaçlardır. Zoledronik asit (ZA) osteoporoz tedavisinde kullanılan ve imidazol grubu içeren bifosfonat türü ilaçtır. Osteoporoz tedavisinde kullanılmasının yanı sıra, kanser hücreleri üzerinde anti kanser etkisi olduğu düşünülmekte ve ayrıca etki mekanizması baz alınarak ZA'nın Alzheimer, Huntington gibi sinir sistemi hastalıklarının tedavisinde de kullanılabileceğine yönelik çalışmalar bulunmaktadır. Bu çalışmada amaç, ZA'nın SH-SY5Y hücrelerinde sitotoksisite ve oksidatif stres üzerindeki etkisinin araştırılmasıdır.

Gereç ve Yöntem: Sitotoksisite analizi için SH-SY5Y hücrelerine ZA 25, 50, 100, 200, 400, 600, 800 ve 1000 µM konsantrasyonlarında 24 saat süresince uygulandı ve 3-[4,5-dimetilltiazol-2-yl]-2,5 difenil tetrazolyum bromid (MTT) testi ile sitotoksisite değerlendirmesi yapıldı. Oksidatif stres analizi için total oksidan statü (TOS) ve total antioksidan statü (TAS) ELİZA testleri uygulandı. Oksidatif stres indeksi (OSI) hesaplandı.

Bulgular: ZA'nın IC50 değeri 615,996 µM ve IC30 değeri 466,275 µM olarak hesaplandı. TAS, TOS ve OSI değerleri açısından gruplar arasında istatistiksel olarak anlamlı bir fark gözlenmedi.

Sonuç: ZA maruziyeti SH-SY5Y hücrelerinde oksidatif stresi indüklememektedir ve sitotoksisik konsantrasyonları yüksek değerler olarak karşımıza çıkmaktadır. Bu nedenle sinir sistemi hastalıklarında hücrelere zarar vermeden etkin bir tedavi seçeneği olarak düşünülebilir, ancak detaylı moleküler mekanizmaların değerlendirildiği *in vivo* çalışmaların yapılması gerekmektedir.

Anahtar kelimeler: Zoledronic asit, SH-SY5Y hücreleri, oksidatif stres, MTT

Abstract

Objective: Bisphosphonates are drugs that are effectively used for treating osteoporosis. Zoledronic acid (ZA) is a bisphosphonate type drug containing the imidazole group, used for treating osteoporosis. In addition to its use for treating osteoporosis, it is thought to have an anticancer effect on cancer cells, and studies have shown that ZA can also be used for treating nervous system diseases such as Alzheimer's and Huntington's, based on its mechanism of action. Aim this study was to investigate the effect of ZA on cytotoxicity and oxidative stress in SH-SY5Y cells.

Materials and Methods: For cytotoxicity analysis, ZA 25, 50, 100, 200, 400, 600, 800 and 1000 µM concentrations were exposed to SH-SY5Y cells for 24 h and cytotoxicity assessment was performed using 3-[4.5-dimethylthiazol-2-yl]-2.5 diphenyl tetrazolium bromide (MTT) test. Total oxidant status (TOS) and total antioxidant status (TAS) ELISA tests were applied to oxidative stress analysis. The oxidative stress index (OSI) was calculated.

Results: The IC50 value of ZA was calculated as 615.996 µM and the IC30 value was calculated as 466.275 µM. No statistically significant difference was observed between the groups in terms of TAS, TOS and OSI values.

Conclusion: ZA exposure did not induce oxidative stress in SH-SY5Y cells and its cytotoxic concentrations appear as high values. For this reason, it can be considered an effective treatment option in nervous system diseases without damaging the cells. However, *in vivo* studies that evaluate detailed molecular mechanisms are required.

Keywords: Zoledronic acid, SH-SY5Y cells, oxidative stress, MTT

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Giriş

Osteoporoz kemik kütlesinin azalması ile karakterize bir hastalıktır. Osteoporozun tedavisinde genellikle iki yaklaşım uygulanır; ilki kemik yıkımın önleyici tedavi seçenekleri, ikincisi ise anabolizan etki gösteren ilaçların kullanılmasıdır. Bifosfonatlar iyi tolere edildikleri düşünüldüğünden yaygın olarak osteoporoz tedavisinde kullanılmaktadırlar (1). Bifosfonatların çoğu, kırıkları önlemek amaçlı oral olarak uygulanan ilaçlardır. Oral uygulama zorluğu bulunan hastalarda intravenöz uygulama avantajlı bir seçenektir (2). Bifosfonatlar kemik yıkımını osteoklast hücrelerini inhibe ederek önlerler ve kemik yapısını korurlar. Bifosfonatlar kalsiyum hidroksifosfat çözünmesini inhibe eder ve osteolizisi engellerler. Bifosfonatlar vücutta uzun yarı ömüre sahiptirler. Bifosfonatların genel gözlenen yan etkileri ateş, bulantı, kusma, kalsiyum magnezyum gibi elektrolit dengesizlikleri, göz semptomları, böbrek yetmezliği ve çene kemik nekrozudur (1-4). Zoledronik asit (ZA), alendronat ve rizedronat ile birlikte üçüncü nesil bifosfonatlardandır. Bu ilaçlar kemik yıkımını azaltmak için kemik döngüsünü yavaşlatırlar (3). ZA, primer, sekonder ve hafif osteoporoz durumlarında kullanılmaktadır. Uzun yarı ömre sahip olduğu için yılda bir kez kullanım imkanı bulunmaktadır. ZA tedavisi ile kemik kırılmaları, özellikle de omurga kemiklerinde kırılmaların dramatik şekilde azaldığı bildirilmiştir (5). ZA, tersiyer nitrojen içeren bifosfonattır ve postmenopozal osteoporoza yönelik kullanılmaktadır. Ayrıca ZA malign ilişkili hiperkalsemi ve multipl myeloma gibi metastatik kemik hastalıklarının tedavisinde de kullanılmaktadır. ZA, postmenopozal osteoporoz için önerilen yılda bir kez 5 mg dozuna kıyasla, onkolojiyle ilişkili osteoporoz için daha yüksek dozlarda kullanımı önerilmektedir (2,6).

ZA, intravenöz uygulamadan sonra mineralize kemiklere yüksek afinite gösterir, hızlıca kemikte yüksek döngünün bulunduğu alanlarda birikir. Kemik hücrelerine endositoz ile alındığı düşünülmektedir. Kemik rezopsiyonunu farnesil pirofosfat sentazı inhibe ederek ve protein prenilasyonunu önleyerek inhibe etmektedir. ZA, hidroksiapatitlere diğer bifosfonat grubu ilaçlardan daha yüksek bir afinite ile bağlanmaktadır. Yapılan çalışmalarda ZA'nın farmakokinetik özellikleri detaylandırılmıştır. İntravenöz uygulamadan sonra hızlıca kandan kemiklere geçişi olur ve plazma miktarı hızlıca azalır. ZA, sitokrom P450 enzimleri ile metabolize olmaz ve doğrudan idrar ile atılır. ZA'nın çalışmalarda genellikle iyi tolere edildiği bildirilmiştir. İnfüzyon sonrası en yaygın gözlenen advers etkiler ateş yükselmesi (preksi), miyalji, influenza benzeri semptomlar ve artralji olarak bildirilmiştir. Daha az sıklıkta da göz enflamasyonu, bulantı, kusma gibi gastraintestinal sistem semptomları ve baş ağrısı bildirilmiş. Renal yetmezlik ve serumda kreatinin artışı diğer advers etkileri arasındadır. Ayrıca çene kemiğinde nekroza da neden olduğu bildirilmiştir (5,7).

Literatürde ZA'nın sinir sistemi veya sinir hücreleri üzerine etkisini bildiren çalışmalar kısıtlıdır (8-10). ZA kullanımında retrobulbar optik nöropati gelişimine yönelik vaka raporu literatürde yer almaktadır (11). Ancak yeni tedavi yaklaşımlarında bifosfonatların çeşitli nörolojik hastalıkların tedavisinde de kullanılabileceği gündeme gelmektedir. Yapılan preklinik çalışmalarda nitrojen içeren bifosfonatların, beyinde kalsifikasyon ile ilişkili olan Alzheimer, Huntington gibi hastalıklarda mevalonat yolağını hedefleyerek tedavi seçeneği olabileceği bildirilmiştir. Bu ilaçlar izoprenoid sentezinin inhibisyonunda rol alabilmekle birlikte bunların, çeşitli nörolojik bozuklukların ayırt edici özelliği olan bilişsel işlevlerin bozulması için kritik faktörler olarak kabul edilen beyindeki asetil kolinesteraz enzimini ve kolesterol sentezini inhibe ettiği gösterilmiştir. Bifosfonatların merkezi sinir sistemi üzerine ve görev alan moleküler yolaklar üzerine etkilerine yönelik bilgiler kısıtlıdır (12).

Bu çalışmada amaç, osteoporoz tedavisinde kullanılan ZA'nın sinir hücrelerinde sitotoksisitesinin ve oksidatif strese yönelik etkisinin total oksidan statü (TOS) ve total antioksidan statü (TAS) analizleri ile belirlenmesidir.

Gereç ve Yöntem

Kimyasallar

ZA, (toz şeklinde) Centurion Pharma (İstanbul, Türkiye) firması tarafından hediye edildi. Total Oksidan Statüs Kit ve Total Antioksidan Statüs Kitleri Elabscience Biotechnology Co., Ltd (Houston, Texas, ABD) firmasından alındı. 3-(4,5-dimetilltiazol-2-yl)-2,5 difenil tetrazolyum bromid (MTT) ve dimetisüfoksit (DMSO) Merck (Münih, Almanya) firmasından alındı.

Hücre Kültürü Uygulamaları

SH-SY5Y (CRL2266) nöroblastoma hücreleri Amerikan Tip Kültür Koleksiyonu'ndan (American Type Culture Collection) alındı. Hücrelerin kültürü bu firmanın önerdiği doğrultuda gerçekleştirildi. Hücreler 37 °C ve %5 CO_2 koşullarında kültüre edildi. Kültür medyumu %10 oranında ısı ile inaktive edilmiş fötal sığır serumu ve %1 oranında antibiyotik (100 U/mL penisilin ve 100 µg/mL streptomisin) içeren Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12 besiyeri içerisinde kültüre edildi. Hücreler ko-fluent duruma geldiklerinde 3-4 günde 1 olacak şekilde pasajlandı. Bu çalışmada tüm analizler üç tekrar ve üç ayrı gün olacak şekilde uygulandı.

Sitotoksisite Testi

Sitotoksisite değerlendirmesi için MTT testi uygulandı. ZA maruziyeti uygulanmadan önce SH-SY5Y hücreleri 96 kuyucuklu mikroplakalarda 1×104 hücre/100 µL besiyeri olacak şekilde kültüre edildi ve 24 saat hücrelerin adezyonu için inkübe edildi. Sonrasında hücreler ZA ile muamele edildi. ZA stok çözeltisi 10 mm olarak hazırlandı. MTT testi için 25, 50, 100, 200, 400, 600, 800 ve 1.000 µM konsantrasyonlarında ZA hücrelere uygulandı ve 24 saat 37 °C ve %5 CO_2 koşullarında inkübe edildi. Yirmi dört saat inkübasyon sonrasında 20 µl MTT çözeltisi eklendi ve 3 saat daha inkübe edildi. Sonrasında üst sıvı atılarak DMSO eklendi ve 570 nm'de absorbanslar mikroplaka okuyucu ile (Biotek, Epoch, Vermont, ABD) ölçüldü.

Total Oksidan Statü ve Total Antioksidan Statü Analizleri

MTT testi sonucunda belirlenen yarı maksimum inhibitör konsantrasyon (IC50) değerinden daha düşük ZA konsantrasyonları (400 µM, 200 µM, 100 µM ve 50 µM) TAS ve TOS analizi için 25'lik flasklarda kültüre edilmiş hücrelere 24 saat süresince uygulandı. Maruziyet uygulanan hücreler ve kontrol grubu hücreleri 37 °C ve %5 CO_2 koşullarında inkübe edildi. TAS ve TOS analizi Elabscience Biotechnology Co., Ltd (Houston, Texas, ABD) firmasından alınan ELİZA kitleri ile üretici firmanın talimatlarına göre değerlendirildi. Tripsin-EDTA uygulaması ile kaldırılan hücre süspansiyonları 1.000xg'de (2-8 °C) 20 dakika süresince santrifüj edildi. Süpernatant ile çalışmaya devam edildi. Hem TAS hem de TOS analizleri için 1, 2, 4, 8 ve 16 U/mL standart seriler kit içeriğindeki çözeltiler ile hazırlandı ve çizilen standart eğriye göre deney maruziyet konsantrasyonlarında TAS ve TOS miktarları hesaplandı. TOS seviyeleri, TOS'ye karşı biyotinlenmiş antikorlar ve TAS seviyeleri, TAS'ye karşı biyotinlenmiş antikorların spektrofotometrik olarak ölçülmesi ile belirlendi. Sonuçlar hem TAS hem de TOS analizleri için U/mL olarak ifade edildi. Daha kesin bir gösterge olarak oksidatif stres indeksi (OSI), TOS'nin TAS'ye oranı olarak hesaplandı (13,14).

İstatistiksel Analiz

Veriler tek yönlü varyans analiz ANOVA ile analiz edildi, ardından post hoc Dunnett testi ve ortalama ± standart sapma olarak ifade edildi. istatistik anlamlılık seviyesi p<0,05 olarak belirlendi. Tüm analizler Windows için istatistiksel paket SPSS sürüm 20.0 (SPSS Inc., Chicago, Illinois, ABD) kullanılarak gerçekleştirilmiştir.

Bulgular

Uygulanan 25, 50, 100, 200, 400, 600, 800 ve 1.000 µM ZA konsantrasyonlarından yapılan MTT analizi sonucuna göre, SH-SY5Y hücrelerinde ZA'nın IC50 değeri 615.996 µM ve IC30 değeri 466.275 µM olarak hesaplandı. ZA'nın MTT testine göre hücre canlılığı üzerine etkisi Şekil 1'de gösterilmiştir.

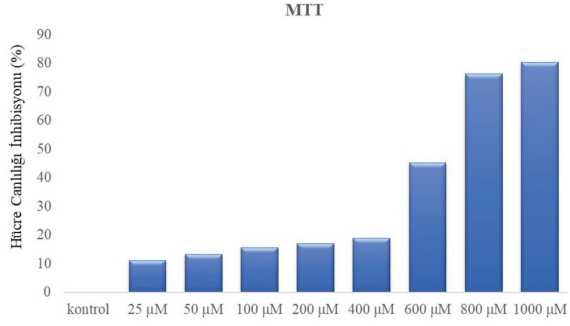
TAS ve TOS analizi için IC30 değeri olan 466.275 µM'den daha düşük konsantrasyonlar (400 µM, 200 µM, 100 µM ve 50 µM) çalışmada kullanıldı. TOS analizine göre uygulanan konsantrasyon arttıkça oksidatif stres artmış görünse de istatistiksel olarak gruplar arasında anlamlı fark gözlenmedi. TAS analizi sonuçlarına göre istatistiksel olarak gruplar arasında anlamlı fark gözlenmedi. OSI'ya göre de istatistiksel olarak gruplar arasında anlamlı fark gözlenmedi (p>0,05) (Tablo 1, Şekil 2).

Tartışma

Bifosfonatların osteoporoz endikasyonu dışında çeşitli kanserler ve merkezi sinir sistemi hastalıklarında da kullanımı gündemde yer almaktadır (12,15-17). Literatürde, bifosfonatların ve ZA'nın değişik hücre hatlarında sitotoksisite değerlendirmesine yönelik, hedeflenen hücre ve doku grubu ve tedavi stratejisini değerlendirmek amacı ile çok sayıda çalışma yer almaktadır (12,18-20).

Bu çalışmada bifosfonat grubu ilaç olan ZA'nın SH-SY5Y hücrelerindeki sitotoksisite ve oksidatif stres mekanizması üzerine etkisini değerlendirdik. Çalışmamızda MTT testine göre IC50 değeri 615.996 µM olarak hesaplandı. Ayrıca TAS, TOS ve OSI analizine göre ZA'nın SH-SY5Y hücrelerinde 24 saat maruziyeti ile oksidatfi stresi indüklemediği ve hücrelerin antioksidan kapasitesini düşürmediği gözlendi.

Wang ve ark. (21) (2014) HeLa, SiHa, and CaSki servikal kanseri hücrelerinde ZA'nın 5, 50 ve 100 uM uygulamasında her üç hücre hattında da konsantrasyona bağlı olarak hücre canlılığının azaldığını bildirmişlerdir. 100 uM konsantrasyonda ise %60'dan fazla hücre canlılık inhibisyonu her 3 hücre hattında da gözlenmiştir. Singireesu ve ark. (22), 2018 Vero ve MDCK



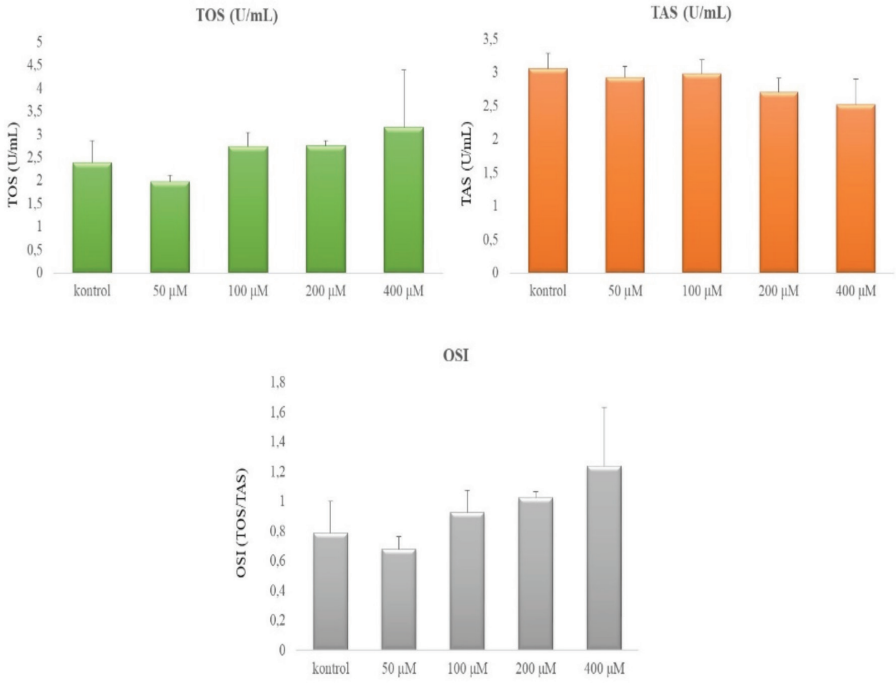
Şekil 1. MTT analizine göre 25, 50, 100, 200, 400, 600, 800 ve 1.000 µM ZA konsantrasyonlarının SH-SY5Y hücreleri üzerinde % inhibisyon değerleri

MTT: Difenil tetrazolyum bromid, ZA: Zoledronik asit

Tablo 1. ZA maruziyeti sonucunda SH-SY5Y hücrelerinden elde edilen TOS, TAS ve OSI değerleri

Parametreler	TOS (U/mL)			TAS (U/mL)			OSI		
Gruplar	**Ort.**	**± SS**	**p**	**Ort.**	**± SS**	**p**	**Ort.**	**± SS**	**p**
Kontrol	2,38	0,47		3,05	0,22		0,78	0,21	
50 µM	1,98	0,13	p>0,05	2,92	0,17	p>0,05	0,68	0,08	p>0,05
100 µM	2,74	0,29	p>0,05	2,97	0,21	p>0,05	0,92	0,14	p>0,05
200 µM	2,76	0,1	p>0,05	2,7	0,21	p>0,05	1,02	0,04	p>0,05
400 µM	3,15	1,24	p>0,05	2,52	0,38	p>0,05	1,23	0,39	p>0,05

ZA: Zoledronik asit, Ort: Ortalama, SS: Standart sapma, OSI: Oksidatif stres indeksi, TOS: Total oksidan statü, TAS: Total antioksidan statü, p değerleri kontrol grubuna kıyasla değerlendirmeleri göstermektedir.



Şekil 2. Yirmi dört saat ZA maruziyeti sonucu SH-SY5Y hücrelerinde TOS, TAS ve OSI değerleri. Bu değerler sonucuna göre ZA 24 saat maruziyetinde hücrelerde anlamlı bir oksidatif stres artışı veya antioksidan kapasite azalması gözlenmemiştir

TOS: Total oksidan statü, TAS: Total antioksidan statü, OSI: Oksidatif stres indeksi, ZA: Zoledronik asit

hücrelerinde ZA'nın IC50 değerini MTT testi ile yaptıkları analizde sırası ile 7,41 ve 109.58 µM olarak bildirmişlerdir. Yapılan başka bir çalışmada insan osteosarkoma MG-63 ve U-2 OS hücrelerine 0, 25, 50,100 ve 200 µM ZA 24, 48 ve 72 saat olarak uygulanmış ve hücre canlılığının her iki hücre türünde de hem konsantrasyon hem de süre ile ilişkili olarak azaldığını göstermişlerdir (16). Lang ve ark. (23), 2016, HUVEC hücrelerinde 24 saat 0 ile 500 µM konsantrasyon aralığında ZA maruziyetinin, ZA konsantrasyonu arttıkça hücre canlılığının istatistiksel anlamlı olarak azaldığını göstermişlerdir. Yapılan başka bir çalışmada SH-SY5Y hücrelerinde ZA'nın 24 saat maruziyetinde büyüme inhibisyon 50 (GI50) değeri 34,1 µM olarak bildirilmiştir (24). Bizim çalışma sonuçlarımız ile bu çalışmalardaki IC50 değer farklılıkları çalışılan hücre tipi farklılığı, maruziyet uygulama süresi farklılığı ve deney ortamları farklılığı ile ilişkili olabilir.

ZA'nın oksidatif stres mekanizması üzerine etkisine yönelik çalışmalarda birbiri ile çelişkili sonuçlar yer almaktadır. Bazı çalışmalarda oksidatif stresi azalttığı bazı çalışmalarda ise artırdığına yönelik veriler yer almaktadır. Bazı çalışmalarda özellikle kemik hücrelerinde ZA uygulamasının hücresel oksidatif stresi çeşitli moleküler yolaklar üzerinde azalttığı gösterilmiştir. Ancak literatürdeki bazı çalışmalarda ise ZA uygulamasının oksidatif stres indüklü apoptoz ve otofajiyi uyardığı gösterilmiştir (25-28). Bu çalışmada ise SH-SY5Y hücrelerinde 24 saat ZA maruziyetinde oksidatif stres artışı veya antioksidan kapasite azalması gözlenmemiştir.

Yapılan çalışmalardaki sitotoksisite ve hücresel oksidatif stres verileri ZA'nın antikanser çalışmalarında etkin bir ilaç olabileceğini düşündürmektedir. Ancak, bu çalışmadan elde edilen IC50 değerinin yüksek olması, ZA uygulamasının sinir hücrelerinde sitotoksik etkisini daha yüksek konsantrasyonlarda gösterdiğini ve nöroblastoma kanser türünde etkinliğine yönelik daha detaylı araştırmalar gereksinimi olduğunu ortaya çıkarmaktadır. Başka bir açıdan bakıldığında ZA'nın Alzheimer, Huntington gibi sinir sistemi hastalıklarında da aday tedavi yaklaşımı olarak kullanılabileceğini düşünürsek, ZA'nın sinir hücrelerine hasar vermeden ve hücrelerde hücresel stres mekanizmasını tetiklemediğinden etkin tedavi seçeneği olarak karşımıza çıktığı görülmektedir.

Sonuç

Sonuç olarak, ZA'nın sinir sistemi hastalıklarında bir tedavi seçeneği olarak etkinliği, hangi moleküler mekanizmaları etkilediği ve tedavinin sonucunun kalıcılığına yönelik daha detaylı *in vitro* ve *in vivo* model çalışmalarının yapılmasına ihtiyaç duyulmaktadır. Bu çalışma literatürde SH-SY5Y nöroblastoma hücrelerinde ZA'nın sitotoksisite derecesini ve hücresel oksidatif stres ve antioksidan kapasite üzerindeki etkisini gösteren ilk çalışmadır.

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Etik

Etik Kurul Onayı: Çalışmamız *in vitro* çalışma olduğundan etik kurul onayına gerek yoktur.

Hasta Onayı: Çalışma hasta onamı gerektirmemektedir.

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Relationships Among 10-Year Fracture Risk Assessment, Comorbidity Burden, and Functional Status in Ischemic Stroke Survivors

İskemik İnmeden Sağ Kalanlar Arasında 10 Yıllık Kırık Riski Değerlendirmesi, Komorbidite Yükü ve Fonksiyonel Durum Arasındaki İlişkiler

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Abstract

Objective: Poststroke disabilities and comorbidities pose serious problems among the stroke survivors. We thought that the comorbidity burden and functional status may impact determining the fracture risk of patients with ischemic stroke. The aim of this study was to investigate the effect of comorbidity burden and functional status in determining the 10-year fracture risk of patients with ischemic strokes.
Materials and Methods: The cross-sectional study included 138 ischemic stroke survivors. Functional status [Functional Independence Measure (FIM)], comorbidity burden [Charlson Comorbidity index (CCI)] and fracture risk [The Fracture Risk Assessment Tool (FRAX)] were evaluated.
Results: The median age of the cases was 64 (49-83) years (53.6% male). As the CCI increased, motor (FIM-motor) and cognitive (FIM-cognitive) functions decreased. The decrease in FIM-motor and FIM-cognitive and the increase in the CCI increased statistically significantly the risk of major osteoporotic fracture (FRAX-MOFR) and hip fracture (FRAX-HFR) ($p<0.05$). The patients with a history of osteoporotic fractures were older, had lower FIM-motor and FIM-cognitive, and higher CCI ($p<0.05$). There was a significant relationship between FIM-motor, FIM-cognitive, and CCI, and FRAX-MOFR and FRAX-HFR. CCI was the independent variable.
Conclusion: In stroke survivors, levels of the motor and cognitive functions and comorbidity burden could predict the risk of hip and major osteoporotic fractures. Comorbidity burdens are independent variables.
Keywords: Comorbidity burden, functional status, fracture risk, FRAX, ischemic stroke

Öz

Amaç: İnme sonrası özürlülük ve komorbiditeler hayatta kalanlar arasında ciddi problemler oluşturmaktadır. İskemik inme hastalarında komorbidite yükü ve fonksiyonel durumun kırık riskini belirlemede etkili olabileceğini düşündük. Bu çalışmanın amacı iskemik inmeli hastalarda 10 yıllık kırık riskini belirlemede komorbidite yükü ve fonksiyonel durumun etkisini araştırmaktır.
Gereç ve Yöntem: Bu kesitsel çalışmaya 138 iskemik inmeli hasta dahil edildi. Fonksiyonel durum [Fonksiyonel Bağımsızlık Ölçütü (FIM)], komorbidite yükü [Charlson Komorbidite indeksi (CCI)] ve kırık riski [Kırılma Riski Değerlendirme skoru (FRAX)] değerlendirildi.
Bulgular: Olguların ortanca yaşı 64 (49-83) yıl (%53,6 erkek) idi. CCI arttıkça motor (FIM-motor) ve bilişsel (FIM-bilişsel) fonksiyonlar azaldı. FIM-motor ve FIM-bilişseldeki azalma ve CCI'daki artış, majör osteoporotik kırık (FRAX-MOFR) ve kalça kırığı (FRAX-HFR) riskini istatistiksel olarak anlamlı bir şekilde artırdı ($p<0,05$). Osteoporotik kırık öyküsü olan hastalar daha yaşlıydı, daha düşük FIM-motor ve FIM-bilişsel ve daha yüksek CCI'ya sahipti ($p<0,05$). FIM-motor, FIM-bilişsel ve CCI ile FRAX-MOFR ve FRAX-HFR arasında anlamlı bir ilişki vardı ve CCI bağımsız değişkendi.
Sonuç: İnmeden kurtulanlarda motor ve bilişsel işlev seviyeleri ve komorbidite yükü, majör osteoporotik kırık ve kalça kırığı riskini öngörebilir. Komorbidite yükü bağımsız değişkenlerdir.
Anahtar kelimeler: Komorbidite yükü, fonksiyonel durum, kırık riski, FRAX, iskemik inme

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Introduction

Stroke is one of the most important causes of morbidity and mortality worldwide. The most common type of stroke is an ischemic stroke, and its incidence increases with age (1,2). The overwhelming majority of stroke patients have at least one comorbidity. About 25% of them have five or more comorbidities. The most common stroke-related comorbidities are advanced age, hypertension, dyslipidemia, diabetes, obesity, atrial fibrillation, and smoking. Poststroke morbidity and comorbidities pose serious problems among survivors (2,3). Studies have reported a negative relationship between comorbidity burden and functional outcomes (4,5). It is essential to determine the comorbidity burden in predicting functional prognosis after acute diseases like stroke and hip fractures (5). It is not well understood how comorbidities affect stroke patients (3). Comorbidities such as heart diseases, chronic obstructive pulmonary disease, and dementia create the risk of falling and affect the incidence of fractures (6). Stroke is a significant risk factor for hip fracture, which increases the risk of hip fracture up to four times (7,8). Poststroke hip fracture has a negative effect on clinical outcomes. The rehabilitation program is delayed, recovery and hospital stay are prolonged, and the risk of morbidity and mortality increases (9). Studies have shown that stroke can increase the risk of falling, resulting in a hip fracture (8). The rate of stroke survivors experiencing a fracture in the first year after stroke is 3-6% (7). Moreover, the risk of hip fractures in stroke survivors is higher than that in healthy adults of the same age (10). It is estimated that 50% of stroke survivors fall within the first year after being discharged from the hospital, and as many as 40% fall repeatedly (11). High fracture rates among stroke survivors are not solely due to their high risk of falling. Additionally, stroke survivors have an increased risk of osteoporotic fractures due to sarcopenia and decreased bone mineral density (BMD), especially on the paretic side (8). However, the results of previously published studies are conflicting and the relationship between stroke and hip fracture risk is unclear (8,12). The Fracture Risk Assessment Tool (FRAX) approved by the World Health Organization (WHO) predicts the 10-year probability of hip and major osteoporotic fractures (13). One study linked severe disability after stroke and a higher FRAX risk score with an increased risk of hip fractures (7). The need to prevent post-stroke fractures, including the prevention of both falls and osteoporosis, and identify stroke patients at risk of fractures was emphasized (14). We thought that the burden of comorbidity and functional status in ischemic stroke patients might impact the prediction of their 10-year fracture risk. We could not find any research in this direction in the literature. This study aimed to investigate the effects of comorbidity burden and functional status in determining 10-year fracture risk in ischemic stroke survivors.

Materials and Methods

This cross-sectional study was performed at the Physiotherapy and Rehabilitation Clinic of a Training and Research Hospital (between 2019 and 2021). The study was planned in compliance with the principles of the Declaration of Helsinki and was approved by the Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee (decision no: 2011-KAEK-25 2019/05-03, date: 22.05.2019). All Patients and/or their legal representatives were informed about the study, and they gave written and signed informed consent.

Male and female patients aged 40-85 years, with a stroke duration of six months or more, diagnosed with ischemic stroke, attending their rehabilitation programs in the physiotherapy and rehabilitation clinic, and not receiving osteoporosis treatment were included in the study. The exclusion criteria were determined as not having a significant cognitive function, being in a vegetative state, and having a stroke type other than ischemic stroke. Other exclusion criteria were refusal to participate in the study, being <40 years old, and being >85 years old.

The age, body mass index (BMI, kg/m²), and demographic data of each participant were recorded. The patient's comorbidities (such as diabetes, hypertension, dyslipidemia, chronic heart failure, myocardial infarction, cardiovascular disease, atrial fibrillation, cancer, chronic lung-liver-kidney diseases, peptic ulcer, and dementia) were learned from the patient or their companion. These data were verified using the necessary testing and imaging methods during clinical follow-ups, and these were obtained and recorded from the hospital records. The same investigator made the clinical observations and evaluations.

Data collection

Functional Independence Measure (FIM): It was used to assess functional status (15). FIM, which includes 13 motor and five cognitive elements, measures independence in daily life. The score for each item ranges from 1 (total dependency) to 7 (total independence). The maximum total motor score is 91, the maximum total cognitive score is 35, and the maximum total FIM score is 126. The Turkish version of FIM was found reliable and valid (16).

Charlson Comorbidity index (CCI): CCI contains 19 chronic diseases and has been used to predict mortality and functional outcomes in stroke cases (17). There is a weighted score between 1 and 6 determined for each disease. Additionally, 1 point is added for every ten years over the age of 40. The higher the overall score, the greater the burden of comorbidity. In this study, the patients were divided into four subgroups according to their CCI scores: group 1 (CCI score 2-3), group 2 (CCI score 4-5), group 3 (CCI score 6-7), and group 4 (CCI score ≥8) (18).

FRAX: Approved by the WHO, the FRAX tool predicts the 10-year probability of hip fractures (HFR) and major osteoporotic fracture (MOFR) (fracture of the hip, clinical spine, wrist, and humerus) (13). FRAX can be used in clinical practice in men or women aged 40 and above. Clinical risk factors for FRAX are as follows:

- Age,
- Sex,
- Weight (kg),
- Height (cm),
- Previous fragility fracture,
- Parent fractured hip,
- Glucocorticoid treatment,
- Current smoking,
- Alcohol consumption,
- Rheumatoid arthritis,
- Conditions causing secondary osteoporosis,
- Optional; BMD of the femoral neck.

Clinical risk factors are entered into the country-specific calculator, and the probability of fractures is calculated (https://www.sheffield.ac.uk/FRAX). The femoral neck BMD T-score was not included in the calculation in this study. The clinical risk factors were learned with the declaration of the patients and/or their companions. They were confirmed with the results of the necessary testing and imaging methods obtained from the hospital records. The patients were classified for MOFR according to FRAX: low- (<10%), moderate- (10-20%), and high-risk (≥20%). Additionally, classification was made for HFR: high-risk ≥3%, and low-risk <3% (19). The patients were divided into those with and without a history of fractures. Intra-group comparisons of the evaluation parameters were made.

Statistical Analysis

The IBM SPSS 23.0 statistical software was used in statistical analysis of data. Descriptive statistical methods such as frequency, percentage, mean, standard deviation, median, and min-max were used while analyzing the data. The data's compliance with normal distribution was evaluated using Shapiro-Wilk tests. Independent-samples t-test (t-test for independent groups) was used in the inter-group comparisons of the normally distributed variables. For the non-normally distributed variables, the Wilcoxon signed-rank test was used for the intra-group comparisons, and the Mann-Whitney U test was used for the inter-group comparisons. A comparison of different risk groups was made with the Kruskal-Wallis test. The relationships between the variables were analyzed using the Spearman correlation test. Multivariate regression analysis was used to analyze the independent predictors of HFR and MOFR. $p<0.05$ was considered significant.

Results

This study included 138 patients who survived ischemic strokes (Figure 1). Of the 153 stroke survivors, seven were excluded

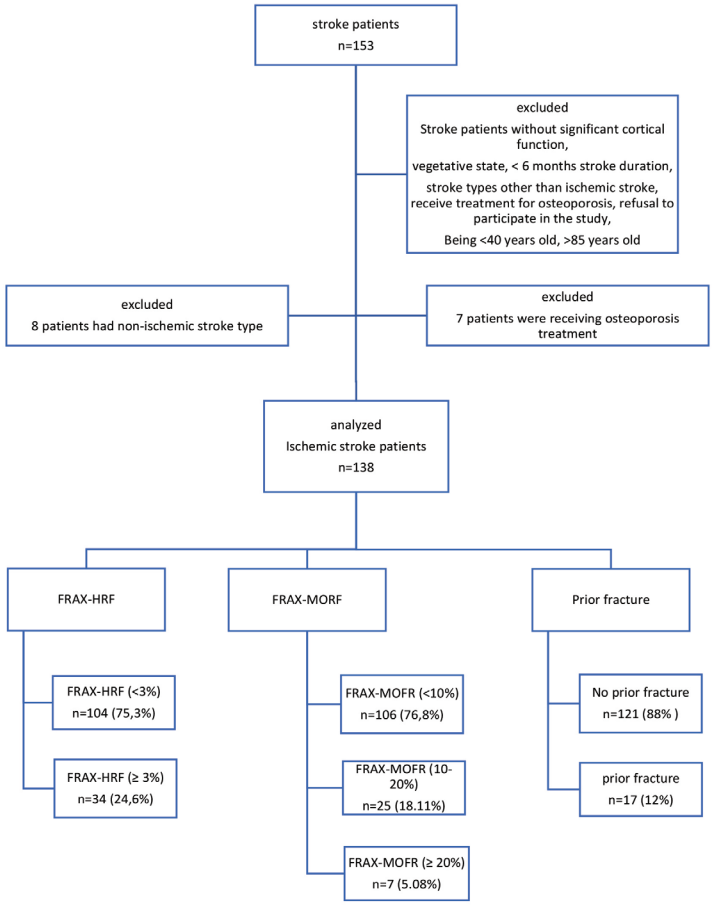

Figure 1. Flow chart

FRAX-HFR: Fracture Risk Assessment Tool-hip fracture, FRAX-MOFR: Fracture Risk Assessment Tool-major osteoporotic fracture

because they received treatment for osteoporosis, and eight were excluded because they had a non-ischemic stroke. The median age of the cases was 64 (49-83) years, 53.6% were male, and 46.4% were female. The median stroke duration was 14 (5-36) months, and the median length of stay in the intensive care unit was 2 (0-90) days. The demographic data, functional status, comorbidity burden, and FRAX scores of the cases are given in Table 1.

The functional statuses of the patients according to their CCI levels are shown in Figure 2: As CCI levels increase, a decrease is observed in motor and cognitive functions.

FRAX scores were obtained in 138 patients, and the patients were grouped according to their MOFR values (Table 2): 76.8% of the patients had a low risk (<10%), 18% had a moderate risk (10-20%), and 5% had a high risk of MOFR. There was an increase in MOFR with increasing age. While 40.6% of the low-risk patients were women, 56% of the intermediate-risk patients and all high-risk patients were women (p<0.05). There was no significant difference between the groups regarding their BMI values (p>0.05). As MOFR increased, FIM motor, FIM cognitive, and FIM total scores decreased, while CCI total scores increased significantly (p<0.05) (Table 2).

According to the classification of the patients according to their HFR values, 75.36% had a low risk (<3%) and 24.63% had a high risk (≥3%) (Table 3). There was no significant difference between the low- and high-risk groups in terms of their sex

Table 1. Demographic data, functional status, comorbidity burden and FRAX scores of patients with ischemic stroke

		n=138
Age		64 (49-83)
Gender n; %	Male n; %	74; 53.6%
	Female n; %	64; 46.4%
BMI (kg/m^2)		27.50 (19.80-41.39)
Smoker n; %	Current smoker n; %	30; 21.7%
	Ex-smoker n; %	40; 29%
	Non-smoker n; %	68; 49.3%
Income n; %	High n; %	33; 23.9%
	Moderate n; %	55; 39.9%
	Low n; %	50; 36.2%
Stroke side n; %	Right n; %	76; 55.1%
	Left n; %	62; 44.9%
Stroke duration (months)		14 (5-36)
Number of strokes		1 (1-4)
Intensive care period		2 (0-90)
Atrial fibrillation n; %		21; 15.2%
Hypertension n; %		117; 84.8%
Hyperlipidaemia n; %		50; 36.2%
FIM-motor		65.50 (13-91)
FIM-cognitive		31 (5-35)
FIM-total		97 (18-126)
CCI-total		4.5 (2-11)
CCI 2-3 n; %		42; 30%
CCI 4-5 n; %		52; 38%
CCI 6-7 n; %		11; 8%
CCI≥8 n; %		33; 24%
FRAX-MOFR		6 (2.2-31)
FRAX-HFR		1.4 (0-16)
History of osteoporotic fracture n; %		17; 12.3%
Dominant hand	Right n; %	134; 97.1%
	Left n; %	4; 2.9%

Median (minimum-maximum); percentage: %, BMI: Body mass index, FIM: Functional Independence Measure, CCI: Charlson Comorbidity index, FRAX: Fracture Risk Assessment Tool, MOFR: Major osteoporotic fracture risk, HFR: Hip fracture risk

(p>0.05). The high-risk group had significantly lower BMI values (p<0.05). As HFR increased, FIM motor, FIM cognitive, and FIM total scores decreased, while CCI total scores increased significantly (p<0.001) (Table 3).

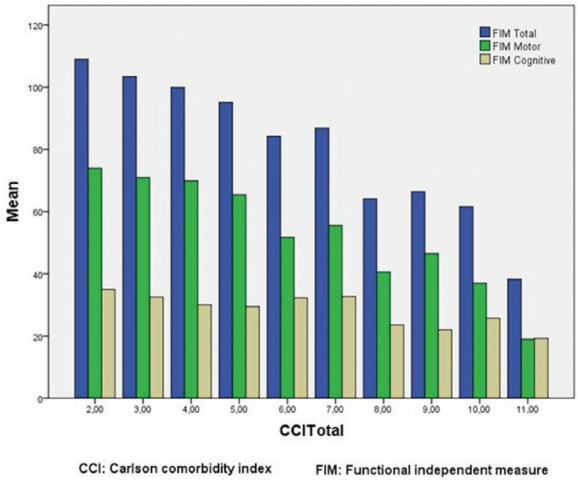

Figure 2. Functional status according to comorbidity rates
CCI: Charlson Comorbidity index, FIM: Functional independence measure

Cases with a history of osteoporotic fractures were significantly older. They had significantly lower FIM motor, FIM cognitive, and FIM total scores and significantly higher CCI total scores (p<0.05) (Table 4).

While MOFR showed a positive correlation with CCI total and age, it was negatively correlated with FIM motor, FIM cognitive, and FIM total scores. The multivariate regression analysis model was found to be significant for the CCI total scores of the patients. In the regression analysis, the following results were obtained: p<0.001, R= 0.747, regression model: FRAX - MOFR = -1.834+0.846 CCI total (Table 5).

While HFR showed a positive correlation with CCI total and age, it was negatively correlated with BMI, FIM motor, FIM cognitive, and FIM total scores. The multivariate regression analysis model was found to be significant for the CCI total scores of the patients. In the regression analysis, the following results were obtained: p<0.001, R=0.735, regression model: FRAX - HFR= -1.057+0.514 CCI total (Table 5).

Discussion

Our results showed that the functional status and comorbidity burden of stroke survivors could significantly predict their ten-

Table 2. Comparison of data according to major osteoporotic fracture risk levels

		FRAX-MOFR (<10%)	FRAX-MOFR (10-20%)	FRAX-MOFR (≥20%)	p
n; %		106; 76.81%	25; 18.11%	7; 5.08%	
Gender	Male n; %	63; 59.4%	11; 44%	-	0.005*
	Female n; %	43; 40.6%	14; 56%	7; 100%	
Age		63 (49-82)	69 (57-83)	72 (65-83)	<0.001*
BMI (kg/m^2)		26.95 (19.80-41.30)	25.80 (20.80-36.70)	25.70 (23-33.30)	0.565
FIM-motor		68 (13-91)	40 (15-86)	32 (13-73)	<0.001*
FIM-cognitive		32.50 (5-35)	30 (5-35)	26 (5-35)	0.001*
FIM-total		98 (18-126)	68 (22-121)	52 (18-108)	<0.001*
CCI-total		4 (2-10)	8 (3-11)	10 (8-11)	<0.001*

Median (minimum-maximum), percentage: %; *p<0.05 significant, BMI: Body mass index, FIM: Functional Independence Measure, CCI: Charlson Comorbidity index, FRAX: Fracture Risk Assessment Tool, MOFR: Major osteoporotic fracture risk

Table 3. Comparison of data according to hip fracture risk levels

		FRAX-HFR (≥ 3%)	FRAX-HFR (<3%)	p
n; %		34; 24.63%	104; 75.36%	
Gender	Male n; %	20; 58.8%	54; 51.9%	0.487
	Female n; %	14; 41.2%	50; 48.1%	
Age		73 (60-83)	62 (49-82)	<0.001*
BMI (kg/m^2)		25.75 (19.90-34)	27 (19.80-41.30)	0.028*
FIM-motor		37.50 (13-81)	69 (13-91)	<0.001*
FIM-cognitive		27 (5-35)	32.50 (5-35)	<0.001*
FIM-total		64 (18-101)	99 (18-126)	<0.001*
CCI-total		9 (6-11)	4 (2-9)	<0.001*

Median (minimum-maximum), percentage: %, *p<0.05 significant, BMI: Body mass index, FIM: Functional Independence Measure, CCI: Charlson Comorbidity index, FRAX: Fracture Risk Assessment Tool, HFR: Hip fracture risk

year fracture risk. Comorbidity burden was the independent variable in this study. The decreases in motor and cognitive functions and the increases in comorbidity burden increased the risk of hip and major osteoporotic fractures calculated by the FRAX tool. The patients with a history of osteoporotic fractures were older than those without a history of such fractures. Additionally, the patients with a history of osteoporotic fractures had lower cognitive and motor functions and higher comorbidity burdens than those without a history of such fractures.

An association has been established between stroke and an increased risk of low-trauma fractures (7,8,20). Post-stroke bone fractures are associated with higher morbidity and mortality (9). Although Lai et al. (12) found no relationship between stroke and hip fracture, the consensus is that stroke significantly and independently increases the risk of hip fractures (8). A population-based study demonstrating a significantly higher risk of hip fractures in all stroke types than controls, albeit at higher rates in hemorrhagic stroke, reported that stroke patients had a higher rate of comorbidity than controls. Additionally, a multivariate analysis was performed to adjust for age, sex, geographic area, and comorbidities, and again, stroke patients were shown to have a significantly higher HFR than controls. Using the National Health Insurance Survey Database, the aforementioned retrospective study did not assess the functional status of patients or the degree of osteoporosis risk (2). Although one study of 186,171 men found that CCI≥3 was associated with increased HFR (21), another study in older people found no relationship between CCI and fracture risk (19). Additionally, the results of a meta-analysis showed a negative relationship between comorbidity burden and functional outcomes in stroke patients (5). Studies have reported that comorbidity burden and immobilization cause a significant increase in fracture risk (22,23). One study listed the independent predictors of poor rehabilitation outcomes after ischemic stroke as CCI>3, atrial fibrillation, and previous myocardial infarction (4). In this study, cognitive and motor functions were evaluated with FIM. Consistent with the literature, there was a negative correlation between comorbidity burden and functional outcomes. Furthermore, as the MOFR and HFR of the patients measured with the FRAX tool increased, it was observed that their comorbidity burden increased, and

Table 4. Comparison of data in patients with and without previous osteoporotic fractures

		No prior fracture n=121; 88%	Prior fracture n=17; 12%	p
Gender	Male n; %	65; 53.7%	9; 52.9%	0.952
	Female n; %	56; 46.3%	8; 47.1%	
BMI (kg/m^2)		26.70 (19.80-41.30)	27.70 (20.80-36.70)	0.460
Age		64 (49-83)	68 (60-83)	0.003*
Stroke duration (months)		14 (5-36)	15 (6-33)	0.963
Intensive care period		4 (0-5)	2 (0-4)	0.699
FIM-motor		67 (13-91)	42 (15-86)	0.001*
FIM-cognitive		32 (5-35))	30 (5-35)	0.262
FIM-total		97 (18-126)	75 (22-121)	0.003*
CCI-total		4 (2-11)	8 (4-11)	<0.001*

Mean ± standard deviation, median (minimum-maximum), percentage: %, *p<0.05significant, BMI: Body mass index, FIM: Functional independence measure, CCI: Charlson Comorbidity index

Table 5. A- The relationships between FRAX-MOFR and data. B- The relationships between FRAX-HFR and data

	FRAX-MOFR				FRAX-HFR			
	Spearman correlation analysis		Multivariate regression analysis		Spearman correlation analysis		Multivariate regression analysis	
	r	p	β	p	r	p	β	p
Age	0.497	<0.001*	0.020	0.768	0.683	<0.001*	0.098	0.163
BMI (kg/m^2)	-0.131	0.126	0.052	0.360	-0.290	0.001*	-0.071	0.219
Stroke duration	0.025	0.773	-0.022	0.660	0.048	0.580	-0.019	0.705
FIM-motor	-0.388	0.000*	-0.615	0.139	-0.499	<0.001*	-0.506	0.234
FIM-cognitive	-0.349	0.000*	-0.197	0.226	-0.412	<0.001*	-0.177	0.288
FIM-total	-0.445	0.000*	0.725	0.159	-0.570	<0.001*	0.521	0.322
CCI-total	0.590	0.000*	0.393	<0.001*	0.768	<0.001*	0.504	<0.001*

Mean ± standard deviation, median (minimum-maximum), percentage: %, *p<0.05 significant, BMI: Body mass index, FIM: Functional independence measure, CCI: Charlson Comorbidity index, FRAX: Fracture Risk Assessment Tool, MOFR: Major osteoporotic fracture risk, HFR: Hip fracture risk

their functional status decreased. Both HFR and MOFR increased in direct proportion to age. This result differed from studies reporting a higher incidence of hip fractures after stroke in those of a younger age (2). In the multivariate analysis including age, BMI, stroke duration, FIM, and CCI, the effect of CCI was significant for both MOFR and HFR.

A study performed on the elderly population reported that retardation in cognitive and physical functions was associated with higher FRAX scores (19). Additionally, studies have reported an inverse relationship between changes in BMD and the functional statuses of stroke survivors. As a person's functional status deteriorates, the degree of bone density loss increases (7,24). Previous studies with male and female participants have reported a relationship between overall fracture risk and severity of stroke, but no significant relationship has been found between hip fracture risk and stroke severity (20,25). In a cohort of postmenopausal women, worse functional outcome after stroke and a higher FRAX score were associated with an increased risk of subsequent hip fractures (7). Our results showed that those with a high risk of hip and major osteoporotic fractures had significantly lower motor and cognitive functionality levels. The population of our study consisted of men and women who survived strokes; however, the majority of those with high MOFR and HFR values were female. The mean age of the patients in our study was lower than that in the cohort study mentioned above.

Post-stroke fracture risk has been linked to decreased BMD and increased susceptibility to falls. The reduction in skeletal loading on the affected side causes an increase in osteoclastic activity. The decrease in postural stability and muscle strength due to immobility may indirectly lead to decreased skeletal mass and increased risk of falling. BMD may be lower in postmenopausal women (7,23). Studies have also shown that chronic diseases and related drugs can affect bone metabolism, predispose individuals to bone loss (osteoporosis), and thus, increase the risk of bone fractures (2). The incidence of any fracture was previously reported as 9%, while the incidence of hip fractures was 52% in a mean follow-up period of 2.54 years (maximum ten years) after stroke. In the same study, a >7-fold increased risk of fractures, including hip fractures, was found in the first year after hospitalization due to stroke. After this, the fracture risk decreased towards baseline risk levels except for people aged ≥80 years, but it still did not completely reach the baseline. The risk ratio for any fracture and hip fracture was reported to be the highest in younger age groups and women. In the study, X-ray or other independent assessments did not confirm fractures. All patients characterized by stroke were included, regardless of whether they were hemiplegic (23). In our study, the patient population consisted of hemiplegic stroke patients. Those with a history of osteoporotic fractures confirmed by imaging constituted 12% of the cases, they were older, and women had a higher proportion. Moreover, the mean stroke duration in this study was 17 months.

According to our knowledge, this is the first prospective study to assess 10-year fracture risk with the FRAX tool in ischemic stroke survivors and investigate the relationship of this variable with comorbidity burden and functional status levels. Previous studies have focused more on the risk of hip fractures in stroke survivors and followed a retrospective data collection path for this. This study also addressed the risk of major osteoporotic fractures. Although it is known that comorbidities such as atrial fibrillation and hypertension are common in stroke patients (26), the use of CCI did not allow us to consider these comorbidities. We thought that standardization might not be achieved in the measurement of femoral BMD, and confusion could occur since there is a difference between the hemiplegic side and hip fractures in those who had hip surgery. For this reason, femoral BMD was not included in the calculation in the FRAX tool. Future studies should target objective data, including BMD.

Conclusion

Currently, the evaluation and treatment of stroke survivors for fracture and/or osteoporosis is a neglected topic. Osteoporosis treatment is indicated if the FRAX index is ≥20% for significant osteoporotic fracture risk and ≥3% for hip fracture risk. Our results showed that motor and cognitive function and comorbidity burden could predict 10-year fracture risk (major osteoporotic fracture risk and hip fracture risk) measured by the FRAX index in stroke survivors. We think that assessing the functional status and comorbidities of stroke survivors may be as crucial as the FRAX index for predicting fracture risk. Future studies may focus on developing a new index, including functional status and comorbidity burden, on determining the risk of osteoporotic fractures and indications for treatment in stroke survivors.

Ethics

Ethics Committee Approval: The study was planned in compliance with the principles of the Declaration of Helsinki and was approved by the Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee (decision no: 2011-KAEK-25 2019/05-03, date: 22.05.2019).

Informed Consent: All patients and/or their legal representatives were informed about the study, and they gave written and signed informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Case Report / Olgu Sunumu

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Case Report: Acute Unilateral Uveitis Induced by Infusion of Zoledronic Acid

Olgu Raporu: Zoledronik Asit İnfüzyonuyla İndüklenen Akut Unilateral Üveit

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Abstract

Bisphosphonates are a group of drugs that inhibit osteoclast-mediated bone resorption, used for treating osteoporosis, Paget's disease, metastatic bone disease, and hypercalcemia caused by malignancy. Zoledronic acid treatment, which is the most potent member of the group and is administered annually, is frequently preferred due to high patient compliance. The most common side effect in the first 3 days after administration is transient flu-like syndrome, which has also been reported to cause serious ocular adverse events. Although the most common ocular side effect is nonspecific conjunctivitis, it can also cause serious symptoms such as uveitis and scleritis. A limited number of cases diagnosed as uveitis triggered by zoledronic acid have been reported in the literature. In this article, we presented the occurrence of unilateral anterior uveitis 24 h after the application in a 62-year-old female patient who was under oral letrozole therapy for breast cancer diagnosed previously and was treated with zoledronic acid for osteoporosis. A detailed ophthalmologic medical history should be taken for patients who will be prescribed zoledronic acid. Additionally, recent bisphosphonate use should be questioned in patients presenting with symptoms of uveitis. Clinicians should warn patients about symptoms that may develop related to uveitis, which is a very rare but serious side effect of bisphosphonates and should promptly evaluate patients by an ophthalmologist when any symptoms develop.
Keywords: Bisphosphonates, zoledronic acid, uveitis, side effect, osteoporosis

Öz

Bifosfonatlar; osteoporoz, Paget hastalığı, metastatik kemik hastalıkları ve ayrıca malignite kaynaklı hiperkalsemi tedavisinde kullanılan osteoklast aracılı kemik rezorpsiyonunu inhibe eden bir ilaç grubudur. Grubun en potent üyesi olan ve yıllık intravenöz olarak uygulanan zoledronik asit tedavisi hasta uyumunun yüksekliği nedeniyle sıkça tercih edilmektedir. Uygulamadan sonra ilk 3 günde en sık görülen yan etkisi geçici grip benzeri sendrom olup bunun dışında ciddi oküler advers olaylara da yol açtığı bildirilmiştir. En sık görülen oküler yan etkisi non-spesifik konjunktivit olsa da üveit ve sklerit gibi ciddi semptomlara yol açabilen durumlara da sebep olabilir. Literatürde kısıtlı sayıda zoledronik asit tarafından tetiklenen üveit tanısı alan olgular raporlanmıştır. Bu yazıda daha önce tanısı koyulmuş meme kanseri nedeniyle oral letrozol tedavisi altında olan ve gelişen osteoporoz nedeniyle zoledronik asit tedavisi uygulanan 62 yaşında bir kadın hastada, uygulamadan 24 saat sonra unilateral ön üveitin ortaya çıkışını sunmayı amaçladık. Zoledronik asit reçete edilecek hastalarda detaylı oftalmolojik medikal öykü alınmalıdır. Ayrıca üveit semptomları ile başvuranlarda yakın zamanlı bifosfonat kullanımı sorgulanmalıdır. Klinisyenler bifosfonatların çok nadir ama ciddi bir yan etkisi olan üveit ile ilgili gelişebilecek semptomlar açısından hastaları uyarmalı, herhangi bir semptom geliştiğinde hastaların oftalmolog tarafından ivedilikle değerlendirilmesini sağlamalıdır.
Anahtar kelimeler: Bifosfonatlar, zoledronik asit, üveit, yan etki, osteoporoz

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Introduction

Bisphosphonates (BP) are frequently used in the treatment of osteoporosis, Paget's disease, metastatic bone diseases and malignancy induced hypercalcemia (1). Zoledronic acid (ZA) is the most preferred BP, especially for patient compliance, because it is used intravenously once a year owing to its potency. The most common adverse event is an acute-phase reaction, which occurs in nearly half of the patients following ZA infusion, despite that the symptoms generally last briefly with less intensity (2). Hypocalcemia, changes in other serum electrolyte and creatinine levels, bone pain, emesis, constipation, and osteonecrosis of the jaw are mostly known side effects (3). Although ocular side effects have been reported, their frequency is very low. Conjunctivitis, scleritis, episcleritis and uveitis have been identified among the ocular side effects of ZA (4). Few cases of ZA infusion-associated uveitis (ZAIU) have been reported in the literature since 2005 (5-22). According to our database research, the only case published from Turkey is a case of uveitis after ZA infusion for the treatment of bone metastasis of breast cancer by Kilickap et al. (22). We describe a case accompanied by unilateral uveitis occurring during the management of drug-induced osteoporosis with ZA infusion. This case report aims to increase clinicians' awareness of ZAIU and to review the treatment for osteoporosis in patients describing ocular adverse events.

Case Report

A 62-year-old female who still using letrozole 2.5 mg orally because of breast cancer history (diagnosed in 2016) was prescribed 5 mg ZA iv for drug-induced osteoporosis. She had no previous history of oral BP therapy. Approximately 6 hours after the infusion, severe muscle pain consistent with myalgia started, and after 24 hours unilateral pain, blurry vision, and redness in her right eye developed**.** She was admitted to ophthalmology outpatient clinic with these complaints. She had no medical history of ocular diseases. On ocular examination, the ophthalmologist found reduced visual acuity (Snellen charts of right eye: 3/10, left eye: 10/10), normal intraocular pressure for both eyes, ciliary and conjunctival injection and a medium number of cells and flare in the anterior chamber. Additionally, the existence of a 2 mm blood-clothed hypopyon was noted. She was also evaluated for any other situations that may induce acute anterior uveitis such as rheumatological diseases, viral infections, and lung diseases. These laboratory and radiological investigations did not represent any aberrancy. When all these findings were reviewed and there was no additional concomitant drug use, the patient was diagnosed with ZAIU. Topical hydrocortisone and dexamethasone were started for three weeks. After the topical steroid therapy was completed, her ocular symptoms resolved completely. Because of this situation, denosumab treatment was planned for drug-induced osteoporosis in the second application of the patient to our clinic. The patient was informed that her data would be used in a scientific publication and her consent was obtained.

Discussion

BP increase bone mineral density and reduce the risk of fracture in benign skeletal system diseases such as osteoporosis, Paget's disease and malignant conditions affecting the skeletal system such as malignancy and multiple myeloma. ZA is the most potent member of the BP that inhibits osteoblast-mediated bone resorption. ZA is administered as a once-a-year intravenous (IV) therapy IV infusion in patients with postmenopausal or drug-induced osteoporosis in cases where there is a lack of tolerance or benefit of oral BP. In addition, ZA was featured as the member with the highest drug adherence among BP (23). One of the most known side effects is the appearance of temporary flu-like symptoms characterized by nausea, arthralgia, and low-grade fever, especially within the first three days (2). It has been reported that ZA infusion may also cause ocular inflammation of varying location and severity in the same periodic process. Most of the typical ocular involvement is typically mild and limited to nonspecific conjunctivitis (24). However, although rare, more serious ocular pathologies such as uveitis and scleritis can be observed. According to a multicenter prospective randomized trial, patients treated with ZA had a significant increase in inflammatory ocular adverse events, most commonly conjunctivitis, compared to the control group two weeks after infusion (25). Several cases diagnosed with ZAIU have been reported in the past. In a previous incidence study, the frequency of ZAIU was reported as 0.8%-1.1%. In the same study, risk factors for ZAIU could not be demonstrated due to its low incidence (26,27).

Although the pathophysiology of ZAIU has not been clarified yet, it is thought that ocular inflammation is triggered by the release of IL-1 and IL-6 cytokines originating from T cells due to the similar structure of BP to pyrophosphate molecules (28,29).

In similar cases reported in the literature, although topical steroid administration was initially given, more than half of the patients required oral or iv steroid management. In a study, re-administration of ZA with prophylactic steroid therapy has been tried in patients with a history of ZAIU and it has been reported that it can provide tolerance (6). In one review, no ocular adverse events were reported in subsequent infusions with or without steroid prophylaxis in patients who developed ocular toxicity after initial exposure. For this reason, re-administration of BP in patients diagnosed with ZAIU was not considered an absolute contraindication (5). However, considering the seriousness of possible ocular side effects and the reducing effect of high-dose steroids on bone mineral density, the benefit-risk relationship should be evaluated separately for each patient. When necessary, drugs that increase bone mineral density other than BP should be preferred.

In this article, we presented a case of unilateral anterior uveitis after the infusion of ZA at a patient who was diagnosed with drug-induced osteoporosis. Clinicians should be aware of this rare side effect. The fact that ZA, which is used in many indications by clinicians today, can cause ocular inflammatory

pathologies should be considered. A detailed medical history of ocular pathologies should be included in the clinicians' questioning of patients before BP therapy. Likewise, detailed drug history should be questioned in patients presenting with uveitis symptoms. Therefore, patients should be warned about possible ocular side effects. If necessary, the clinicians should see the patient again after ZA administration and appropriate patients should be evaluated quickly by the ophthalmologist.

Ethics

Informed Consent: The patient was informed that her data would be used in a scientific publication and her consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Bilateral Pleural Effusion as the Initial Manifestation of Rheumatoid Arthritis Without Articular İnvolvement: Case Report and Literature Review

Eklem Tutulumu Olmadan Romatoid Artritin Başlangıç Bulgusu Olarak Bilateral Plevral Efüzyon: Olgu Sunumu ve Literatür Taraması

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Abstract

Pulmonary involvement due to rheumatoid arthritis (RA) usually occurs after articular involvement, and pleural involvement is rarely seen before articular involvement. A 62-year-old male patient was complaining of exertional dyspnea. He had bilateral pleural effusion on chest radiograph and high C-reactive protein and erythrocyte sedimentation rate in laboratory tests. As a result of exclusion of other etiologies of bilateral pleural effusion and positive results of rheumatoid factor and anti-cyclic citrullinated peptide antibody in the serum, the patient was diagnosed with RA. This case emphasizes that RA, which is a systemic rheumatic disease, should always be among the preliminary diagnoses in the presence of bilateral pleural effusion, even if there is no known RA diagnosis.
Keywords: Anti-cyclic citrullinated peptide antibody, rheumatoid arthritis, pleural effusion

Öz

Romatoid artrite (RA) bağlı pulmoner tutulum genellikle eklem tutulumundan sonra gözlenirken, plevral tutulum nadiren eklem tutulumundan önce görülür. Altmış iki yaşında erkek hasta efor dispnesi şikayeti ile başvurdu. Akciğer grafisinde bilateral plevral efüzyon, laboratuvar tetkiklerinde yüksek C-reaktif protein ve eritrosit sedimentasyon hızı mevcuttu. Bilateral plevral efüzyon yapabilecek diğer etiyolojilerinin dışlanması ve serumda romatoid faktör ve antisiklik sitrüline peptid antikorunun pozitif çıkması sonucu hastaya RA tanısı konuldu. Bu olgu, bilinen bir RA tanısı olmasa bile bilateral plevral efüzyon varlığında sistemik bir romatizmal hastalık olan RA'nın her zaman ön tanılar arasında olması gerektiğini vurgulamaktadır.
Anahtar kelimeler: Anti-siklik sitrüline peptid antikoru, romatoid artrit, plevral efüzyon

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune systemic disease with a frequency of approximately 1% (1). This disease, the etiology of which is not fully known, primarily affects the small joints of the hands and feet polyarticularly and may also show extra-articular systemic involvement at a rate of 50% (2). Pulmonary involvement is important in terms of systemic involvement, because the most common cause of mortality in RA is pulmonary involvement (1). Symptoms of pulmonary involvement in RA occur after arthritis with a frequency of about 85% (1). As in our case, RA, which was diagnosed with pulmonary involvement before articular involvement, is a rare condition (3-10). Here, a case diagnosed with RA while being examined with bilateral pleural effusion is presented.

Case Report

A 64-year-old male patient was admitted to chest diseases department due to chest pain, fatigue and exertional dyspnea. The patient was diagnosed with bilateral pleural effusion, prominent on the right side. In this state, the patient was consulted to our clinic to be evaluated in terms of rheumatological diseases. Chest pain increased with breathing, was stinging, especially on the

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right side, and there was dyspnea that increased with exertion. The patient had an intermittent cough for the last 1 year, which did not affect his daily life, but his cough had increased in the last 1 month. Bilateral pleural effusion, more on the right side, was detected in the postero-anterior (P-A) chest X-ray. There was no pleural effusion in the thorax computed tomography (CT) taken 1 year ago with the complaint of cough. The patient applied to an external center with similar complaints; he received moxifloxacin (400 mg/day, 7 days) treatment, but his complaints did not regress. As a result of the evaluations made by the cardiology department, it was determined that there was no congestive heart failure (ejection fraction: 65%). Diuresis was recommended to the patient by the cardiology to remain at 0 to -500 mililiters together with the fluid intake follow-up, but despite the diuretic treatment, the patient's complaints did not improve, and it was found that the pleural effusion increased minimally on the right side in the control X-ray. Thoracentesis was recommended to the patient by chest diseases department, but the patient refused; thereupon, empirical 32 mg/day (for 10 days) methylprednisolone treatment was started, and the patient was informed that thoracentesis would be performed if no response was obtained. After methylprednisolone treatment, the patient's cough, weakness and fatigue decreased, and bilateral significant regression was observed in effusions in the P-A chest X-ray. The C-reactive protein (CRP) value was 72.94 mg/L (0-5 mg/L) in the first outpatient clinic application, it decreased to 7.83 mg/L in the control. Thoracentesis was abandoned due to regression in the patient's imaging, clinical and laboratory findings. Steroid therapy was tapered off. The patient did not have any complaints for 2 months, but he admitted to our hospital when the shortness of breath started again, and the patient was hospitalized for further examination and treatment. The patient had no complaints except exertional dyspnea. He had a history of thyroidectomy and hypertension. He was using levothyroxine sodium 100 mcg/day and verapamil hcl + trandolapril 180/2 mg per day. In the rheumatological evaluation of the patient, there was no significant finding other than pain in the small joints of both hands and short-term morning stiffness that had been intermittent for 3 years, there was no arthritis or arthralgia, and there was no deformity in the hand and foot joints (Figure 1). In respiratory examination, respiratory sounds were decreased in the lung bases and there were crepitant rales. Costodiaphragmatic sinuses were closed and dull on percussion. In laboratory examinations; CRP was 20.8 mg/L (0-5 mg/L), erythrocyte sedimentation rate was 65 mm/h (0-20 mm/h), D-dimer was 3.73 ug/mL (0-0.5 ug/mL). The patient's complete blood count, kidney and liver function tests were normal. On thorax CT, there were lymph nodes in the mediastinum with a short axis not exceeding 1 cm, and pleural effusion reaching a thickness of 18 mm in the widest part on the right and 15 mm in the widest part on the left, and compression atelectasis adjacent to it in both hemithoraces (Figure 2). There was an obstruction pattern in the pulmonary function test [FEV1: 62.3% (3.25L), FVC: 72.4% (4.16L), FEV1/FVC: 67.23]. In the examinations of the patient, anti-nuclear antibody, anti-ds DNA, anti-SSA were detected as negative; rheumatoid factor was 85.4 IU/mL (0-14 IU/mL) and Anti-cyclic citrullinated peptide antibody was 266.8 U/mL (0-17 U/mL) with high positivity for RA. Although the patient's findings did not meet the 2010 ACR/EULAR classification criteria, considering that these criteria are designed for patients presenting with synovitis, the absence of a more appropriate diagnosis to explain bilateral pleural effusion, mild joint complaints and laboratory findings were considered together with RA pulmonary involvement in the patient. Although patient's joint complaints were not severe enough to require treatment, chest pain and pleural effusion completely regressed in the follow-up with hydroxychloroquine sulfate and methylprednisolone treatment for systemic involvement.

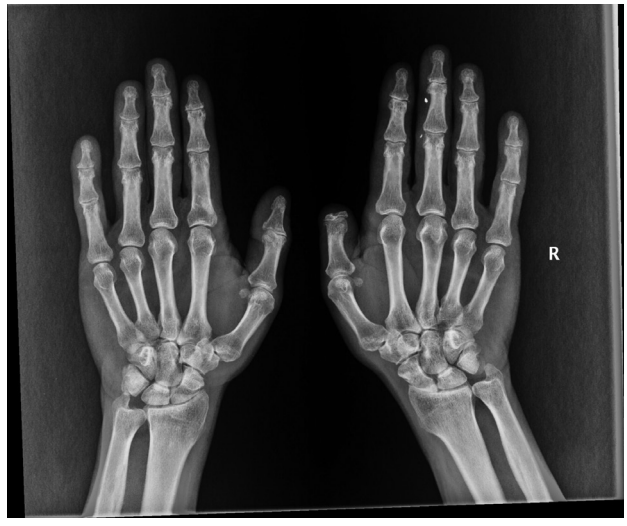

Figure 1. X-rays of both hands of the patient. There was no deformity in the hands

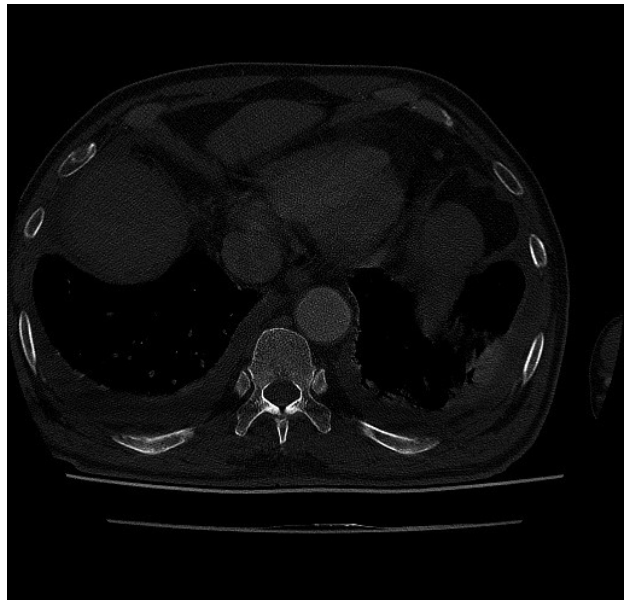

Figure 2. An image from the patient's thorax computed tomography. Areas marked with arrows show bilateral pleural effusion

Informed consent was obtained from the patient regarding the case report. The patient is being followed by physical medicine and rehabilitation and chest diseases departments.

Discussion

Pulmonary involvement of RA is manifested by parenchyma and airway involvement, especially obliterative bronchiolitis, multiple nodules, interstitial pneumonitis, and fibrosis. Pleural involvement can be observed at a rate of 3-5% (2). Different pleura-related lung diseases such as exudative rheumatoid effusion, cholesterol-rich chyliform effusion, drug use (methotrexate and infliximab) related pleuritis, empyema and pyopneumothorax, bronchopleural fistula, pneumothorax or hemopneumothorax can also be observed in RA (11-13). When pleural effusion occurs in the course of RA, 80% is unilateral; It manifests bilaterally at a rate of 20%, as in this case, and its amount is low (1). Pleural involvement in RA is more common in middle-aged men with high RF values, and may be associated with subcutaneous nodules, interstitial lung disease, and pericarditis (1). Although the demographic characteristics of our patient were compatible with literature, no additional findings such as subcutaneous nodules, interstitial lung disease or pericarditis were present in our patient.

In rheumatoid pleuritis, chest pain and/or fever are the most common additional findings. Patients with severe pleural effusions may present with dyspnea. No findings may be seen on physical examination, or decreased breath sounds, pleural rubbing, or unilateral or bilateral dullness to percussion may be detected. The presence of dyspnea that is disproportionate to the size of the effusion may be a clue to any underlying pulmonary or cardiac pathology (14). The approach to pleural effusion in RA is not different from the approach to pleural effusion in general. First of all, it follows the steps such as exclusion of infection and malignancy and alleviation of dyspnea. Ultrasound-guided thoracentesis is an important diagnostic method in patients with RA and pleural effusion. The purpose of pleural fluid analysis is to detect that the pleural fluid is an exudate of rheumatoid effusion and to rule out other etiologies such as infection, malignancy, cholesterol effusion. Therefore, pleural fluid can be sent for glucose, lactic dehydrogenase, cell count, protein, triglycerides, cholesterol, Gram stain, cytology and cultures (11,14). In our case, thoracentesis could not be performed due to the patient's refusal and the rapid regression of the effusion with treatment. The first choice for the diagnosis of pleural effusion is direct radiography, but CT and pulmonary function tests also help in the diagnosis to show the involvement of the pulmonary parenchyma. Because to reveal RA lung involvement, P-A chest X-ray yields approximately 10%, high-resolution CT 70-80% and pulmonary function tests 10-20% (2). Although the pulmonary function tests were expected in a restrictive pattern, our patient's findings were compatible with the obstructive pattern, suggests that our patient's cough that has been going on for the past 1 year may be associated with an undiagnosed obstructive pulmonary disease.

In RA, joint complaints generally occur first and then pulmonary involvement is expected, but rarely pulmonary involvement can be detected before articular involvement (3-10). Thus, the diagnosis of RA can be made after pulmonary involvement. Common features of patients with RA diagnosed with pleural involvement in the literature; pulmonary symptoms are more severe than joint symptoms, other causes of effusion are excluded, a good response to RA treatment and then the diagnosis is clarified, and pleural involvement is accompanied by parenchymal involvement. The general characteristics of the cases diagnosed with RA after pleural effusion are; consists of middle-aged men, musculoskeletal complaints are less than 1 year and lung symptoms are less than 6 months, occur as unilateral effusion, pleural fluid is exudate after thoracentesis, accompanied by parenchymal involvement; in pleural fluid analysis, high adenosine deaminase level, very low glucose level, lymphocyte dominance; and presence of high positive RF, CRP and erythrocyte sedimentation rate in serum (7-10). Since thoracentesis could not be performed in our case, no interpretation of pleural fluid similarities could be made, but other clinical findings were compatible with the literature, except the absence of parenchymal involvement. Pleural effusions due to RA usually do not require specific treatment as they often regress spontaneously or regress 1 to 36 months (mean 14 months) after treatment of articular symptoms of RA, but larger effusions are more likely to be symptomatic and require treatment. When rheumatoid pleuritis is symptomatic and does not improve without treatment, non-steroidal anti-inflammatory drugs (NSAIDs), oral or intrapleural glucocorticoids, and therapeutic thoracentesis for immediate control of dyspnea can be performed (14). In addition, other immunosuppressive drugs can be used in the treatment of RA. If treatment is to be given in the presence of pleuritic chest pain or because of the size of the effusion, NSAIDs are the first choice and recovery is observed in an average of one week with treatment (15). On the other hand, it should not be forgotten that some drugs used in the treatment of RA can cause pulmonary complications. Therefore, more care should be taken in drug selection in patients with pulmonary involvement during the post-diagnosis treatment process. Especially in patients with pulmonary parenchyma involvement, RA and other rheumatological diseases are often questioned, but it should not be forgotten that there may also be extraparenchymal pulmonary findings related to RA.

In conclusion, the possibility of the presence of RA in patients with pulmonary pathology should be kept in mind and the patient should be questioned in terms of RA. In addition, regression of pulmonary signs and symptoms after RA treatment will also make it possible to reach a diagnosis from treatment. In our case, there was a progressive regression of the effusion with glucocorticoid therapy before admission to our clinic, but it later relapsed. Therefore, it was thought that a long-term immunosuppressive or anti-inflammatory treatment should be used in our case. By presenting this case, our aim is to emphasize that although RA is a disease that stands out with its articular

findings, we should not forget that it is a systemic rheumatic disease, and there may be RA patients diagnosed with extra-articular involvements.

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Ethics

Informed Consent: Informed consent was obtained from the patient regarding the case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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