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AMAÇ VE KAPSAM

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

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

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

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

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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.osteoporozdunyasindan.com. 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:
Bu dergide yayınlanmış makaleler hakkında yapılan değerlendirme yazılarıdır. Editör gönderilmiş mektuplara yanıt isteyebilir. Metnin bölümleri yoktur.
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5) Eğitim Yazıları:
Bu kategoride otörler osteoporoz, metabolik kemik hastalıkları ve rehabilitasyon konularındaki güncel bilgileri özetlerler.

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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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All manuscripts are reviewed by editor, related associate editor and at least three experts/referees. The authors of the accepted manuscript for publication have to accept that the editor and the associate editors are authorized to make corrections without changing the main text of the paper.

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The style for title page, references, figures and tables should be unique for all kind of articles published in this journal.

Original Articles

1) Title Page (Page 1)

This page should include the Turkish and English titles of the manuscript, affiliation of author(s), key words and running titles.
The English title should take place in the title page. Likely, Turkish title should be mentioned for articles in foreign language. Turkish and English key words and running titles should also be included in the title page.
The names and full postal addresses of authors and the corresponding author should be indicated separately. Especially as e-mail addresses will be used for communication, e-mail address of the corresponding author should be stated. In addition, telephone and fax numbers must be notified.
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If there are any grants and other financial supports by any institutions or firms for the study, information must be provided by the authors.

2) Summary (Page 2)

In the second page, Turkish and English summaries of the manuscript (maximum 200 words for each), and the key words should take place.
The summary consists of the following sections separately: Objective, Materials and Methods, Results, Conclusion. Separate sections are not used in the summaries for the review articles, case reports and educational articles. For these articles, the summaries should not exceed 200 words and briefly present the scope and aims of the study, describe the salient findings and give the conclusions. The references should not be cited in the summary section. As far as possible, use of abbreviations are to be avoided. If any abbreviations are used, they must be taken into consideration independently of the abbreviations used in the text.

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The typical main headings of the text are as follows: Introduction, Materials and Methods, Results, Discussion.
The introduction part should include the rationale for investigation and the background of the present study. Results of the present study should not be discussed in this part.
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c) Chapter of a book:
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These are preliminary reports presenting new ideas, inventions or findings of scientific interest that do not constitute original research. They aim to determine possible interest to future articles related to this topic. There are no separate sections in the text.

5) Educational articles:

In this category, authors summarize the present state of knowledge regarding physical medicine, rheumatology and rehabilitation.

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Türk Osteoporoz Dergisi
TURKISH JOURNAL OF OSTEOPOROSIS

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Türk Osteoporoz Dergisi
TURKISH JOURNAL OF OSTEOPOROSIS

Editörden / Editorial

Değerli Meslektaşlarımız,

22-25 Kasım 2018 tarihlerinde Türkiye Osteoporoz Derneği ev sahipliğinde, International Society for Clinical Densitometry (ISCD) ve International Osteoporosis Foundation (IOF) ortak uluslararası kursu yapılacaktır. Kursun uluslararası ismi Osteoporosis: Essentials of Densitometry, Diagnosis and Management olup, kemik dansitometri bilgisi ile ilgili en yeni teknoloji ve bilgileri içerir. Aynı zamanda osteoporoz tedavisi ile ilgili bilgiler de sunulacaktır. Bu kursun sonunda arzu edenler sınava girip, uluslararası bir sertifika alabilecektir. Bu kurs ile birleştirilecek Osteoporoz Tedavisinde Güncellemeler Sempozyumu'nda da osteoporoz tedavisindeki son gelişmeler paylaşılacaktır.

Bu kurs çok değerli üç konuşmacı tarafından verilecektir. Prof. Dr. John Carey ISCD bir önceki dönem başkanıdır. Dr. Basel Masri IOF Board üyesidir. Prof. Dr. Didier Hans ise ISCD geçmiş dönem başkanlarından olup, osteoporoz değerlendirmesinde son yıllardaki en güncel konu olan Trabeküler Kemik Skoru'nu bulan ve geliştiren kişi olup, kurs sırasında bu konu ile ilgili detaylı bilgi kendisi tarafından verilecektir.

Ülkemizde osteoporoz tanı ve tedavisi ile ilgilenen hekimlerimiz için çok önemli bir fırsat olan sertifikalı bu kursa ve sempozyumumuza katılımınızı bekler, sevgi ve saygılarımızı sunarız.

Editör
Prof. Dr. Yeşim Kirazlı

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The Quality of Life Level in Female Patients with Fibromyalgia Syndrome and the Associated Factors

Fibromiyalji Sendromlu Kadın Hastalarda Yaşam Kalitesi Düzeyi ve İlişkili Faktörler

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Abstract

Objective: In our study, we were examined the quality of life and its relationship with socio-demographic characteristics in female patients with Fibromyalgia syndrome (FMS) who applied to outpatient clinic.

Materials and Methods: In the study, 108 female patients applying to physical therapy outpatient clinic between May 1, 2017 and September 1, 2017, and diagnosed with FMS were included. The data collection tool used in the study was the questionnaire developed by the researcher based on the literature information. The questionnaire consisted of two parts. The first part of the form consisted of the question set querying the socio-demographic characteristics (15 questions), and the second part consisted of the quality of life bref scale used to assess the quality of life of the cases.

Results: When the quality of life scores of the individuals according to their economic status were examined; the emotional role functioning, physical functioning, physical role functioning, and physical indicator scores of individuals with middle income level were significantly higher than other income groups ($p<0.05$).

Conclusion: Consequently, we can say that the quality of life is better in female patients who have a high income level with education, normal body mass index, regular sleeping and diagnosis of fibromyalgia.

Keywords: Fibromyalgia, quality of life, clinical characteristics

Öz

Amaç: Çalışmamızda, polikliniğe başvuran Fibromiyalji sendromlu (FMS) kadın hastalarımızda yaşam kalitesini ve yaşam kalitesinin sosyo-demografik özellikler ile ilişkisini inceledik.

Gereç ve Yöntem: Çalışmada, 1 Mayıs 2017 - 1 Eylül 2017 tarihleri arasında fizik tedavi polikliniğine başvuran ve FMS tanısı alan 108 kadın hasta alındı. Araştırmada kullanılan veri toplama aracı literatür bilgilerine dayanarak araştırmacı tarafından geliştirilen anket formudur. Anket formu, iki bölümden oluşmaktadır. Formun birinci bölümü sosyo-demografik özellikleri sorgulayan soru takımından (15 soru), ikinci bölümü ise, olguların yaşam kalitesini değerlendirmek için kullanılan yaşam kalitesi kısa ölçeğinden oluşmuştur.

Bulgular: Bireylerin ekonomik durumlarına göre yaşam kalitesi puanları incelendiğinde; orta gelir düzeyine sahip olan bireylerin emosyonel rol güçlüğü, fiziksel fonksiyon, fiziksel rol güçlüğü ve fiziksel göstergeler skorları diğer gelir gruplarına göre anlamlı derecede yüksektir ($p<0,05$).

Sonuç: Sonuç olarak; eğitim ile gelir düzeyi yüksek olan ve beden kitle indeksi normal olup, düzenli uyuyan fibromiyalji tanısı alan kadın hastalarda yaşam kalitesinin daha iyi olduğunu söyleyebiliriz.

Anahtar kelimeler: Fibromyalji, yaşam kalitesi, klinik özellikler

Introduction

Fibromyalgia is a disease characterized by widespread chronic musculoskeletal pain. Peripheral and central pain mechanisms are thought to have a role in genetic basis at fibromyalgia etiopathogenesis (1). The etiology and mechanisms of Fibromyalgia syndrome (FMS) are not exactly understood, however, central pain mechanisms and central sensitization as well as neuroendocrine dysfunctions are the most important factors in the development of FMS (2). Fibromyalgia affects 1-2% of the community and most of them are female patients aged between 40-55 years (3,4). The quality of life briefly defines "how the person perceives his/her own health subjectively in the environment he/she is in". This concept is not a quantity measured by medical techniques and laboratory processes, but it is a quality experienced subjectively. The quality of life is multidimensional and the criteria used are affected by the disease itself and its severity. The quality of

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life is an important measure in the effect, treatment and follow-up process of the chronic diseases such as rheumatic disease on a person. One of these diseases is FMS (5). FMS disturbs the physical and emotional quality of life by causing significant difficulties in the person's functional capacity and activities of daily living. For this reason, the quality of life scales are often used. The scales developed to measure quality of life include physical and occupational functions, social interaction, psychological and economic conditions. Numerous scales used for this purpose are involved in the literature and among them the scale which is most frequently used in the health researches is "the quality of life scale" which has 36 questions and 8 subscales short form-36 (SF-36) (6). Being widely used in Turkey and in the world in order to measure the quality of life, the SF-36 evaluates the health status with its positive and negative aspects. The high scale score signifies a good quality of life (7). Determining the factors affecting the quality of life in FMS seems important at the stage of directing the treatment of the disease. In the present study, the quality of life of female patients with FMS applying to outpatient clinic and the correlation between the quality of life and socio-demographic characteristics were examined.

Materials and Methods

Necessary written permissions were obtained from related institutions before the study. A total of 108 female patients who applied to the Bingöl State Hospital Physical Medicine and Rehabilitation outpatient clinic that diagnosed of FMS according to 1990 American College of Rheumatology FMS classification criteria and filled out of informed voluntary consent were included in this study. The study was performed in accordance with the principles of Declaration of Helsinki. The ethical approvals were taken from Bingöl University Scientific Research Publications Ethics Committee (dated 09.05.2016 and numbered 29). All participants gave written and verbal permission to participate in this study. The sample of the study consisted of the patients who were followed-up with the diagnosis of FMS, were able to communicate and were voluntary to participate in the study. Patients whose complete blood count, complete urine test, sedimentation rate and serological tests (Syphilis, Brucella, Hepatitis markers, human immunodeficiency virus) were in the normal limits and who had no significant systemic disease were included in the study. In addition, attention was paid so that all the cases included in the study had no additional disease like systemic and inflammatory diseases. The data collection tool used in the study was the Questionnaire developed by the researcher based on the literature information. The questionnaire consisted of two parts. While the first part of the questionnaire consisted of a question set checking the socio-demographic characteristics (15 questions), the second part was the quality of life scale (SF-36) used for evaluating the quality of life of the cases. It is a widely used quality of life measure and has high reliability (8). It is not only intended for a single disease but also it can be used for all chronic diseases. Therefore, in the present study investigating the female patient group with FMS, the use of SF-36 was preferred in evaluating the quality of lives of the patients.

Statistical Analysis

The data were prepared for analysis on SPSS, Version 22.0 following export from Qualtrics. Mean scores were given with standard deviation and the value of $p<0.05$ was determined as significance level. Frequency was benefited in presentation of the descriptive data, while Kruskal-Wallis Variance analysis from nonparametric hypothesis tests used to compare more than two groups was used in the evaluation of statistical significance of the other data.

Results

Table 1 shows the general characteristics of the individuals participating in the study. The majority of the individuals were illiterate (28.7%), had a middle income level (75.9%), and were mostly housewives (49.1%). 45.4% of the individuals did not smoke and reported the disease as the event affecting their life (24.1%). In addition, it was also found that 76.4% of them had irregular sleep and 60.2% had no illness. When the status of having a psychological disease was examined, 86.1% of them were observed to have no disease. A great majority of the patients received physical therapy (43.5%) and physical therapy+medication together (39.8%). Table 2 shows the distribution of scores of the life quality according to educational status. According to this, all the quality of life components other than general health were higher in the individuals whose educational level was university than individuals in the other educational levels and it was statistically significant ($p<0.05$). The general health component was significantly lower in illiterate individuals than other groups ($p<0.05$); this score of the other groups was close to each other.

When the quality of life scores of the individuals according to their economic status were examined (Table 3); the emotional role functioning, physical functioning, physical role functioning, and physical sign scores of individuals with middle income were significantly higher than other income groups ($p<0.05$). The pain score was found to be higher in the individuals with high income than the other groups and it was statistically significant ($p<0.05$). Table 4 shows the distribution of quality of life scores according to body mass index (BMI) groups. According to this, a significant difference in terms of BMI groups was seen only in the physical role functioning component ($p<0.05$). Physical role functioning score of obese individuals was significantly lower than others. Table 5 shows the distribution of mean and standard deviation values of the quality of life scores according to the sleep pattern. While no significant correlation was found between the sleep pattern and physical signs except for physical role functioning score; whereas, the difference between the vitality and mental health from mental signs and total mental sign scores was significant. The physical role functioning score

Table 1. Distribution of individuals in terms of their socio-demographic characteristics (%)

Characteristics	Number (n)	Percentage (%)
Educational status		
Illiterate	31	28.7
Primary school	28	25.9
Secondary school	18	16.7
High school	9	8.3
University	22	20.4
Economic status		
Low	22	20.4
Middle	82	75.9
High	4	3.7
Profession		
Housewife	53	49.1
Worker	6	5.6
Civil servant	20	18.5
Student	10	9.3
Retired	6	5.6
Self-employed	13	12.0
Smoking status		
Never	49	45.4
Sometimes	34	31.5
Addicted	25	23.1
Experiencing the event that will affect your life		
Death	21	19.4
Accident	5	4.6
Disease	26	24.1
Economic difficulty	7	6.5
Other	23	21.3
Disease, economic difficulty	8	7.4
Death, accident	4	3.7
Accident, economic difficulty	3	2.8
Death, economic difficulty	4	3.7
Death, accident, disease	5	4.6
Death, disease	2	1.9
Sleep pattern		
Regular	11	10.2
Some nights	14	13.0
Irregular	83	76.9
Disease status		
No	65	60.2
Yes	43	39.8
Disease name		
Heart	14	13.0
Diabetes	2	1.9
Kidney	2	1.9
Waist, neck, joint and muscular disease	6	5.6
Heart, diabetes	8	7.4
Digestive system	4	3.7
Respiratory tract	5	4.6
Celiac	2	1.9
Status of having psychological disease		
No	93	86.1
Yes	15	13.9
Patient		
Mother	22	20.4
Father	2	1.9
My spouse	17	15.7
Parents and siblings	2	1.9
Mother father	5	4.6
Treatment		
Medication	10	9.3
Physical therapy	47	43.5
Other	8	7.4
Physical therapy, medication	43	39.8
Duration of Fibromyalgia disease (years)	**3.5±3.2**	

was higher in individuals with regular sleep than the others and it was statistically significant ($p<0.05$). While the mental health score was high in individuals sleeping irregularly at some nights; vitality score and mental signs score are significantly high in individuals sleeping regularly than the other groups ($p<0.0$).

Discussion

All the quality of life components of the individuals, whose educational level was university, other than general health were higher than the individuals in the other educational levels and it was statistically significant ($p<0.05$). The general health component was significantly low in the illiterate ones compared to the other groups ($p<0.05$); this score of the other groups was close to each other. It was stated that FMS was seen more frequently especially in those who were female, had low educational level, and had low socio-economic level (9,10). The effect of low educational level may be interpreted

as not only being a stress factor but also affecting coping strategies, causing somatization to be used more by reducing the expression of emotions. When the quality of life scores of the individuals in terms of their economic levels were examined; emotional role functioning, physical function, physical role functioning and physical sign scores of the individuals with moderate income level were significantly higher than the other income groups ($p<0.05$). The pain score on the other hand was higher in the individuals with high income compared to the other groups and this was statistically significant ($p<0.05$). In a previous study, female gender, middle age, low educational level, low family income and being divorced in patients with fibromyalgia were reported to be the risk factors for Turkey (11). Lower educational levels, income levels, and future concerns may have caused adverse effects on the quality of life and psychological status of individuals. Giving nutrition training and performing the diet follow-up for individuals diagnosed with FMS and enabling them to acquire a physical activity habit gain importance (12). In a study conducted in the United States of America to determine the overweight and obese prevalence in female patients diagnosed with FMS, obesity prevalence of the patients diagnosed with FMS (61%) was higher than the obesity prevalence (38%) in the society (13). According to results of the present study; significant difference according to the BMI groups of the female patients participating in the study was only seen in the physical role functioning component ($p<0.05$). Physical role functioning scores of the obese individuals were significantly low compared to the others. In the literature, it was determined that the quality of life in overweight and obese patients diagnosed with FMS was negatively affected

Table 2. Distribution of mean and standard deviation values of quality of life scores according to educational status

SF-36 components	Educational status					p value
	Illiterate (n=31)	Primary school (n=28)	Secondary school (n=18)	High school (n=9)	University (n=22)	
	(x ± SD)	(x ± SD)	(x ± SD)	(x ± SD)	(x ± SD)	
Mental signs	28.7±15.9	32.1±19.2	31.2±11.1	41.7±19.0	**53.5±17.1**	0.001*
Vitality	29.7±14.3	29.5±18.9	38.1±9.1	50.6±17.8	**50.5±19.1**	0.001*
Social role functioning	29.0±21.3	41.5±25.9	37.5±26.8	44.4±21.8	**54.5±27.4**	0.015*
Emotional role functioning	14.0±26.9	21.4±27.5	0.0±0.0	29.6±35.1	**54.5±40.6**	0.001*
Mental health	42.1±24.1	36.1±23.5	49.3±15.9	42.2±14.4	**54.5±15.9**	0.013*
Physical signs	22.4±11.6	36.4±20.7	31.1±11.1	43.0±18.9	**53.5±24.2**	0.001*
Physical functioning	25.5±19.9	41.9±19.9	39.9±22.9	51.1±8.9	**65.2±26.0**	0.001*
Physical role functioning	0.0±0.0	25.0±34.0	2.8±8.1	33.3±50.0	**44.3±45.6**	0.001*
Bodily pain	29.3±16.3	31.9±16.9	33.2±17.0	39.7±20.8	**55.5±21.6**	0.001*
General health	34.8±20.3	46.6±22.4	49.4±18.1	47.8±15.8	48.9±20.1	0.049*

Kruskal-Wallis analysis of variance was performed, *p<0.05, SF-36: Short form-36, SD: Standard deviation, x: Mean

Table 3. Distribution of mean and standard deviation values of quality of life scores of the individuals according to their economic status

SF-36 components	Economic status			p value
	Low (n=22)	Middle (n=82)	High (n=4)	
	(x ± SD)	(x ± SD)	(x ± SD)	
Mental signs	28.6±10.5	37.9±20.5	42.2±9.7	0.150
Vitality	34.3±12.0	37.0±20.0	52.5±8.7	0.099
Social role functioning	29.5±23.9	43.1±26.4	37.5±14.4	0.076
Emotional role functioning	6.1±13.2	**28.0±36.4**	16.7±19.2	0.038*
Mental health	44.5±18.3	434±21.8	62.0±25.4	0.372
Physical signs	25.1±11.4	**38.4±22.2**	33.4±9.7	0.036*
Physical functioning	30.5±17.3	**45.4±26.6**	42.5±2.9	0.036*
Physical role functioning	2.3±7.4	**24.1±38.2**	0.0±0.0	0.026*
Bodily pain	29.0±23.9	38.0±20.7	**56.3±13.0**	0.015*
General health	38.9±21.7	46.2±20.2	35.0±23.1	0.202

Kruskal-Wallis analysis of variance was performed, *p<0.05, SF-36: Short form-36, SD: Standard deviation, x: Mean

and their pain scores and physical dysfunction were higher (14,15). Some authors concluded that the body weight was not related with the pain (16). Most patients with fibromyalgia (75-90%) complain of non-deepening, non-restful sleep disorder. The presence of the alpha waves that should not normally be seen in delta wave sleep in the deepest phase of sleep in fibromyalgia patients causes sleep deprivation (17). Although sleep disorders are common in patients with FMS, the number of studies showing its relationship with the quality of life is limited (5). In the present study, while no significant correlation was found between the sleep pattern and the physical signs except for physical role functioning score, the difference between the vitality and mental health from mental signs and total mental sign scores was found to be significant. Physical role functioning score was found to be higher in those with regular sleep than the other individuals and this was statistically significant ($p<0.05$). While mental health score was found to be high in individuals who had an irregular sleep at some nights; vitality score and mental sign score of the individuals who slept regularly were significantly high compared to the other groups ($p<0.0$). In the study by Wagner et al., (18) the quality of life of patients with sleep disorder was found to be significantly lower than those without sleep disorder. Recent studies also suggest a multidisciplinary approaches including pharmacological treatment, psychotherapy, training programs, pain and fatigue control, sleep pattern improvement, mood control, and psychosocial reintegration in FMS treatment (19,20).

Table 4. Distribution of mean and standard deviation values of quality of life scores of the Individuals according to the body mass index

SF-36 components	BMI classification				p value
	Underweight (n=2)	Normal (n=40)	Overweight (n=40)	Obese (n=26)	
	(x ± SD)	(x ± SD)	(x ± SD)	(x ± SD)	
Mental signs	**46.0±0.0**	**36.3±19.9**	**37.7±20.0**	**32.8±16.2**	**0.504**
Vitality	40.0±0.0	40.2±19.5	35.8±19.5	33.8±15.4	0.642
Social role functioning	62.5±0.0	35.6±26.6	45.3±27.8	37.5±21.1	0.218
Emotional role functioning	33.3±0.0	25.0±37.6	25.8±32.5	15.4±30.2	0.338
Mental health	48.0±0.0	44.3±20.6	44.0±22.3	44.5±22.5	0.994
Physical signs	**36.9±0.0**	**39.3±21.9**	**37.9±23.7**	**25.9±9.6**	**0.121**
Physical functioning	45.0±0.0	49.9±26.8	38.6±27.9	35.8±14.7	0.050
Physical role functioning	25.0±0.0	20.6±37.9	28.8±39.0	0.0±0.0	0.002*
Bodily pain	32.5±0.0	39.0±20.0	38.9±23.0	30.6±16.2	0.399
General health	45.0±0.0	48.8±23.0	45.4±18.7	37.1±20.0	0.186

Kruskal-Wallis analysis of variance was performed, *p<0.05, SD: Standard deviation, x: Mean, BMI: Body mass index, SF-36: Short form-36

Table 5. Distribution of mean and standard deviation values of quality of life scores according to sleep pattern

SF-36 components	Sleep pattern			p value
	Regular (n=11)	Some nights (n=14)	Irregular (n=83)	
	(x ± SD)	(x ± SD)	(x ± SD)	
Mental signs	46.6±23.5	43.8±16.3	33.5±18.0	0.032*
Vitality	55.0±22.2	45.4±13.9	33.2±16.8	0.001*
Social role functioning	36.4±23.4	50.0±24.5	39.0±26.4	0.459
Emotional role functioning	45.5±45.4	19.0±36.3	20.9±33.6	0.177
Mental health	49.5±**23.8**	60.9±**13.4**	40.8±**20.8**	0.002*
Physical signs	48.8±**27.6**	33.1±**17.4**	34.2±**19.9**	0.315
Physical functioning	47.7±**27.6**	36.1±**25.4**	42.5±**24.9**	0.346
Physical role functioning	54.5±**52.2**	10.7±1**8.9**	15.4±**31.4**	0.017*
Bodily pain	42.7±1**9.3**	38.2±**23.0**	35.8±**20.1**	0.437
General health	50.0±**19.4**	47.5±**16.0**	43.0±**21.6**	0.352

Kruskal-Wallis analysis of variance was performed, *p<0.05, x: Mean, SD: Standard deviation, SF-36: Short form-36

Conclusion

Consequently, it can be asserted that the quality of life was better in female patients diagnosed with fibromyalgia who had high educational and income levels, normal BMI, and a regular sleeping. In other words, female patients with these characteristics had a better quality of life. In general, studies have revealed that education, income status, BMI and sleep quality are important and remarkable concepts.

Further studies are needed with more groups of participants to extend the results of the present study and increase the value of evidence. Thus, we think that the life quality level of women with fibromyalgia, from which sociodemographic characteristics it is affected can be more easily determined and the exact results can be demonstrated.

Ethics

Ethics Committee Approval: The ethical approvals were taken from Bingöl University Scientific Research Publications Ethics Committee (dated: 09.05.2016 and numbered 29).

Informed Consent: All participants gave written and verbal permission to participate in this study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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The Relationship Between Interleukin-17 and Osteoporosis in Patients with Rheumatoid Arthritis

Romatoid Artrit Tanılı Hastalarda İnterlökin-17 ile Osteoporoz Arasındaki İlişki

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Abstract

Objective: In this study; it is aimed to compare interleukin-17 (IL-17) levels in rheumatoid arthritis (RA) and osteoporosis (OP) patients compared to healthy controls, and to determine the relationship between IL-17 and disease activity, functional status and presence of OP in RA.

Materials and Methods: Eighty five patients were classified in four groups. Group 1: RA + OP (n=21), group 2: RA (n=22), group 3: 20 healthy volunteers, and group 4: OP (n=22). Demographical data, bone densitometry values, serum 25-hydroxy vitamin D and IL-17 levels were recorded. The disease duration, medications, pain levels of the patients and the disease activities were noted, and the disease activities of patients were evaluated by the health assessment questionnaire.

Results: No difference was detected between IL-17 levels of patients with and without RA (p>0.05). Likewise, we could not establish a relationship between disease activity and IL-17 levels. However, IL-17 levels of RA patients with OP were significantly higher when compared with patients without OP. Rheumatoid factor and IL-17 levels were higher for RA patients with OP. While a significant, negative correlation was established between IL-17 and lumbar T-score with femoral bone mineral density, no correlation was detected between other variables in RA patients.

Conclusion: IL-17 levels are elevated in RA and OP. While there is no relationship between IL-17 and disease activity and functional status in RA; IL-17 levels are high in RA patients with OP.

Keywords: Interleukin-17, rheumatoid arthritis, osteoporosis

Öz

Amaç: Bu çalışmada; romatoid artrit (RA) ve osteoporoz (OP) hastalarında interlökin (IL)-17 düzeylerinin sağlıklı kontrollere göre karşılaştırılması ve RA da hastalık aktivitesi, fonksiyonel durum ve OP varlığının IL-17 ile arasındaki ilişkisinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Seksen beş hasta 4 grupta sınıflandırıldı. Grup 1: RA + OP (n=21), grup 2: RA (n=22), grup 3: 20 sağlıklı gönüllü, grup 4: OP (n=22). Demografik veriler, kemik dansitometresi değerleri, serum 25-hidroksi vitamin D ve IL-17 düzeyleri kaydedildi. Hastaların hastalık süreleri, ilaçları, ağrı düzeyleri ve hastalık aktiviteleri de kaydedildi ve hastalık aktiviteleri sağlık değerlendirme anketi ile değerlendirildi.

Bulgular: RA olan ve olmayan hastaların IL-17 düzeyleri arasında fark saptanmadı (p>0,05). Benzer şekilde, hastalık aktivitesi ile IL-17 düzeyleri arasında bir ilişki saptamadık. Bununla birlikte, OP'si olmayan hastalarla karşılaştırıldığında, OP'li RA hastalarının IL-17 düzeyleri anlamlı olarak yüksek bulundu. OP'li RA hastalarında romatoid faktör ve IL-17 düzeyleri daha yüksekti. IL-17 ve lumbar T skoru ile femoral kemik mineral yoğunluğu arasında anlamlı, negatif korelasyon saptanırken, RA hastalarında diğer değişkenler arasında korelasyon saptanmadı.

Sonuç: RA ve OP'de IL-17 seviyeleri yüksektir. RA'da IL-17 ile hastalık aktivitesi ve fonksiyonel durum arasında ilişki saptanmaz iken, OP'si olan RA'lı hastalarda IL-17 düzeyleri yüksektir.

Anahtar kelimeler: İnterlökin-17, romatoid artrit, osteoporoz

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Introduction

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease, characterised by marginal bone erosion and cartilage destruction of unknown aetiology due to synovial inflammation (1). The deformation on remodelled bones in RA causes not only bone erosion, but also development of systemic osteoporosis (OP). OP is one of the most common comorbidies encountered in RA. The risk of vertebral fracture regardless of bone mineral density and corticosteroid administration is increased in patients with RA (2). The fracture risk is 10%-56% in RA, this percentage is higher in comparison to general population (3,4). Thus, OP and associated fractures in RA patients lead to an impaired quality of life and an increased health expenditures (5).

Although there are several factors, which may cause OP in RA, the imbalance of inflammatory cytokines in receptor activator of nuclear factor kB (RANK)-RANK ligand (RANKL)-osteoprotegerin (OGP) system is considered to be the most common reason (5). The principal cytokines that lead to increase in bone resorption are tumor necrosis factor (TNF), interleukin (IL)-1 and IL-6. The role of IL-17 in joint inflammation and damage has also been detected recently (6,7). IL-17 is a recently defined cytokine family with its six members (8). IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F belong to this cytokine group (9). IL-17 is mainly produced by so called T-helper (Th)-17 cells, which are actually CD4 + T cells (10). The primary function of Th-17 cells is to eliminate pathogens and to induce inflammation with IL-17. On the contrary to IL-17, IL-17 receptor may be produced everywhere. Therefore, many different cells may be targeted to IL-17 (11). Five receptors are defined for IL-17 so far [IL-17 receptor (IL-17 R) A, IL-17 RB, IL-17 RC, IL-17 RD, and IL-17 RE]. IL-17 RA binds IL-17A. The specifity between IL-17 and IL-17 R has not been clearly enlightened yet. However, it has been shown that IL-17 RA and IL-17 RC bind IL-17A and IL-17F (12,13). In autoimmune diseases, IL-17 has a crucial role for osteoclast formation. The binding of IL-17 to its receptor activates nuclear factor-kB (NF-kB) and mitogen-activated protein kinase (MAPK). IL-17 is also required for activated clotting time (ACT)-1, which is the activator of NF-kB pathway. The studies regarding RA, have revealed that Th-17 cells not only provide production of RANKL but also ensure secretion of RANKL by stimulating osteoblasts and induce osteoclast differentiation (14). IL-17 plays a major role at the early onset and late progression phases in RA pathogenesis. It induces collagen destruction, decreases collagen synthesis in synovium and cartilage, and reduces bone formation by increasing bone destruction (15,16). The inhibition of IL-17 may prevent joint inflammation and bone destruction. In this study, we aimed to evaluate the correlation between IL-17 level and OP in RA patients. We would like to show whether there exists a correlation between IL-17 levels, disease activities, and functional situations in RA patients.

Materials and Methods

Patients

This cross-sectional study comprised 85 patients who were visiting the outpatient rheumatic disease clinics of the physical medicine and rehabilitation department of our universities. The patients were divided into four groups. Group 1 was composed of 21 patients diagnosed with RA in accordance to 2010 criteria of the American College of Rheumatology (ACR) and who had OP according to the World Health Organisation. Group 2 was composed of 22 patients, who only had RA but did not suffer from OP. Group 3 was composed of 20 healthy volunteers who neither suffered from an autoimmune disease nor received concomitant treatment nor had OP. Group 4 was composed of 22 volunteers who neither suffered from an autoimmune disease nor received any concomitant treatment however had OP. The inclusion criteria were; an RA diagnosis according to the ACR criteria, the exclusion criteria were as follows: 1) RA patients who had secondary OP (patients with cancer, untreated thyroid and parathyroid diseases, end-stage renal disease, and hypogonadism), 2) metabolic bone disease, 3) primary bone tumour or bone metastasis, 4) osteomyelitis, 5) patients receiving anti-TNF therapy.

Data Collection

Patients' demographic data [age, sex, height, weight, body mass index (BDI), marital status, education] and clinical data (duration of the disease, medications used for treatment, duration of morning stiffness) were obtained from patient files and through face-to-face interviews. Smoking, alcohol consumption, fracture history, and family history for fracture were also noted. Bone densitometry values were evaluated with dual-energy X-ray absorptiometry (DEXA). Total lumbar (L2-4) measurement and femoral neck T scores were registered. The patients with T score ≥-1 standard deviation (SD) were evaluated as normal; T score between -1 and -2.5 as osteopenia; T score ≤2.5 SD as OP; and those patients, who have one or more fragility fractures, were assessed as severe OP in accordance to World Health Organisation's evaluations. Blood serum 25-hydroxy vitamin D, parathyroid hormone, and calcium levels were assessed in the scope of laboratory analysis. Double antibody sandwich ELISA test was utilised for IL-17 analysis in all patients. (Sunred Biological Technology Human IL-17 Elisa Kit Catalogue no: 201-12-0143) At the end of study, absorbents were read at 450 nm wavelength, and results were given as pg/mL. The disease duration for RA, the medications used for RA, and the number of sensitive and swollen joints were noted. The pain levels of patients were evaluated by visual analogue scale (VAS); the disease activities by disease activity score (DAS) 28 score; and the functional situation by health assessment questionnaire (HAQ). The disease activities were determined in accordance to DAS 28 scores. The scores of DAS 28 >5.1 is evaluated as high; from 5.1 to 3.2 as average, and from 2.6 to 3.2 as low, and if it is <2.6, it was evaluated as in remission (17).

Functional situations of patients were assessed in accordance to HAQ for disability index score. Score <0.3 is normal (18). Written informed consent was obtained from all patients. The study was approved by the Adnan Menderes University Hospital Ethics Committee (protocol no: 2015/750). Informed consent form was signed for all patients.

Statistical Analysis

SPSS for Windows 15.00 software package has been used for analyzing the data. The descriptive statistics for categorical variables were shown as %, and chi-square tests were utilised for comparison in accordance to groups. The compatibility of continuous variables to normal distribution was analysed by Kolmogorov-Smirnov test. The descriptive statistics of normal distribution variables were shown by mean ± SD, and t-tests were used for independent groups for the comparison in accordance to groups. The descriptive statistics of non-normal distribution variables were shown by median (25%-75%), and Mann-Whitney U test was used for the comparison in accordance to the groups. Pearson correlation analysis was performed for determination of relation between continuous variables.

Results

The comparison of the characteristics of patients with arthritis and without arthritis is shown in Table 1. No significant correlation could be established among genders, ages, BMI, smoking and alcohol consumption, DEXA measurement scores, laboratory tests (25-hydroxy vitamin D, parathyroid hormone, calcium), and notably IL-17 (p>0.05). The comparison of non-RA patients with and without OP is shown in Table 1. Age, Lumbar T score, lumbar bone mineral density (BMD), femoral T score, and 25-hydroxy vitamin D levels were found significantly different from healthy individuals (p=0.03, p<0.001, p<0.001, p=0.008, and p=0.005, respectively). No correlation between other variables and OP was established (p>0.05). For IL-17 levels, no differentiation was distinguished between the two

Table 1. Baseline demographic and clinical characteristics of the patients

	RA patients (n=43)	Non RA patients (n=42)	p*	Healty colunteers (n=20)	OP patients (n=22)	p**
Gender (female, n, %)	37 (84.1)	37 (90.2)	0.60	19 (95.0)	19 (86.4)	0.61
Age (years, min-max)	57 (49.0-63.0)	59 (52.0-66.3)	0.29	53.10±10.57	62.45±8.65	**0.03**
BMI (kg/m^2, min-max)	30.4 (26.1-33.8)	29 (25.9-36.0)	0.89	32.22±7.38	29.39±4.56	0.15
Smoker (yes, n, %)	9 (20.5)	4 (9.8%)	0.28	2 (10)	2 (9.1)	1.00
Alcohol (yes, n, %)	0 (0)	2 (4.9)	0.23	1 (5)	1 (4.5)	1.00
Fracture (yes, n, %)	4 (9.1)	6 (14.6)	0.51	1(5)	5 (22.7)	0.19
Number of births (n, min-max)	2 (2-3)	2 (2-3)	0.44	2.0 (2.0-3.0)	2.5(1.7-4.0)	0.77
Age at menopause (years, min-max)	47 (44-51)	46 (40-48)	0.27	46.5 (43.2-48.0)	45.0 (38.0-49.2)	0.75
Lumbar total T score (min-max)	-2.2 [(-2.6)-(-1.4)]	-2.0 [(-2.7)-(-1.2)]	0.71	-1.4 [(-1.6)-(-0.3)]	-2.6 [(-3.1)-(-2.5)]	**<0.001**
Lumbar BMD (g/cm^2, min-max)	0.816 (0.764-0.905)	0.817 (0.717-0.891)	0.78	0.89 (0.87-1.00)	0.73 (0.65-0.77)	**<0.001**
Femoral T score (min-max)	-1.2 [(-2.0)-(-0.4)]	-1.4 [(-1.9)-(-0.7)]	0.50	-0.9 [(-1.5)-(-0.4)]	-1.5 [(-2.5)-(-1.1)]	**0.008**
Femoral BMD (g/cm^2, mean ± SD)	0.717±0.117	0.714±0.128	0.56	0.75±0.10	0.67±0.13	0.057
25-hydroxy vitamin D (ng/mL, mean ± SD)	23.4±8.70	20.9±10.09	0.24	16.50±8.15	25.06±10.11	**0.005**
Parathyroid hormone (pg/mL, mean ± SD)	96.9±45.48	92.63±36.59	0.14	86.5 (70.7-116.8)	91.3 (53.1-126.1)	0.86
Serum calcium (mmol/L, mean ± SD)	9.3±0.43	9.3±0.49	0.12	9.39±0.55	9.25±0.43	0.35
IL-17 (pg/mL, min-max)	409.2 (307.2-465.9)	412.9 (369.9-804.0)	0.40	425.0 (364.0-963.0)	400.7 (369.5-729.6)	0.55

BMD: Bone mineral density, BMI: Body mass index, IL-17: Interleukin-17, RA: Rheumatoid arthritis, OP: Osteoporosis, SD: Standard deviation, Min: Minimum, Max: Maximum, *Differences between rheumatoid arthritis and non-rheumatoid arthritis patients, **Differences between healty volunteers and osteoporotic patients, Independent samples t-test and Mann-Whitney U test used

groups. In comparison to the normal healthy volunteers the patients with OP were significantly younger although their weights and heights were significantly higher. The comparison of RA patients with and without OP is shown in Table 2. The height, menopausal age, lumbar T score, lumbar BMD, femoral T score, femur BMD and IL-17, RF levels were considered significantly high in patients with RA and OP, and in only RA patients (p=0.035, p=0.012, p<0.001, p<0.001, p<0.001, p<0.001, p=0.027, p=0.010, respectively). No significant correlation was found between the other variables (p>0.05). According to this finding RA patients with OP were shorter, had earlier menopausal age, and their DEXA results were lower as expected. RF levels and IL-17 levels were higher for RA patients with OP. Correlation between IL-17 level with different variables in patients with RA is shown in Table 3. While a significant negative correlation was established between IL-17, lumbar T score, and femoral BMD (p=0.045, p=0.044, respectively), no correlation was detected between the other variables in RA patients (p>0.05).

Discussion

In this study; we aimed to compare IL-17 levels in RA and OP patients compared to healthy controls, and to determine disease activity, functional status and relationship of OP with IL-17 in RA, and we found no difference between IL-17 levels of patients with and without RA. Likewise, we could not establish a correlation between disease activity and IL-17 levels. In several studies, IL-17 levels in RA patients have been found to be elevated (6,15,16,19-22). In a study conducted by Tofiq and Merza (22) in which 45 RA patients and 45 healthy people were compared, IL-17A was found significantly high in RA group. In the same study, no difference was detected in IL-17A levels among groups who received or did not receive biological treatment. No significant elevation was detected in serum IL-17

Table 2. Comparison of rheumatoid arthritis patients with and without osteoporosis

	RA patients with OP (group 1) n=21	RA patients without OP (group 2) n=22	p
Gender (female, n, %)	19 (90.5)	17 (77.3)	0.41
Age (years, min-max)	59.0 (54.0-65.0)	56.0 (43.7-60.7)	0.08
BMI (kg/m^2, mean ± SD)	30.5±6.5	30.5±6.2	0.98
Smoker (yes, n, %)	4 (19)	5 (22.7)	1.00
Alcohol (yes, n, %)	0 (0)	0 (0)	-
Fracture (yes, n, %)	3 (14.3)	1 (4.5)	0.35
Age at menopause (years, min-max)	45.0 (43.0-49.0)	50.5 (45.5-52.0)	**0.012**
Lumbar total T score (min-max)	-2.6 [(-3.1)-(-2.5)]	-1.7 [(-2.1)-(-0.6)]	**<0.001**
Lumbar BMD (g/cm^2, mean ± SD)	0.74±0.07	0.91±0.09	**<0.001**
Femoral T score (mean ± SD)	-1.98±0.88	-0.67±0.62	**<0.001**
Femoral BMD (g/cm^2, mean ± SD)	0.63±0.09	0.79±0.08	**<0.001**
25-hydroxy vitamin D (ng/mL, mean ± SD)	22.74±5.50	24.09±11.03	0.62
Parathyroid hormone (pg/mL, mean ± SD)	101.48±51.77	92.55±39.29	0.53
Serum calcium (mmol/L, min-max)	9.4 (9.1-9.6)	9.3 (8.9-9.4)	0.11
IL-17 (pg/mL, min-max)	416.3 (396.8-883.9)	374.9 (157.1-430.8)	**0.03**
Duration of RA (years, min-max)	10.0 (2.5-14.5)	6.0 (1.0-10.0)	0.19
Corticosteroid use (n, %)	20 (95.2)	16 (72.7)	0.09
DAS 28 (min-max)	3.4 (2.9-4.5)	3.2 (2.4-4.1)	0.08
HAQ score (mean ± SD)	0.61±0.41	0.41±0.38	0.11
VAS (cm, min-max)	5 (2.0-6.5)	5 (1.7-5.0)	0.54
RF (U/mL, min-max)	87.8 (38.0-194.8)	24.1 (3.15-88.7)	**0.010**
Anti-CCP (min-max)	126 (13.0-200)	31.0 (2.2-165.5)	0.090
ESR (mm/hour, mean ± SD)	33.19±14.38	25.81±12.59	0.081
CRP (mg/L, mean ± SD)	10.56±8.94	7.46±5.77	0.183

Anti-CCP: Anticyclic citrullinated peptide, OP: Osteoporosis, BMD: Bone mineral density, BMI: Body mass index, SD: Standard deviation, CRP: C-reactive protein, ESR: Eritrosit sedimentation rate, DAS: Disease activity score, IL-17: Interleukin-17, OP: Osteoporosis, RA: Rheumatoid arthritis, RF: Rheumatoid factor, VAS: Visual analog scale, HAQ: Health assesment questionnaire, Min: Minimum, Max: Maximum, Independent samples t-test and Mann-Whitney U test used

levels in a study conducted by Ziolkowska et al. (23) in which 15 RA patients and eight osteoarthritis patients were compared. IL-17 was detected to be significantly high in synovial fluid of RA patients. As the major source of IL-17, Th-17 cell levels in peripheral blood were not also found different in RA patients in comparison to control groups in other studies (24,25). In our study, we observed that there was no significant difference in IL-17 levels for 43 RA patients and the control group of 42 individuals without RA. Moreover, we discovered that IL-17 levels were not different for 43 RA patients and 20 normal healthy (without RA and OP) volunteers. We examined IL-17 in our study, however, other studies have investigated IL-17A. This might be the reason why IL-17 was not different for RA patients in the current study.

Table 3. Correlation between interleukin-17 level with different variables in patient with rheumatoid arthritis (n=43)

	IL-17	
	r	p
Age	0.209	0.178
Weight	-0.042	0.788
Height	-0.149	0.339
BMI	0.032	0.840
Rheumatoid arthritis duration	0.027	0.862
Number of births	-0.154	0.371
Menopausal age	-0.112	0.548
Lumbar T score	-0.307	**0.045**
Lumbar BMD	-0.298	0.052
Femoral T score	-0.293	0.057
Femoral BMD	-0.309	**0.044**
DAS 28	0.027	0.865
Morning stiffness	0.131	0.402
Sensitive joint	0.198	0.204
Swollen joint	-0.048	0.762
VAS	0.031	0.844
HAQ	0.097	0.535
ESR	-0.151	0.335
CRP	0.014	0.930
RF	0.063	0.689
Anti-CCP	0.022	0.888
25-hydroxy vitamin D	0.063	0.687
Serum parathyroid hormone	-0.161	0.301
Serum calcium	0.085	0.590
Serum phosphorus	0.047	0.766

Anti-CCP: Anticyclic citrullinated peptide, BMD: Bone mineral density, CRP: C-reactive protein, ESR: Eritrosit sedimentation rate, HAQ: Health assesment questionnaire, RF: Rheumatoid factor, VAS: Visual analog scale, DAS: Disease activity score, IL-17: Interleukin-17, BMI: Body mass index, Pearson correlation analysis used

In a recent study conducted by Fischer et al. (26) the anti-inflammatory activity of combined TNF alpha and IL-17 blockage were researched on human mesenchymal cells. It was detected that blockage of both TNF alpha and IL-17 was more effective than blockage of single cytokine. Both cytokines are influential in bone destruction. TNF alpha and IL-17 have additive and synergic effects for production of IL-6, IL-8, granulocyte colony stimulating factor, and matrix metalloproteinase from fibroblast-like synoviocytes (27). Better results were obtained when bone was remodelled with combined blockage of these cytokines. We excluded RA patients receiving anti-TNF therapy from our study in order to search for only the effect of IL-17 on OP. The major target of RA is skeleton system where bone erosions and generalised OP may develop. OP and associated fracture are important disability causes which result in an impaired quality of life and increase in health expenditures. There are several factors for the development of OP in RA, however, IL-6 and other inflammatory cytokines are considered to be the main reason for OP by impairing OGP/RANK/RANKL system (5). IL-17 has a crucial role for osteoclast formation in autoimmune diseases. The binding of IL-17 to its receptor activates NF-kB and MAPK. IL-17 is required for ACT 1 which is the activator of NF-kB pathway. In studies carried out with RA, it was observed that Th-17 cells not only provide production of RANKL (NF-kB ligand-activated receptor), but also ensure secretion of RANKL by stimulating osteoblasts and induce osteoclast differentiation (14). Likewise, it was shown that IL-17A increased production of RANKL in osteoblasts and decreased OGP production, and therefore, caused osteoclast formation and bone erosion in mouse models of arthritis (27,28).

In a recent prospective study, the correlation between OP and IL-17A levels was analysed. It was detected that serum IL-17A levels were higher in postmenapausal patients with OP, and that there was a negative correlation between IL-17A levels and BMD. Therefore, it was concluded that IL-17A is influential in pathogenesis of postmenopausal OP (29). There are only few studies in which IL-17 levels in patients with OP were evaluated. The existing studies are usually limited to cell cultures and animal models. In a study conducted by Tyagi et al. (30) on ovariectomised rats, it was found that oestrogen insufficiency resulted in an increase in Th-17 cels within bone marrow and an increase in IL-17 levels within peripheral blood. DeSelm et al. (31) showed that deletion in IL-17 RA prevented bone loss. When we compared RA patients without OP, with healthy volunteers in the scope of our study, we observed that there was no significant difference between both groups in terms of IL-17. Based on its role in pathogenesis of RA, we compared IL-17 levels in RA patients with and without OP. We detected a significant elevation in IL-17 levels for RA patients with OP (group 1, n=21) in comparison to RA patients without OP (group 2, n=22). In line with the study conducted by Molnar et al. (32) we detected a statistically significant negative correlation between IL-17, lumbar spine T scores, and femoral BMD. No correlation between IL-17 levels and disease activity,

DAS 28, erythrocyte sedimentation rate, C-reactive protein (CRP) of patients with RA, was detected in a study conducted by Al-Saadany et al. (33). In a study performed by Metawi et al. (16) they found out the positive correlation between IL-17A levels and DAS 28 score, and the number of sensitive joint and number of swollen joints. Likewise, a significant correlation was observed within disease activity and IL-17 levels in a study conducted on 22 RA patients by Melis et al. (19). Yamada et al. (25) could not establish a significant correlation between DAS scores, number of sensitive joints and swollen joint in their study in which 69 RA patients were admitted. Moreover, no significant correlation was detected between serum IL-17 levels, swollen joints, and HAQ in the scope of study performed on 41 RA patients (20). There are also studies in which no significant correlation was established between results of global pain scale (by VAS) and IL-17 levels (20). In this study, although a positive correlation was detected between IL-17 and DAS 28, VAS, HAQ and CRP levels, the results were not statistically significant.

Conclusion

In this study, no difference was detected between IL-17 levels of patients with and without RA. Likewise, we could not establish a correlation between rheumatoid disease activity and IL-17 levels. However, IL-17 levels of RA patients with OP were significantly elevated in comparison to those patients without OP. The subgroups of IL-17 (such as IL-17A, F, etc) may be more influential in RA pathogenesis. Special attention should be paid to this difference during the studies performed with cytokines, and it will be more convenient to monitor the bone formation and destruction markers.

Ethics

Ethics Committee Approval: This study was approved by the Adnan Menderes University, Clinical Research Ethics Committee (protocol no: 2015/750).

Informed Consent: Informed consent form was signed for all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Yaşlı Postmenapozal Osteoporozlu Hastalarda Tedavi Sonuçlarımız: Oral ve Parenteral Bifosfonatların Karşılaştırılması

Outcomes of Treatment in Patients with Elderly Postmenopausal Osteoporosis: Comparision of Oral and Parenteral Bisphosphonates

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Öz

Amaç: Bu çalışmamızda postmenopozal osteoporoz (OP) tedavisinde kullanılan oral ve parenteral bifosfanatların etkinliğini karşılaştırmayı amaçlamaktadır.
Gereç ve Yöntem: 2010-2015 yılları arasında postmenopozal OP tanısı konularak, oral ya da parenteral bifosfonat ile tedavi edilen 65 yaş üstü hastalar çalışmaya dahil edildi. Tedaviye göre oral bifosfonat alan 72 hasta grup O ve parenteral bifosfonat alan 52 hasta grup P olarak iki gruba ayrıldı. Tedavilerini düzenli alan ve en az 2 yıl takibi yapılabilen 124 hastanın tedavinin 2. yıldaki sonuçları değerlendirilerek karşılaştırıldı.
Bulgular: Her iki grupta tedavi öncesine göre; vertebra ve femur kemik mineral yoğunluğu (KMY) ve T-skorlarında anlamlı düzelme olduğu görüldü. Vertebra ve femur T-skorundaki ve femur KMY değerindeki ortalama düzelme bakımından grup P daha iyiydi ve istatistiksel olarak anlamlı fark vardı. Oral bifosfonat grubunda femur T-skorunda alendronat lehine gruplar arasında istatistiksel anlamlı fark olduğu ve parenteral bifosfonat grubunda ise vertebra ve femur T-skorundaki düzelme zoledronat alt grubunda daha iyiydi ve istatistiksel olarak anlamlıydı.
Sonuç: Çalışmamızın sonuçları; postmenopozal OP'nin tedavisinde oral ve parenteral bifosfonatların etkili olduğunu göstermektedir. Bununla birlikte vertebra ve femur T-skorlarında ve femur KMY ortalama düzelme bakımından parenteral bifosfonatlar daha etkili bulundu.
Anahtar kelimeler: Postmenopozal osteoporoz, tedavi, bifosfonat

Abstract

Objective: In this study, we aim to compare the efficacy of oral and parenteral bisphosphonates used in postmenopausal osteoporosis (OP) treatment.
Materials and Methods: Between 2010 and 2015, patients older than 65 years who were diagnosed with postmenopausal OP and treated with oral or parenteral bisphosphonate were included in the study. According to treatment, 72 patients receiving oral bisphosphonate and 52 patients receiving parenteral bisphosphonate were divided into two groups as group O and group P respectively. The results of the second year treatment of 124 patients who were treated regularly and at least two years follow up were evaluated and compared.
Results: According to the pre-treatment state in both groups; bone mineral density (BMD) of vertebral and femoral, and T-scores showed significant improvement. The mean improvement in vertebral and femoral T-scores and femoral BMD values was better in group P and there was statistically significant difference. In the oral bisphosphonate group, there was a statistically significant difference between the groups in favor of alendronate in the femoral T-score and the improvement in the vertebral and femoral T-score in the parenteral bisphosphonate group was better in the zoledronate subgroup and statistically significant.
Conclusion: The results of this study demonstrate that oral and parenteral bisphosphonates are effective in the treatment of postmenopausal OP. Nevertheless, parenteral bisphosphonates were found to be more effective in terms of vertebral and femoral T-scores and femoral BMD average improvement.
Keywords: Postmenopausal osteoporosis, treatment, bisphosphonates

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Giriş

Osteoporoz (OP), düşük kemik kitlesi ile kemik mikro mimarisinde bozulmayla karakterize ve kırıklara yatkınlıkta artışa neden olan sistemik metabolik bir kemik hastalığıdır (1-3). Ülkemizde yapılan geniş çaplı ve güncel iki çalışmada OP sıklığı 12,9-19,6 olarak bildirilmiştir (2-4). Osteoporotik kırıklar hem morbidite ve mortaliteyi artırmakta hem de önemli bir sosyo-ekonomik maliyet oluşturmaktadır (5). OP'yi önleme, teşhis ve tedavisindeki uygulamalar, kırıkları ve sekellerini engelleyebilir (6). Bifosfonatlar (BF), vertebra, kalça ve vertebra dışı kırık riskini azaltmak için etkinliği kanıtlanmış ilk basamak ilaçlardır. Amerikan Gıda ve İlaç Dairesi (FDA) tarafından OP'nin önlenmesi ve tedavisinde kullanılması onaylanan BF, alendronat, ibandronat, risedronat ve zoledronik asitdir (6-8).

OP tedavisinde oldukça yaygın olarak kullanılan BF kemikte hidroksiapatite bağlanıp, pirofosfatazların etkisine direnç oluşturarak kemik yıkımını azaltırlar. OP tedavisinde kullanılan BF'lerin oral ya da parenteral formları mevcuttur. Çeşitli çalışmalarda değişik etkinlik ve yan yen etki oranları bildirilmiştir (5-8). Diğer yandan tedavide seçilen ilacın etkinliği yan etkisi ve hastanın uyumu önemlidir (9,10). Bununla birlikte farklı BF'lerin, değişik formalarının etkinlik, yan etki ve ilaç kullanım uyumunu karşılaştıran az sayıda çalışma mevcuttur (11-13).

Bu çalışmamızda postopmenopozal OP tedavisinde kullanılan oral ve parenteral BF'lerin etkinliğini karşılaştırmayı amaçladık.

Gereç ve Yöntem

Yazarın çalıştığı kliniklerde, 2010-2015 yıllarını kapsayan 5 yıllık dönemde postmenopozal OP tanısı konularak, oral ya da parenteral BF ile tedavi edilen 65 yaş ve üstü kadın hastalar çalışmaya dahil edildi. Hastaların tıbbi ve demografik bilgileri kaydedildi. Sekonder OP olguları ve dahil etmeme kriterlerinden olan (5); ek hastalığı olanlar (metabolik, endokrin, nöropsikiyatrik, malignensi gibi) veya alkol, sigara ve uzun süreli steroid kullanımı (≥5 mg ve ≥3 ay) olanlar, yatalak hastalar, kemik dansitometri taraması yapılacak bölgesinde (kalça ve vertebra) implant olan hastalar ve BF intoleransı veya diğer ciddi yan etkiler nedeniyle tedaviyi yarım bırakan hastalar çalışmaya dahil edilmedi. Lunar-DPX IQ cihazı ile kemik yoğunluğu taraması yapılan ya da Lunar değerlerine dönüştürülen (14) sonuçlar çalışmaya dahil edildi. Bu çalışmada 2013 yılında revize edilen 1964 Helsinki Deklarasyonu'nda bildirilen etik kurallara uyulmuştur. Hastalara sonuçlarının bilimsel amaçla kullanılacağı belirtilerek onamları alındı [Afyon Kocatepe Üniversitesi Girişimsel Olmayan Etik Kurulu'ndan onay alınmıştır (sayı ve karar no: B.30.2.AKÜ.0.20.0504/08 ve 2013/1)].

Kemik yoğunluğu taraması: Ön-arka yönde vertebra (L1-L4) ve femur üst uç (Total) ölçümlerinde dikkat edilecek hususlar, cihazın bakım ve kalibrasyonları; Uluslararası Klinik Dansitometri Kurumu (15) ve Türkiye Nükleer Tıp Derneği (16) önerilerine göre yapıldı. Cihazların kalibrasyonları, testleri, kontrolleri ve fantom ölçümleri, sertifikalı teknisyenlerce düzenli olarak yapıldı. Katılımcıların boyları ve kaba giysileri çıkarılarak boy ve kiloları ölçüldü ve sonrasında Dual enerji X-ray absorbsiyometri (DEXA) ile taramaları yapıldı. OP'li olgular T-skorlarına göre Dünya Sağlık Örgütü (DSÖ) ölçütleriyle belirlendi (5,15-17). Hastaların tedavisinin belirlenmesinde; hastanın tercihi (tablet ya da iğne kullanma isteği), eşlik eden rahatsızlığı (gastrit, ülser ve benzer nedenlerle BF intoleransı), Sosyal Güvenlik Kurumu (SGK) kriterleri ve hekimin tercihi etkili oldu. Tanı ve tedaviler için SGK geri ödeme kriterleri dikkate alındı.

Hastalar aldıkları tedaviye göre retrospektif olarak iki gruba ayrıldı. Oral BF alan 72 hasta grup O [alendronat 70 mg/hafta (n=25), ibandronat 150 mg/ay (n=24)], risedronat 35 mg/hafta veya 150 mg/ay (n=23) uygulandı). Parenteral BF alan 52 hasta grup P 25 hastaya yılda bir kez 5 mg zoledronat 15 dakika intravenöz infüzyon şeklinde ve 27 hastaya ise her üç ayda bir 3 mg intravenöz (İV) ibandronat İV infüzyon şeklinde hastane şartlarında uygulandı. İlaç uygulaması öncesi biyokimyasal testler değerlendirilerek renal fonksiyon bozukluğu olan hastalara uygulanmadı ve ayrıca tedavi sonunda oluşan yan etkiler kaydedildi. Ek olarak tedavi öncesi D vitamini replasman tedavisi yapılmadı ancak BF tedavisi başlanan tüm hastalara 800 IU/gün D3 vitamini, 1,200 mg/gün kalsiyum tedavisi verildi.

Hastalar periyodik kontrollere çağrıldı. Hastaların yakınmalarında artma ya da azalma ve yan etkiler not edildi. Ayrıca kapsamlı fizik inceleme yapıldı. Tedavilerini düzenli alan ve en az 2 yıl takibi yapılabilen 124 hastanın tedavinin 2. yıldaki sonuçları değerlendirildi. Kemik mineral yoğunluğu (KMY) ve T-skorları DXA ile değerlendirildi.

İstatistiksel Analiz

Elde edilen veriler sayısal ve kategorik olarak sınıflandırılarak Excel'e kaydedildi. Tedavi öncesi ve ikinci yıl sonundaki değerleri istatistiksel olarak analiz edildi. Tanımlayıcı istatistikler; ortalama ± standart sapma ve yüzde olarak belirtildi.

Verilerin normal dağılıma uygunluğu Kolmogorov-Smirnov testiyle yapıldı. Anlamlılık analizlerinde: Grupların karşılaştırılmasında KMY ve T-skorundaki düzelme ortalamaları bağımsız t-testi ile karşılaştırıldı. Alt grup karşılaştırılmalarında ikiden fazla grup için Kruskal-Wallis, post-hoc analiz ve/veya iki grubun karşılaştırılmalarında ise Mann-Whitney U testi kullanıldı. Grup içi karşılaştırmalarda ise; tedaviden yararlanma düzeylerini değerlendirmek için tedavinin başlangıcındaki ve kontroldeki değerleri Paired t-test kullanılarak karşılaştırıldı. P<0,05 değeri anlamlı kabul edildi.

Bulgular

Grup O (n=72) ve grup P (n=52) arasında ortalama yaş (71,5±6,14 ve 75,14±6,61) ve ortalama vücut kitle indeksi (VKİ) (26,73±5,73 ve 27,29±5,13) açısından istatistiksel anlamlı fark bulunamadı (sırasıyla; p=0,362 ve p=0,347).

Her iki grupta 2 yıllık tedavi sonucu tedavi öncesine göre; vertebra ve femur KMY ve T-skorlarında anlamlı düzelme olduğu görüldü (Paried t-test; Tablo 1). Hastaların her iki tedavi yönteminden fayda gördüğü değerlendirilmiştir.

Tablo 1. Grupların kemik mineral yoğunluğu ve T-skorundaki düzelme bakımından gruplar arası ve grup içi karşılaştırılması

Parametreler	Group 1 n=72 (oral bifosfonat)	Group 2 n=52 (parenteral bifosfonat)	p*
Vt	-3,104±0,92	-2,596±1,07	
Vt2	-2,811±0,96	-1,838±0,89	
p**	0,000	0,000	
Vt düzelme	0,293±0,05	0,758±0,10	0,002
VKMY	0,735±0,17	0,884±0,11	
VKMY2	0,792±0,13	0,974±1,17	
p**	0,002	0,005	
VKMY düzelme	0,057±0,018	0,089±0,16	0,064
Ft	-2,361±1,15	-2,346±1,01	
Ft2	-2,174±1,09	-1,573±0,93	
p**	0,001	0,000	
Ft düzelme	0,186±0,06	0,773±0,11	0,000
FKMY	0,688±0,19	0,754±0,13	
FKMY2	0,724±0,15	0,844±,15	
p**	0,018	0,001	
FKMY düzelme	0,037±0,06	0,090±0,02	0,034

Vt: Vertebra L1-L4 t skoru, Vt2: İki yıl sonraki vertebra L1-L4 t skoru, VKMY: Vertebra kemik mineral yoğunluğu, VKMY2: İki yıl sonraki kemik mineral yoğunluğu, Ft: Femur total T-skoru, Ft2: İki yıl sonraki femur total T-skoru, FKMY: Femur kemik mineral yoğunluğu, FKMY2: İki yıl sonraki femur kemik mineral yoğunluğu, Düzelme: Tedavi sonrası iki yıldaki KMY ve T-skorundaki tedavi öncesine göre fark
*Independent Samples t-test, **Paried t-test

Diğer yandan vertebra ve femur T-skorundaki ortalama düzelme bakımından grup P değerlerindeki düzelme daha iyiydi ve gruplar arasında istatistiksel olarak anlamlı fark vardı (sırasıyla p*=0,002 ve p=0,000; Tablo 1). Femur KMY değerindeki düzelme grup P'de daha iyiydi ve gruplar arasında istatistiksel olarak anlamlı fark vardı (p*=0,0034; Tablo 1). Buna karşın Vetebra KMY değerleri bakımından gruplar arasında anlamlı farklılık bulunamadı (p=0,064; Tablo 1).

Alt grup karşılaştırmalarında; oral BF grubunda femur T-skorunda alendronat lehine gruplar arasında istatistiksel anlamlı fark olmasına rağmen (p=0,031; Tablo 2), vertebra T-skoru, vertebra ve femur KMY değerlerindeki düzelme bakımından oral alt gruplar arasında istatistiksel anlamlı fark bulunamadı (sırasıyla p=0,129, p=0,902 ve p=0,197; Tablo 2). Ayrıca alt grup karşılaştırılmasında hem grup O hem de grup P'de yaş ve VKİ bakımından gruplar arasında anlamlı fark bulunamadı (Tablo 2, 3).

Parenteral BF grubunda vertebra ve femur T-skorundaki düzelme zoledronat alt grubunda daha iyiydi ve istatistiksel olarak anlamlıydı (sırasıyla p=0,035 ve p=0,025; Tablo 3). Buna karşın vertebra ve femur KMY değerindeki ortalama düzelme zoledronat grubunda daha iyi olmasına rağmen istatistiksel olarak anlamlı fark bulunamadı (sırasıyla p=0,091 ve p=0,068; Tablo 3).

Bu çalışmada oral BF'lerin tolere edilebilen gastrointestinal yan etkileri ve parenteral BF'lerin İV uygulanması sonrası görülen ve hastalar tarafından tolere edilebilen influenza benzeri semptomlar dışında ciddi yan etkiler nedeniyle tedaviyi yarım bırakan hastaların sonuçları değerlendirilmedi.

Tablo 2. Grup O'da alt grup karşılaştırması

Parametreler	Alendronat (n=25)	İbandronat (n=24)	Risedronat (n=23)	p*
Yaş (yıl; anlamlılık ± ss)	69,98±3,91	72,67±6,74	71,94±7,29	0,571
Vücut kitle indeksi (anlamlılık ± ss)	26,37±6,36	26,26±4,94	27,59±5,93	0,617
Vt düzelme	0,448±0,09	0,175±0,08	0,248±0,09	0,129
VKMY düzelme	0,103±0,05	0,0258±0,01	0,038±,01	0,902
Ft düzelme	0,252±0,06	0,2875±0,13	0,013±,08	0,031**
FKMY düzelme	0,074±0,04	0,0279±0,06	0,005±,01	0,197

*Kruskal-Wallis test, **Aledronat grubu anlamlı olarak daha fazla düzelme (post-hoc Mann-Witney U test), Vt: Vertebra L1-L4 t skoru, Ft: Femur total T-skoru, FKMY: Femur kemik mineral yoğunluğu, VKMY: Vertebra kemik mineral yoğunluğu, SS: Standart sapma

Tablo 3. Grup P'de alt grup karşılaştırması

Parametreler	Zoledronat (n=25)	İbandronat (n=27)	p*
Yaş (yıl; anlamlılık ± ss)	75,74±6,96	74,59±6,36	0,647
Vücut kitle indeksi (anlamlılık ± ss)	27,09±5,71	27,49±4,63	0,420
Vt düzelme	0,959±0,17	0,540±0,11	0,035
VKMY düzelme	1,015±0,18	0,512±0,10	0,091
Ft düzelme	0,282±0,33	0,089±0,02	0,025
FKMY düzelme	0,020±,037	0,155±0,03	0,068

*Mann-Witney U test, Vt: Vertebra L1-L4 t skoru, Ft: Femur total T-skoru, FKMY: Femur kemik mineral yoğunluğu, VKMY: Vertebra kemik mineral yoğunluğu, SS: Standart sapma

Tartışma

OP taraması ve tanısı için en yaygın kullanılan DXA yöntemi ile kalça ve lomber bölgeden KMY ölçümüdür. DSÖ tanı kriterlerine göre -2,5 ve altı OP tanısı koydurur (6,15-17). Ülkemizde uygulanan tedavi giderleri geri ödeme sisteminde de OP tedavisi DXA sonuçlarına göre değerlendirildiğinden, DXA ölçümleri ile elde edilen KMY ve T-skorları tanı ve tedavi devam için önemlidir (6,18). Postmenopozal OP tedavisinde etkinliği ve kırık riskini azalttığı kanıtlanmış çeşitli ilaçlar kullanılmaktadır. OP'nin farmakolojik tedavisinde en yaygın kullanılan ajanlar; alendronat, risedronat ve ibandronat gibi BF'ler, selektif östrojen reseptör modülatörü olan raloksifen, denosumab ve paratroid hormonudur (6-8). OP'de kullanılan tedavi seçeneklerinden antirezorptif ve anabolik ajanların farklı dozları ve uygulama şekilleri mevcuttur. Bununla birlikte halen BF'ler OP'de temel tedavidir (8,12,13).

Biz bu retrospektif kesitsel çalışmada; DXA ile belirlenen T-skorları dikkate alınarak DSÖ kriterlerine göre tanısını koyduğumuz postmenopozal OP'li 124 hastada uyguladığımız ve iki yıl izlediğimiz oral (alendronat, ibandronat ve risedronat) veya parenteral (zoledronat, ibandronat), BF tedavi protokolünün etkinliğini vertebra ve kalça KMY ve T skorlarıyla değerlendirdik.

OP tedavisinde oral ve parenteral ilaçların maliyet-etkiniliğinin değerlendirildiği güncel bir sistematik derleme ve meta-analiz çalışmasında (12): Oral aledronat ve parenteral zoledronatın postmenopozal OP tedavisinde en iyi başlangıç tedavisi seçeneği olduğu belirtilmiştir. Ayrıca aynı çalışmada kalça kırıklarını önlemek için mevcut ilaçların etkinliği açısından istatistiksel bir fark olmadığı rapor edilmiştir. Osteoporotik kırığı önlemede farklı BF'lerin etkinliğinin araştırıldığı başka bir güncel meta-analizde ise (13): Kalça, vertebral ve nonvertebral osteoporotik kırıkların önlenmesinde alendronat ve zoledronik asit en etkili ajanlar olduğu belirtilmektedir.

Bizim çalışmamızda her iki grupta 2 yıllık tedavi sonucu tedavi öncesine göre; vertebra ve femur KMY ve T skorlarında anlamlı düzelme olduğu mevcuttu (Tablo 1). Hastaların oral ya da parenteral BF tedavi yönteminden fayda gördüğü değerlendirilmiştir. Diğer yandan vertebra ve femur T-skorundaki ortalama düzelme bakımından grup P değerlerindeki düzelme daha iyiydi ve gruplar arasında istatistiksel olarak anlamlı fark vardı (Tablo 1). Femur KMY değerindeki düzelme grup P'de daha iyiydi ve gruplar arasında istatistiksel olarak anlamlı fark vardı, buna karşın vertebra KMY değerleri bakımından gruplar arasında anlamlı farklılık bulunamadı (Tablo 1).

Çok sayıda oral BF bileşiği olmasına rağmen, günümüzde BF'lerden en yaygın olarak 3. kuşak BF'ler (neridronat, alendronat, olpadronat, risedronat, ibendronat) tercih edilmektedir. BF'lerin postmenopozal kadınlardaki OP tedavisindeki etkinliği çalışmalarla kanıtlanmıştır (6-8,19). Yapılan bir meta-analizde alendronatın OP'li postmenopozal kadınlarda kalça kırıklarını %55 dolayında azalttığını göstermiştir (20). Vertebral fraktürlerde klinik gözlemde tedavinin ilk yılın sonunda bir azalma saptanmıştır. Bir meta-analizde kalça kırığından korunmanın tedaviden 18 ay sonra sağlandığı bildirilmiştir (21). Kalça kırıklarını önleyici etkisi, vertebra kırıkları olan ve olmayan kadınlarda 18. aydan itibaren anlamlı olup, bu etki 36. ay boyunca korunmuştur (22,23). Aslan ve ark. (6) postmenopozal OP'li 144 hastada 6 farklı ilacın (alendronat, ibandronat, risedronat, kalsitonin, stronsiyum ve raloxifen) etkinliğini vertebra ve kalça KMY ve T-skorlarıyla değerlendirdikleri çalışmalarında; aledronatın özellikle vertebra KMY ve T-skorları üzerinde anlamlı olarak etki ettiğini belirtmişlerdir.

Bizim çalışmamızda alt grup karşılaştırmalarında; oral BF grubunda femur T skorunda alendronat lehine gruplar arasında istatistiksel anlamlı fark mevcuttu (Tablo 2). Ancak vertebra T-skoru, vertebra ve femur KMY değerlerindeki düzelme bakımından oral alt gruplar arasında istatistiksel anlamlı fark bulunamadı (Tablo 2).

OP tedavisinde parenteral kullanılan zoledronat osteoporotik kalça kırığı sonrasında yeni gelişecek kırıkların engellemesinde FDA onayı almış bir ajandır. Zoledronik asidin postmenopozal OP'de etkinliğini saptamak amacıyla geniş bir seriyle yapılan HORIZON-PFT çalışmasında hastalara başlangıç, 12 ve 24 aylarda zoledronik asit uygulaması yapılmıştır. Hastalar 3 yıl boyunca izlenmişler ve plasebo grubu ile karşılaştırılmışlardır (24). Bu çalışmada primer son nokta olarak yeni vertebra kırığı ve kalça kırığı alınmıştır. Zoledronik asit grubunda morfometrik vertebra kırığı riski 3 yıl içinde %70, kalça kırığı riski %41 azalmıştır (25). Doz İçi Venöz İdare (Dosing IntraVenous Administration, DİVA) çalışmasında, ikili İV ibandronat (3 ayda bir 3 mg, 2 ayda bir 2 mg) başlangıç lomber KMY'sine göre benzer artış görülmüş olup (%5,1 ve %4,8), günlük oral 2,5 mg ibondronat tedavisinde ise başlangıç değerlerine göre lomber KMY'de %3,8'lik bir artış görülmüştür (26).

Parenteral zoledronat ve ibandronat tedavisi verilen 82 hastanın karşılaştırıldığı hiçbir çalışmada ise; zolendronat ve ibandronat uygulanan her iki grupta bir yıllık takipte uygulama öncesine göre KMY değerlerinde istatistiksel olarak anlamlı artış olduğu, ancak gruplar arasında bir yıllık takipte KMY ortalama değerleri bakımından anlamlı fark saptanamadığı rapor edilmiştir. Yazarlar sonuç olarak; zoledronat ve ibandronat tedavisini OP hastalarında KMY değerlerinde anlamlı düzelme sağladığını, etkinlik ve görülen yan etkiler arasında anlamlı fark olmadığını belirtmişlerdir (7).

Bizim çalışmamızda; parenteral BF grubunda vertebra ve femur T-skorundaki düzelme zoledronat alt grubunda daha iyiydi ve istatistiksel olarak anlamlıydı (Tablo 3). Buna karşın vertebra ve femur KMY değerindeki ortalama düzelme zoledronat grubunda daha iyi olmasına rağmen istatistiksel olarak anlamlı fark bulunamadı (Tablo 3).

OP'nin önlenmesi ve tüm tedavi stratejilerinde en az 1000 mg kalsiyum ve 600 IU D vitamini önerilmektedir. Son yıllarda kalsiyum takviyesi, güvenliği, kalsiyum ve D vitamininin uygun dozu ile ilgili tartışmalara rağmen, kalsiyum ve D vitamini kemik

sağlığının önemli bir parçası olmaya devam etmektedir (8). Bizim çalışmamızda da tüm hastalara 800 IU/gün D3 vitamini, 1,200 mg/gün kalsiyum tedavisi verildi.

Çalışmanın Kısıtlılıkları

Takip süremizin azlığı bir kısıtlılık olabilir. Diğer bir kısıtlılık ilaç gruplarının etkinliğini sadece DXA ile belirlenen KMY ve T-skoruyla değerlendirmiş olmamızdır. Biz her ne kadar yapmamış olsak da kemik yıkım belirteçleri ve D vitamini seviyeleri takipte kullanılmakta olan önemli belirteçlerdir (6,18,27). Diğer yandan çalışmamızda tedavi sırasında görülen yan etkilerin değerlendirilmesini bu çalışmaya dahil etmedik. Üst gastrointestinal semptomları genellikle oral BF tedavisinde, geçici influenza benzeri semptomlar ise nitrojen içeren parenteral BF uygulama sırasında sıklıkla gözlenir (5,6). KMY ölçümlerinde kullanılan DXA cihazlarının farklı olması değişik bölgelerde yapılan KMY ölçümlerinde farklılıklara neden olabilmektedir. Ayrıca üreticilerin kullandığı farklı alan ve yoğunluk belirleme algoritmaları ve farklı kalibrasyon uygulamaları standartlaştırma çalışmalarını daha da güçleştirmektedir. Son olarak, ülkemizde DXA uzun yıllardır tanı ve tedavi amaçlı kullanılmasına rağmen operatör (teknisyen) eğitiminin standardizasyonu, taramanın elde edilmesinde, analiz ve yorumlanmasında hatalara yol açabilir (28). Bu hususlar bizim çalışmamız için de geçerlidir ve sonuçlarımızı etkilemiş olabilir.

Sonuç

Bu çalışmanın sonuçları; postmenopozal OP'nin farmakolojik tedavisinde oral ve parenteral BF'lerin etkili olduğunu göstermektedir. Bununla birlikte vertebra ve femur T-skorlarında ve femur KMY ortalama düzelme bakımından parenteral BF'ler daha etkili bulundu. Ayrıca oral BF'lerden aledronatın femur T-skorlarında anlamlı olarak daha iyi bir düzelme sağladığı, parenteral BF'lerden ise zoledronatın hem femur hem de vertebra T-skorlarında anlamlı olarak daha iyi bir düzelme sağladığı değerlendirilmiştir. Çalışmamızın orijinal yönü özellikle Türkçe literatürde oral ve parenteral BF'lerin etkinliğinin karşılaştırıldığı yeni bir çalışma olmasıdır. Konuyla ilgili daha uzun süreli ve daha kapsamlı karşılaştırılmalı çalışmalara ihtiyaç vardır.

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Pathological Femoral Fracture due to Osteoporosis and Hypophosphatemic Osteomalacia Following Adefovir Therapy in a Patient with Chronic Hepatitis B

Kronik Hepatit B'li Hastada Adefovir Tedavisi Sonrası Gelişen Osteoporoz ve Hipofosfatemik Osteomalaziye Bağlı Patolojik Femur Kırığı

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Abstract

Adefovir dipivoxil (ADV) is a nucleotide analogue used in the chronic hepatitis B treatment. Proximal renal tubular dysfunction is one of the adverse effects of this agent and characterized with hypophosphatemia and osteomalacia. However, reduced bone mineral density with fracture due to ADV therapy has not been reported before. We aimed to report a 55-year-old male patient with proximal femur fracture who developed hypophosphatemic osteomalacia while using low dose of adefovir (10 mg/day) for chronic hepatitis B treatment for 10 years.
Keywords: Adefovir dipivoxil, hypophosphatemia, osteomalacia, osteoporosis, fracture

Öz

Adefovir dipivoksil (ADV), kronik hepatit tedavisinde kullanılan bir nükleotid analoğudur. Proksimal renal tübüler fonksiyon bozukluğu, bu ajanın yan etkilerinden biridir ve hipofosfatemi ve osteomalazi ile karakterizedir. Bununla birlikte, ADV tedavisine bağlı kırık ile kemik mineral dansitesinde azalma daha önce bildirilmemiştir. Burada 10 yıldır kronik hepatit B tedavisi için düşük dozda adefovir kullanan (10 mg/gün) 55 yaşındaki erkek hastada hipofosfatemik osteomalazi sonucu gelişen proksimal femur kırığı olan bir hastayı bildirmeyi amaçladık.
Anahtar kelimeler: Adefovir dipivoksil, hipofosfatemi, osteomalazi, osteoporoz, kırık

Introduction

Adefovir dipivoxil (ADV) is an adenine dinucleotide analog, used in lamivudine-resistant hepatitis B virus (HBV) infection therapy. Adefovir causes dose-related renal toxicity due to renal tubular dysfunction. Although low-dose ADV therapy (10 mg/day) has been reported to be safe (1,2), there is an increasing number of case reports demonstrating hypophosphatemic osteomalacia caused by proximal renal tubular dysfunction, a feature of Fanconi's syndrome (3-7). However, pathological fractures related to low dose ADV therapy is still uncommon. According to literature, there are two cases with hypophosphatemic osteomalacia and fracture due to low-dose ADV use (8,9). We aimed to present a case with hypophosphatemic osteomalacia caused by Fanconi's syndrome, resulting in osteoporosis and right hip fracture due to low-dose ADV therapy for 10 years.

Case Report

A 55-year-old man admitted to our clinic with 2-years of bilateral groin pain history referring to anterior thighs exacerbated on weight-bearing. The groin pain gradually increased and he had ambulatory difficulty in the last 3 months. He started to spend most of the his time in the bed. At the time of his admission, he was receiving ADV therapy. He had 18-years of chronic hepatitis history due to HBV infection. He had received lamivudine therapy for 8 years. Since the virus developed resistance to lamivudine, he received ADV 10 mg daily for 10 years. In his locomotor examination; there was a widespread bone tenderness with palpation. Range of motion of hips was limited and painful in all directions, especially on the right side. All lumbar spinous processes and ribs were painful with palpation. The patient was walking antalgic using one cane.

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He had hypophosphatemia (1.9 mg/dL; normal range, 2.3-4.7 mg/dL) and increased alkaline phosphatase (ALP: 363 IU/L; normal range: <150 IU/L) and serum creatinine (1.79 mg/dL; normal range: 0.8-1.2 mg/dL) level. Furthermore, he had normal blood urea nitrogen (BUN: 22 mg/dL; normal range: 7-18 mg/dL), intact parathyroid hormone (PTH: 41.4 pg/mL; normal range: 10-65 pg/mL), 25 hydroxyvitamin D (29.2 ng/mL), 1,25-dihydroxyvitamin D3 (24.3 pg/mL; normal range, 16-65 pg/mL), serum glucose (91 mg/dL) and serum calcium (9.1 mg/dL; normal range: 8.5-10.5 mg/dL) levels. Urinalysis revealed proteinuria and glucosuria. A 24-h urine analysis showed increased urinary excretion of phosphate (2070 mg/day; normal range: 400-1300 mg/day), calcium (586.0 mg/day; normal range: 100-300 mg/day), hyper micro albuminemia (607.2 mg/day; normal range: 0-30 mg/day), and proteinuria (3.06 g/day; normal range: 0-150 mg/day). Detailed blood sample tests are shown in Table 1. These findings indicated hypophosphatemia and hyperphosphaturia. However, because the patient had normal levels of 25-dihydroxyvitamin D3, we considered that the impaired phosphate reabsorption could have been caused by proximal renal tubule dysfunction.

X-ray graphy was suspicious for right femoral neck fracture. Magnetic resonance imaging (MRI) of right hip joint showed fracture across femoral neck and revealed generalized bone marrow edema around the femoral head and collum which were observed as low intensity on T1-weighted images and high intensity on T2-weighted images and effusion in the hip joint and around the femoral neck (Figure 1a, b).

We examined the bone mineral density (BMD) by dual-X-ray absorptiometry. The BMD was 0.5373 g/cm^2 at femur neck and 0.8573 g/cm^2 at lumbar region. T score was -4.57 at femur neck and -1.65 at L1-L4 lumbar vertebrae. Z score was -2, 98 at femur neck and -1,48 at L1-L4 vertebrae.

On the basis of these findings, we made a diagnosis of osteoporosis, osteomalacia and pathologic fractures due to Fanconi's syndrome secondary to ADV therapy (10 mg/day).

Orthopedic surgeons considered to treat the patient conservatively and follow the patient. The patient was treated conservatively for femoral neck fracture with bed rest and bilateral cane use for daily activities when needed. At the end of 10 months of follow up, a new MRI was issued. The new MRI showed minimal bone marrow oedema at subchondral area of right femoral neck which had low intensity on T1-weighted images and high intensity on T2-weighted images (Figure 1c, d) representing the healing of the fracture.

After diagnosis, ADV was switched with entecavir 1 mg/day and alendronate sodium hydrate 70 mg 2 weeks were administered because of the high creatinine clearance levels (33.2 mL/min) combined with calcium and vitamin D supplementation. After 10 months, we observed that these treatments normalized the blood phosphate (2.4 mg/dL) and ALP (258 IU/L) levels. Glycosuria resolved and proteinuria reduced significantly. Clinical symptoms such as groin pain and ambulatory difficulty disappeared. He was able to walk without any assistance.

The consent approval of the patient was received.

Table 1. Laboratory examination of the patient

	Baseline assessment	10 months follow-up
25 hydroxy vitamin D (ng/mL)	29.2	37.5
1.25 dihydroxy vitamin D (pg/mL) (16-65)	24.3	33.9
Alkaline phosphatase (IU/L) (<150)	363	258
Alanine aminotransferase (IU/L) (<42)	24	18
Phosphate (mg/dL) (2.3-4.7)	1.9	2.7
Calcium (mg/dL) (8.5-10.5)	9.1	9.6
Serum glucose (mg/dL)	91	92
Blood urea nitrogen (mg/dL) (7-18)	22	19
Creatinine (mg/dL) (0.8-1.2)	1.79	1.62
Magnesium (mg/dL) (1.6-2.6)	2.35	2.46
Uric acid (mg/dL) (3.5-7.2)	2.1	3.2
Parathyroid hormone (pg/mL) (10-65)	41.4	49.8
Albumin (g/dL)	4.4	4.5
Urine examination	2+proteinuria, 3+glucosuria	Trace amount of protein, glucose negative
Microalbumin excretion/24 hours urine examination (0-30)	607.2 mg/day	85.1 mg/day
Protein excretion/24 hours urine examination (0-150 mg/day)	3.06 g/day	0.49 g/day
Phosphate excretion/24 hours urine examination (400-1300)	2070 mg/day	44.8 mg/day
Calcium excretion/24 hours urine examination (100-300)	586 mg/day	216 mg/day

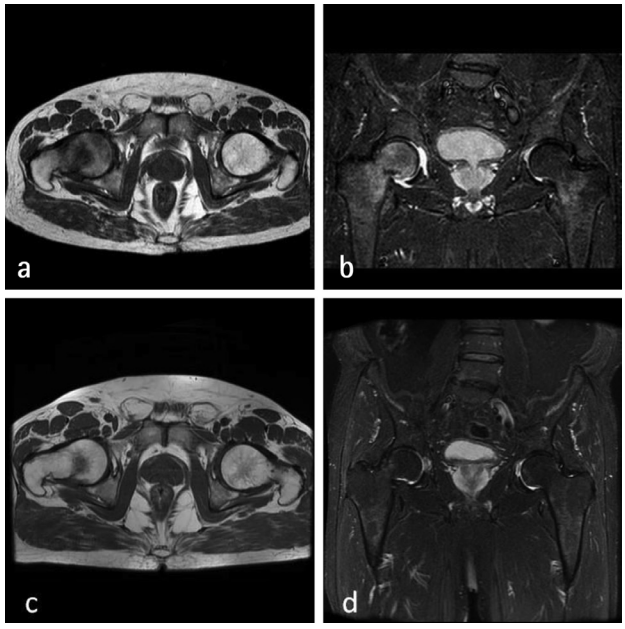

Figure 1. a) Coronal T2W STIR image demonstrating the nondisplaced femoral neck fracture at the right proximal femur medial side, with associated generalized bone marrow oedema at the level of femoral caput and collum. b) Axial T1W images demonstrating fracture line at medial side of the right femoral neck and bone marrow oedema at the level of femoral caput and collum. c) Coronal T2W STIR image demonstrating minimal marrow oedema at subchondral area of right femoral neck posterior side. d) Axial T1W images demonstrating slight bone marrow oedema at subchondral region of right femoral neck posterior side

Discussion

ADV is a nucleotide analog which is widely used in the treatment of lamivudine-resistant HBV infection. Although it has been reported to be safe (1,2), there is an increasing number of ADV-induced nephrotoxicity reported even at low doses on long-term uses (2-7). Eighteen cases (6 cases in China, 6 cases in Korea, 3 cases in Japan and 1 cases in France, Australia and Italy) have been reported on adefovir induced hypophosphatemic osteomalacia since 2008 (4).

ADV-induced nephrotoxicity is characterized by a decrease in the level of phosphate and a slight increase in creatinine level due to renal proximal tubular dysfunction (10). Adefovir is thought to cause cell necrosis and stop oxidative phosphorylation by inhibiting DNA synthesis in the proximal tubule epithelial cell mitochondria. This renal tubular dysfunction leads to renal phosphate wasting and osteomalacia. Osteomalacia is common in Fanconi's syndrome. Muscle weakness and generalized bone pain are the major symptoms (11). Although pseudo fractures are expected to be seen in osteomalacia, fractures may also be observed in some cases.

Management of ADV-induced osteomalacia includes phosphate supplementation and switching antiviral drug. This management may correct the serum phosphate, ALP and creatinine levels. In our case, the therapy has been switched to entecavir. Dietary phosphate supplementation normalized the serum phosphate levels, reduced the serum ALP and creatinine levels at the end of 10- month follow up. Kim et al. (12) reported a 54-year-old male patientwho had been taking adefovir (10 mg/day) for 59 months due to lamivudine-resistant HBV. Adefovir was replaced with entecavir due to adefovir induced hypophosphatemic osteomalacia. After 8 week phosphate supplementation, symptoms has been improved.

Poh et al. (9), reported a 53-year old patient with multifocal insufficiency fractures including subtrochanteric femoral insufficiency fracture, required surgical fixation, due to ADV-induced hypophosphatemic osteomalacia. The patient received ADV therapy for 59 months. Tanaka et al. (8), reported a 62-year-old man with femoral neck fracture associated with ADV-induced osteomalacia and underwent total hip arthroplasty. The patient had received ADV therapy for 60 months. Our case was 55 year-old man receiving ADV therapy for 120 months. Chen et al. (13) have studied ADV induced hypophosphatemic osteomalacia in Chinese and non Chinese patients and found out that middle aged men are affected more in both groups and its not associated with nationality. Our case was also a 55 year old male supporting the results of Chen et al. (13). We observed right hip fracture and treated the patient conservatively. We noticed that, recent reports did not evaluate the BMD of the patients with fractures. When we evaluated the BMD, we observed severe osteoporosis. According to our literature search, this is the first case presented with osteoporosis and fracture due to ADV therapy for chronic HBV infection. We considered that examining BMD in such patients with fractures is necessary to treat osteoporosis and to avoid potential fractures. Furthermore, we concluded that patients receiving ADV therapy should be monitored for osteoporosis to take precautions before fracture occurs. After diagnosing osteoporosis and fracture, we prescribed alendronate 70 mg every 2 weeks period because of the renal impairment.

Chronic hepatitis B virus (CHB)-associated inflammation could inhibit bone formation and increase bone resorption, leading to a decrease in BMD (14,15). However, nucleotide analogue (NA) therapies used for CHB treatment also may reduce the BMD. In a study of 319 patients on NA therapy, osteoporosis was present in 19%, osteopenia in 49%, with an overall 68% reduction in BMD. Age, gender, and NA therapy were independently associated with reduced BMD (16). Maggi et al. (17) evaluated the patients who treated with lamivudine plus adefovir therapy at the time of switch to tenofovir therapy. They found reduced BMD values in 52.7% of the patients at baseline especially in femur neck region. Therefore, the patients with CHB, depending on the disease itself or due to the antiviral therapy, seems carrying fracture risk.

In conclusion, physicians prescribing ADV therapy should be aware of the late onset of these complications and should carefully monitor the renal function, phosphate level, bone mineralization and density thus avoid high-risk femur fractures.

Ethics

Informed Consent: The patient aproval was received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.B., D.G.K., B.Ç.R., H.G., Concept: S.B., N.M., Z.Ş., Design: S.B., N.M., Z.Ş., Analysis or Interpretation: S.B., H.G., Literature Search: S.B., D.G.K., B.Ç.R., Writing: S.B., D.G.K.

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Complex Regional Pain Syndrome After Herpes Zoster: A Case Report

Herpes Zoster Sonrası Kompleks Bölgesel Ağrı Sendromu: Olgu Sunumu

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Abstract

A 78-year-old male patient, diagnosed with herpes zoster infection, had color change, stiffness, swelling and burning pain on his left hand. Hand joints were painful, joint range of motion decreased and hyperpigmented, macular lesions on the left C5-C6 dermatome region was determined. After the medical and physical therapy programme, symptoms decreased significantly. Complex regional pain syndrome (CRPS) is a painful disorder with swelling, stiffness in joints, vascular instability, and dystrophic skin changes. Symptoms most commonly occur after trauma, stroke, surgery, myocardial infarction, fracture, cancer. In this case, an unusual cause of complex regional pain syndrome, herpes zoster, was reported. Only a few cases have been reported to date. In this case report, it is emphasized that CRPS can occur as a complication of many conditions. Early diagnosis and appropriate treatment lead to better outcomes.
Keywords: Complex regional pain syndrome, herpes zoster, rehabilitation

Öz

Herpes zoster enfeksiyonu tanılı 78 yaşında erkek hastanın sol elinde renk değişikliği, tutukluk, şişlik ve yanıcı ağrısı mevcuttu. El eklemleri ağrılı, eklem hareket açıklığı azalmış ve hiperpigmente, sol C5-C6 dermatomal bölgede maküler lezyonlar tespit edildi. Medikal ve fizik tedavi programı sonrası semptomlar anlamlı şekilde azaldı. Kompleks bölgesel ağrı sendromu (KBAS) şişlik, eklemlerde tutukluk, vasküler instabilite, distrofik deri değişiklikleriyle ağrılı bir bozukluktur. Semptomlar sıklıkla travma, inme, cerrahi, miyokard enfarktüs, kırık, kanser sonrası görülür. Bu olguda kompleks bölgesel ağrı sendromunun olağandışı bir nedeni olan herpes zoster bildirilmiştir. Bugüne kadar sadece birkaç olgu rapor edilmiştir. Bu olgu sunumunda KBAS'nin birçok durumun komplikasyonu olarak görülebileceği vurgulanmaktadır. Erken teşhis ve tedavi, olumlu sonuçlara yol açmaktadır.
Anahtar kelimeler: Kompleks bölgesel ağrı sendromu, herpes zoster, rehabilitasyon

Introduction

Complex regional pain syndrome (CRPS) (reflex sympathetic dystrophy) is a painful disorder that affecting the hands but also arms, legs and limbs. The clinical features are spontaneous pain, hyperalgesia, stiffness, impairment of motor function, swelling and autonomic abnormalities. Symptoms most commonly occur after trauma. Other causes include infection, stroke, surgery, myocardial infarction, fracture, cancer (1). Although herpes zoster was first described by Sudeck (2) as a complication in 1901, only a few reports of herpes zoster as the cause of this syndrome has been reported (3-7). We describe this case of a patient with CRPS features after an herpez zoster infection.

Case Report

A 78 years old male patient, with a vesicular rash that is limited to C4-C5-C6 dermatomes, was diagnosed with herpes zoster infection in dermatology clinic. The patient had been treated 3000 mg/day valacyclovir for ten days. After ten days, swelling of the dorsum of the left hand and burning pain in the hand and fingers evolved gradually. The patient had gabapentin, tramadol and nonsteroidal anti-inflammatory drugs (NSAID) therapy, but symptoms increased. The patient was seen in our clinic three months later, with burning pain in the left hand and fingers, stiffness in the fingers, decrease of nail growth. He had no systemic disease. In physical examination, hyperpigmented, maculer lesions in on the left C5-6 dermatome, blue colored cold skin and dryness in on the hand, fragile nails were seen (Figure 1). The wrist, metacarpophalangeal, distal and proximal interphalangeal joints were painful and decreased range of motion were determined. All of the laboratory test values (hemogram, biochemistry, sedimentation, C-reactive protein, rheumatoid factor, thyrotrophin-stimulating hormone levels) were in normal limits, only 25 hidroxy vitamin D3 level was

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22 ng/mL. Patchy osteoporosis were seen in the radiographs on the left hand (Figure 2). The patient was diagnosed as CPRS after herpes zoster and given Vitamin D3 1000 IU/per day, pentoxifylline 400 mg/day, pregabalin 75 mg/day, acemetacin 90 mg/day. Physical therapy was planned for 30 sessions, which included contrast bath, left hand, wrist transcutaneous electrical nerve stimulation, stretching and strengthening exercise. Six weeks later, the complaints of the patients were markedly resolved and, dryness, blue color of skin were disappeared (Figure 3).
Written informed consent was obtained from the patient.

Discussion

Herpes zoster is a self-limiting disease, with pain quenching at the end of vesicular eruption in dermatomal distribution.

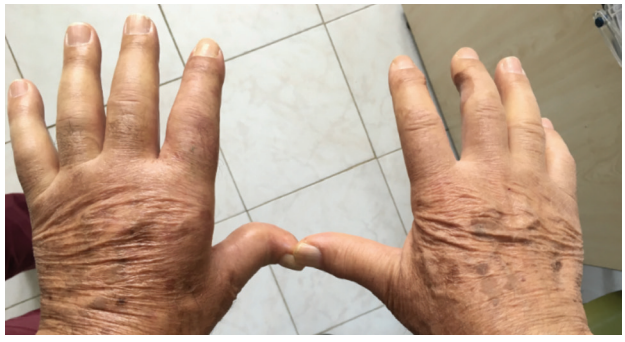

Figure 1. Hyperpigmented, maculer lesions in on the left C5-6 dermatome, blue colored cold skin and dryness in on the hand, fragile nails are seen

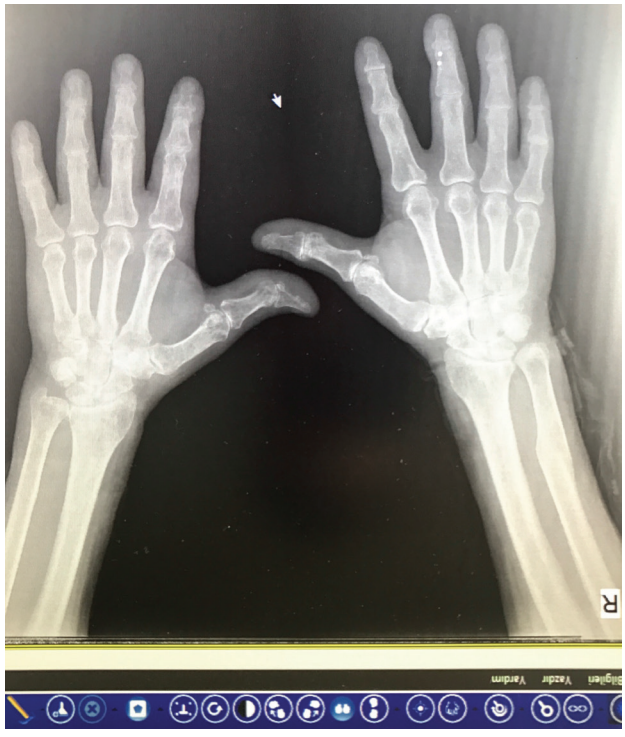

Figure 2. Patchy osteoporosis are seen in the radiographs on the left hand

Herpes zoster results from reactivation of latent varicella-zoster virus within the sensory ganglia (8-10). The incidence and severity of herpes zoster increase with advancing age and immunodeficiency or cancer (11); more than half of all persons are older than 60 years. Also our patient was 78 years old, had no systemic disease. The most frequent debilitating complication is postherpetic neuralgia, a neuropathic pain syndrome that persists or develops after the dermatomal rash has healed (9,10,12). Other neurologic complications are peripheral motor neuropathy, cranial nerve palsy, myelitis, encephalitis, cerebral thrombotic vasculopathy, acute polyradiculitis and aseptic meningitis (13,14). CRPS is a rare complication and only a few reports have been described in the literature (3-7). A case was a 65 years woman with characteristic signs and symptoms of CRPS in the right upper limb. CRPS was appeared four weeks after a herpes zoster infection. Intranasal calcitonin and physiotherapy lead to progressive functional and pain improvements (3). Similarly to the previous case, a 64-year-old woman with CRPS in the right hand that appeared four weeks after she had a herpes zoster infection, had medical treatment (diclofenac sodium, deltacortril, gabapentin, and lansoprazole) and physical therapy. She achieved a progressive improvement with early diagnosis and treatment (4). In our patient, CRPS development time was shorter from above cases. Despite different treatment options, progressive improvements were obtained in all studies. Several hypothesis can explain the mechanism of herpes zoster in causing CRPS, the first mechanism is, herpes zoster causes intense pain. This initial afferent nociceptive stimulus can sensitize multiple sympathetic neurons, resulting sympathetic outflow. The second mechanism is secondary inflamation due to cytopathic changes of herpes zoster infection. The third mechanism is spontaneously abnormal synapses between the efferent sympathetic nerves and afferent sersory nerves due to herpes zoster infection (15-17). Specific criteria for the diagnosis of CPRS were adopted in 2013 as the new international standard by the International Association for the Study of Pain (Table 1) (18). A comprehensive, integrated multidisciplinary

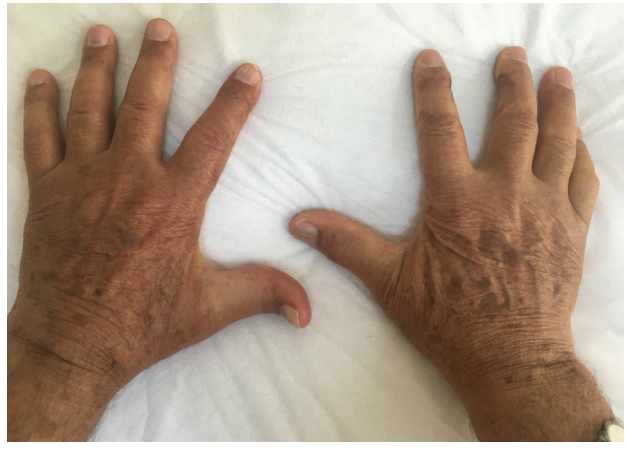

Figure 3. The hands of the patient six week after the treatment

Table 1. Research diagnostic criteria for complex regional pain syndrome
Continuing pain, which is disproportionate to any inciting event
At least one symptom in three of the four following categories*: Sensory: Hyperalgesia and/or allodynia Vasomotor: Temperature asymmetry and/or skin color changes and/or skin color asymmetry Sudomotor/edema: Edema and/or sweating changes and/or sweating asymmetry Motor/trophic: Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)
At least one sign at time of evaluation in two or more of the following categories*: Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch or deep somatic pressure, or joint movement) Vasomotor: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry Sudomotor/edema: Evidence of edema and/or sweating changes and/or sweating asymmetry Motor/trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)
There is no other diagnosis that better explains the signs and symptoms

treatment that includes medical, psychological, and physical and occupational therapy is needed in the treatment of CPRS. Randomized trials suggest that steroids, NSAID, opioids, immun modulators, analgesic antidepressants, bisphosphonates, calcitonin, anticonvulsants, NMDA receptor antagonists, calcium channel blockers, block therapies, surgical sympathectomy, and spinal cord stimulation may be effective treatments (18,19). In our patient, oral and topical NSAIDs, anticonvulsants, physical therapy and Pentoxifylline was used. Physical therapy increases patients range of motion, flexibility and strength (20). NSAIDs are used to treat pain plus inflammatory involvement in CRPS (21). Most often used as anticonvulsants, several have efficacy in neuropathic pain (22,23). Also Pentoxifylline, a cytokine inhibitor, was used in our treatment to reverse nociceptive sensitization and vascular abnormalities (24). It is clinically accepted that early diagnose and treatment in CRPS will lead to better outcomes. Also our patient,showed a progressive improvement with early medical treatment and physical therapy. Although CPRS is a self limited clinical course in most cases, some patients may progress for years leading a major functional disability of the affected extremity. The early management of this clinical entity is very important in daily clinical practice.

Ethics

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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