E-ISSN: 2147-2653

Türk Osteoporoz Dergisi

TURKISH JOURNAL OF OSTEOPOROSIS

Cilt / Vol.: 30 Sayı / Issue: 1 Nisan / April 2024

www.turkosteoporozdergisi.org

TÜRKİYE OSTEOPOROZ DERNEĞİ
1998
www.osteoporoz.org.tr

Türk Osteoporoz Dergisi

TURKISH JOURNAL OF OSTEOPOROSIS

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Türkiye Osteoporoz Derneği "International Osteoporosis Foundation" Üyesidir.
"Web tabanlı danışma kurulu ve hakem listesi www.turkosteoporozdergisi.com adresinde yer almaktadır"
Derginin eski adı 'Osteoporoz Dünyasından Dergisi'dir.

Yayınevi İletişim/Publisher Contact
Adres/Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
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Web: www.galenos.com.tr
Yayıncı Sertifika No/Publisher Certificate Number: 14521

Online Yayınlanma Tarihi/Online Publishing Date: Nisan 2024/April 2024
E-ISSN: 2147-2653
Üç ayda bir yayımlanan süreli yayındır.
International scientific journal published quarterly.

Türk Osteoporoz Dergisi

TURKISH JOURNAL OF OSTEOPOROSIS

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Dergi, çevrimiçi olarak yayınlanmaktadır.

Sahibi: Türkiye Osteoporoz Derneği

Sorumlu Yönetici: Yeşim Kirazlı

Please refer to the journal's webpage **(https://www.turkosteoporozdergisi.org/)** for "Ethical Policy" and "Instructions to Authors".

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The journal is published online.

Owner: Turkish Osteoporosis Society

Responsible Manager: Yeşim Kirazlı

Türk Osteoporoz Dergisi
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Türk Osteoporoz Dergisi
TURKISH JOURNAL OF OSTEOPOROSIS

Editörden / Editorial

Sevgili Meslektaşlarımız,

Öncelikle değerli meslektaşlarımıza akademik çalışmaların meyvesi olarak hazırladıkları araştırma makalesi ve olgu sunumlarını yayınlanmak üzere Emerging Sources Citation Index (ESCI) tarafından indekslenen dergimize düzenli olarak ilettikleri için çok teşekkür ederiz.

Dergimizin 2024 yılının ilk sayısında da bu akademik çalışmaları yayınlamaktan büyük mutluluk duyuyoruz.

Dünya Osteoporoz Kongresi (WCO-IOF-ESCEO) 11-14 Nisan 2024 tarihlerinde Londra'da yapılmıştır. International Osteoporosis Foundation (IOF) ve European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) tarafından hazırlanan bu kongrenin bilimsel komitesi 9755 katılımcı sayısıyla kongrenin çok başarılı geçtiğini ifade etmiştir. Bu kongrede Türkiye Osteoporoz Derneği tarafından 'Atletlerde Kemik Sağlığı' konulu bir sempozyum gerçekleştirilmiştir. Ayrıca Dernek Başkanımız Prof. Dr. Şansın Tüzün'ün Ulusal Dernekler Komitesi Başkan Yardımcısı olarak atandığı bilgisi bu kongre sırasında verilmiştir. Kendisini bu onurlu görev için gönülden kutluyoruz.

Uluslararası katılımlı 8. Ulusal Osteoporoz Kongresi 21-24 Kasım 2024 tarihlerinde Antalya'da yapılacaktır. Ajandanıza kaydetmenizi rica ediyoruz. Bu kongre için kas-iskelet sistemi sağlığına yönelik heyecan verici bir bilimsel program hazırlanmaktadır.

Siz değerli meslektaşlarımıza mutluluğun ve başarının yaşamınızdan eksik olmamasını dileyerek, sevgi ve saygılarımı sunarım.

Editör
Prof. Dr. Yeşim Kirazlı

DOI: 10.4274/tod.galenos.2023.24392
Turk J Osteoporos 2024;30:1-15

Osteoporosis in Pregnant and Lactating Females: An Update

Gebe ve Emziren Kadınlarda Osteoporoz: Bir Güncelleme

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Abstract

The purpose of writing this review is to provide an update on recent advances in pregnancy and lactation-associated osteoporosis (PLO) research and summarize the current evidence for specific treatments. PLO is a transient and rare form of osteoporosis that affects women of childbearing age during the third trimester of pregnancy and post-partum. Though the pathophysiology of the PLO is poorly understood, several case series, case studies, and fewer cohort studies are available highlighting the role of pregnancy and lactation apart from conventional risk factors in the progression of PLO. Approximately 300 research and review articles related to PLO have been read from 1996 to 2023 which include several case studies, case series, cohort studies, meta-analyses, and narrative reviews from PubMed, Embase, Scopus, Google Scholar, World Health Organization regional databases. Common clinical manifestations include lower back and hip pain and rarely vertebral compression fractures. During pregnancy and lactation, women undergo reversible changes in mineral homeostasis and skeletal metabolism. Increased calcium absorption and urinary excretion during pregnancy and increased bone resorption along with renal calcium reabsorption in lactation are the main maternal metabolic adaptations that support the skeletal growth and development of the fetus and newborn respectively. Management of the PLO depends upon proper diagnosis and prognosis using biochemical bone turnover markers and bone histomorphometry. Conventional methods include calcium and vitamin D supplementation, giving up breastfeeding, physiotherapy, supportive braces, and bed rest. Bisphosphonates, denosumab, and teriparatide are commonly prescribed medications, assuring the recovery of bone mineral density besides certain side effects. Considering the transient nature, and underreporting of the cases, treatment recommendations should be personalized based on the parity, duration of lactation, presence or absence of fractures, societal status, age, ethnicity, and race.
Keywords: Osteoporosis, pregnancy, lactation, PTHrP, prolactin, teriparatide, bisphosphonates

Öz

Bu derlemenin yazılma amacı, gebelik ve laktasyonla ilişkili osteoporoz (PLO) araştırmalarındaki son gelişmeler hakkında bir güncelleme sağlamak ve spesifik tedaviler için mevcut kanıtları özetlemektir. PLO, gebeliğin üçüncü trimesterinde ve doğum sonrası dönemde doğurganlık çağındaki kadınları etkileyen geçici ve nadir bir osteoporoz şeklidir. PLO'nun patofizyolojisi tam olarak anlaşılamamış olsa da, PLO'nun ilerlemesinde geleneksel risk faktörlerinin yanı sıra gebelik ve laktasyonun rolünü vurgulayan birkaç olgu serisi, olgu çalışması ve daha az sayıda kohort çalışması mevcuttur. 1996-2023 yılları arasında PubMed, Embase, Scopus, Google Scholar, Dünya Sağlık Örgütü bölgesel veri tabanlarından gebelik ve laktasyonla ilişkili osteoporozla ilgili çeşitli olgu çalışmaları, olgu serileri, kohort çalışmaları, meta-analizler ve anlatı incelemelerini içeren yaklaşık 300 araştırma ve inceleme makalesi incelenmiştir. Yaygın klinik belirtiler arasında bel ve kalça ağrısı ve nadiren vertebral kompresyon kırıkları yer almaktadır. Hamilelik ve emzirme döneminde kadınlar mineral homeostazında ve iskelet metabolizmasında geri dönüşümlü değişikliklere maruz kalırlar. Gebelik sırasında artan kalsiyum emilimi ve idrarla atılımı ve laktasyonda renal kalsiyum geri emilimi ile birlikte artan kemik rezorpsiyonu, sırasıyla fetüsün ve yenidoğanın iskelet büyümesini ve gelişimini destekleyen ana maternal metabolik adaptasyonlardır. PLO'nun yönetimi, biyokimyasal kemik döngüsü belirteçleri ve kemik histomorfometrisi kullanılarak doğru tanı ve prognoza bağlıdır. Geleneksel yöntemler arasında kalsiyum ve D vitamini takviyesi, emzirmenin bırakılması, fizyoterapi, destekleyici breysler ve yatak istirahati yer almaktadır. Bisfosfonatlar, denosumab ve teriparatid yaygın olarak reçete edilen ilaçlardır ve bazı yan etkilerinin yanı sıra kemik mineral yoğunluğunun iyileşmesini sağlarlar. Olguların geçici doğası ve az bildirilmesi göz önünde bulundurularak, tedavi önerileri parite, laktasyon süresi, kırık varlığı veya yokluğu, toplumsal statü, yaş, etnik köken ve ırka göre kişiselleştirilmelidir.
Anahtar kelimeler: Osteoporoz, gebelik, laktasyon, PTHrP, prolaktin, teriparatid, bifosfonatlar

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Received/Geliş Tarihi: 07.07.2023 **Accepted/Kabul Tarihi:** 19.10.2023

Introduction

Osteoporosis is manifested by weakening of bone tissue, and disruption of bone microarchitecture leading to compromised bone strength, low bone mineral density (BMD), and an increase in fracture risk. It is estimated that there are more than 200 million osteoporosis affected people worldwide (1). Risk factors responsible for escalating the incidences of osteopenia and osteoporosis include pre-existing low BMD, aging, low calcium intake, smoking, low body mass index, estrogen deficiency, poor health, personal and family history of low trauma fractures due to osteoporosis, pregnancy and lactation (2,3).

Among all, conditions of osteopenia [T-score - between -1 and -2.50 standard deviation (SD)] and osteoporosis (T-score <-2.5 SD) are more prevalent in perimenopausal and postmenopausal women (4-6). The global prevalence of osteoporosis in women (perimenopausal and postmenopausal) is 23.1%, in premenopausal women between 2-4.7%, and in women below 40 years of age between 0.9-3% (7-9).

Pregnancy and lactation-associated osteoporosis (PLO) is a transient pathophysiological state characterized by back and hip pain, loss of height, lower BMD, and deteriorated bone micro-architecture. It is seldom presented with vertebral compression fractures. It is considered a rare form of osteoporosis however; the actual number of cases may be much higher due to less number of studies, poor awareness, and under-diagnosis. This may result in a poor prognosis of the disease (10,11). The PLO onset time is the third trimester of pregnancy to the early postpartum period during lactation (12). In the third trimester of pregnancy and during lactation, the skeleton experiences accelerated bone remodeling to meet growing calcium demands for fetal and neonatal skeletogenesis, apart from increased intestinal calcium absorption and urinary calcium excretion during pregnancy. This causes increased calcium release from the maternal skeleton leading to PLO (13).

In contrast to developed nations, the prevalence of PLO in developing countries could be more due to under-diagnosis, under-treatment, lack of awareness, multiparity along with prolonged lactation period, and malnutrition (11,14-16). The PLO can be more severe if the pre-pregnancy period has been with poor general nutrition including low calcium intake in the diet, low BMD along with positive family health history for osteoporosis (17). Though, bone loss associated with pregnancy and breastfeeding is transient and recovers fully at the same rate after weaning. However, in some cases, the skeletal calcium storehouse was depleted during lactation at the microstructural level and not fully replenished afterward (18,19).

Recent studies showed that frequent multiple pregnancies or multiparity and breastfeeding for longer duration is positively associated with vertebral fracture risks (14,20). In the case of multiparity, it has been observed that PLO with vertebral fractures may occur in any number of pregnancies (21). On the contrary, in one prospective cohort study which was carried out over 10 to 16 years of follow-up, parity and lactation each showed largely no correlation with the risk of osteoporotic fragility fractures, morphometric or morphological vertebral fractures, and changes in areal bone mineral density (22). Some studies also suggest that the patterns of parity and length of lactation have little or no impact on fracture risk or of pre- and post-menopausal women (23,24) instead length of lactation can provide protection against hip fracture in middle-aged and older women (25). One plausible explanation for this is that pregnancy and lactation may not be the risks for developing osteoporosis in long term.

A timely diagnosis of PLO and proper treatment can ensure a substantial recovery. To maintain skeletal homeostasis and normal during pregnancy and lactation, several preventive measures and management strategies can be suggested after reviewing biochemical and physiological parameters and BMD T-score. Some Food and Drug Administration (FDA)-approved drugs that are commonly prescribed are bisphosphonates, teriparatide, and denosumab. Currently, these drugs are prescribed along with calcium and vitamin D supplements for the management of osteoporosis in lactating females (26,27). The present review provides a holistic definition of PLO and discusses the likely mechanism involved in its onset, systematic investigations, and diagnostic tools with a brief discussion on the management of the disease. This present review is an effort to emphasize the significance of maintaining bone health in pregnant and lactating females and the need for carrying out epidemiological studies to arrive at conclusions necessary for setting up and/or updating guidelines.

Pathophysiology of PLO

In an adult, 99% of calcium is present in the bones as hydroxyapatite crystals [$Ca_{10}(PO_4)_6(OH)_2$] and the remaining 1% calcium is localized in the extracellular fluid and in the cell's cytoplasm either in ionized form or bound to albumin and in other chemical complexes (28). It is the ionized form that is physiologically relevant and is maintained in the narrow range of 4.65 to 5.25 mg/dL (1.16 to 1.31 mM). Calcium homeostasis is essential to life and is precisely regulated by the calciotropic action of four hormones: hypercalcemic factors -parathyroid hormone (PTH), parathyroid-hormone related peptide (PTHrP), and 1,25-dihydroxycholecalciferol (1,25-DHC popularly known as calcitriol) and the hypocalcemic factor calcitonin (CT). Calcium homeostasis is achieved by: 1) the absorption of the mineral by the small intestine; 2) bone formation and resorption, and 3) urinary and fecal excretion and renal reabsorption.

Mammals are viviparous, and have evolved costly postnatal care in terms of energy expenditure. Maternal physiology has developed a variety of reproductive adaptations. To fulfill the calcium requirement for the skeletal growth of the developing fetus and the newborn, maternal bone metabolism and mineral homeostasis comes into effect.

Bone is the major storage site for minerals and proteins in the body and is continuously renewed by a process called skeletal remodeling throughout one's life span. A bone remodeling cycle

involves the action of the osteoblasts or the bone-forming cells, which are responsible for the secretion of bone matrix proteins and bone mineralization; while osteoclasts are responsible for resorption by dissolving extracellular matrix and demineralization; whereas, post-mitotically converted osteoblasts or osteocytes send mechano-sensory signals (29).

At term, ~30 g of calcium gets accumulated in the skeleton of the newborn (13). About 80% of this accretion takes place during the third trimester at which time maximum fetal skeletal growth occurs. The maternal serum ionized calcium concentration remains unchanged throughout pregnancy. During pregnancy, intestinal calcium absorption gets doubled and urinary excretion is increased with a moderate increase in bone turnover (30). PTH level declines below normal in the first two trimesters and then rises to mid-normal in the third trimester in women with adequate calcium intake. CT, PTHrP, calcitriol, estradiol, progesterone, prolactin (PL), and placental lactogen all increase during pregnancy. All of these hormones directly or indirectly contribute to elevated maternal intestinal calcium absorption through active and passive pathways (31). *In vitro* and *in vivo* animal studies confirm that both PTH and PTHrP modulate the transplacental flux of calcium to the fetus and their production is regulated by calcium-sensing receptor (32,33). Under the condition of insufficient maternal intestinal calcium absorption, unable to fulfill the combined calcium requirements of the mother and fetus, the maternal skeleton experiences increased resorption during the third trimester (13).

After birth, neonatal mineral homeostasis becomes progressively efficient due to metabolic adaptations involving bone, intestine, kidneys, and liver (30,34). Generally, a lactating female transfers 200-300 mg of calcium/day from breast milk (35). During lactation, ionized calcium and total calcium remain normal to the non-pregnant values. Renal calcium reabsorption and to a larger extent calcium ion mobilization from the bone through increased resorption enhance calcium in the milk. The hormonal milieu is generally characterized by low estradiol and progesterone, increased PTHrP, PL, and oxytocin. PTH level falls to the lower end of the normal range, whereas calcitriol and CT fall within the normal range. These hormonal changes affect calcium metabolism and lead to changes in the bone remodeling process, eventually the rate of bone resorption increases (30,36,37). Bone resorption is independent of maternal calcium intake during lactation and causes a 5-10% loss of trabecular mineral content in order to deliver calcium to milk (31). Bone resorption mainly promotes the activation of osteoclasts and affects the BMD of breastfeeding women (38).

During lactation resorption of bone occurs mainly by two pathways:

(i) Upregulated Osteoclast-mediated Bone Resorption

In upregulated osteoclast-mediated bone resorption, serum levels of PTH and PTHrP have been reported to increase during lactation (39,40). Elevated PTH level promotes osteoclastogenesis followed by an increase in bone resorption, and serum calcium levels which in turn reduces bone mass (40).

(ii) Osteocytic Osteolysis

It is a phenomenon when osteocytes behave like osteoclasts to resorb minerals from bone matrix. Negative feedback by CT or a high-calcium diet can suppress osteocytic osteolysis. Low-calcium diet, and PTH are the positive modulators of this process during late pregnancy (41,42).

There is a "Brain-Breast-Bone-Circuit" which gets activated by suckling (39). PL hormone secreted by anterior pituitary lactotrophs causes a decrease in the levels of Gonadotropin-Releasing Hormone (GnRH) which leads to low circulating levels of follicle stimulating hormone, and luteinizing hormone and subsequently low concentrations of estrogen and progesterone (43). PTH level helps osteoblasts to increase the secretion of receptor activator of nuclear factor kappa B ligand (RANKL) and reduce the formation of an antiresorptive cytokine, osteoprotegerin (also known as osteoclastogenesis inhibitory factor) (44). PL is an important regulator of the bone remodeling process. It has mainly two receptor isoforms, namely prolactin receptors (PRLR) short and long, expressed in osteoblasts but not in osteoclasts. In an *in vitro* study, it was found that the PL hormone upregulated the expression of various osteoclastogenic modulators such as monocyte chemo-attractant protein-1, cyclooxygenase-2, tumor necrosis factor-alpha, interleukin-1 and ephrin-B1 which eventually lead to increased skeletal resorption during lactation (45). The accessory parathyroid gland in the breast produces abundant PTHrP which enters the maternal circulation, binds with its receptor present on osteoclasts, and accelerates the process of bone matrix resorption (36). Suckling activates the PTHrP expression and release (39). Thus, both PL and PTHrP are responsible for maternal skeletal calcium release (46). At the basolateral side of epithelial cells of mice mammary glands, PTHrP helps in the transcellular flux of calcium in milk (43). The calcium then reaches the neonatal circulation and gets immobilized along with collagen and other non-collagenous bone matrix proteins as a result of bone modeling.

Approximately, 6% loss in occurs during 6 months of exclusive breastfeeding, and this loss causes microarchitectural deterioration, though the bone loss is normally silent and does not lead to fragility fractures (10,36,47). Irrespective of the duration of lactation, the length of postpartum amenorrhea is an important determinant of bone loss (30). The rate of bone loss differs by skeletal sites (42), and the resorption rate is higher from the trabecular-rich spine and hip as compared to that of the appendicular skeleton (30,40).

Management of Pregnancy and Lactation Associated-osteoporosis

Biochemical Markers of Bone Turnover

Several changes have been observed in calcium metabolism and bone remodeling during pregnancy and lactation, and it is now important to understand the severity level of osteoporosis using several bone resorption and bone formation markers in serum and urine. These biochemical markers have been used

to gain a better understanding of the bone turnover dynamics during pregnancy and lactation (Table 1). Changes in the levels of PTH and 1,25-dihydroxyvitamin D do not play a role in reflecting the degree of bone loss during pregnancy (30,55) and during lactation (61). However, circulating level of calcitriol increases during the first trimester of pregnancy and influences the intestinal absorption of calcium (55). Serum concentrations of PTHrP increase during pregnancy which eventually results in bone resorption and increased urinary levels of pyridinoline and deoxypyridinoline significantly in the second and third trimesters (55). Increased levels of serum PTHrP and PL and decreased levels of estradiol are reported to be associated with lactation-induced bone loss during the first 6 months of exclusive breastfeeding (30). Increased bone resorption was studied by observing the increase in serum C telopeptide of type I collagen (CTX) which was twofold higher in lactating females than those of non-pregnant females, serum N-telopeptide of type I collagen (NTX) and urinary deoxypyridinoline also increases (13). Bone specific alkaline phosphatase and osteocalcin concentrations were higher in the lactating group than those in the control group (57).

During lactation, progressive loss of BMD can be assessed by dual-energy X-ray absorptiometry (DXA), and changes in bone histomorphometry can be assessed with the help of micro-computed tomography. High resolution-peripheral quantitative computed tomography is widely used for microarchitectural deterioration of bone tissue in breastfeeding females (Table 1) (58,62).

Prevention

Guidelines of various agencies worldwide (Table 2) recommend regular intake of calcium (1500 mg per day) through diet and/or with oral supplements during pregnancy and lactation. Similarly, for vitamin D, diet is sufficient but if deficiency occurs supplements of vitamin D (1000-2000 IU per day) can be recommended (68). In developed countries like the USA, there are several programs being run to fulfill the dietary need of pregnant and lactating females by considering the need of each socioeconomic group (64). In the developing world, where PLO is underestimated, under-diagnosed, and under-treated, such programs need to be developed and are necessary to run with proper assessment of socioeconomic status and needs of pregnant and lactating females. Assessment of biochemical bone turnover markers during pregnancy and after should be

Table 1. Biochemical and radiological bone turnover markers of pregnancy and lactation associated-osteoporosis

Phase	Bone turnover and histomorphometry	Vicissitudes	References
Pregnancy	Bone resorption markers	• Free pyridinoline and DPD (↑) • PTH (↓) • PTHrP (↑ in II and III trimester) • CTX (↑) • NTX (↑) • Calcitriol (↑ in I trimester)	(48-53)
	Bone formation markers	• BAP (↑) • P1NP (↑) • OCN (↓ in II trimester and ↑ in III trimester)	(49-53)
	Bone histomorphometry	• BMD (↓) • Tb. No. (↓) • Tb. Sp. (↑) • Tb. Th. (↓)	(48,49,54)
Lactation	Bone resorption markers	• Free pyridinoline and DPD (↑) • PTHrP (↑) • PL (↑) • NTX (↑) • CTX (↑) • Estradiol (↓)	(49,53,55,56)
	Bone formation markers	• BAP (↑) • P1NP (↑) • OCN (↔)	(49,53,55-57)
	Bone histomorphometry	• BMD (↓) • BV/TV (↓) • Tb. No. (↓) • Tb. Sp. (↑) • Tb. Th. (↑) • Cortical porosity (↑)	(49,58-60)

DPD: Deoxypyridinoline, CTX: Serum C-terminal cross-linked telopeptide of type I collagen, NTX: Serum cross-linked N-telopeptide of collagen I, PTHrP: Parathormone related peptide, PTH: Parathormone, BAP: Bone specific alkaline phosphatase, P1NP: Procollagen type I N-terminal propeptide, OCN: Osteocalcin, PL: Prolactin, BMD: Bone mineral density (g/cm^2), BV/TV: Bone volume fraction (%), Tb. No.: Trabecular number (mm^{-1}); Tb. Sp.: Trabecular separation (mm), Tb. Th.: Trabecular thickness (mm), cortical porosity (%)

Table 2. Recommendations for dietary calcium and vitamin D in pregnant and lactating females by different agencies

Serial number	Agency	Recommendations	Population	References
1.	CDC	Dietary recommendation of inclusion of low fat milk, cheese, yogurt etc.	American	(63,64)
2.	WHO	Dairy products for calcium in three portion of a day Vitamin D supplements in winter months and Northern Europe; Calcium supplements are available as tablets or capsules. Tablets (soluble tablets, effervescent tablets, chewable tablets for use in the mouth and modified-release tablets) are solid dosage forms containing one or more active ingredients.	For Europe and developing countries	(65,66)
3.	National Health Mission, Government of India	Swallowable tablets of 500 mg elemental calcium and 250 IU vitamin D3 in each tablet to be taken with meals two times a day.	Indian	(67)

CDC: Centre for Disease Control and Prevention, WHO: World Health Organization

carried out at regular time intervals. If required, DXA or pQCT can be recommended for BMD assessment postnatally. If the symptoms of osteoporosis appear, weaning off breastfeeding should be the first recommendation. However, it is important to mention here that all the above-mentioned guidelines are for general requirements of calcium and vitamin D during pregnancy and lactation and are not specific to PLO.

Therapeutic Interventions

The majority of case studies have reported that BMD recovers spontaneously after breastfeeding females have given up lactation within a year after weaning if no other causes are involved (69-71). On the other hand, secondary causes of PLO should be identified and treated. Some conservative strategies for the management of PLO include weaning off, calcium and vitamin D supplementation as per the above-mentioned guidelines (Table 2), avoiding lifting heavy weights, and physiotherapy (72,73). Patients with severe cases of osteoporosis (BMD T-score <-2.5 SD) or with vertebral compression fractures may be advised for using supporting vertebral corsets and bed rest to relieve back and hip pain (72,74). Along with weaning, certain medications can be given to treat these cases, though; no specific treatment guidelines have been developed for PLO as yet. PLO patients have commonly been treated either with anti-resorptive agents like bisphosphonates or anabolic agents like teriparatide depending on the severity of the case or the stage of the disease and sometimes these are used in combination or in a sequential manner (Table 3).

Bisphosphonates

Bisphosphonates are nitrogen-containing anti-resorptive compounds which show strong binding affinity to bone and are the most commonly used drugs. They inhibit the proliferation of osteoclasts, promote osteoclasts apoptosis, and modulate the bone turnover process so as to promote mineralization density (89). Commonly used bisphosphonates are alendronate, zoledronate and risedronate (49,90).

Therapeutic safety considerations of bisphosphonates treatment include complications of the upper gastrointestinal tract, fever, joint pain, transplacental transport, etc. (49,91,92). Data from animal and clinical studies suggest that they circulate in maternal serum, subsequently reach the placental barrier, and may have negative effects on pregnancy outcomes (early delivery, low birth weights, hypocalcaemia, and skeletal retardations of the newborns) (91,93). Generally, these drugs accumulate in the skeleton after their administration due to their high affinity with hydroxyapatite crystals (89,92).

Denosumab

Denosumab is a type of humanized monoclonal antibody which suppresses the RANKL-RANK signaling pathway of osteoclastogenesis. Denosumab binds to RANKL and prevents it from activating RANK thus helping in the suppression of bone resorption (94).

Accumulation of denosumab in breast milk has not been reported yet, but the drug can cross the placenta and affect fetal bone development (95). It can be used either alone or in combination with teriparatide as sequential therapy during lactation with satisfactory clinical efficacy (21).

Teriparatide

An osteoanabolic recombinant formulation, teriparatide shares similarities with the first 34 amino acids of PTH. Numerous case reports and cohort studies on the treatment with teriparatide of PLO patients belonging to different ethnicities and races are available (Table 3). It has been used to treat cases of PLO with a remarkable increase in the BMD at the lumbar spine, femoral neck, and hip with no new fracture and reduction in bone resorption markers (26,85,96-98).

This drug is commonly used due to its clinical efficacy and short half-life. However, the potential side effect is the risk of bone tumors, which is dependent on the dosage of teriparatide (21).

Table 3. Summary of some case reports, case series and cohort studies done in recent past including the important specifications related to the disease and treatment regimens

No. of cases (n) & age (yrs)	Period	Symptoms	Affected region	Tests
7 (30-39)	Pregnancy or lactation	Vertebral compression fractures or transient osteoporosis of the hip	T-score, lumbar spine =-3.2±1.0; left femur =-2.2±0.5; right femur =-1.9±0.5. Reduced trabecular and cortical thickness, no change in the trabecular number. Three novel mutations in LRP5, COL1A1, and COL1A2.	DXA (BMD), HR-pQCT, blood tests. DNA sequencing using MiSeq system
32 (31.3±2.6) (retrospective cohort study)	Third trimester/early postpartum	Vertebral fracture	Low lumbar spine BMD (Z-score =-2.5±0.7); femur neck (Z-score =-1.6±0.8) and total hip (Z-score =-1.5±0.8) BMD were less affected.	HR-pQCT, DXA, blood tests
107 (average 39.5) (Retrospective cohort study)	Third trimester/early postpartum	Vertebral fracture (at least one);	Most affected area are lumber and hip.	DXA
12 (31±5)	Pregnancy and lactation	Severe back pain, multiple vertebral compression fractures in 10 patients, 10 patients had vitamin D insufficiency	Mean BMD =0.894±0.153 g/cm^2 at lumbar spine, 0.728±0.090 g/cm^2 at femoral neck, and 0.728±0.080 g/cm^2 at total hip.	X-rays, DXA, blood tests for biochemical parameters
93 (18-40)	First month postpartum	Severe low back pain	Low BMD in relation to body mass index (BMI) in lumber, femoral neck and femoral overall.	DXA, blood tests (including level of vitamin D)
20 (33.9±4.6)	Postpartum	Vertebral fracture (5.4 fractures on an average) few have shown subsequent fractures in following years; Hip pain due to hip edema in a few, mental distress	Low BMD (lumbar spine T-score -3.3±0.9 and total femur T-score -2.3±1.0.	DXA, MRI, X-rays

Table 3. Continued

Treatments	Other specifications	Follow up duration	Region	References
Weaning, Ca and vitamin D supplements and teriparartide and denosumab.	Inclusion criteria-atraumatic or low traumatic cause, a temporal connection to the pregnancy and/or lactation. Skeletal risk factors-dental problems, drugs, endocrine disorders, historical height loss, immobility, previous fractures, (nutrition habits) as well as pregnancy and lactation.	–	Germany	(75)
27 patients were treated with teriparatide, Ca and vitamin D supplements; while 5 were treated only with Ca and vitamin supplements.	No evidence of secondary osteoporosis.	12 months	Korea	(26)
75.7% patients received bisphosphonates and/or parathyroid hormone derivatives (PTH) including vitamin D supplementation.	Included incident fracture cases and excluded patients with endocrine disorders known to affect bone metabolism such as osteogenesis imperfecta, osteomalacia, etc.	6 yrs	Germany	(47)
Alendronate or zoledronic acid.	Inclusion criteria: (1) occurrence of osteoporosis during terminal pregnancy or within 18 months post-delivery; (2) BMD Z-scores ≤-2.0; Exclusion criteria: (1) diagnosis of osteoporosis prior to pregnancy; (2) with other secondary osteoporosis.	24 months	China	(49)
Ca and vitamin D supplementation.	Exclusion criteria: (1) all individuals using antiresorbtive drugs, (2) taking vitamin D or calcium supplements, (3) with acute or chronic infections, (4) history of trauma or psychiatric disorders, (5) any secondary causes of inflammation.	6-12 months	Turkey	(76)
All patients received vitamin D (1000 IE/day). At baseline, 9 patients received teriparatide (for 2 yrs), 8 treated with bisphosphonates (for 5 yrs), 1 with denosumab, and 2 patients received no further medications. Two patients received teriparatide followed by 5 years of bisphosphonates treatment. All patients underwent a 3-week inpatient rehabilitation.	Excluded other causes of secondary osteoporosis.	2-16.3 yrs	Germany	(77)

Table 3. Continued

No. of cases (n) & age (yrs)	Period	Symptoms	Affected region	Tests
14 fracture subjects +79 non-fracture subjects (31-44)	Third trimester and early postpartum	Vertebral fractures	Low BMD (lumbar spine T-score -2.6 and femur neck T-score -2.0.	DXA, X-rays, biochemical examinations (urine and blood tests)
1 (24)	Postpartum	Severe back pain reduced vertebral height (T11-L5)	L1-4 T-score was -3.6 and femoral neck T-score was -3.1.	DXA, MRI, biochemical examinations
1 (35)	2 months postpartum (third pregnancy)	Back pain, multiple vertebral fragility fractures and height loss	Total lumbar Z-score -3.7, lumbar BMD =0.687 g/cm^2, total femur Z-score -1.5, total femur BMD =0.815 g/cm^2.	DXA, MRI, biochemical examinations
1 (33)	Early postpartum period	Severe back pain, multiple vertebral bodies with mild compression, especially in T12	The lumbar (L1-L4) BMD =0.602 g/cm^2 (Z-score =-4) and total hip BMD =0.741 g/cm^2 (Z-score =-1.6).	BMD, X-rays, MRI, CT, biochemical examinations
1 (33)	10 months postpartum	Low back pain and hip pain, left intertrochanteric fracture after falling from standing	L1-L4 (T-score is -2.8 to -3.5); hip neck (-2.7); hip trochanter (-2.2).	DXA, MRI, X-rays, biochemical tests
1 (36)	37 weeks of gestation 3 week postpartum diagnosis	Barton fracture at 37 weeks of gestation. Swelling and deformity of the wrist; restricted range of motion, lumber tenderness	Lumbar (L1-L4) BMD =0.714 g/cm^2 (Z-score =-2.9) and total hip BMD =0.717 g/cm^2 (Z-score =-1.7).	MRI, X-ray, DXA, biochemical examinations
42 (34.3±4.9)	Third trimester and postpartum lactation period	Vertebral compression fractures; transient osteoporosis of the hip or peripheral fractures	Z-score =-2.7±0.9 at the lumbar spine; pronounced reduction of trabecular and cortical thickness.	Genetic study, DXA, HR-pQCT, MRI biochemical examinations
27 (34.2±5.4)	Postpartum period	Severe back pain due to low energy vertebral fractures (VFs)	Low BMD of lumber and hip region (below -4.0) and trabecular region.	DXA, MRI, biochemical examination of bone turnover markers

Table 3. Continued

Treatments	Other specifications	Follow up duration	Region	References
Weaning, Ca and vitamin D supplement.	Study with fracture subjects started from postpartum visit while study with others started from pregnancy for before and after partum bone turnover markers.	-	Japan	(40)
Weaning, calcium and vitamin D and teriparatide 20 µg/day.	Anemia due to iron deficiency.	18 months	Iran	(78)
Weaning, calcium and vitamin D and teriparatide 20 µg/day.	No secondary cause of osteoporosis.	12 months	Turkey	(12)
Weaning, calcium carbonate 1200 mg/day, vitamin D3 650 IU/day, and alendronate 70 mg/week.	Never smoke or consumed alcohol. Followed a balanced diet during her pre-pregnancy and pregnancy. Neither experienced menstrual irregularities before pregnancy, nor pregnancy complications such as preeclampsia.	6 months	China	(79)
Weaning, calcium 600 mg/day, and vitamin D 1200 IU/day; underwent open reduction and internal fixation. Administered dalteparin sodium (0.2 mL/day, 2500 IU) to prevent deep vein thrombosis during the perioperative period and pain was alleviated with celecoxib (cyclooxygenase 2 inhibitor). Instructed to perform muscle strengthening exercises and moderately improve the range of motion in the hip and knee joints.	Breastfeeding at the time of presentation of fracture. Discontinued calcium and vitamin D after delivery.	–	China	(80)
Open reduction and internal fixation; weaning, calcium and vitamin D supplementation.	No family history of osteoporosis, and causes of secondary osteoporosis; no medical history of consuming alcohol, smoking, or using drugs. Discontinued taking calcium and vitamin D during pregnancy.	1 yr	China	(81)
Calcium and vitamin D supplementation recommended to all. Eleven patients with multiple vertebral compression fractures and a low bone turnover state treated with teriparatide (20 µg per day). Eighteen women received a bone-specific therapy 4 patients with the predominant occurrence of transient osteoporosis of the hip or a high turnover state treated with denosumab (60 mg every 6 months). Three patients treated with a combined approach (teriparatide + denosumab) due to severity (12, 5 and 6 vertebral compression fractures, respectively).	Loss of function mutations in LRP5 and WNT1 in 21 patients.	3 yrs	Germany	(56)
19 women received teriparatide (20 µg/day) (group A) plus calcium and vitamin D, 8 women with calcium and vitamin D only (group B)	Two cases identified with hyperthyroidism, one with anorexia nervosa, and one with inflammatory bowel disease. Nine had a positive family history of osteoporosis and nine received low molecular weight heparin during pregnancy.	2 yrs	Greece	(82)

Table 3. Continued

No. of cases (n) & age (yrs)	Period	Symptoms	Affected region	Tests
67 (31±2)	Postpartum period	Multiple vertebral fractures and lower back pain	Low spine and hip BMD.	DXA, X-rays, biochemical examinations
7 (30.6±3.3)	Pregnancy and postpartum	6 suffered vertebral fractures postpartum and 1 developed a hip fracture during the seventh month of gestation	Lumbar spine aBMD =0.772±0.115 g/cm^2, and Z-score =-3.2±0.7 SD. At the femoral neck, aBMD =0.683±0.133 g/cm^2 and Z-score =-2.0±0.9 SD. Low vBMD at distal radius.	HR-pQCT, DXA, biochemical examinations
1 (33)	Postpartum	Severe back pain, vertebral compression fracture	Low BMD (L1 & L4) femoral neck and total hip.	MRI, DXA, quantitative ultrasonometry (QUS) and an Xtreme-CT® (HR-pQCT)
47 (34.2±4.8)	Postpartum	Spinal fractures (mean: 4 fractures)	-	DXA, MRI, X-ray
9 (20-41)	Postpartum	Vertebral compression fractures (1 patient)	Four of nine cases were diagnosed with low bone mas; one case [accumulated doses of MgSO (4): 1,260 g] was diagnosed with PLO.	DXA
1 (29)	6 month pregnancy and 6 month postpartum	Severe back pain was located in the lower thoracic and lumbar regions since the sixth month of pregnancy	Kyphosis at L1 and L2 with mild scoliosis in the thoracolumbar region.	DXA, X-ray, MRI, biochemical tests
1 (47)	1 month postpartum	Severe low back pain, multiple vertebral fractures	Low bone marrow density (BMD) and a loss of height at the L1-L4 vertebrae.	DXA, MRI, biochemical tests
1 (34)	Pregnancy & postpartum	Leg pain during second trimester, severe hip and back pain during third trimester; multiple compression fracture postpartum	Multiple vertebral compression fractures (Th8 and Th12), height loss of all mid and low thoracic vertebra osteoporosis T-score lumbar spine =-4.2; total hip =-2.7.	DXA (aBMD), HR-pQCT, X-ray, MRI, biochemical tests; Genetic analysis (exome sequencing)

Table 3. Continued

Treatments	Other specifications	Follow up duration	Region	References
teriparatide (20 µg/day) with or without sequential antiresorptive therapy (ART).	Patients with osteogenesis imperfecta, osteomalacia, pre-existing osteoporosis, and secondary osteoporosis were excluded before PLO diagnosis.	3 yrs	Korea	(83)
-	At least one of the risk factors for osteoporosis (positive family history of osteoporosis, smoking, low calcium intake, hyperprolactinemia, kidney stones with hypercalciuria, treatment with high doses of glucocorticoids) was present.	-	Argentina	(48)
Denosumab was administered postpartum with 3000 IE vitamin D and 1000 mg of calcium daily.	No history of a secondary amenorrhea was found. The patient had always at normal weight/BMI. She had three abortions in the first trimester, an MTHFR polymorphism (C677C, heterozygous as well as a lipoprotein-a elevation) was found. A treatment with low-molecular heparin was initiated.	1.5 yrs	Germany	(84)
Subcutaneous injection of 20 µg teriparatide daily along with individually adapted vitamin D supplementation.	4 patients (7.8%) sustained a subsequent fracture, two after 3-5 months of treatment and two at >6 months of treatment.	2 yrs	Germany	(85)
-	Patients underwent long-term tocolysis with $MgSO_4$ (more than 8 days) for treatment of threatened preterm birth. (The accumulated doses of $MgSO_4$ were between 168 and 3,756 g). A positive smoking history (n=3). No family history of osteoporosis.	-	Japan	(86)
The patient was advised 2.5 mg of bromocriptine for the cessation of breastfeeding with 600 mg of calcium twice a week and vitamin D (6000 IU) once a week for 10 months. Bisphosphonate (alendronic acid) 70 mg pill weekly was advised as well.	History of miscarriage at four months of her pregnancy two years ago.	4 month	India	(87)
Romosozumab for 12-month, after 4 months of teriparatide injection.	Positive family history of osteoporosis; undergone a laparoscopic partial oophorectomy for the treatment of endometriosis.	1 yrs	Japan	(88)
Advised cessation of breastfeeding; calcium and vitamin D supplementation. Teriparatide 20 µg/day for 1 year followed by one dose of zoledronic acid (ZA).	No monogenic mutation; no secondary causes of osteoporosis.	7-40 months	Netherlands	(27)

aBMD: Areal bone mineral density, DXA: Dual-energy X-ray absorptiometry, HR-pQCT: High resolution-peripheral quantitative computed tomography

Other Anabolic Medications

Romosozumab and abaloparatide are two more FDA-approved anabolic interventions for the management of osteoporosis (99). Abaloparatide shares 76% homology to PTHrP and selectively activates PTHR1 favoring bone formation (100). Romosozumab is a monoclonal antibody that targets sclerostin secreted by osteocytes. The canonical Wnt/β-catenin pathway plays a crucial role in osteoblasts proliferation and differentiation. Sclerostin suppresses the canonical Wnt/β-catenin pathway by binding to low density lipoprotein receptor-related protein 5/6 (LRP5/6) co-receptors (101). Romosozumab binds to sclerostin and prevents inhibition of bone formation with mild adverse events (102).

Various clinical studies highlight the role of romosozumab and abaloparatide in improving BMD and bone turnover markers and a concomitant relief from back pain with no further fractures in postmenopausal osteoporosis (100,103,104). A 23.6% increase in lumbar spine, a 6.2% increase in femoral neck, and an 11.2% increase in total hip BMD of a 34-year-old woman who presented with severe low back pain and multiple vertebral fractures after she received romosozumab for 12 months has been reported (88). There were no reports on abaloparatide treatment of PLO women.

Kyphoplasty and Vertebroplasty

Kyphoplasty and vertebroplasty were reported for treating pregnancy and lactation-associated osteoporotic vertebral fragility fractures and compression fractures with other therapeutic interventions. Kyphoplasty and vertebroplasty are a very successful treatments for short-term pain relief for vertebral fractures (59,74,105,106).

Conclusion and Future Perspective

PLO is a rare disease and the number of cases is low, possibly due to underreporting and ignorance in the population about the situation mainly in the developing world. This calls for the need to reassess the societal status of the population while formulating new guidelines and public health policies. Further investigations into the correlation between pregnancy, lactation, and BMD, and subsequent risk of osteoporosis will provide new opportunities for early intervention, timely management, and prevention of PLO.

Treatment recommendations should be personalized based on number of parities, duration of lactation, presence or absence of fractures, societal status, age, ethnicity and race. By integrating the systems biology with P4 (predictive, preventive, personalized and participatory) medicine care social, psychological, economic and healthcare related burden can be reduced towards a more productive society.

Acknowledgments: We thank Dr. MD. Arshad and Dr. Rahul Gupta for critical reading of the manuscript and providing valuable suggestions.

Ethics

Authorship Contributions

Concept: N.M., M.G., Design: N.M., M.G., Literature Search: N.M., H.M., M.G., Writing: N.M., H.M., M.G.

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

Financial Disclosure: ICMR; file No. 3/1/3(24)/Endo-fellowship/22-NCD-III to HM.

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Original Investigation / Orijinal Araştırma

DOI: 10.4274/tod.galenos.2023.54036
Turk J Osteoporos 2024;30:16-21

Evaluation of the Relationships Between Bone Mineral Density and Anthropometric Measurements in Women with Postmenopausal Osteoporosis

Postmenopozal Osteoporozu Olan Kadınlarda Kemik Mineral Yoğunluğu ile Antropometrik Ölçümler Arasındaki İlişkilerin Değerlendirilmesi

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Abstract

Objective: There are various factors that affect bone mineral density (BMD) in postmenopausal women. The aim of this study was to evaluate the relationships between anthropometric characteristics and BMD in women with postmenopausal osteoporosis (PMO).
Materials and Methods: Demographic features of the participants including age, menopause age, smoking habits, comorbidities, educational and marital status were recorded. Anthropometric characteristics such as height, weight, body mass index (BMI), waist-to-hip ratio (WHR), digit ratio of dominant hand (2D:4D), skeletal muscle mass index (SMI), hand and thigh circumferences were measured. In addition to L1-L4, femur neck (FN), femur total (FT) T-scores, serum calcium and 25(OH) vitamin D levels were noted.
Results: This study included a total of 181 women with PMO (mean age 62.78±7.81 years, menopause age 45.69±5.58 years and BMI 27.24±4.87 kg/m²). 64.6% of the participants had at least one systemic disease and 71.8% were non-smokers. The mean values of serum calcium and 25(OH) vitamin D were 9.71±0.73 mg/dL and 26.22±15.34 ng/mL, respectively. Weight and BMI showed significant positive correlations with T-scores at L1-L4 total, FN and FT. While thigh circumference and SMI significantly correlated with T-scores at FN and FT, hand circumference only correlated with T-score at FN. On the other hand, no correlations were found between T-scores and other anthropometric measurements (height, WHR, 2D:4D).
Conclusion: These findings have shown that the patients with lower weight and BMI have lower T-scores at lumbar spine and femur. Additionally, thigh circumference and SMI correlated positively with femur T-scores. Further studies are warranted to reveal the role of these anthropometric measurements in determining the risk of osteoporosis in postmenopausal women.
Keywords: Anthropometric measurements, bone mineral density, postmenopausal osteoporosis

Öz

Amaç: Postmenopozal kadınlarda kemik mineral yoğunluğunu (KMY) etkileyen çeşitli faktörler vardır. Bu çalışmanın amacı, postmenopozal osteoporozu (PMO) olan kadınlarda antropometrik özellikler ile KMY arasındaki ilişkileri değerlendirmektir.
Gereç ve Yöntem: Katılımcıların yaş, menopoz yaşı, sigara içme alışkanlığı, ek hastalıkları, eğitim durumu ve medeni durumu gibi demografik özellikleri kaydedildi. Boy, kilo, vücut kitle indeksi (VKİ), bel kalça oranı (BKO), dominant elin parmak oranı (2P:4P), iskelet kası kütle indeksi (İKKİ), el ve uyluk çevreleri gibi antropometrik özellikler ölçüldü. L1-L4'e ek olarak femur boyun (FB), femur total (FT) T-skorları, serum kalsiyum ve 25(OH) D vitamini seviyeleri not edildi.
Bulgular: Bu çalışmaya PMO'lu toplam 181 kadın dahil edildi (ortalama yaş 62,78±7,81 yıl, menopoz yaşı 45,69±5,58 yıl ve VKİ 27,24±4,87 kg/m²). Katılımcıların %64,6'sının en az bir sistemik hastalığı vardı ve %71,8'i sigara kullanmıyordu. Serum kalsiyum ve 25(OH) D vitamini ortalama değerleri sırasıyla 9,71±0,73 mg/dL ve 26,22±15,34 ng/mL idi. Ağırlık ve VKİ, L1-L4 total, FB ve FT'deki T-skorları ile anlamlı pozitif korelasyon gösterdi. Uyluk çevresi ve İKKİ, FB ve FT'de T-skorları ile anlamlı korelasyon gösterirken, el çevresi sadece FB'de T-skoru ile koreleydi. Öte yandan, T-skorları ile diğer antropometrik ölçümler (boy, BKO, 2P:4P) arasında bir korelasyon bulunmadı.

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Received/Geliş Tarihi: 28.10.2023 **Accepted/Kabul Tarihi:** 06.11.2023

Presented in: This study has been presented in OSTEO 2021 Osteoporosis, Osteoarthritis and Musculoskeletal Pain Congress 8-10 October 2021.

Öz

Sonuç: Bu bulgular, kilosu ve VKİ'si düşük olan hastaların lomber omurga ve femurda daha düşük T-skorlarına sahip olduğunu göstermiştir. Ek olarak, uyluk çevresi ve İKKİ, femur T-skorları ile pozitif korelasyon gösterdi. Postmenopozal kadınlarda osteoporoz riskini belirlemede bu antropometrik ölçümlerin rolünü ortaya çıkarmak için daha ileri araştırmalar gereklidir.
Anahtar kelimeler: Antropometrik ölçümler, kemik mineral yoğunluğu, postmenopozal osteoporoz

Introduction

The hallmarks of osteoporosis (OP), a systemic disease, are low bone mass and deterioration in the microarchitecture of bone tissue in addition, these result in bone fragility and an increase in the risk of fracture (1-5). It is a preventable, underdiagnosed, under-treated, and silent disease until complicated by fractures (2,5-10). As a public health issue, osteoporotic fractures may have fatal or severe disabling effects (1,5-7). All risk factors for OP and fractures with an impact on quality of life that crosses medical, social, and economic lines, should be considered and addressed thoroughly when managing a patient with suspected or diagnosed bone loss (1,5).

The factors affecting bone mineral density (BMD) vary widely in postmenopausal osteoporosis (PMO). Body composition, weight, alcohol consumption, smoking, exposure to sunlight, nutritional status, eating habits and physical activities are known to have a significant impact on BMD (11-13). Tools for population screening and early illness identification, the anthropometric measurements are straightforward, non-invasive, affordable, and useful (14,15). Some studies have been carried out to assess the relationships between anthropometric traits and BMD in PMO (10,13,16-22). It has been reported that weight, height and body mass index (BMI) were found to be positively associated with BMD parameters (16-22). On the other hand, there are conflicting results regarding the relationships between waist circumference (WC) and BMD as well as waist-to-hip (WHR) and BMD in PMO (10,13,16-19). There are very few studies evaluating the relationships between BMD and other anthropometric measurements including skeletal-muscle-mass-index (SMI), digit ratio of dominant hand (2D:4D), and hand circumference (10,18). This study sought to assess the associations between anthropometric parameters and BMD in PMO.

Materials and Methods

This cross-sectional research was conducted with 181 consecutive patients. Inclusion criteria were as follows: Aged over 50 years, being postmenopausal and having OP in accordance with World Health Organization (WHO) recommendations. The following were the exclusion criteria: The presence of conditions and/or drug usage that could lead to secondary OP, neurological disorders, vestibular diseases, malignancy, cardiac disorder, instrumentation in the spine and/or joints in the lower extremities.

Written informed consent was obtained prior to the study from all subjects. Approval for the study was granted by Hacettepe University Non-invasive Clinical Research Ethics Committee (decision no: GO 16/209-02, date: 12.04.2016). The study was carried out according to the principles of the Declaration of Helsinki.

Age, menopause age, smoking habits, comorbidities, educational and marital status were recorded as participant demographic characteristics. After then anthropometric characteristics such as height, weight, BMI, WC, hip circumference (HC), WHR, SMI, 2D:4D, hand and thigh circumferences were measured. WHR was calculated by dividing the standing-position measured WC by HC. Skeletal muscle mass (SM) was first computed to calculate SMI using the following formula (15):

SM=0.244×weight+7.80×height
+6.6×sex-0.98×age+race-3.3

(sex =1 for male and 0 for female, race =-1.2 for Asian, 1.4 for African American, and 0 for white and Hispanic). SM (kilogram) was divided by squared height (square meter) to determine SMI. The 2D:4D ratio was determined by dividing the length of the second finger by the length of the fourth finger. Hand circumference measurement was measured using tape at the widest part of the palm and wrapping it around the palms. Lastly, thigh circumference was measured from the largest part of the dominant leg in the standing position.

Using a dual-energy X-ray absorptiometry system from Hologic, BMD was calculated, and OP was identified in accordance with WHO standards. T-scores were recorded at the femur neck (FN), femur total (FT), and lumbar spine (LS, L1-L4 total).

Statistical Analysis

The IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA) was used to conduct the statistical analysis. The mean and standard deviation or median (minimum-maximum) were used for continuous variables, whereas percentages and numbers were used for categorical variables. The Kolmogorov-Smirnov test revealed that the data were normal distribution, and the Pearson correlation was performed to ascertain the relationship between parametric variables. A p-value of 0.05 was taken into account.

Results

The study comprised a total of 181 postmenopausal women with a mean age of 62.78±7.81 years. Table 1 displays the patients' demographic details, clinical traits, and anthropometric characteristics. The average values of calcium and 25-hydroxyvitamin D levels were 9.7±0.73 mg/dL and 26.2±15.34 ng/mL, respectively. The correlations between BMD

and anthropometric measurements are shown in Table 2. With respect to the L1-L4 total, FN and FT T-scores, weight and BMI significantly correlated positively. While the thigh circumference and SMI were significantly correlated with both the femoral neck and total T-scores, hand circumferences showed significant correlation only with FN T-score. No correlation was found between height, WHR, 2D:4D ratio and T-scores of all regions.

Discussion

Anthropometric measurements are usually chosen for population screening because they are affordable and simple to implement in clinics. The relationships between anthropometric traits and BMD in postmenopausal women have not been thoroughly investigated in many research (10,13,16-22). In most of the previous studies, it has been found that weight, height, and BMI positively correlate with BMD parameters (16-22). In line with earlier findings, we reported that LS and femur BMD were positively associated with weight and BMI in postmenopausal women. The associations between WC and BMD, as well as WHR and BMD, in PMO are contradictory (10,13,16-19). In a cross-sectional population-based study, Hasani-Ranjbar et al. (16) showed that BMI and WC were positively associated with BMD in three different bone areas, while WHR had a negative correlation with BMD in postmenopausal women. According to Kim et al. (17), body weight was favorably correlated with all regions of BMD, while WC was adversely correlated with all regions of BMD in a study with 907 postmenopausal healthy female participants aged 60 to 79 years. According to a population-based study with 4,445 subjects by Aghaei Meybodi et al. (13), it has been shown that BMD was significantly correlated to weight, height, BMI and WHR. Unlike prior inquiries, we found that there was no relationship between WHR and LS or femur T-scores. There exists very little research that investigates the connections between BMD and other anthropometric parameters such as SMI, digit ratio of the dominant hand (2D:4D), and hand circumference (10,18). In a cross-sectional study consisting of 482 patients who attended the geriatric outpatient clinic, Murat et al. (18) established that LS and FN T scores were considerably associated with weight, BMI, WC, and SMI. It has been demonstrated that SMI provides the most contribution to predicting FN and LS T-scores in multiple regression analysis (18). Arazi et al. (10) reported that 97 postmenopausal women's anthropometric characteristics, including WHR, SMI, 2D:4D, and calf circumference, were associated with BMD. In the scope of the same study, no relationship was found between hand circumference and BMD. Consistent with previous reports, our results have shown that some anthropometric characteristics (weight, BMI, SMI, thigh and hand circumference) were associated with T-scores in PMO. Similar to the results of other studies, we found LS and femur BMD positively correlated with weight and BMI in postmenopausal women, as well as positive correlations between femur T-scores (both neck and total) and thigh circumference and SMI in postmenopausal women. Moreover, we also determined that hand circumference was only related to the FN T-score. Contrary to the previous results, we could not find a correlation between WHR, 2D:4D ratio and T-scores.

It has been demonstrated that the risk of bone fracture decreases with increasing BMI (17,23-26). Obesity is usually thought to be preventive against fractures by reducing the impact of falls owing to higher BMD and more soft tissue padding (23,27). In contrast, obese people may have an increased risk of falling due to their decreased physical mobility and muscle strength. Although it was previously believed that obesity guarded against OP, recently a high percentage of fat has been shown to negatively affect bone health (18). Premaor et al. (25) found that obesity was common among those who presented to the Fracture Liaison Service with a low-trauma fracture even though the majority of these postmenopausal women had BMDs that were within the normal range. Particularly, they reported that obese women had considerably more hip fractures than non-obese women. In a multinational, population-based cohort of postmenopausal women, Compston et al. (27) showed that the

Table 1. The demographic features, clinical properties and anthropometric characteristics of the patients

	n=181
Age (years) (mean ± SD)	62.78±7.81
Marital status	
Married	117 (64.6%)
Single	21 (11.6%)
Widow	43 (23.8%)
Education	
Illiterate	32 (17.7%)
Primary school	100 (55.3%)
High school	27 (14.9%)
University	22 (12.2%)
Height (cm) (mean ± SD)	156.20±5.95
Weight (kg) (mean ± SD)	66.20±11.61
Body mass index (kg/m²) (mean ± SD)	27.24±4.87
Age of menopause (years) (mean ± SD)	45.69±5.58
Waist-to-hip ratio (mean ± SD) (median)	0.88±0.90 0.88
Skeletal-muscle-mass-index (kg/m²) (mean ± SD)	9.06±1.31
Digit ratio (2D:4D)	0.99±0.07
Thigh circumference (cm) (mean ± SD)	52.29±9.59
Hand circumference (cm) (mean ± SD)	19.44±1.06
BMD in different bone areas (mean ± SD)	
Femoral neck T-score	-1.98±0.77
Total hip T-score	-1.66±0.85
Lumbar L1-L4 total T-score	-2.97±0.66

SD: Standard deviation, 2D:4D: Digit ratio of dominant hand

Table 2. The correlations between BMD and anthropometric measurements

	Lumbar L1-L4 total T-score	Femoral neck T-score	Total hip T-score
Height	r=0.102 p=0.176	r=0.015 p=0.840	r=-0.070 p=0.354
Weight	**r=0.203** **p=0.007**	**r=0.310** **p<0.001**	**r=0.256** **p=0.001**
Body mass index	**r=0.164** **p=0.029**	**r=0.324** **p<0.001**	**r=0.288** **p<0.001**
Waist-to-hip ratio	r=0.050 p=0.510	r=0.014 p=0.853	r=-0.023 p=0.766
Thigh circumference	r=0.038 p=0.616	**r=0.464** **p<0.001**	**r=0.411** **p<0.001**
Skeletal-muscle-mass-index	r=0.125 p=0.098	**r=0.308** **p<0.001**	**r=0.290** **p<0.001**
Digit ratio (2D:4D)	r=0.071 p=0.345	r=0.021 p=0.775	r=-0.002 p=0.984
Hand circumference	r=0.074 p=0.325	**r=0.148** **p=0.048**	r=0.061 p=0.425

BMD: Bone mineral density, 2D:4D: Digit ratio of dominant hand

risk of fractures in the ankle and upper leg was considerably higher in obese women compared to non-obese females. They emphasized that obesity is related to an increased risk of ankle and upper leg fractures and does not protect against fractures in postmenopausal females. Gnudi et al. (28) reported that increased BMI and wrist or ankle fractures were not correlated in a study of postmenopausal women with fractures but increased BMI was linked to a considerably higher risk of humerus fracture and a lower risk of hip fracture.

The gynecoid fat distribution model with a low WHR provides significant advantages for women. It is stated that high WHR is associated with high androgen and cortisol levels and low estrogen (29). WC increases significantly during menopause due to the drop in estrogen levels (30). Estrogen may directly reduce WHR by enhancing the accumulation of fat in the hips and thighs and the accelerated lipolysis of abdominal fat. It appears likely that there is a strong correlation between WHR and bone density given the link between WHR and androgen and estrogen (29). Aghaei Meybodi et al. (13) found a correlation between WHR and BMD. In the study of Kim et al. (17), WC was demonstrated to be significantly larger in the postmenopausal group with fractures than in the postmenopausal group without fractures. It was also emphasized that WC was related to BMD and osteoporotic vertebral fractures (17). Arazi et al. (10) revealed a negative correlation between WHR and LS and hip BMD. In the study of Abbasi et al. (31), it has been demonstrated that osteoporotic females have a smaller WC and WHR than non-osteoporotic females. However, we could not find a relationship between WHR and T-scores.

The findings of Arazi et al. (10) demonstrated a significant positive association between SMI and BMD. Similarly, Murat et al. (18) showed that LS and FN T-scores were significantly related to SMI. In addition, they emphasized the importance of SMI in predicting FN and LS T-scores (18). Similarly, we found a positive correlation between SMI and femoral neck and total T-scores.

It is known that women's second fingers are typically equal to or longer than their fourth fingers, whereas men's second fingers are typically shorter than their fourth digit. It has been proposed that 2D:4D has an adverse relationship with prenatal testosterone and a positive relationship with prenatal estrogen (10,32). Zheng and Cohn (32) showed that the 2D:4D ratio was related to the equilibrium of the androgen and estrogen receptors. These receptors are more determinative of the length of the fourth finger than the second finger. The androgen receptor inactivation decreases the ring finger's growth rate, whereas the estrogen receptor inactivation increases the ring finger's growth rate, decreasing the 2D:4D ratio. The 2D:4D ratio is thought to reverberate circulating androgen and estrogen levels. Genetic studies have shown that certain genes regulated by sex steroids play significant roles in finger growth. Wnt5a has been demonstrated to organize the rate of growth and maturation of chondrocytes in long bones. It is also known that aging-related bone loss is caused by a decrease in estrogen (10,32). In a previous study, it was reported that 2D:4D was associated with LS and hip BMD in postmenopausal women (10). On the contrary, we found no relationship between the 2D:4D ratio and T-scores in our study.

Many studies have indicated that BMD and handgrip strength (HGS) have a positive association (10,33-36). It is thought that hand circumference and HGS have a strong favorable association (37). Accordingly, it is assumed that hand circumference can be utilized as an anthropometric measurement to estimate BMD. Nevertheless, Arazi et al. (10) reported that the hand

circumference was not related to LS and hip BMD. We found that hand circumference was related to FN T-scores but not lumbar and FT T-scores.

Study Limitations

Our study's limitations include a small sample size and the fact that we did not document the patients' fracture histories. If we had examined the relationship between fracture and anthropometric characteristics, the data could have enriched our research. Our study's strength is that a sample of postmenopausal osteoporotic women was examined using a variety of anthropometric characteristics. More study is needed to investigate the relationships between BMD and other anthropometric characteristics such as SMI, 2D:4D, and hand circumference. We contributed to the restricted literature by finding that there was no correlation between WHR and LS or femur T-scores, nor between 2D:4D ratio and T-scores.

Conclusion

In conclusion, we found that anthropometric measurements including weight, BMI, SMI, thigh and hand circumference significantly correlated with T-scores at LS and or femur. BMD in PM women is a complex issue, and a comprehensive evaluation that includes the anthropometric element will be beneficial in terms of clinical practical applications. Further research is needed to reveal the act of anthropometric measurements in determining the OP risk in postmenopausal women.

Ethics

Ethics Committee Approval: Approval for the study was granted by Hacettepe University Non-invasive Clinical Research Ethics Committee (decision no: GO 16/209-02, date: 12.04.2016).

Informed Consent: Written informed consent was obtained prior to the study from all subjects.

Authorship Contributions

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

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

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

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Original Investigation / Orijinal Araştırma

DOI: 10.4274/tod.galenos.2023.14892
Turk J Osteoporos 2024;30:22-9

Systemic Immune Inflammation Index in Ankylosing Spondylitis Patients

Ankilozan Spondilit Hastalarında Sistemik İmmün Enflamasyon İndeksi

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Abstract

Objective: Our objective was to assess the relationship between disease activity and the systemic immune-inflammation index [SII; (platelet count × neutrophil count / lymphocyte count)] in individuals with ankylosing spondylitis (AS).
Materials and Methods: A total of 201 participants (130 AS patients and 71 healthy volunteers) aged 18-65 years were included in this single center cross-sectional study. Based on their ratings on the Bath Ankylosing Spondylitis Disease Activity index (BASDAI), patients with AS were split into two groups: remission (n=90, those with BASDAI <4) and active disease (n=40, those with BASDAI >4). The study employed Spearman correlation analysis to assess the relationship between SII and C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), BASDAI, Ankylosing Spondylitis Disease Activity score-ESR (ASDAS-ESR), and ASDAS-CRP. The effectiveness of SII and other measures in evaluating the disease activity in the active AS and remission AS groups was ascertained using receiver operating characteristic curve analysis.
Results: SII values were significantly higher in the AS group than healthy controls, as well as in the active AS group than AS patients in remission (p<0.001 for each). SII values were positively correlated with CRP [Spearman correlation coefficient (rs): 0.384, p<0.001], ESR (rs: 0.243, p=0.005), BASDAI (rs: 0.668, p<0.001), ASDAS-ESR (rs: 0.619, p<0.001) and ASDAS-CRP (rs: 0.700, p<0.001) values. The optimal cut-off value for the determination of AS disease activity was found to be 530.22×10^9/L (area under the curve: 0.902, 95% confidence interval: 0.838-0.947, sensitivity: 72.50% and specificity: 92.22%).
Conclusion: When assessing the activity of AS disease, SII appears to be a useful biomarker.
Keywords: Ankylosing spondylitis, C-reactive protein, neutrophil to lymphocyte ratio, systemic immune-inflammation index

Öz

Amaç: Ankilozan spondilit (AS) hastalarında sistemik immün-enflamasyon indeksi [SII; (platelet sayısı × nötrofil sayısı / lenfosit sayısı)] ile hastalık aktivitesi arasındaki ilişkiyi değerlendirmeyi amaçladık.
Gereç ve Yöntem: Tek merkezli kesitsel çalışmamıza 18-65 yaş arası toplam 201 katılımcı (130 AS hastası ve 71 sağlıklı gönüllü) dahil edildi. AS hastaları Bath Ankilozan Spondilit Hastalık Aktivite indeksi (BASDAI) skorlarına göre remisyon grubu (n=90, BASDAI <4 olanlar) ve aktif hastalık grubu (n=40, BASDAI ≥4 olanlar) olmak üzere iki gruba ayrıldı. SII'nin C-reaktif protein (CRP), eritrosit sedimantasyon hızı (ESH), BASDAI, Ankilozan Spondilit Hastalık Aktivite skoru-ESH (ASDAS-ESH) ve ASDAS-CRP ile korelasyonu Spearman korelasyon analizi ile değerlendirilmiştir. Aktif AS ve remisyondaki AS gruplarında SII ve diğer parametrelerin hastalık aktivitesini değerlendirmedeki performansını belirlemek için alıcı işletim karakteristik eğrisi analizi kullanıldı.
Bulgular: SII değerleri AS grubunda sağlıklı kontrollere göre ve aktif AS grubunda remisyondaki AS hastalarına göre anlamlı derecede yüksekti (her biri için p<0,001). SII değerleri CRP [Spearman korelasyon katsayısı (rs): 0,384, p<0,001], ESH (rs: 0,243, p=0,005), BASDAI (rs: 0,668, p<0,001), ASDAS-ESH (rs: 0,619, p<0,001) ve ASDAS-CRP (rs: 0,700, p<0,001) değerleri ile pozitif korelasyon gösterdi. AS hastalık aktivitesini belirlemek için optimal kesme değeri $530,22 \times 10^9$/L olarak bulunmuştur (eğri altındaki alan: 0,902, %95 güven aralığı: 0,838-0,947, duyarlılık: %72,50 ve özgüllük: %92,22).
Sonuç: SII, AS hastalık aktivitesini değerlendirmede etkili bir biyobelirteç gibi görünmektedir.
Anahtar kelimeler: Ankilozan spondilit, C-reaktif protein, nötrofil/lenfosit oranı, sistemik immün-enflamasyon indeksi

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Presented in: Our study was presented as an oral presentation at the North South Marmara Rheumatology Meetings congress held on 14-16 October 2022.

Introduction

Ankylosing spondylitis (AS), a chronic inflammatory rheumatic disease, is characterized by inflammatory low back pain resulting from spondylitis and sacroiliitis. The condition typically peaks in the second and third decades of life (1). Apart from spinal involvement, other musculoskeletal findings (i.e., arthritis, enthesitis and dactylitis) and findings related to extra-articular involvement (i.e., anterior uveitis, psoriasis and inflammatory bowel disease) may also accompany the clinical picture (2). In the advanced stages of the disease, kyphosis and limited spine mobility may appear with the development and progression of syndesmophytes in the vertebrae (3). These conditions likely to occur in the course of the disease may limit physical functions and impair quality of life in AS patients (4). When monitoring AS patients, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly used to gauge the level of inflammation (5). Besides the conventional acute phase reactants, other markers calculated from complete blood count parameters such as neutrophil-to-lymphocyte ratio (NLR) and platelet (PLT)-to-lymphocyte ratio (PLR) have also been investigated in many studies (6-11).

The Ankylosing Spondylitis Disease Activity score-CRP (ASDAS-CRP), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and the ASDAS-ESR are the current measures used to evaluate AS disease activity.

Systemic immune-inflammation index (SII), calculated from complete blood count parameters using a formula of "PLT x neutrophil count / lymphocyte count", was firstly defined as a useful index in hepatocellular cancer patients (12). Later on, its potential utility has also been considered for other malignancies, ulcerative colitis, uveitis, Bell's palsy, irritable bowel syndrome, hidradenitis suppurativa, psoriasis and obstructive sleep apnea syndrome (13-24). In the setting of rheumatic diseases, SII is suggested to be used as a novel index in assessment of disease activity in rheumatoid arthritis, Behçet's disease, adult-onset Still's disease and anti-neutrophil cytoplasmic antibody-associated vasculitis (25-28). Already there are 2 studies evaluating the SII in relation to disease activity in AS patients (29,30). In one of these studies, only 50 AS patients were evaluated (30). In the other study, correlation of SII with CRP, ESR and BASDAI was evaluated, correlation assessment was not performed with ASDAS (29).

Therefore, the purpose of our study was to assess the relationship in a larger group of AS patients between ASDAS and SII values in addition to ESR, CRP, and BASDAI.

Materials and Methods

This single center cross-sectional study included 130 patients (aged 18-65) who were being followed at rheumatology outpatient clinics of Bursa Uludağ University Faculty of Medicine, Department of Physical Medicine and Rehabilitation and who had been diagnosed with AS based on Modified New York criteria (31).

Patients with comorbid diseases such as hypertension, diabetes mellitus, coronary artery disease, metabolic syndrome, malignancy, infection, anemia, parathyroid diseases, thyroid dysfunction, chronic obstructive respiratory disease, obstructive sleep apnea syndrome, allergic rhinitis, asthma, active smoking and other inflammatory rheumatic diseases were excluded from the study. A total of 71 healthy volunteers with no pathological findings on physical examination and laboratory tests on their admission to outpatient clinics served as the control group. The study protocol was approved by the Bursa Uludağ University Faculty of Medicine Clinical Research Ethics Committee (approval date: February 23, 2022, decision no: 2022-4/25). Informed consent was obtained from all subjects in accordance with the Declaration of Helsinki. Data on patient demographics (age, gender), educational status, occupational status, disease duration, medical treatments, CRP and ESR levels, neutrophil, lymphocyte and PLT counts were recorded. SII, NLR and PLR values were calculated.

Disease activity was assessed with BASDAI, ASDAS-ESR and ASDAS-CRP scores. Based on exhaustion, spinal pain, joint pain/swelling, areas of localized soreness, morning stiffness length, and morning stiffness intensity, the 6-item BASDAI index is used to assess disease activity. Higher total scores indicate increased disease activity. The score ranges from 0 to 10 (32). BASDAI scores ≥4 denotes the active disease. Patients classified as being in remission were those with a BASDAI <4, and patients classified as having active disease were those with a BASDAI >4.

Statistical Analysis

The conformity of continuous variables to the normal distribution was examined using the Shapiro-Wilk test. Continuous variables were expressed using mean ± standard deviation or median (minimum:maximum) values; categorical variables were expressed as n (%). The Mann-Whitney U test and the independent samples t-test were used to compare the groups based on the findings of the normality test. Categorical variables were analyzed using the chi-square test. The correlation of SII values with CRP, ESR, BASDAI, ASDAS-ESR and ASDAS-CRP values were examined with Spearman correlation analysis. SPSS (Version 26.0. Armonk, NY: IBM Corp.) program was used for statistical analysis. Power analysis is calculated to be 99% and the effect size was 0.66. Type I error was accepted as 5% and $p<0.05$ was considered to be statistically significant.

Results

In total, 201 people were included in our study: 130 patients with AS diagnoses and 71 healthy controls. Age and gender differences between the AS group and the healthy control group were not statistically significant ($p>0.05$). When comparing the AS group to the healthy control group, the values of SII, neutrophil, PLT, and NLR were considerably greater ($p<0.05$). Regarding PLR and lymphocyte levels, there was no discernible difference between the two groups ($p>0.05$).

Demographic and clinical characteristics and laboratory results of all participants are summarized in Table 1.

When AS patients were evaluated with respect to BASDAI score, 90 patients with a score <4 were considered in the remission group, and 40 patients with a score ≥4 were in the active group. There was no statistically significant difference between active AS and remission AS groups in terms of age, gender, disease duration, education level and occupational status (p>0.05). SII, neutrophil, lymphocyte, PLT, CRP, ESR, NLR, PLR, BASDAI, ASDAS-ESR and ASDAS-CRP values were significantly higher in the active AS group than in the AS in remission (p<0.05). The clinical and demographic characteristics and laboratory results of the active AS and the remission AS groups are summarized in Table 2.

SII values were found to be positively correlated with CRP [Figure 1a: Spearman correlation coefficient (rs): 0.384, p<0.001], ESR (Figure 1b: rs: 0.243, p=0.005), BASDAI (Figure 1c: rs: 0.668, p<0.001), ASDAS-ESR (Figure 1d: rs: 0.619, p<0.001) and ASDAS-CRP (Figure 1e: rs: 0.700, p<0.001) values. Data on correlation analysis of SII values with ESR, CRP, BASDAI, ASDAS-ESR and ASDAS-CRP values are shown in Table 3 and Figure 1.

Receiver operating characteristic (ROC) curve was used to evaluate disease activity in AS patients. Area under the ROC curve was found to be 0.902 for SII [95% confidence interval (CI): 0.838-0.947], 0.837 for NLR (95% CI: 0.762-0.896), 0.812 for PLR (95% CI: 0.734-0.875), 0.728 for ESR (95% CI: 0.643-0.802) and 0.732 for CRP (95% CI: 0.647-0.806). The optimal cut-off point for SII in evaluation of disease activity was found to be 530.22×10^9/L (sensitivity: 72.50%, specificity: 92.22%). ROC curve analyses are shown in Table 4 and Figure 2.

Discussion

In AS, similar to the other inflammatory rheumatic diseases, indicators are needed to determine and monitor disease activity. ESR, CRP, BASDAI, ASDAS-ESR and ASDAS-CRP are routinely used for this purpose in AS patients. In order to evaluate AS disease activity, studies have been conducted on new indicators that can be calculated from complete blood count parameters (6-11,29,30). In order to offer a new indicator, we studied SII and found that it is positively correlated with inflammation and disease activity in AS patients.

Table 1. Clinical, demographic and laboratory parameters of AS patients and healthy controls

	AS (n=130)	Control (n=71)	p-value
Age (year)	44 (26-63)	43 (18-64)	0.583
Sex, n (%)			
Female	34 (26.2)	25 (35.2)	0.197
Male	96 (73.8)	46 (64.8)	
Level of education, n (%)			
Primary education	50 (38.5)	-	-
High school	47 (36.1)	-	
University	33 (25.4)	-	
Job, n (%)			
Housewife	14 (10.8)	-	-
Retired	32 (24.6)	-	
Employee	56 (43.1)	-	
Officer	20 (15.4)	-	
Freelancer	8 (6.2)	-	
Medications, n (%)			
NSAIDs	24 (17.5)	-	-
bDMARDs	111 (81)	-	
Sulfasalazine	2 (1.5)	-	
Neutrophils ($\times10^9$/L)	4.26 (2.08, 8.30)	3.44 (2.11, 5.86)	**<0.001**
Lymphocytes ($\times10^9$/L)	2.50 (1.21, 4.85)	2.44 (1.51, 3.82)	0.494
PLT ($\times10^9$/L)	261.40 (157.00, 499.80)	236.90 (135.00, 339.00)	**0.007**
NLR	1.58 (0.73, 4.48)	1.48 (0.79, 2.82)	**0.007**
PLR	107.67 (42.69, 251.97)	98.04 (39.82, 160.31)	0.143
SII ($\times10^9$/L)	435.33 (177.74, 1297.02)	371.54 (163.73, 532.23)	**<0.001**

Data are reported as mean ± standard deviation and median (minimum:maximum). AS: Ankylosing spondylitis, bDMARDs: Biological disease-modifying antirheumatic drugs, NLR: Neutrophil-to-lymphocyte ratio, NSAIDs: Non-steroidal anti-inflammatory drugs, PLR: Platelet-to-lymphocyte ratio, PLT: Platelet, SII: Systemic immune-inflammation index. P<0.05= statistical significance level

Table 2. Clinical, demographic, and laboratory parameter comparisons between the AS patient population in remission and the active group

	Active AS (n=40)	Remission AS (n=90)	p-value
Age (year)	44.70 (SD:9.56)	44.42 (SD:8.47)	0.869
Sex, n (%)			
Female	14 (35.0)	20 (22.2)	0.136
Male	26 (65.0)	70 (77.8)	
Disease duration (year)	12 (1-37)	12 (1-41)	0.340
Level of education, n (%)			
Primary education	12 (30.0)	38 (42.2)	0.431
High school	17 (42.5)	30 (33.3)	
University	11 (27.5)	22 (24.4)	
Job, n (%)			
Housewife	5 (12.5)	9 (10.0)	0.707
Retired	8 (20.0)	24 (26.7)	
Employee	19 (47.5)	37 (41.1)	
Officer	7 (17.5)	13 (14.4)	
Freelancer	1 (2.5)	7 (7.8)	
Medications, n (%)			
NSAIDs	15 (36.6)	9 (9.4)	**<0.001**
bDMARDs	26 (63.4)	85 (88.5)	
Sulfasalazine	0 (0)	2 (2.1)	
Neutrophils ($\times10^9$/L)	5.01 (2.61-8.30)	4.04 (2.08-7.57)	**<0.001**
Lymphocytes ($\times10^9$/L)	2.23 (1.21-3.73)	2.57 (1.42-4.85)	**<0.001**
PLT ($\times10^9$/L)	298.00 (178.10, 499.80)	244.25 (157.00, 446.00)	**<0.001**
NLR	2.21 (1.15, 4.48)	1.43 (0.73, 3.77)	**<0.001**
PLR	139.55 (68.58, 246.87)	92.30 (42.69, 251.97)	**<0.001**
SII ($\times10^9$/L)	665.14 (384.32, 1297.02)	380.29 (177.74, 1237.39)	**<0.001**
CRP (mg/L)	6.93 (2.00, 198.30)	2.00 (0.4, 19.90)	**<0.001**
ESR (mm/h)	12.50 (4, 88)	4 (2, 46)	**<0.001**
BASDAI	4.85 (4.00, 8.00)	1.20 (0.00, 3.20)	**<0.001**
ASDAS-ESR	2.99 (2.00, 5.30)	1.41 (0.50, 3.20)	**<0.001**
ASDAS-CRP	3.30 (2.10, 5.60)	1.45 (0.60, 2.50)	**<0.001**

Data are reported as mean ± standard deviation (SD) and median (minimum:maximum). ASDAS-ESR: Ankylosing Spondylitis Disease Activity score-erythrocyte sedimentation rate, ASDAS-CRP: Ankylosing Spondylitis Disease Activity score-C-reactive protein, AS: Ankylosing spondylitis, BASDAI: Bath Ankylosing Spondylitis Disease Activity index, bDMARDs: Biological disease-modifying antirheumatic drugs, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil-to-lymphocyte ratio, NSAIDs: Non-steroidal anti-inflammatory drugs, PLR: Platelet-to-lymphocyte ratio, PLT: Platelet, SII: Systemic immune-inflammation index. P<0.05= statistical significance level

In the presence of inflammation, an increase in neutrophil and PLT counts and a decrease in lymphocyte counts are expected (33). The increase in neutrophil count in AS patients is suggested to be associated with an increase in the differentiation and maturation of hematopoietic progenitor cell through many cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6, IL-8 and granulocyte macrophage colony stimulating factor (6). Decrease in lymphocyte counts in AS patients is considered to occur as a result of apoptosis; and although the exact mechanism is not clear, the increase in PLT counts has been suggested to be mediated by factors such as thrombin, histamine, TNF-α and IL-12 (29). Given the association of inflammation with increase in neutrophil and PLT counts and decrease in lymphocyte counts, the NLR, PLR and SII values as calculated from neutrophil, lymphocyte and PLT values can also be expected to be high, in relation to inflammation, in AS patients.

While neutrophil and PLT values were found to be greater in AS patients compared to the healthy control group (p<0.001 for each), no significant difference was identified in lymphocyte values (p=0.336) in a study by Liang et al. (11). Regarding the values of lymphocytes, PLT, and neutrophils, our findings are

consistent with this research. Liang et al. (11) also reported significantly higher PLR and NLR values in the AS group compared to the healthy control group (p values: p<0.001, p=0.006, respectively). In our results, NLR values were significantly higher (p=0.007) in the AS group compared to the healthy control group in line with the study by Liang et al. (11), however, no significant difference was found in terms of our PLR values (p=0.143). Also, while Liang et al. (11) reported that PLR values (p=0.045) but not NLR values (p=0.086) were significantly higher in patients with BASDAI ≥4 compared to those with BASDAI <4, our findings revealed that both PLR and NLR values (p<0.001 for each) were significantly higher in active AS group than in the remission AS group.

Hence, we obtained similar results with the study of Liang et al. (11) in terms of PLR but different results in terms of NLR.

In a study conducted in AS patients by Coşkun et al. (6), neutrophil, PLT and NLR values were reported to be significantly higher (p<0.001 for each) in the AS vs. control group, and our results are in line with this study. In terms of lymphocyte values, while Coşkun et al. (6) reported significantly lower lymphocyte counts in the AS group (p=0.012), our findings revealed no significant difference in terms of lymphocyte values.

Similar to our results, Gökmen et al. (10) reported significantly higher neutrophil and NLR values in AS patients vs. control

Table 3. SII and CRP, ESR, BASDAI, ASDAS-ESR, and ASDAS CRP correlations in AS patients

AS (n=130)		
	rs	**p-value**
CRP	0.384	<0.001
ESR	0.243	0.005
BASDAI	0.668	<0.001
ASDAS-ESR	0.619	<0.001
ASDAS-CRP	0.700	<0.001

AS: Ankylosing spondylitis, ASDAS-ESR: Ankylosing Spondylitis Disease Activity score-erythrocyte sedimentation rate, ASDAS-CRP: Ankylosing Spondylitis Disease Activity score-C-reactive protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SII: Systemic immune-inflammation index, rs: Spearman correlation coefficient; p<0.05= statistical significance level.

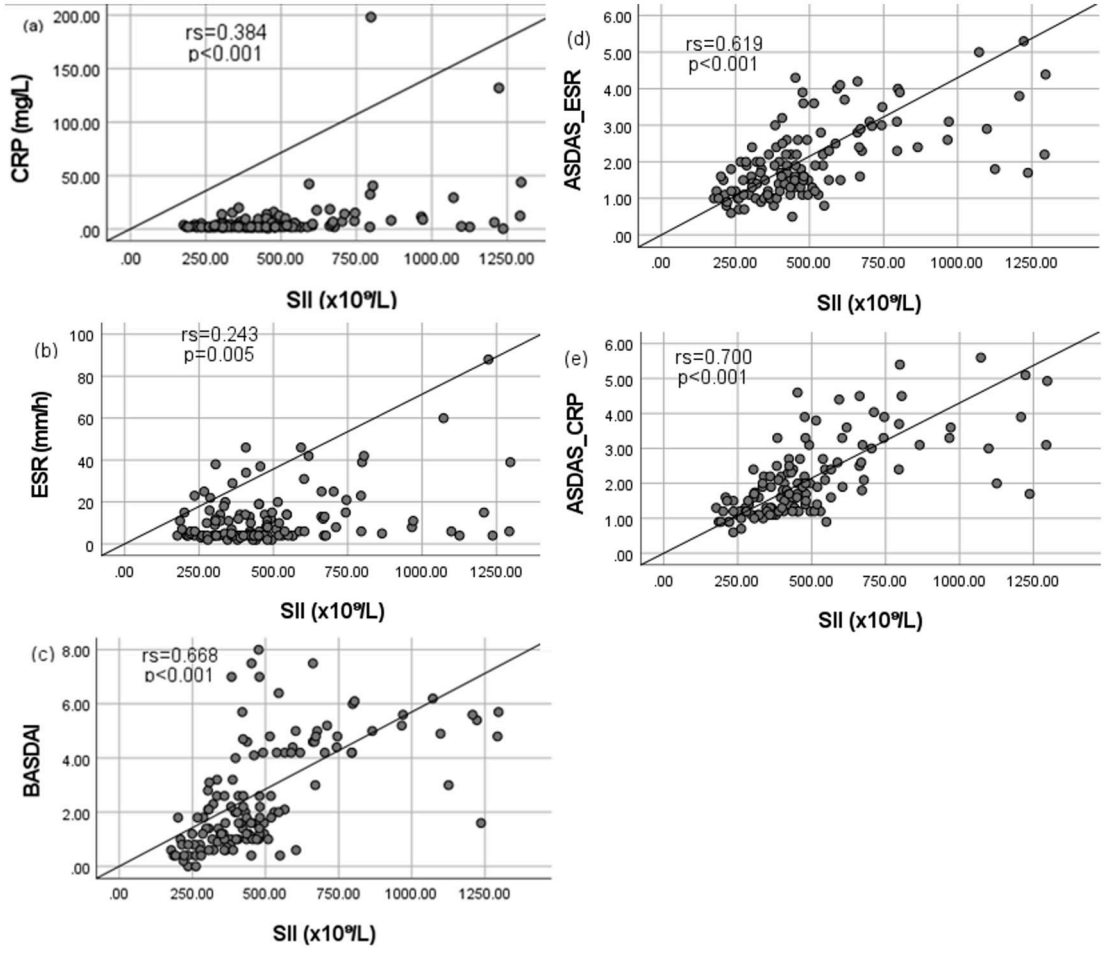

Figure 1. SII correlations with CRP (a), ESR (b), BASDAI (c), ASDAS-ESR (d), and ASDAS-CRP (e)
ASDAS-ESR: Ankylosing Spondylitis Disease Activity score-erythrocyte sedimentation rate, ASDAS-CRP: Ankylosing Spondylitis Disease Activity score-C-reactive protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SII: Systemic immune-inflammation index

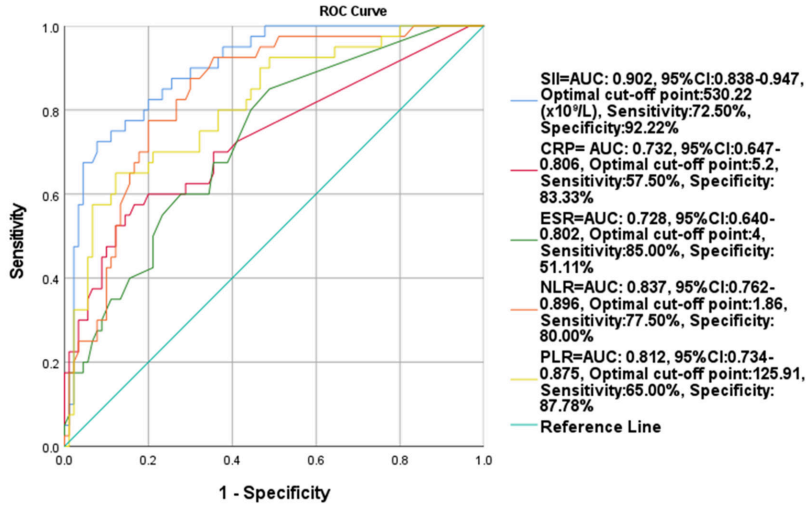

Figure 2. SII, NLR, PLR, CRP, and ESR receiver operating characteristic (ROC) curves to distinguish AS patients from those who are in remission
AS: Ankylosing spondylitis, AUC: Area under the curve, CI: Confidence intervals, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index

Table 4. Receiver operating characteristic curves analysing of the SII, CRP, ESR, NLR, and PLR

	AUC	95% CI	Optimal cut-off point	Sensitivity	Specificity
SII	0.902	0.838-0.947	530.22 (×10⁹/L)	72.50%	92.22%
CRP	0.732	0.647-0.806	5.2 (mg/L)	57.50%	83.33%
ESR	0.728	0.643-0.802	4 (mm/h)	85.00%	51.11%
NLR	0.837	0.762-0.896	1.86	77.50%	80.00%
PLR	0.812	0.734-0.875	125.91	65.00%	87.78%

AUC: Area under the curve, CI: Confidence intervals, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index

group (p<0.001 for each), along with no significant difference between groups in terms of lymphocyte values (p=0.23).

In a study by Zeb et al. (7), on NLR and PLR values in AS patients and control subjects, NLR and PLR values were reported to be significantly higher in AS patients than in healthy controls, as well as in the active AS (BASDAI ≥4) vs. remission AS (BASDAI <4) group (p<0.01 for each). Our results support this study in terms of NLR values. When PLR values are taken into account, our investigation indicated that, in contrary to Zeb et al.'s (7) work, there was no significant difference (p=0.143) between the AS group and the control group. However, PLR values were considerably greater (p<0.001) in the active AS group compared to the remission AS group.

Seng et al.'s (8) investigation on axial spondyloarthritis patients revealed no discernible difference in NLR and PLR values (p=0.60 and p=0.40, respectively) between the groups with active and inactive illness. The neutrophil, lymphocyte, PLT, NLR and PLR values seem to vary across different studies, including the present study. Instead of using NLR and PLR values calculated from lymphocyte with neutrophil or PLT counts only, usage of SII value, obtained by a calculation including all of these parameters (neutrophil, lymphocyte and PLT), seems to be more valuable tool in determining the disease activity.

Two previous studies to date have investigated the SII, as a novel marker, in AS patients (29,30). One of them evaluated the indexes calculated from complete blood count parameters in inflammatory rheumatic diseases. The authors reported significantly higher SII levels in AS patients compared to healthy controls (p<0.001), and also in active AS patients compared to inactive AS patients (p=0.013). It was also noted that SII values were correlated with ESR (p=0.003), CRP (p=0.001) and ASDAS (p=0.013) values. In ROC curve analysis, the cut-off value for SII was reported to be 697.66 [area under the curve (AUC): 0.674, 95% CI: 0.504-0.845, sensitivity: 71.4%, specificity: 53.3%] (30). Our findings also revealed significantly higher SII values in AS patients vs. healthy controls, and in active AS group vs. remission AS group (p<0.001 for each), in addition to correlation of SII values with ESR (p=0.005), CRP (p<0.001), ASDAS-ESR (p<0.001) and ASDAS-CRP (p<0.001) values. We also found a correlation of SII with BASDAI (p<0.001), which was not evaluated in the above-mentioned study. In the ROC curve analysis, we determined the cut-off value for SII as 530.22×10⁹/L (AUC: 0.902, 95% CI: 0.838-0.947, sensitivity: 72.50%, specificity: 92.22%).

SII values were shown to be considerably higher in AS patients compared to the healthy control group and in the active AS

group compared to the AS group in remission in Wu et al.'s (29) other AS study (p<0.001 for both). The data also showed a positive correlation between SII levels and CRP (rs=0.483, p<0.001), ESR (rs=0.374, p<0.001), and BASDAI (rs=0.667, p<0.001) values, as reported by the authors. The best indicator for assessing disease activity was found to be SII, with a reported cut-off value of 513.2 in ROC curve analysis (AUC: 0.877, 95% CI: 0.813-0.941, sensitivity: 86.84%, specificity: 83.33%). Our findings also revealed correlations between SII and ESR, CRP, BASDAI. We have also found correlation of SII with ASDAS-ESR and ASDAS-CRP, which was not assessed in the study by Wu et al. (29).

The single-center design and the relatively small sample sizes for the AS and healthy control groups are the two main limitations of our investigation. Owing to the cross-sectional design of our investigation, it was not possible to assess how patient-taken drugs affected SII levels. To ascertain whether SII is a useful tool for evaluating AS disease activity, more extensive prospective multi-center trials are required.

Conclusion

Our findings revealed that SII, which can easily be calculated from readily available complete blood count parameters routinely ordered in the follow up of AS patients, is a simple useful and efficient index in assessment of disease activity in AS patients, without causing any additional cost.

Ethics

Ethics Committee Approval: The study protocol was approved by the Bursa Uludağ University Faculty of Medicine Clinical Research Ethics Committee (approval date: February 23, 2022, decision no: 2022-4/25).

Informed Consent: Informed consent was obtained from all subjects in accordance with the Declaration of Helsinki.

Authorship Contributions

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

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

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

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Original Investigation / Orijinal Araştırma

DOI: 10.4274/tod.galenos.2023.69335
Turk J Osteoporos 2024;30:30-6

Osteoporosis Awareness and Knowledge in Postmenopausal Breast Cancer Survivors

Postmenopozal Meme Kanseri Hastalarında Osteoporoz Farkındalığı ve Bilgi Düzeyleri

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Abstract

Objective: To determine the awareness and knowledge levels of osteoporosis in postmenopausal breast cancer survivors (PBCS) who have completed adjuvant chemoradiotherapy, are under hormonal therapy, or are being monitored, and to examine potentially related factors.
Materials and Methods: Between March 2022 and December 2022, 73 breast cancer patients with clinically and biochemically proven menopause were included in the study. The demographic characteristics and clinical findings of the patients were recorded. The participants' osteoporosis knowledge level (OKL) regarding osteoporosis was evaluated with the osteoporosis knowledge test and their osteoporosis awareness level (OAL) was evaluated with the osteoporosis awareness test. P values <0.05 were considered statistically significant.
Results: The mean age of the patients was 59.8±9.4 years (minimum-maximum: 32-75). Their OKL's were categorized as follows: 9.6% poor, 58.9% moderate and 31.5% good. Nutrition knowledge level (NKL) was distributed as follows: 9.6% poor, 37.3% moderate and 52.1% good. Exercise knowledge level (EKL) was distributed as follows: 13.7% poor, 31.5% moderate and 54.8% good. As the patient's age increased, it was observed that OAL, OKL, NKL and EKL decreased. A statistically significant correlation was found between higher education level and higher OAL (r=0.246, p=0.036). There was a significant inverse correlation between menopausal duration and OKL (r=-0,280, p=0.017). There was no significant difference in OAL, OKL, NKL and EKL between patients who received hormone therapy and those who did not.
Conclusion: Our study, which assessed the awareness level of osteoporosis for the first time in PBCS, indicates the need for further research on the development of patient education programs for osteoporosis prevention and the improvement of methodological approaches specific to measuring awareness and knowledge levels in cancer patients.
Keywords: Osteoporosis knowledge test, osteoporosis awareness test, postmenopausal breast cancer survivors

Öz

Amaç: Adjuvan kemoradyoterapisi tamamlanan, hormonoterapi altında veya izlemde postmenopozal meme kanseri hastalarında (PMKH) osteoporoz farkındalık ve bilgi düzeylerini belirlemek ve ilişkili olabilecek faktörleri incelemektir.
Gereç ve Yöntem: Mart 2022 ile Aralık 2022 tarihleri arasında menopozu klinik ve biyokimyasal olarak kanıtlanmış 73 meme kanseri hastası çalışmaya dahil edildi. Hastaların demografik özellikleri ve klinik bulguları kayıt altına alındı. Katılımcıların osteoporoza yönelik bilgi düzeyi (OBD) osteoporoz bilgi testi, osteoporoz farkındalık düzeyi (OFD) osteoporoz farkındalık testi ile değerlendirildi. P değerleri <0,05 istatistiksel olarak anlamlı kabul edildi.
Bulgular: Çalışmamızda hastaların yaş ortalaması 59,8±9,4 yıl (minimum-maksimum: 32-75) idi. OBD'leri %9,6'sı kötü, %58,9 orta, %31,5 iyi idi. Beslenme bilgi düzeyi (BBD); %9,6 kötü, %37,3 orta,%52,1 iyi seviyedeydi. Egzersiz bilgi düzeyi (EBD); %13,7 kötü, %31,5 orta, %54,8 iyi seviyedeydi. Hasta yaşı arttıkça; OFD, OBD, BBD ve EBD'nin düştüğü gözlemlendi. Eğitim düzeyi yüksek olan PMKH'de OFD de yüksek bulundu ve istatistiksel olarak anlamlı görüldü (r=0,246, p=0,036). Menopoz süresi ile OBD arasında anlamlı ters korelasyon görüldü (r=-0,280 p=0,017). Hormonoterapi alan ve almayan hastalar arasında OFD ve OBD; BBD ve EBD açısından anlamlı bir fark görülmedi.
Sonuç: PMKH'de ilk kez OFD'nin değerlendirildiği çalışmamız; osteoporozun önlenmesine ilişkin hasta eğitim programının oluşturulması için çok daha fazla çalışmaya ve kanser hastalarının özelinde farkındalık ve bilgi düzeyini ölçen metodolojik yöntemleri geliştirmeye ihtiyaç olduğunu göstermektedir.
Anahtar kelimeler: Osteoporoz bilgi testi, osteoporoz farkındalık testi, postmenopozal meme kanseri hastaları

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Received/Geliş Tarihi: 01.08.2023 **Accepted/Kabul Tarihi:** 16.10.2023

Introduction

Breast cancer is the most common cancer worldwide among women. According to the 2020 GLOBOCAN database, it has the highest incidence rate at 11.7% (1). The rate and magnitude of bone resorption caused by cancer treatment are higher than age-related bone loss (2). Approximately 80% of breast cancer patients experience bone loss (3). Breast cancer survivors have specific risk factors for osteoporosis, such as aromatase inhibitor (AI) therapy lasting over 6 months, age over 65 years, early menopause, radiotherapy, tamoxifen use during the premenopausal period, chemotherapy-induced menopause, low body mass index (BMI) below 20 kg/m^2, a history of hip fracture among first-degree relatives, a history of spontaneous or low-energy trauma associated fracture, oral glucocorticoid use at a dose of ≥7.5 mg per day for 3 months or longer, alcohol abuse (consuming more than 3 standard alcohol units per day) and smoking. In this population, calcium and vitamin D deficiencies are common, which further increases the risk of osteoporosis (4). The risk of early-stage osteoporosis developing as a result of cancer treatment poses a significant economic burden and leads to higher healthcare costs (5). Understanding the specific effects on bone health in breast cancer survivors and increasing their awareness and knowledge about osteoporosis can potentially prevent complications and morbidities.

According to the accessible literature, there is no existing study regarding the awareness level of osteoporosis in breast cancer survivors. However, in a study conducted on a smaller number of patients, it was found that breast cancer patients had lower osteoporosis knowledge levels (OKL) compared to cancer-free individuals (6). The objective of this study is to measure the previously unexplored osteoporosis awareness level (OAL) and OKL in postmenopausal women who have undergone breast cancer treatment.

Materials and Methods

This is a prospective study conducted between March 2022 and December 2022 at the tertiary health institution/oncology training and research hospital. The study included 73 patients who were diagnosed with breast cancer, had clinically and biochemically confirmed menopause, completed adjuvant treatments (chemotherapy, radiotherapy, hormone therapy), and/or continued hormone therapy. None of the patients included in the study were found to have metachronous metastasis/local recurrence during the diagnostic process. The demographical data and risk factors of the patients, such as age, education status, time since surgery, menopause duration, smoking, alcohol use, and presence of comorbidities, were recorded. Additionally, the bone mineral density (BMD) BMI (kg/m^2), and vitamin D levels of all participants were evaluated. Dual hip and lumbar energy X-ray absorptiometry scans were used to assess BMD.

The study assessed the OAL, OKL, hormone therapy, the use of medications for osteoporosis treatment, and the presence of a history of known fractures in the participants.

Patient Evaluation Methods

Osteoporosis Knowledge Level

The osteoporosis knowledge test (OKT) was applied to assess patients' knowledge on various topics related to osteoporosis prevention, such as calcium intake, exercise, and activity levels. The test was initially developed by Kim et al. (7) as a multiple-choice questionnaire aimed at measuring the knowledge level about osteoporosis. In 2011, it was revised and the number of questions increased to 32. The revised OKT consists of two subgroups: The nutrition subgroup [nutrition knowledge test (NKT)] with 26 questions (1-11 and 18-32) and the exercise subgroup [exercise knowledge test (EKT)] with 20 questions (1-17 and 30-32). Fourteen questions are common to both subgroups (1-11 and 30-32). All questions are multiple-choice. Correct answers are scored as 1 and all incorrect or "don't know" answers are scored as 0.

The EKT score ranges from 0 to 20 points and the NKT score ranges from 0 to 26 points (8). The upper third of scores represents good knowledge, the middle third represents moderate knowledge and the lower third represents insufficient knowledge regarding osteoporosis preventive behaviors (9). The Turkish validity and reliability study of the revised OKT was conducted by Şimşir Atalay et al. (10).

Osteoporosis Awareness Test

The Turkish version of the "osteoporosis awareness test" (OAT) was administered to assess patients' awareness level regarding osteoporosis and its validity and reliability have been demonstrated (11). The OAT is evaluated using a 4 point likert scale. As the total score obtained from the scale increases [minimum (min) =31, maximum (max) =124], the awareness of osteoporosis also increases. The scale consists of five subscales and does not contain reverse items or cutoff points.

Statistical Analysis

The data of the study were recorded with the statistical package for the social sciences (SPSS) version 25 (IBM corporation. New York. United States) program and statistical analyses were made. Frequency tables and descriptive statistics were used to interpret the findings for statistical analysis. The "Student's t-test" value was used to compare the scale score averages of the independent variables with normal distribution. Pearson correlation "r" coefficient was used for normally distributed averages in the comparison of the relationship between the scale point averages according to the research question. P values <0.05 were considered statistically significant. Ethical approval for this study was obtained from the University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Health Education Application and Research Center Non-Interventional Clinical Research Ethics Committee (no: 2022-02/47, date: 10.03.2022). Written informed consent was obtained from all patients after providing them with detailed information about the study.

Power Analysis

Power analysis is a valuable tool in medical research for determining the minimum sample size needed to detect a clinically significant effect at a specific level of statistical significance. In our study, a post hoc power analysis was performed using the G Power 3.1.9.2 program. We pre-determined an effect size (Cohen's d) of 0.5, which represents the magnitude of the effect we wanted to detect. The alpha level (type I error) was set at 0.05, which is the significance level we chose to accept for our statistical tests. The power level was set at 0.95, indicating our desired probability of correctly rejecting a false null hypothesis. After conducting the power analysis, it was determined that a sample size of 70 patients would be sufficient to achieve a power level of 0.951 with a 5% margin of error. This means that our study should have adequate statistical power to detect the effect size we specified.

Results

The study included a total of 73 postmenopausal female patients diagnosed with breast cancer, with an average age of 59.8±9.4 years (min-max =32-75). Out of the participants, 13 were smokers. It was observed that a significant portion of the participants had quit smoking after being diagnosed with breast cancer. Table 1 provides a summary of the demographical and clinical characteristics of all patients. Out of the participants, 65 were hormone receptor positive, and the most commonly used hormone therapy was letrozole with 44 patients (60.3%), followed by 14 patients (19.2%) on anastrozole, 3 patients (4.1%) on tamoxifen, and 4 patients (5.5%) on gonadotropin-releasing hormone analog + AI. It was observed that a significant portion of the patients included in the study, 84.9% (62 patients), were using AI. Out of the patients who received hormone therapy, 59 of them (90.7%) had a treatment duration of less than 5 years. In the study, 39 patients (53.4%) had not received osteoporosis treatment before. Among the participants, 34 patients (46.6%) had previously undergone osteoporosis treatment, with an average treatment duration of 2.42±1.3 years. The relationship between patients' BMD levels and risk factors such as age, smoking status, BMI, vitamin D levels and hormone therapy duration was evaluated and summarized in Table 2. It is worth noting that there were no patients in the study who reported alcohol consumption. The OAT and OKT were evaluated, and it was found that the average OAT level for all patients was 77.7±20.3 (range =31 to 124), and the average OKT level was 18.71±5.55 (OKT is scored between 0 and 32). Patients' OKT scores were evaluated as follows: 7 patients (9.6%) had a poor knowledge level (0-10.7), 43 patients (58.9%) had a moderate knowledge level (10.08-21.4), and 23 patients (31.5%) had good knowledge level (21.5-32). When looking at the OKT subgroup analysis, the average EKT score was 10.27±3.69 (ranging from 0 to 16), and the average NKT score was 14.00±3.35 (ranging from 0 to 21).

The EKT results showed that 10 patients (13.7%) had a poor knowledge level (scored between 0-5.3), 23 patients (31.5%) had a moderate knowledge level (scored between 5.4-10.6), and 40 patients (54.8%) had a good knowledge level (scored between 10.7-16). Regarding the NKT, 7 patients (9.6%) had a poor knowledge level (scored between 0-7), 28 patients (37.3%) had a moderate knowledge level (scored between 8-14) and 38 patients (52.1%) had a good knowledge level (scored between 15-21). The correlation of osteoporosis risk factors, which may be related to the OKT and OAT values of the patients, was examined in Tables 3 and 4 below.

Table 1. Sociodemographic and clinical characteristics of the patients

Age (years), mean ± SD (min-max)	59.8±9.4 (32-75)
BMI (kg/m^2), mean ± SD	28.9±4.3
Current smokers, n (%)	13 (17.8)
Comorbidity, n (%)	44 (60.3)
Hypertension (HT)	13 (17.8)
Diabetes mellitus (DM)	2 (2.7)
HT + DM	16 (21.9)
Hypothyroidism + HT	4 (5.5)
Asthma	4 (5.5)
Rheumatic disease	5 (6.8)
Education level, n (%)	
Semiliterate	9 (12.3)
Primary school	40 (54.8)
High school	16 (21.9)
University	8 (11.0)
Mean time elapsed postmastectomy (years)	4.18±2.30
Average age of menopause (years)	45.5±4.13
Average menopause times (years)	14±8.07
Mean serum 25(OH)D levels (ng/mL)	20.66±12.0
Lumbar BMD T-score	-1.83±0.97
Total hip BMD T-score	-1.02±0.93

Min-max: Minimum-maximum, SD: Standard deviation, BMD: Bone mineral density, BMI: Body mass index

Table 2. Correlation between BMD level and osteoporosis risk factors

	Lumbar BMD T-score (mean: -1.83±0.97)	Total hip BMD T-score (mean: -1.02±0.93)
Age	r=0.076, p=0.523	r=0.178, p=0.132
Smoking	r=0.178, p=0.132	r=0.132, p=0.791
Vitamin D	r=-0.118, p=0.329	r=-0.235, p=0.050
BMI	r=0.323, p=0.005	r=0.357, p=0.002
Hormone therapy period	r=-0.082, p=0.506	r=0.037, p=0.764

Pearson correlation, BMD: Bone mineral density, BMI: Body mass index

Table 3. Comparison of test scores of those in the case group				
	OAT	**OKT**	**EKT**	**NKT**
Hormone therapy + (n=65)	78.1±20.1	18.82±5.59	10.34±3.82	14.14±4.39
Hormone therapy - (n=65)	74.88±23.37 p=0.674	17.88±5.54 p=0.655	9.75±2.43 p=0.674	12.88±4.12 p=0.443
Fracture history + (n=6)	80.00±10.71	21.51±4.73	12.17± 3.86	16.50±3.39
Fracture history - (n=67)	77.57±21.07 p=0.295	18.51±5.60 p=0.782	10.10±3.66 p=0.192	18.13±4.38 p=0.143
Osteoporosis tx. + (n=34)	79.71±21.81	18.38± 6.09	10.18±3.95	13.71±5.07
Osteoporosis tx. - (n=39)	76.08±19.17 p=0.452	19.00±5.09 p=0.639	10.36±3.49 p=0.835	14.26±3.66 p=0.594
Student's t-test done, OAT: Osteoporosis awareness test, OKT: Osteoporosis knowledge test, EKT: Exercise knowledge test, NKT: Nutrition knowledge test				

Table 4. Correlation between test scores and osteoporosis risk factors				
	OAT	**OKT**	**EKT**	**NKT**
Age	r=-0.279 p=0.017	r=-0.278 p=0.017	r=-0.282 p=0.016	r=-0.265 p=0.023
Smoking	r=-0.011 p=0.924	r=0.053 p=0.656	r=0.008 p=0.945	r=-0.082 p=0.489
Education level	r=0.246 p=0.036	r=0.159 p=0.18	r=0.222 p=0.059	r=0.193 p=0.102
Duration of menopause	r=-0.189 p=0.109	r=-0.280 p=0.017	r=-0.212 p=0.072	r=-0.190 p=0.108
Pearson correlation, OAT: Osteoporosis awareness test, OKT: Osteoporosis knowledge test, EKT: Exercise knowledge test, NKT: Nutrition knowledge test				

Discussion

In our study, which primarily consisted of hormone receptor-positive postmenopausal breast cancer patients, a significant and consistent correlation was observed between BMI and lumbar as well as total hip BMD. These findings align with existing literature and provide valuable insights into the relationship between BMI and BMD in this patient population.

Interestingly, we found no direct association between factors such as hormone therapy usage, osteoporosis treatment, or fracture history and the osteoporosis knowledge and awareness levels of the patients.

Furthermore, we observed statistically significant correlations between age and both osteoporosis knowledge and awareness levels. Additionally, educational level was found to be significantly associated with osteoporosis awareness, while menopausal duration was related to OKL. These results underscore the importance of considering these demographic factors in assessing and addressing osteoporosis-related knowledge and awareness in postmenopausal breast cancer patients.

In a previous study conducted on postmenopausal breast cancer survivors (PBCS), the OKL was found to be lower than healthy participants ($p<0.01$) (6). Similarly, in our study, the majority of breast cancer survivors had a moderate level of total osteoporosis knowledge (58.9%), while 9.6% had a low knowledge level. Regarding exercise knowledge, 13.7% of the patients had a low level, 31.5% had a moderate level, and 54.8% had a good level. For nutrition knowledge, 9.6% had a low level, 37.3% had a moderate level, and 52.1% had a good level.

According to accessible literature, our study is the first to use the OAT (Osteoporosis Awareness scale) in PBCS. This novel application of the OAT in our study contributes to the understanding of osteoporosis awareness and knowledge level specifically in breast cancer survivors, which was previously unexplored in the literature. By utilizing this assessment tool, we aimed to assess and enhance the level of awareness and knowledge about osteoporosis among PBCS patients, potentially leading to better preventive measures and improved bone health outcomes in this population.

There are studies suggesting that high levels of vitamin D may reduce the risk of progression in breast cancer patients. Vitamin D is believed to inhibit tumor angiogenesis (formation of new blood vessels that feed tumors) and modulate the immune system. It has been proposed in studies that it could potentially reduce the risk of estrogen receptor-positive breast cancer by lowering estrogen levels (12). Therefore, the treatment of vitamin D deficiency in PBCS should be a priority.

In a systematic meta-analysis published in the Cancer Causes & Control Journal in 2016, the prevalence of vitamin D deficiency was examined among postmenopausal women with breast cancer. The analysis showed that the prevalence of vitamin D deficiency ranged from approximately 25% to 86%, with an

overall estimate of approximately 55% based on the included studies (13). Consistent with the literature, our study also found that the average serum 25(OH)D levels in the participating patients were insufficient.

The most common comorbidities observed in PBCS patients, consistent with our study, are hypertension and diabetes mellitus. Chemotherapy-induced hypertension is known to be associated with elevated blood pressure, especially in postmenopausal women with increased obesity and insulin resistance (14). These factors may contribute to the development and exacerbation of hypertension and diabetes mellitus in breast cancer survivors, warranting close monitoring and management of these conditions to optimize the overall health and well-being of the patients.

In the literature, studies conducted on PBCS patients have shown a decrease in total lumbar and hip BMD values (15,16). Similarly, in our study, the mean lumbar BMD value was found to be lower, indicating osteopenia in both lumbar and average total hip BMD values. These findings highlight the importance of monitoring bone health in postmenopausal breast cancer survivors and implementing appropriate measures to prevent further bone loss and reduce the risk of osteoporosis-related complications.

In our study, we observed a statistically significant decrease in the total hip T-score in PBCS who had low serum 25(OH)D levels. However, we did not find a significant correlation between the decrease in lumbar T-score and these factors. These findings suggest that vitamin D deficiency may have a more significant impact on bone health in the hip region compared to the lumbar region in PBCS. Further research and larger sample sizes may be needed to better understand the complex relationship between bone health and various factors in this population.

In the study, no significant relationship was found between smoking and BMD in both lumbar and total hip T-scores. This suggests that smoking may not have a direct impact on bone health in postmenopausal breast cancer survivors. However, it is important to note that smoking is associated with various other health risks and can have detrimental effects on overall health. The lack of a significant relationship with BMD in this study might be due to various other factors affecting bone health in this specific population. Further research and larger studies may be necessary to explore the potential long-term effects of smoking on bone health in PBCS.

Obesity is known to increase the risk of breast cancer in postmenopausal women. Higher levels of adipose tissue can lead to an increase in estrogen levels in the body. Estrogen is a hormone that can promote the growth of hormone receptor-positive breast cancer cells. Additionally, adipose tissue can produce inflammatory substances and hormones, such as insulin, that may play a role in the development of breast cancer (17).

However, it is also true that low BMI (<20 kg/m^2) is a risk factor for fractures in PBCS. In our study, when BMI was compared with BMD, a significant relationship was observed in both lumbar T-score and total hip T-score. This suggests that, in line with the literature, an increase in BMI has a protective effect against osteoporosis (18).

In postmenopausal breast cancer patients, it is a well-known fact that chemotherapy and long-term hormone therapy can increase bone resorption and lead to bone loss. Chemotherapy can have negative effects on bone cells, while hormone therapy can decrease estrogen levels, contributing to bone loss.

Consistent with the literature, our study also observed a significant decrease in lumbar T-score in patients undergoing long-term hormone therapy. These findings are important evidence for preserving bone health and reducing the risk of osteoporosis in postmenopausal women diagnosed with breast cancer.

Therefore, it is recommended to initiate antiresorptive treatments in postmenopausal breast cancer patients who start AI therapy, regardless of whether they have a history of fractures or not, at the early stages of breast cancer diagnosis. These treatments can help prevent bone loss and protect bone health (19).

In March 2016, a guideline was published by the European Panel of Leading Experts in the Field of Breast Cancer Management, which addressed the prevention of treatment-related bone loss and metastasis in breast cancer treatment. The guideline recommended the use of adjuvant bisphosphonates, lifestyle recommendations, and pharmacological interventions.

Regarding dietary intake, the guideline suggested calcium supplementation (1000 mg per day) and vitamin D supplementation (800-1000 IU per day) if intake is insufficient. Additionally, all patients at risk were advised to engage in regular exercise and reduce smoking and alcohol consumption.

For women with an increased risk of fractures, antiresorptive treatments were recommended. It emphasized that women with a lumbar or total hip T-score ≤-2 or those with two or more clinical risk factors for fractures should be considered for treatment.

This guideline highlights the importance of addressing bone health in breast cancer patients and offers recommendations to prevent bone loss and reduce the risk of fractures and metastasis. It underscores the significance of a comprehensive approach in breast cancer management, including lifestyle modifications and pharmacological interventions, to improve patient outcomes and quality of life (20).

PBCS who receive aromatase AI as part of their treatment may experience an annual bone loss rate of approximately 2.5% (21). In addition to spinal and hip fractures, patients undergoing AI therapy may also be at risk for fractures in peripheral joints (22). In our study, we observed that 6 patients (8.2%) with a history of fractures experienced fractures while under AI treatment. Among these patients, 4 (66%) had fractures in the distal end of the radius, and 2 (33%) had a history of proximal humerus fractures.

However, when comparing patients with and without a history of fractures, we did not find any statistically significant differences in the OAT score (p=0.295), OKT score (p=0.782), EKT score (p=0.192), and NKT score (p=0.143). This indicates that the

level of osteoporosis awareness and knowledge, as well as exercise and nutrition knowledge, was not significantly different between patients with and without a history of fractures in our study. Further research may be needed to explore other potential factors contributing to the development of fractures in this population.

In a previous study, it was observed that advanced age in PBCS is associated with lower levels of osteoporosis awareness and knowledge, as well as reduced exercise capacity (20). Similarly, in our study, we also found a statistically significant negative correlation between age and osteoporosis awareness and knowledge in advanced age PBCS. This suggests that as age increases, the level of awareness and knowledge about osteoporosis decreases in this population.

Given these findings, it is crucial to develop specialized exercise programs aimed at increasing BMD for the advanced-age postmenopausal breast cancer patient group. These exercise programs should include activities such as walking, aerobic exercises, running, dancing, and resistance exercises (weight training) that can improve bone health. By promoting regular and appropriate exercise, healthcare professionals can enhance osteoporosis awareness and knowledge, and potentially mitigate the risk of fractures in this vulnerable population.

In one study, it was found that cancer patients with higher education levels had higher levels of osteoporosis knowledge (22). In our study, we also observed a weak statistically significant improvement in OAT scores among women with higher education levels (r=0.246, p=0.036). However, when we analyzed the OKT and its subgroups, we did not find a significant correlation between education level and exercise knowledge (r=0.222, p=0.059) or nutrition knowledge (r=0.193, p=0.102).

In conclusion, although women with higher education levels had higher osteoporosis knowledge among postmenopausal breast cancer survivors, their exercise and nutrition knowledge levels were not significantly affected positively. This suggests that while education level may play a role in overall osteoporosis knowledge, it may not have a direct impact on specific knowledge areas related to exercise and nutrition. Further research may be needed to better understand the factors influencing knowledge levels in different domains of osteoporosis prevention and management among this patient population.

Study Limitations

This study aims to measure the knowledge and awareness levels of breast cancer patients only. Therefore, the findings may not apply to all cancer patients. It should be noted that the study was conducted in a comprehensive oncology center, which means that it may represent a patient group with higher awareness levels compared to cancer patients treated in general hospital settings.

Conclusion

After breast cancer treatment (surgery, chemotherapy, radiotherapy, hormone therapy), postmenopausal women are at risk for skeletal health issues. Considering the potential risk of bone metastasis in PBCS, it is essential to recognize that the risk of osteoporotic fractures may be higher compared to other postmenopausal women. Therefore, every woman diagnosed with breast cancer should be evaluated for their fracture risk.

The assessment of fracture risk involves evaluating clinical risk factors for fractures. In PBCS, it is crucial to focus on behavior changes and developing a patient education program aimed at preventing osteoporosis. However, more research is needed in this area, especially to develop methodological approaches that measure awareness and knowledge levels in cancer patients specifically.

The prevention of osteoporosis and the implementation of educational programs for breast cancer patients should be a priority to improve skeletal health outcomes and reduce fracture risk. It is crucial to address the unique needs of breast cancer survivors and implement strategies that can help them maintain bone health throughout their survivorship journey.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Health Education Application and Research Center Non-Interventional Clinical Research Ethics Committee (no: 2022-02/47, date: 10.03.2022).

Informed Consent: Written informed consent was obtained from all patients after providing them with detailed information about the study.

Authorship Contributions

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

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

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

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DOI: 10.4274/tod.galenos.2023.23500
Turk J Osteoporos 2024;30:37-43

Awareness of Orthopedic Surgeons and Neurosurgeons About Fragility Fractures and Fracture Liaison Services: A Survey Study

Ortopedistlerin ve Beyin Cerrahlarının Frajilite Kırıkları ve Fraktür Liyezon Servisleri Üzerine Farkındalıkları: Bir Anket Çalışması

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Abstract

Objective: The aim of this study was to investigate the awareness of neurosurgeons and orthopedic surgeons working in Eskişehir about fragility fractures and fracture liaison services.
Materials and Methods: A total of 50 surgeons (21 neurosurgeons, 29 orthopedic surgeons) responded to a survey about fragility fractures and fracture liaison services.
Results: More than 95% of all the surgeons stated that they considered osteoporosis in patients who had a fracture with a low-level trauma. However, only 69% of the orthopedic surgeons and 61% of the neurosurgeons stated that they requested dual-energy X-ray absorptiometry in patients with fragility fractures. The rate of knowledge about the FRAX® algorithm was 17% in the orthopedic surgeons and 0% in the neurosurgeons. While 38% of the orthopedic surgeons stated that they performed both the treatment and follow-up of osteoporosis in patients with fragility fractures, 62% stated that they referred these patients. All the neurosurgeons stated that they did not perform osteoporosis treatment or follow-up and referred all their patients. Only one orthopedic surgeon was aware of fracture liaison services, while the other surgeons had no knowledge.
Conclusion: The awareness of both the orthopedic surgeons and neurosurgeons about the management of fragility fractures and fracture liaison services was lower than expected.
Keywords: Fragility, neurosurgery, orthopedics

Öz

Amaç: Bu çalışmanın amacı Eskişehir'de çalışan beyin cerrahları ve ortopedistlerin frajilite kırıkları ve fraktür liyezon servisleri hakkındaki farkındalıklarını araştırmaktır.
Gereç ve Yöntem: Toplam 50 cerraha (21 beyin cerrahı, 29 ortopedist) frajilite kırıkları ve fraktür liyezon servisleri hakkında sorular içeren anket uygulandı.
Bulgular: Tüm cerrahların %95'den fazlası düşük seviyeli travma ile oluşmuş kırıklarda osteoporoz düşündüğünü belirtti. Ancak sadece %69 ortopedist ve %61 beyin cerrahı, frajilite kırıklı hastalarda dual-enerji X-ışını absorbsiyometri istediğini belirtti. FRAX® algoritması hakkındaki bilgi yüzdesi ortopedistlerde %17, beyin cerrahlarında %0 idi. Ortopedistlerin %38'i frajilite kırığı olan hastalarda osteoporozun hem tedavisini hem de takibini yaptığını belirtirken, %62'si bu hastaları refere ettiğini belirtti. Tüm beyin cerrahları ise osteoporoz takip ve tedavisi yapmadıklarını, tüm hastaları refere ettiklerini belirtti. Sadece bir ortopedistin fraktür liyezon servisleri hakkında bir bilgisi varken, diğer cerrahların herhangi bir bilgisi yok idi.
Sonuç: Ortopedi ve beyin cerrahi hekimlerinin, frajilite kırıklarının yönetimi ve fraktür liyezon servisleri hakkındaki farkındalığı beklenenden düşüktür.
Anahtar kelimeler: Frajilite, beyin cerrahi, ortopedi

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Received/Geliş Tarihi: 05.05.2023 **Accepted/Kabul Tarihi:** 16.10.2023

Introduction

The clinical significance of osteoporosis is that it can lead to fragility fractures occurring in the weakened bone through a low-energy trauma (1). In the FRACTURK study, it was reported that the risk of hip fracture was 3.5% in Turkish men and 14.6% in Turkish women after 50 years old. This means after the age of 50, almost one in seven women will sustain a hip fracture during their remaining lifetime. In 2009, 24,000 hip fractures occurred in Turkey, of which 73% were in women. In 2035, this number is expected to be almost 64,000 (2). Vertebral fractures are two to three times more common than hip fractures; however, only about a third of these are ever diagnosed (3).

Fragility fractures are related to both morbidity and mortality. The mortality rate of patients with hip fractures is approximately one in three, with 4% mortality in hospitalization and 10-24% mortality in the first year (4,5). Besides mortality, fragility fractures are also associated with loss of productivity and independent living, reduced quality-of-life and substantial morbidity (1). Twenty-five percent of patients were also reported to require long-term residential care (6). In addition, these fragility fractures cause a huge burden to the economies of individual countries. In 2005, this burden in Europe amounted to 32 billion Euros per year. In 2025, it is expected to rise to 37 billion Euros (7). Moreover, the full extent of the burden to patients, caregivers and society due to the attendant lifestyle changes and lost productivity is not fully known.

A fragility fracture is the greatest indicator of a future fragility fracture. Patients who have experienced any fracture at any site, are at almost twice the risk of a future fracture (8,9). Furthermore, patients with a fragility fracture of the radius, femur, humerus or ankle have almost four times the risk of suffering a future fracture (9). Half of patients with a vertebral fracture are expected to experience another vertebral fracture within three years, and most of these fractures occurs in the first year afterwards (10,11). It has been reported that starting medical treatment for patients with fragility fractures may decrease their risk of experiencing a new fragility fracture by up to 50% (12,13). In 2012, the International Osteoporosis Foundation (IOF) launched the "Capture the Fracture" campaign, with the aim of making fracture liaison services (FLS), a solution for post-fracture care, more globally widespread (14). FLS centers have been established in Turkey for almost ten years and can currently be found in İstanbul, Ankara, İzmir, Denizli, and Kayseri. The Eskişehir FLS was opened in June 2022, as part of Turkish FLS team run by representatives of the Turkish Osteoporosis Society. Considering the effect of fragility fractures on peoples' lives and society in general, it is important that osteoporosis treatment and rehabilitation programs be started as soon as fragility fractures are detected. Patients with vertebral fragility fractures are frequently referred to neurosurgeons, while patients with non-vertebral fragility fractures are more commonly referred to orthopedic surgeons. Both of these groups of healthcare professionals have the chance to prevent future fractures by recognizing fragility fractures. However, in previous studies, orthopedic practice for both the diagnosis and treatment of osteoporosis was reported to be inadequate in patients with fragility fractures (15-17). No similar study for neurosurgical practice regarding vertebral fragility fractures could be found in the literature. The aim of this study was thus to evaluate (1) the approach to fragility fractures in daily orthopedic and neurosurgical practice, and (2) the awareness about fragility factures and FLS of neurosurgeons and orthopedic surgeons in the province of Eskişehir.

Materials and Methods

This survey study was conducted between March and April 2023 in the department of physical medicine and rehabilitation (PMR) at a university hospital. The inclusion criteria were: Being an orthopedic surgeon or a neurosurgeon in state hospitals, university hospitals and special hospitals in Eskişehir and agreeing to participate in the study. The exclusion criteria were: having medical experience <4 years, being retired and not currently working as a surgeon (Figure 1). The survey data included demographic characteristics (age, duration of medical experience, place of work) of the surgeons, knowledge of fragility fractures, FRAX® and FLS, and questions about whether they administered osteoporosis treatment or referred the patient to PMR or to the internal medicine/endocrinology/geriatric clinics and whether medication prescribed for osteoporosis would impair fracture healing. The survey was filled out by the surgeons themselves.

Ethics approval was received from the Eskişehir Osmangazi University Non-invasive Clinical Research Ethics Committee with the decision dated 21/02/2023 and numbered 16. All surgeons were informed about the study and their verbal consent was obtained.

Statistical Analysis

IBM SPSS Statistics 21.0 (SPSS Inc., Chicago, Illinois) program was used for statistical analysis. The categorical variables were evaluated using chi-square tests and presented as numbers (n) and percentages (%). Descriptive statistics were given as mean (standard deviation). A p-value <0.05 was considered significant.

Results

A total of 50 male surgeons (21 neurosurgeons, 29 orthopedic surgeons) who agreed to participate in the survey were enrolled in this study. The mean age of the orthopedic surgeons was 46.72±9.47 years (minimum age: 29, maximum age: 62), the mean age of neurosurgeons was 44.0±11.23 years (minimum age: 27, maximum age: 65). The mean duration of medical experience was 22.40±9.85 years (minimum: 4, maximum: 38) in the orthopedic surgeons, the mean was 20.28±11.49 years (minimum: 4, maximum: 41) in the neurosurgeons. Of the 29 orthopedic surgeons, 41.4% were working in state hospitals, 31.0% of them were in special hospitals, and 27.6% of them were in university hospitals. Of the 21 neurosurgeons, 42.9%

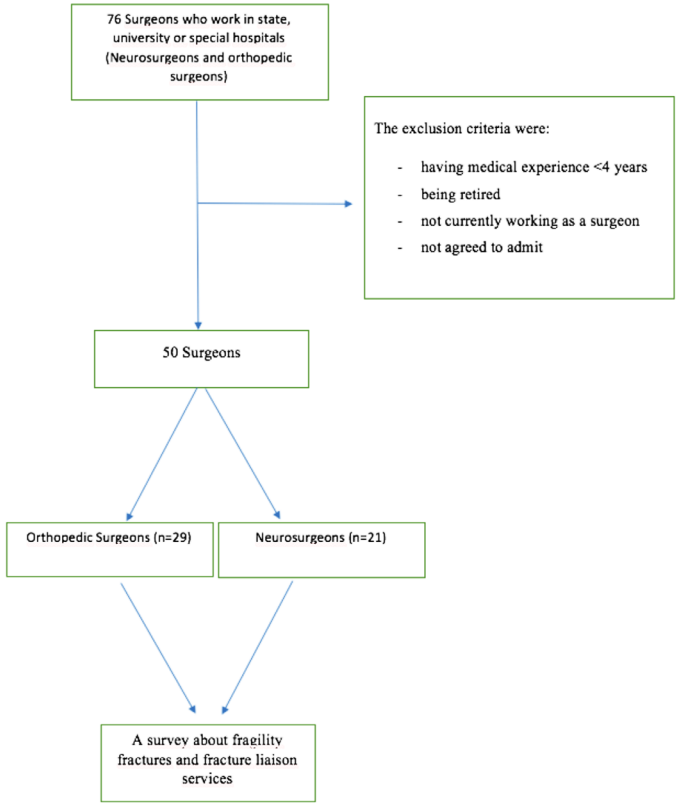

Figure 1. Flow chart of the study

were working in state hospitals, 38.1% of them were in university hospitals, and 19.0% of them were in special hospitals (Table 1, 2).

All surgeons answered "Yes" to the question: "Do you have any knowledge about fragility fractures?". Of the orthopedic surgeons, 96.6% answered "Yes" to: "Do you think that the risk of a new fracture increases in a patient with a fracture from a low-level trauma?" and "Would you consider osteoporosis in a patient who had a fracture from a low-level trauma?", while these percentages were 95.2% and 100% respectively in the neurosurgeons. The most common fragility fractures seen by orthopedic surgeons were those of the femur and forearm, while for the neurosurgeons' fractures were only seen in the vertebrae (Table 1, 2).

To evaluate osteoporosis in fractures caused by low-level trauma in daily practices, 69% of the orthopedic surgeons stated that they would want dual-energy X-ray absorptiometry (DXA), 31% of them stated they would want blood analysis for the level of calcium, phosphorus, albumin, Alkaline phosphatase (ALP), and 44.8% of them stated they would want to know the level of 25 hydroxyvitamin D. Of the neurosurgeons, 61.9% stated that they would want a DXA, while 14.3% of them stated that they would want a blood analysis. The rate of knowledge about the FRAX® algorithm was 17.2% in the orthopedic surgeons and 0% in neurosurgeons. While 37.9% of the orthopedic surgeons stated that they performed both the treatment and follow-up of osteoporosis in patients with fragility fractures, 44.8% referred these patients to PMR, and 17.2% referred them to internal medicine, geriatrics or endocrinology. All the neurosurgeons stated that they did not perform osteoporosis treatment or follow-up and referred all their patients to PMR. To the question "Do you think that starting osteoporosis medication in the early period will impair fracture healing?" 20.7% of the orthopedic surgeons and 9.3% of the neurosurgeons answered "Yes". Only one orthopedic surgeon answered "Yes", while all the neurosurgeons answered "No", to the questions "Do you have any knowledge about FLS?" and "Is there an FLS in Eskişehir?" (Table 1, 2).

Discussion

This is the first study which evaluates the awareness of both orthopedic surgeons and neurosurgeons about fragility fractures. Osteoporosis is mostly a silent disease and these surgeons are often the first to see patients with the condition who have sustained with fragility fractures. The most important risk factor for a future fragility fracture is a previous one. Patients with a vertebral fracture have an approximately four times increased risk of a new vertebral fracture and are at twice the risk of non-vertebral fractures (1,8-11,18). Distal radius fragility fractures occur almost 15 years earlier than hip fragility fractures. Patients who have experienced a distal radius fracture, have two times risk of a future hip fracture (19). In patients with a hip fracture, 10.6% will go on to suffer a fracture in their contralateral hip (20).

The role of orthopedic surgeons and neurosurgeons is thus critical to prevent morbidity, mortality and the large economic burden arising from new fragility fractures.

In an international study (in England, Germany, Spain, Italy, France, New Zealand) conducted by IOF, it was revealed that orthopedic surgeons lack training on osteoporosis and recommended that they receive more education on this topic (15). In Turkey, Moradi and Atik (16) evaluated the rate of the initiation of osteoporotic treatment after surgical fragility fractures in 844 patients between January 2002 and December 2011 and reported that awareness of diagnosis and treatment of fragility fractures declined over time. However, no study could be found in the literature about neurosurgeons' awareness and knowledge of osteoporosis or fragility fractures.

The American National IOF recommends that DXA be requested for all adults over 50 years of age with fractures (21). In the current study, although almost all of the orthopedic surgeons and neurosurgeons stated that they thought the risk

Table 1. Fragility fracture and fracture liaison service assessment survey data in orthopedic surgeons

	Orthopedic surgeons (n=29) n (%)
Age (years) (mean ± SD)	46.72±9.47
Medical experience (years) (mean ± SD)	22.40±9.85
Working place	
State hospital	12 (41.4%)
University	8 (27.6%)
Special hospital	9 (31%)
Survey questions	
Do you have any knowledge about fragility fractures? (yes)	29 (100%)
Which part of the body do you see fragility fractures mostly?	
Femur	21 (72.4%)
Forearm	14 (48.3%)
Vertebra	10 (34.5%)
Shoulder	3 (10.3%)
Costa	0 (0%)
Do you think that the risk of a new fracture increases in a patient with a fracture with a low-level trauma? (yes)	28 (96.6%)
Would you consider osteoporosis in a patient who had a fracture with a low-level trauma? (yes)	28 (96.6%)
Do you know about the FRAX® algorithm? (yes)	5 (17.2%)
Do you want an examination for osteoporosis in fractures caused by a low-level trauma that would not normally cause fractures in your daily practice? (yes)	20 (69.0%)
Which examinations do you prefer?	
DXA	20 (69.0%)
The level of calcium, phosphorus, albumin, ALP	9 (31%)
The level of 25 hydroxyvitamin D	13 (44.8%)
The level of magnesium	1 (3.4%)
Cantitative CT	0 (0%)
Which branch do you refer to for the follow-up and treatment of osteoporosis of a patient with a low-level trauma and fracture?	
Physical medicine and rehabilitation specialist	13 (44.8%)
Internal medicine/endocrinology/geriatrics	5 (17.2%)
No referral, treatment was made by myself	11 (37.9%)
Do you think that starting osteoporosis medication in the early period will impair fracture healing? (yes)	6 (20.7%)
Do you have any information about FLS? (yes)	1 (3.4%)
Is FLS in Eskişehir? (yes)	1 (3.4%)

SD: Standard deviation, ALP: Alkaline phosphatase, DXA: Dual-energy X-ray absorptiometry, CT: Computed tomography, FLS: Fracture liaison services

Table 2. Fragility fracture and fracture liaison service assessment survey data in neurosurgeons	
	Neurosurgeons (n=21) n (%)
Age (years) (mean ± SD)	44.0±11.23
Medical experience (years) (mean ± SD)	20.28±11.49
Working place	
State hospital	9 (42.9%)
University	8 (38.1%)
Special hospital	4 (19.0%)
Survey questions	
Do you have any knowledge about fragility fractures? (yes)	21 (100%)
Which part of the body do you see fragility fractures mostly?	
Vertebra	21 (100%)
Other	0 (0%)
Do you think that the risk of a new fracture increases in a patient with a fracture with a low-level trauma? (yes)	20 (95.2%)
Would you consider osteoporosis in a patient who had a fracture with a low-level trauma? (yes)	21 (100%)
Do you know about the FRAX® algorithm? (yes)	0 (0%)
Do you want an examination for osteoporosis in fractures caused by a low-level trauma that would not normally cause fractures in your daily practice? (yes)	13 (61.9%)
Which examinations do you prefer?	
DXA	13 (61.9%)
The level of calcium, phosphorus, albumin, ALP	3 (14.3%)
The level of 25 hydroxyvitamin D	3 (14.3%)
The level of magnesium	2 (9.5%)
Cantitative CT	0 (0%)
Which branch do you refer to for the follow-up and treatment of osteoporosis of a patient with a low-level trauma and fracture?	
Physical medicine and rehabilitation specialist	100 (100%)
Internal medicine/endocrinology/geriatrics	0 (0%)
No referral, treatment was made by myself	0 (0%)
Do you think that starting osteoporosis medication in the early period will impair fracture healing? (yes)	2 (9.3%)
Do you have any information about FLS? (yes)	0 (100%)
Is there a FLS in Eskişehir? (yes)	0 (100%)
SD: Standard deviation, DXA: Dual-energy X-ray absorptiometry, ALP: Alkaline phosphatase, CT: Computed tomography, FLS: Fracture liaison services	

of a new fracture increased after a fragility fracture, only 69% of the orthopedic surgeons stated that they requested a DXA in patients with fragility fractures, while this rate was 61% in the neurosurgeons. These rates are similar to those found in a previous study which conducted a survey of 166 orthopedic surgeons about osteoporosis in Turkey. Likewise, Aydın (17) reported that 30% of orthopedic surgeons did not request a DXA for any patient. After hip fractures, the rate of initiation of osteoporosis treatment ranges from 5-30% (2). The low rate of post-fracture DXA request by surgeons in two separate studies in Turkey explains the low rates of initiation of post-fracture osteoporosis treatment.

FRAX® is a computer-based algorithm which gives ten-year probability of hip fracture and a major osteoporotic fracture (22). The World Health Organization recommends the use of FRAX® to detect patients' risk of fractures. However, only 17.2% of the orthopedic surgeons, and not a single neurosurgeon, knew about the FRAX® algorithm. Measuring serum vitamin D levels is recommended for diagnosis and follow-up for osteoporosis by the Society of Endocrinology and Metabolism, and measuring calcium, phosphorus, ALP is recommended in vitamin D deficiency (23). Aydın (17) reported that 36% of orthopedic surgeons did not request the vitamin D levels of patients with a fragility fracture. The percentage of those

asking for vitamin D levels was even lower in the present study: 56% of the orthopedic surgeons and 86% of neurosurgeons stated that they did not do this. In addition, 69% of the orthopedic surgeons and 86% of the neurosurgeons stated that they did not request serum levels of calcium, phosphorus, albumin, and ALP. Similar to our study, Aydın (17) reported this rate to be 62%. Given the effect of vitamin D on falls and bone health (24), these low rates were disappointing. Osteoporosis is treated in many different branches of medicine. While physicians working in internal medicine, PMR, rheumatology, gynecology and obstetrics are authorized to write osteoporosis medication for osteoporosis, as are orthopedic surgeons, neurosurgeons in Turkey are not authorized to do so. With regard to patients with fragility fractures, 17% of the orthopedic surgeons stated that they referred these patients to internal medicine physicians and 45% referred them to PMR physicians, while only 38% of them stated that they provided treatment and follow-up osteoporosis themselves. All the neurosurgeons stated that they referred all patients with fragility fractures to PMR. Given that neurosurgeons are not authorized to prescribe osteoporosis medication, this is not a surprising result, because PMR physicians are better able to treat and follow-up these patients. Aydın (17) reported almost the same rates, finding that while 33% of orthopedic surgeons performed the follow-up and treatment of osteoporosis themselves, 60% of them referred patients to PMR. Orthopedic surgeons and neurosurgeons are generally the first physicians who are consulted when a fragility fracture occurs and they should be expected to know osteoporosis well. However, the rate of initiating osteoporosis treatment by orthopedic surgeons is low both in the province of Eskişehir and in Turkey as a whole, and they mostly refer patients with fragility fractures to other clinics for osteoporosis follow-up and treatment. The use of FLS has been an accepted approach to decrease fragility fractures, especially hip fractures, for approximately a decade. These services, which have been established in many countries, including Turkey, provide interventions to combat osteoporosis and to prevent future fragility fractures (25). There should ideally be a close relationship between FLS and neurosurgeons and orthopedic surgeons, who frequently see patients with fragility fractures. However, the results of this study showed that only one surgeon had some knowledge about FLS. This demonstrates the need for FLS to be promoted more in the orthopedics and neurosurgery communities. In this regard, establishing better contact with professional associations and bringing surgeons and physicians together in multidisciplinary conferences and meetings may offer a way forward. In addition, coordinated post-fracture systems should be established, so that when a fracture record in a patient aged 50 and over is entered into system, their contact information should automatically drop into the FLS system in the same city or region. Such a system would also make it easier to reach out to patients. The limitation of this study is that the surgeons filled in the survey by themselves. The actual approaches they used in thus practice could thus not be evaluated. There is a need for objective studies with patient data to determine the rates of initiation of osteoporotic treatment after a fragility fracture.

Conclusion

In both the orthopedic surgeons and neurosurgeons knowledge of FRAX® and FLS, and general awareness about fragility fractures was lower than expected. These surgeons play a very important role in the diagnosis and treatment of osteoporosis after fragility fractures, and further professional training on these issues is required to increase awareness.

Ethics

Ethics Committee Approval: Ethics approval was received from the Eskişehir Osmangazi University Non-invasive Clinical Research Ethics Committee with the decision dated 21/02/2023 and numbered 16.

Informed Consent: All surgeons were informed about the study and their verbal consent was obtained.

Authorship Contributions

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

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

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

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Original Investigation / Orijinal Araştırma

DOI: 10.4274/tod.galenos.2023.30164
Turk J Osteoporos 2024;30:44-8

Ultrasound Examination of the Median Nerve at Different Levels: Inter-rater Reliability Study

Medyan Sinirin Farklı Seviyelerden Ultrason ile İncelenmesi: Değerlendiriciler Arası Güvenilirlik Çalışması

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Abstract

Objective: In this study, we aimed to investigate the inter-rater reliability of the median nerve, evaluated at different levels by ultrasound (US) in asymptomatic subjects.
Materials and Methods: A cross-sectional study. This study included 61 healthy controls. The mediolateral and anteroposterior diameters and cross-sectional area (CSA) of the median nerve at the carpal tunnel inlet were measured. The CSA of the median nerves at the carpal tunnel outlet and forearm level was measured. Flattening ratio, wrist-forearm ratio and wrist-forearm difference were calculated.
Results: In the inter-rater comparison of the measurements, there was a statistically significant difference only in the carpal tunnel outlet cross sectional area ($p<0.048$). There was no statistically significant difference between the observers in terms of other measurements ($p>0.05$). For the median nerve measurement, agreement was also moderate to good inter-rater reliability [intraclass correlation coefficient (ICC) =0.54-0.81] except for the forearm cross sectional area, swelling ratio of the medial nerve. For the median nerve forearm cross sectional area, agreement was excellent inter-rater reliability (ICC =0.91). However, for swelling ratio, agreement was poor interrater reliability (ICC =0.27).
Conclusion: In this study, US showed to be a reliable tool for measuring median nerve dimensions in asymptomatic subjects.
Keywords: Ultrasound, reliability, median nerve

Öz

Amaç: Bu çalışmada asemptomatik bireylerde ultrason (US) ile farklı seviyelerde değerlendirilen medyan sinirin değerlendiriciler arası güvenilirliğinin araştırılması amaçlandı.
Gereç ve Yöntem: Bu çalışma kesitsel bir çalışmadır. Bu çalışmaya 61 sağlıklı kontrol dahil edildi. Medyan sinirin karpal tünel girişindeki mediolateral ve ön-arka çapları ve kesit alanı ölçüldü. Karpal tünel çıkışında ve ön kol seviyesinde medyan sinirlerin kesit alanı ölçüldü. Düzleşme oranı, bilek-ön kol oranı ve bilek-ön kol farkı hesaplandı.
Bulgular: Ölçümlerin gözlemciler arası karşılaştırılmasında sadece karpal tünel çıkış kesit alanında istatistiksel olarak anlamlı farklılık vardı ($p=0,048$). Diğer ölçümler açısından gözlemciler arasında istatistiksel olarak anlamlı bir fark yoktu ($p>0,05$). Medyan sinir ölçümlerinde; ön kol kesit alanı ve medyan sinirin şişme oranı dışında, gözlemciler arası güvenilirlik orta ile iyi düzeydeydi [sınıf içi korelasyon katsayısı (ICC) =0,54-0,81]. Medyan sinir ön kol kesit alanı için güvenilirlik, değerlendiriciler arası mükemmeldi (ICC =0,91). Ancak şişme oranı açısından, gözlemciler arası güvenirlik zayıftı (ICC =0,27).
Sonuç: Bu çalışmada US'nin asemptomatik bireylerde medyan sinir boyutlarını ölçmek için güvenilir bir araç olduğu gösterilmiştir.
Anahtar kelimeler: Ultrason, güvenilirlik, medyan sinir

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Received/Geliş Tarihi: 23.08.2023 **Accepted/Kabul Tarihi:** 16.10.2023

Introduction

The most common type of neuropathy caused by entrapment of the median nerve is carpal tunnel syndrome (CTS). Clinical history, physical examination findings and electrodiagnostic evaluations are used in the diagnosis of CTS (1,2). Although electrodiagnostic evaluation is important in the diagnosis of CTS, it has a false negative rate of 16-34% (3). Ultrasound (US) is often preferred to evaluate the morphological and mechanical properties of the median nerve in the diagnosis of CTS. It has been stated that the US is a highly accurate, effective, and cost-effective diagnostic method for diagnosing CTS, and the evaluation period is a short diagnostic method (1). However, it is emphasized that reference values should be determined for the diagnosis of CTS. One of the most important factors determining the reliability and accuracy of US use in the diagnosis of CTS is the accurate identification of landmarks (2).

There are studies investigating the reliability of the cross-sectional area (CSA) (4-8), flattening ratio (FR) (5,6), anteroposterior (AP), and mediolateral (ML) diameters (4), and carpal tunnel inlet (CTI) to forearm ratio (9). In this study, we aimed to evaluate the reliability of the median nerve CSA at CTI, chronic total occlusion (CTO), and forearm levels, as well as the AP and ML diameters and FR of the median nerve at the CTI level. In addition, we aimed to evaluate the reliability of the CTI/CTO ratio, the CTO/forearm ratio, and the wrist-forearm CSA difference used in the ultrasonographic diagnosis of CTS, but whose reliability was not evaluated.

Materials and Methods

In our inter-rater reliability study, which was carried out as a single center, 66 healthy volunteers who were hospital staff were included. However, five healthy volunteers were not included in the study. A bifid median nerve was detected in three of them; two of them did not want to continue studying after the first measurement. The study continued with 61 healthy volunteers.

Each subject provided written informed consent. The research was carried out in conformity with the Helsinki Declaration's criteria. The study was started after ethical approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital number (date: 07.04.2023, decision no: 90).

Inclusion criteria in the study: Healthy volunteers between the ages of 18 and 65; exclusion criteria in the study: Individuals with clinical signs and symptoms of CTS, diabetes mellitus, thyroid abnormalities, rheumatological disease history, previous surgery, or fractures in the upper extremity. Median nerves that were found to be bifid during the US examination were not included in the study. The dominant extremity of the participants was evaluated.

The gender, height, weight, and body mass indexes (BMI) of all participants in the study were recorded.

Sample Size Calculation: Power Analysis and Sample Size Software 15 (2017) by NCSS, LLC (Kaysville, UT, USA; www.ncss.com/software/pass) was used to calculate the sample size. Using a one-way random-effects analysis of variance model, a random sample of 66 wrists who were tested twice produced a two-sided 95% confidence interval with a width of 0.200 when the estimated intraclass correlation was 0.840 (5).

US Examination: US evaluation was performed by physiatrists with 5 years (B.T.D.) and 4 years (F.K.) experience in the musculoskeletal US. Examinations were performed with a wired US device [MyLab50 (Esaote Biomedica, Genova, Italy)] using a 12 MHz linear probe. The examinations were performed on a table at rest with the elbow in flexion position, forearm in supination, wrist in neutral position and fingers in semi-flexion position. The median nerve was visualized by positioning the US probe transversely approximately 10 cm proximal to the distal wrist line. The probe was shifted distally and the median nerve was visualized at CTI at the scaphoid-pisiform bone level. The probe was shifted slightly distally and the median nerve was visualized at the CTO at the level of the hamate-trapezium bone. Three images were taken from each of the three imaging levels and recorded in the database.

Calculations and measurements were made by taking the arithmetic mean of the data obtained from the three recorded images. If the nerve had an elliptical form, the electronic ellipse function was applied for the CSA measurement (Figure 1a). The continuous tracing method was used if the nerve was not elliptical. During the evaluations, the border of the median nerve was evaluated as the line between the hyperechoic nerve sheath and hypoechoic nerve fascicles (4). CSA measurements were performed at the forearm, CTI and CTO levels. AP and ML diameter measurements were performed only at the CTI level (Figure 1b, c). After the measurements, the ratio of ML diameter to AP diameter, known as FR, was calculated. The swelling ratio is calculated by dividing the CSA of the nerve at the CTO by that of the nerve at the CTI. The ratio of the "CSA of the nerve at the CTO or CTI levels to the CSA of the nerve at the forearm level", also known as the wrist/forearm ratio. CTI CSA-forearm CSA difference and CTO CSA-forearm CSA difference were calculated (wrist-forearm difference) (10).

During this study, in order to the standardization of the measurements, two sessions were conducted with 5 participants before the start of the study and the differences between the observers were discussed and a consensus was reached. However, the data of these 5 participants were not used in the study.

Statistical Analysis

Statistical analysis was carried out using IBM SPSS version 22.0 software (IBM Corp., Armonk, IL, USA). Normal distribution was determined using the Kolmogorov-Smirnov/Shapiro-Wilk test, kurtosis and skewness values and histogram plots. When presenting descriptive analyses, mean and standard deviation values or median and minimum-maximum values are given for quantitative variables. Since the data showed a normal distribution, the correlation between numerical variables

was determined with the parametric Pearson correlation test. After the measurements and calculations, the intraclass correlation coefficient (ICC), minimum detectable change (MDC) and standard error of the mean (SEM) were calculated. SEM=(standard deviation) x√(1-ICC) and MDC=(SEM)x(√2) x(1.96). To evaluate inter- and intra-rater reliability, ICC was used. When analyzing the reliability of ICC, ICC =0.5-0.75 indicates moderate reliability, ICC =0.75-0.90 indicates good reliability and ICC≥0.90 indicates excellent reliability (11).

Results

A total of 61 wrists were evaluated. The mean age of the participants included in the study was 48.0±11.1 years; 25 (78%) were women. The mean BMI was 29.0±5.7.

In the inter-observer comparison of the measurements, there was a statistically significant difference only in the CTO CSA (p<0.048). There was no statistically significant difference between the observers in terms of other measurements (p>0.05) (Table 1).

For the median nerve measurement, agreement was also moderate to good inter-rater reliability (ICC =0.54-0.81), except for the forearm CSA and swelling ratio of the median nerve. For the median nerve forearm CSA, agreement was excellent inter-rater reliability (ICC =0.91). However, for the swelling ratio, the agreement had poor inter-rater reliability (ICC =0.27). The inter-rater ICC's, SEM's, and MDC's for US measurements are displayed in Table 2.

Discussion

This study found the interrater correlation coefficient for the US measurement of the median nerve at different levels. In our study, we obtained excellent inter-rater reliability for forearm CSA. Except for the swelling ratio, we obtained moderate to good inter-rater reliability in other measurements.

Previous studies have shown that the US has higher sensitivity (82%) and specificity (87%) when compared to electrophysiological methods in the diagnosis of CTS (12). In fact, some researchers believe that the US is more sensitive than

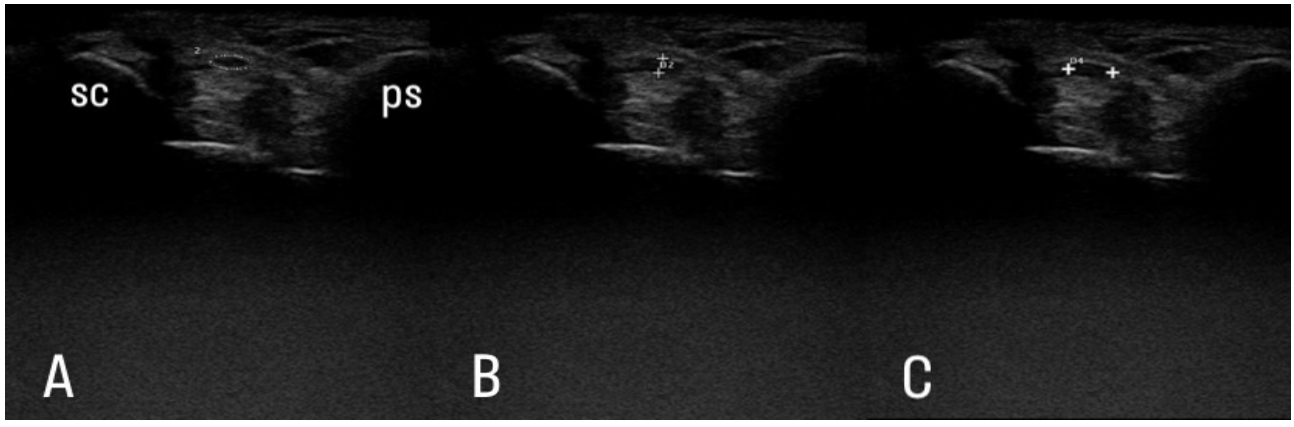

Figure 1. Median nerve measurements in the transverse plane at the scaphoid (sc) and pisiform (ps) bone level A) cross-sectional area, B) anteroposterior diameter, C) mediolateral diameter

Table 1. Comparison of measurements between observers

	Observer 1	Observer 2	p-value
Forearm CSA	1.64±0.26	1.73±0.50	0.756
CTI CSA	6.93±1.51	7.27±1.22	0.170
CTI FR	3.51±0.80	3.32±0.92	0.241
CTI AP diameter	1.64±0.26	1.73±0.50	0.209
CTI ML diameter	5.63±0.92	5.47±0.92	0.325
CTO CSA	6.90±1.44	7.39±1.26	**0.048***
Swelling ratio	1.00±0.12	0.99±0.11	0.456
CTI/forearm ratio	1.83±0.41	1.91±0.36	0.279
CTO/forearm ratio	1.82±0.37	1.93±0.35	0.110
CTI-forearm difference	3.11±1.37	3.42±1.21	0.189
CTO-forearm difference	3.08±1.30	3.52±1.19	0.053

*p<0.05
CSA: Cross-sectional area, CTI: Carpal tunnel inlet, FR: Flattening ratio, AP: Anteroposterior, ML: Mediolateral, CTO: Chronic total occlusion

Table 2. Reliability results of the median nerve measurements at the different levels

	ICC (95% CI)	SEM	MDC
Forearm CSA	0.91 (0.82-0.93)	0.173	0.480
CTI CSA	0.81 (0.68-0.88)	0.578	1.603
CTI FR	0.72 (0.54-0.83)	0.454	1.259
CTI AP diameter	0.54 (0.23-0.72)	0.259	0.718
CTI ML diameter	0.75 (0.58-0.85)	0.460	1.276
CTO CSA	0.78 (0.63-0.87)	0.635	1.760
CTI/CTO ratio	0.27 (-0.20-0.56)	0.100	0.277
CTI/forearm ratio	0.76 (0.61-0.85)	0.189	0.524
CTO/forearm ratio	0.71 (0.51-0.82)	0.195	0.541
CTI-forearm difference	0.78 (0.63-0.86)	0.606	1.679
CTO-forearm difference	0.70 (0.51-0.82)	0.682	1.890

ICC: Intraclass correlation coefficient, CI: Confidence interval, SEM: Standard error of the mean, MDC: Minimum detectable change, CSA: Cross-sectional area, CTI: Carpal tunnel inlet, FR: Flattening ratio, AP: Anteroposterior, ML: Mediolateral, CTO: Chronic total occlusion

electrophysiological methods (13). Wong et al. (1) proposed an algorithm in which sonography for patients suspected of having CTS is the first study and electrodiagnostic tests are performed only in cases where the sonographic results are not confirmatory. Although US is widely used in the diagnosis of CTS, for sonographic evaluation of the median nerve for CTS, there is no universally accepted standard. When the literature is examined, different sonographic techniques and different levels are used in the evaluation of the median nerve. These differences in measurements necessitated the need to assess the reliability of the measurement parameters (9).

According to Junck et al. (9) the median nerve CSA at the CTI level was highly reliable both between and within raters. However, it was less reliable at the pronator quadratus and middle forearm levels. In addition, like our study, they examined the reliability of the wrist/forearm ratio in their studies and found the reliability value to be 0.73 in patients with CTS and 0.69 in the control group. Impink et al. (14) investigated the reliability of the CSA, FR, and swelling ratio of the median nerve at the different levels. In their study, they found that the reliability of the median nerve CSA at the psiform bone level was higher than the CSA at the hamat bone level and the FR measured at the psiform bone level. In their study, they also stated that intra-rater reliability is superior to inter-rater reliability. However, they used generalizability theory, unlike the ICC, to assess the reliability of measurements in their studies. Therefore, it is difficult to compare the data in their study with our study.

Gonzalez-Suarez et al. (4) investigated the reliability of sonographic measures of the median nerve at various levels. In this study, they obtained excellent inter-rater reliability (ICC =0.89) for the median nerve CSA at the forearm level. They found that the inter-rater reliability value of the median nerve CSA at the forearm level was greater than that evaluated at the psiform and hamat bone level (ICC =0.57, ICC =0.75, respectively). In this study, they obtained fair to good inter-rater reliability for the AP diameter and ML diameter of the median nerve, which were evaluated at the psiform bone level (ICC =0.67, ICC =0.58, respectively). Furthermore, it was reported in this study that using external landmarks in sonographic measurements of the median nerve increased inter-rater reliability (4).

In a study, Bueno-Gracia E et al. (5) investigated the reliability of median nerve measurements at the CTI level. In their studies, they obtained good to excellent inter-rater reliability for the median nerve CSA and ML diameter (ICC =0.89, SEM =0.56, MDC =2.07; ICC =0.81, SEM =0.38, MDC =1.70, respectively). However, they obtained moderate to good inter-rater reliability for AP diameter and FR (ICC =0.74, SEM =0.12, MDC =0.98; ICC =0.62, SEM =0.43, MDC =1.81 respectively).

SEM and MDC values were indicated in only two of the studies investigating the reliability of sonographic measurements of the median nerve (5,14). SEM and MDC values are specified because the large SEM value and the small SEM value, respectively, indicate an imprecise and precise estimate. The MDC value is also an important measurement. It indicates the smallest difference that is clinically significant for the measurements made to be considered reliable.

When the literature is examined, the CTI/CTO ratio and the wrist-forearm CSA difference are shown to be significantly different between CTS patients and the control group. However, to the best of our knowledge, the study examining the reliability of these parameters from sonographic measurements of the median nerve was non-existent (10,15,16). In our study, we aimed to contribute to the literature by examining the reliability of these parameters. This aspect makes our study special. However, we state that future studies are needed to support our findings.

Study Limitations

If we list the limitations of our study, the first is that we did not investigate the reliability of measurements of FR, AP diameter, and ML diameter at the forearm level and CTO level; second, our reliability study was only on the control group; and more importantly, we did not investigate intra-rater reliability.

Conclusion

In this study, agreement was also moderate to good, except for the forearm CSA, and swelling ratio of the median nerve. For the median nerve forearm CSA, agreement was excellent inter-rater reliability achieved. As a result, in this study, US was shown to be a reliable tool for measuring median nerve dimensions in asymptomatic subjects.

Ethics

Ethics Committee Approval: Ethical approval to report this case was obtained from Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital number (date: 07.04.2023, decision no: 90).
Informed Consent: Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Authorship Contributions

Surgical and Medical Practices: B.T.D., F.K., Concept: B.T.D., M.O., F.B., E.A., Design: B.T.D., F.K., E.A., Data Collection or Processing: B.T.D. F.K., Analysis or Interpretation: B.T.D. F.K. M.O., E.A., Literature Search: B.T.D., F.B., E.A., Writing: B.T.D., F.K., F.B.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study has received no financial support.

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DOI: 10.4274/tod.galenos.2023.65902
Turk J Osteoporos 2024;30:49-54

Comparison of Functional Status and Depression in Younger and Older Patients with Chronic Low Back Pain: A Multi-center Cross-sectional Survey

Kronik Bel Ağrılı Genç ve Yaşlı Hastaların Fonksiyonel Durum ve Depresyon Açısından Karşılaştırılması: Çok Merkezli Kesitsel Bir Araştırma

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Abstract

Objective: This study compared the differences in functionality and depression between younger and older patients with chronic low back pain (CLBP).
Materials and Methods: This multi-center cross-sectional survey enrolled subjects with CLBP who visited physical medicine and rehabilitation clinics in seven different regions of Turkey. Sociodemographic data were collected via questionnaires. Functional status was evaluated with Roland-Morris Disability index (RMDI), and psychological health was evaluated with Beck Depression inventory (BDI).
Results: The sample included 106 younger [mean age: 24.3 (range: 18-30) years] and 104 older [mean age: 70.5 (range: 65-108) years] subjects. No significant difference was found in the gender distribution between the younger (38 males, 68 females) and older (38 males, 66 females) groups (p=0.917). The BDI was 11.90±10.6 in the younger subjects and 16.17±10.72 in the older subjects (p=0.002), whereas the mean RMDIs were 10.31±6.36 and 16.04±5.36, respectively (p=0.001).
Conclusion: The loss of functional capacity and depression resulting from CLBP are serious threats to public health and are predictive of chronic disability. The development of social programs that address risk factors will reduce the risk of CLBP, improve quality of life, reduce workforce losses and contribute significantly to public health.
Keywords: Low back pain, functional capacity, geriatrics, depression, public health

Öz

Amaç: Bu çalışmada genç ve yaşlı kronik bel ağrılı (KBA) hastaların fonksiyonellik ve depresyon açısından farklılıkları karşılaştırılmıştır.
Gereç ve Yöntem: Bu çok merkezli kesitsel çalışmaya, Türkiye'nin 7 bölgesindeki farklı fiziksel tıp ve rehabilitasyon polikliniklerine başvuran KBA'lı 106 genç 104 yaşlı hasta dahil edilmiştir. Sosyodemografik veriler anketler yoluyla toplanmıştır. Fonksiyonel durum Roland-Morris Dizabilite anketi (RMDA) ile, psikolojik sorgulama ise Beck Depresyon anketi (BDA) ile değerlendirilmiştir. İstatistiksel analizler IBM SPSS Statistics 22 paket programıyla yapılmıştır.

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Received/Geliş Tarihi: 14.09.2023 **Accepted/Kabul Tarihi:** 15.12.2023

Öz

Bulgular: Çalışmamıza 106 genç [ortalama yaş: 24,3 (18-30)] ve 104 yaşlı [ortalama yaş: 70,5 (65-108)] hasta katıldı. Cinsiyet dağılımı açısından genç (68 kadın, 38 erkek) ve yaşlı hasta (66 kadın, 38 erkek) grupları arasında anlamlı bir farklılık yoktu (p=0,917). BDA sonuçları gençlerde 11,90±10,6 iken yaşlı hasta grubunda 16,17±10,72 bulunmuşken (p=0,002), RMDA ortalamaları geçlerde ve yaşlılarda sırasıyla 10,31±6,36 ve 16,04±5,36 olarak bulundu (p=0,001).

Sonuç: KBA sık karşılaşılan, fonksiyonel ve psikolojik problemlere yol açtığı bilinen bir hastalıktır. Bel ağrısı kaynaklı fonksiyon kaybı ve depresyon ciddi halk sağlığı problem ve kronik dizabilitenin belirleyicilerindendir. KBA gelişimini engelleyecek risk faktörlerinin belirlenmesi ve buna yönelik sosyal programların geliştirilmesi, hassas kişilerde yaşam kalitesini artıracak, iş gücü kaybını azaltacak ve halk sağlığına önemli olumlu etkileri olacaktır.

Anahtar kelimeler: Bel ağrısı, fonksiyonel kapasite, geriatri, depresyon, halk sağlığı

Introduction

International Pain Studies Association describes pain as; "An unpleasant sensory and emotional experience associated with actual or potential tissue damage". Chronic pain, lasting more than 3 months, is a subjective and multidimensional experience with sensory, emotional, behavioral and cognitive components that require long-term treatment (1).

Chronic low back pain (CLBP) is a complex disease that we encounter frequently, and is associated with serious consequences, such as physical disability and psychosocial disorders like anxiety, depression, and fear of participating in activities (2). Approximately 80% of people experience low back pain in their lifetime, and most of them will experience a recurrent or new LBP episode within 1 year (3). Depression and anxiety often exist among patients with LBP. Some studies mentioned about mechanisms, especially focusing on the mechanisms in the central and peripheral nervous system, which are commonly seen in herniated intervertebral disc and major depressive disorder (4).

CLBP is a common debilitating problem in people aged 65 and over. The known prevalence of LBP in older populations is between 13% and 49% (3). The incidence CLBP related disability in the general population is 65%, and disability-related factors include the work situation, low self-esteem, and depression (5). Studies comparing the functional status and depression of young and old people with CLBP have increased over time (6-8). Older people are inadequately represented, even when different age categories are compared, and patients over 65 years were clearly excluded in several studies (9).

Information about disability is essential for rehabilitation specialists and other healthcare professionals working with CLBP patients. It may be associated with chronic pain, insomnia, nausea, and depression and may be comorbid or secondary. Leading to a decrease in effectiveness, resulting in medical, social and may emerge as an economic problem. In general, policymakers and healthcare providers assume that the rate of weak-to-moderate disability and depression in the population is the same in young and old people (10,11). It has been reported that the incidence of depression in patients with chronic pain varies between 10-100%, usually above 50% (12). However, these studies are usually performed on samples that are heterogeneous in terms of age or on middle-aged people, and it is doubtful whether the disability and depression levels are the same in young and old populations because they have not been compared. Information from recent epidemiological studies suggests that CLBP influences the physical functioning of younger and older people differently (13,14).

Identifying the factors associated with CLBP can help to improve rehabilitation care and improve patients' quality of life (15). It was aimed to compare functional disability and depression in young and old patients with CLBP and to close a gap in the literature.

Materials and Methods

This was a multi-center cross-sectional survey of patients with CLBP who presented to physical medicine and rehabilitation (PM&R) outpatient clinics in seven different regions of Turkey. The research was prepared in accordance with the Declaration of Helsinki. Ethics committee permissions and preliminary preparation of the study were reviewed and approved by İstanbul Medeniyet University Göztepe Training and Research Hospital Institutional Review Board (decision no: 20/G, date: 20.03.2012). Written informed consent was obtained from all patients to participate in the study.

Patients

The study was conducted by 10 PM&R specialists from seven geographic regions of Turkey (Marmara Anatolian, Marmara European, Central Anatolia, Aegean, Black Sea, Mediterranean, Eastern Anatolia, and Southeastern Anatolia) from August 2012 through January 2013. The study enrolled 210 patients who suffered from mechanical LBP on at least half the days over the previous 3 months. Patients with an acute fracture, neoplasia, infection, or LBP radiating from the abdominal and pelvic organs or due to pregnancy were not included in the study. None of the patients recruited for the study declined to participate.

Outcome Measures

Sociodemographic characteristics (age, gender, and body mass index) and clinical information (diagnosis, duration of disease, and treatments received) were recorded during face-to-face interviews at the first visit. The Roland-Morris Disability index

(RMDI) was used to assess functional status, and the Beck Depression inventory (BDI) was used to assess psychological health. The RMDI and BDI questionnaires filled out by patients after the first visit.

Roland-Morris Disability Index

The RMDI is a reliable, valid health status measure designed to be filled in by patients themselves to assess the physical disability associated with LBP. The index was originally designed to be used in research (i.e., as a benchmark for clinical trials), but it has also been helpful in clinical practice for monitoring patients. The RMDI is short, easy to fill and easily understood by patients. The RMDI score is calculated as the sum of the number of items checked by patients, and scores range from 0 (no disability) to 24 (maximum disability) (16,17).

Beck Depression Inventory

The BDI is a self-reported measure of depressive symptoms including 21 items with confirmed reliability and validity. Each item is scored from 0 to 3, and the maximum possible total score is 63. A score of 0-4 is considered normal, one of 5-13 is considered to reflect borderline clinical depression, one of 14-20 is considered to reflect moderate depression, and one of 21-63 is considered to reflect severe depression. The BDI is a screening tool and is not used for diagnosis (18). The validity and reliability of the BDI for the Turkish population was conducted by Teğin (19).

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics 22 (IBM SPSS, Turkey). The fit of the data to a normal distribution was evaluated using the Shapiro-Wilk test. Quantitative analyses (means, standard deviations, and frequencies) were also performed. Student's t-test was used to compare two groups with normally distributed parameters, and data that were not normally distributed were compared with the Mann-Whitney U test. Qualitative data were compared with the chi-square test and the Yates continuity correction.

Statistical significance was set at $p<0.05$ at $\alpha=0.05$ significance.

Results

In total, 106 patients were younger (18-30 years) and 104 were older (65-88 years). Patients included in the study were diagnosed with chronic mechanical low back pain in accordance with the exclusion criteria. None of them had received any surgical or interventional treatment. There were no differences in the treatments used (non-pharmacological treatments such as physical therapy or bracing, pharmacological treatments such as simple analgesics and non-steroidal anti-inflammatory drugs). Other findings related to demographic characteristics of the patients are shown in Table 1. The mean BDI and RMDI scores are seen in Table 2.

Discussion

Pain helps to regulate object relations and plays a symbolic role in communication with the person's environment. In some patients, pain can be interpreted as punishment. The subconscious is accompanied by a sense of guilt. The death of the person invested with love can initiate pain. Various factors such as childhood neglect and suppressed aggression have also been described in chronic pain patients, and it has been reported that anger and hostility play an important role in the development and continuation of pain. Anger expression is one of the issues emphasized in these patients. According to this view; chronic pain is caused by the patient's desire to suppress

Table 1. Demographic characteristics of patients

	Young patients (n=106) mean ± SD	Geriatric patients (n=104) mean ± SD	p-value
Age (years)	24.3 (±3.99)	70.5 (±5.19)	**0.001****
Height (cm)	167.35 (±8.1)	162.44 (±8.5)	[1]**0.001****
Weight (kg)	65.31 (±12.16)	75.42 (±12.14)	[1]**0.001****
BMI (kg/m^2)	23.28 (±3.86)	28.73 (±5.13)	[1]**0.001****
Duration of LBP (months)	35.54 (±83.33)	90.25 (±126.78)	[2]**0.001****
Sex (female/male)	68/38	66/38	[3]**0.917****

[1]Student t-test, [2]Mann-Whitney U test, [3]Chi-square test ve continuity (Yates) correction, **p<0.01. BMI: Body mass index, LBP: Low back pain, SD: Standard deviation

Table 2. RMDI and BDI scores of groups

	Young patients mean ± SD (median)	Geriatric patients mean ± SD (median)	p-value
RMDI	10.31±6.36 (9)	16.04±5.36 (16.5)	**0.001****
BDI	11.90±10.6 (11)	16.17±10.72 (14)	**0.002****

Mann-Whitney U test, **p<0.01. RMDI: Roland-Morris Disability index, BDI: Beck Depression inventory, SD: Standard deviation

intense anger, and this inward anger is more common than healthy controls (20).

This study examined whether the associations between LBP and depression and disability differ in younger and older individuals. Other studies have revealed a weak-to-moderate association between LBP and physical disability (7,9), and our results are consistent with these findings. In our study, the association between these two variables was significantly stronger in older patients.

To our knowledge, only Houde et al. (21) have evaluated whether the disability status of those with LBP is influenced by age. They enrolled 164 patients with LBP and reported that physical disability (measured using the Oswestry Disability index) was considerably higher in younger patients. However, the groups in their study were divided according to median age into younger (n=82; age: 22-48 years) and older (n=82; age: 49-90 years) groups. We believe that their older group does not represent geriatric patients. Our study groups comprised younger patients, aged 18-30 years, and a geriatric group, aged 65-88 years. Unlike Houde et al. (21), we found considerably higher physical disability scores in the older group. Within the scope of the research, studies in the literature were examined on an empirical basis in order to evaluate chronic pain in elderly patients. A conceptual model has been obtained. In the study conducted to examine the relationship between pain phenotypes and depression, neuroticism, a positive correlation was found between pain and major depression research focuses on studies investigating the molecular features of the comorbid relationship between chronic pain and mood disorders, especially major depressive disorders (12).

Some studies have reported that restriction of activities was directly related to advancing age, and the oldest age groups were those with the highest mobility restrictions (22). In a 2-year prospective study evaluating associations among chronic pain, functioning, depression, and healthcare utilization in 169 older adults, Mossey and Gallagher (23) reported that 37.7% had pain leading to moderately-to-severely impaired functioning. Furthermore, the pain that was present at the beginning of the study process and continued over the 2 years, increasing the risks of depression and impaired functioning and leads to increased use of health services. Back pain is a common condition of major social importance and poorly understood pathogenesis (24). Buchbinder et al. (13) researched the effect of age on the burden of disability in LBP patients and reported a higher burden of disability per capita in geriatric age groups. Our results concur with these studies.

Chronic pain also brings with it psychiatric disorders, most commonly depression. The relationship between chronic pain and depression is complex (25). Corran et al. (26) proposed that younger patients be classified as having a "positive adaption to pain" (high level of pain with low levels of depression and functional impact), "chronic pain syndrome" (high levels of pain with functional impact and depression), or "good pain control" (low levels of pain and low impact). An additional category, called "high impact" and characterized by low levels of pain but high levels of functional impact and relatively high levels of depression, was identified in about 25% of older patients. The most plausible explanation for this discrepancy is the higher incidence of comorbidities in older patients, which alters the effects of pain on functioning and mood. Although we did not check X-rays or the bone mineral densities of our patients, degenerative changes in the spine and osteoporosis are prevalent in older patients and would contribute to their high physical dysfunction and depression scores. Within the scope of the research conducted by Groenveld at al. (27), a method based on behavioral therapy was applied to patients with moderate to severe pain in the pain clinic. Visual reality (VR) practice for at least 10 minutes a day for 4 weeks the control group received standard care. As a result of this application, it was found that anxiety and depression decreased and VR application increased the quality of life (27).

Although we couldn't find an article that compares depression in younger and older CLBP patients, depression frequently accompanies LBP (28) and is commonly associated with increased physical and psychological disability (29). In a review, Linton (30) reported that depression was associated with chronic pain syndromes in 88% of the studies reviewed. Older patients with chronic pain are also at high risk of depression, and this is the case whether they live in a nursing home or the community (31). Onat et al. (32) found that advanced age was a risk factor for depression in older individuals. They showed that the functional situation deteriorates with aging, and poor functioning poses a risk for depression. This vicious cycle is another explanation for our results. Although a strong association between pain and depression has been reported, we could not find any comparative study in terms of age. Mesci et al. (33) investigated the sensitivity of younger and older people to painful stimuli and studied the impact of aging on pain perception and depression. However, they didnot find a difference in pain sensitivity and depression between younger and older individuals. They studied healthy groups, whereas our patients were CLBP patients.

The most important limitation of this study is that our participants were recruited from tertiary health centers. Although we recruited patients from all regions of Turkey, it is possible that our patients were referred for treatment because they were more disabled. However, as the health policies in Turkey allow anyone to visit any hospital they choose, even patients living in a rural area can apply directly to a university hospital. Therefore, our results apply to the entire CLBP population in Turkey.

The design of the study focuses on the depression with only considering the low-back pain aspect. It is known that advanced age is a risk for depression, as well as chronic pain as we emphasized in the article. Moreover, the increased load of comorbidities as well as treatments for both low back pain and these comorbidities can contribute to the severity of the depression. The study lacks a through psychiatric evaluation for possible factors and only rely on an inventory.

Although comorbidities and the treatments received by the patients for their comorbidities are important, no analysis has been performed. Since the main focus of our study was to compare young and elderly patients with CLBP in terms of function and depression, no analysis was made with the assumption that older age naturally comes with more comorbidities. Such an analysis will be needed to evaluate the elderly patient group in itself.

Conclusion

To the best of our knowledge, this is the first study to examine whether there is a relationship between physical disability and depression in patients with CLBP is influenced by age. The results indicate that disability and depression are considerably more common in older patients with CLBP. Limitation of movement and loss of functional capacity caused by LBP are serious threats to public health as they are the precursors of chronic disability and increased risk of mortality. The development of social programs to address risk factors should reduce the risk for CLBP, improve the quality of life of vulnerable individuals, decrease workforce losses, and make a substantial contribution to public health.

Ethics

Ethics Committee Approval: Ethics committee permissions and preliminary preparation of the study were reviewed and approved by İstanbul Medeniyet University Göztepe Training and Research Hospital Institutional Review Board (decision no: 20/G, date: 20.03.2012).

Informed Consent: Written informed consent was obtained from all patients to participate in the study.

Authorship Contributions

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

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

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

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DOI: 10.4274/tod.galenos.2024.04934
Turk J Osteoporos 2024;30:55-63

Assessment of Prevalence of Neck Pain and Related Factors in Nurses Working in a University Hospital

Bir Üniversite Hastanesinde Çalışan Hemşirelerde Boyun Ağrısı Prevalansı ve İlişkili Faktörlerin İncelenmesi

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Abstract

Objective: The aim of this study was to assess the presence of neck pain, which is one of the most common musculoskeletal disorders in nurses, in terms of different work environments, and also to assess the possible relationships of ergonomic, demographic, and psychological factors on their neck pain.
Materials and Methods: Female nurses from our university hospital that worked in outpatient clinics, wards and intensive care units were included in this cross-sectional study. It was carried out between February and July 2020 in different departments of our university. Patient demographics as well as duration and characteristics of neck pain, Short form-36 (SF-36) questionnaire scores were recorded.
Results: A statistically significant relationship was found between units that the subjects worked in and emergence of neck pain due to the presence of triggering factors such as computer use, heavy lifting and the presence of neck pain for the last month ($p<0.05$). The presence of neck pain in the previous month was found to be statistically correlated with presence of comorbid diseases ($p<0.05$), while no statistically significant relationship was found between fatigue, stress, education level, marital status and presence of neck pain ($p<0.05$).
Conclusion: Musculoskeletal pain is reported to be common in healthcare workers. Nurses are also known to be among the occupational groups at serious risk for painful conditions. Lack of proper working conditions and lifestyle are among the causes of neck pain in nurses. In our study, a statistically significant relationship was found between neck pain and conditions that are not suitable for ergonomics such as prolonged computer exposure and heavy lifting.
Keywords: Computer usage, neck pain, nurses, occupational disease, stress

Öz

Amaç: Bu çalışmanın amacı, hemşirelerde sık rastlanan kas iskelet sistemi rahatsızlıklarından biri olan boyun ağrısının farklı çalışma ortamları açısından karşılaştırılması, ergonomik, demografik ve psikolojik faktörlerin boyun ağrısı üzerindeki olası ilişkilerini araştırmaktır.
Gereç ve Yöntem: Bu kesitsel çalışmaya, üniversite hastanemizin poliklinik, servis ve yoğun bakım ünitelerinde görev yapan kadın hemşireler dahil edilmiştir. Şubat ve Temmuz 2020 arasında hastanemizin farklı birimlerinde yürütülmüş olan çalışma kapsamında, katılımcıların demografik özellikleri, boyun ağrısının süresi ve özelliklerine ek olarak Kısa form-36 anketi skorları kaydedilmiştir.
Bulgular: Araştırma sonunda, çalıştığı birim ile ve bilgisayar kullanımı, ağırlık kaldırma gibi tetikleyici faktörlerin varlığı ile boyun ağrısının ortaya çıkması ile son bir aydır boyun ağrısı mevcudiyeti arasında istatistiksel olarak anlamlı ilişki saptanmıştır ($p<0,05$). Ayrıca komorbid hastalıklar ile boyun ağrısı varlığı arasında anlamlı bir korelasyon saptanmıştır ($p<0,05$). Ancak yorgunluk, stres, eğitim düzeyi, medeni durum ile son bir aydır olan boyun ağrısı mevcudiyeti arasında istatistiksel olarak anlamlı bir ilişki saptanmamıştır ($p>0,05$).
Sonuç: Kas iskelet sistemi ağrılarına sağlık çalışanlarında sık rastlanmaktadır. Hemşirelerin ağrılı durumlara yatkın bir meslek grubunda oldukları bilinmektedir. Hemşirelerdeki boyun ağrısı nedenleri arasında uygun çalışma şartlarının oluşturulmaması ve yaşam şartları rol oynamaktadır. Çalışmamızda, uzun süreli bilgisayar kullanımı ve ağır kaldırma gibi uygunsuz ergonomik durumlar boyun ağrısı ile ilişkili bulunmuştur.
Anahtar kelimeler: Bilgisayar kullanımı, boyun ağrısı, hemşireler, meslek hastalığı, stres

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Received/Geliş Tarihi: 04.12.2023 **Accepted/Kabul Tarihi:** 23.01.2024

Introduction

The intricate and highly mobile cervical spine is continually subjected to mechanical stress that predisposes the spinal units to degenerative changes. There are three common symptom complexes associated with the degenerative process of the cervical spine. These include cervical axial pain, radiculopathy, and myelopathy (1,2). These symptoms and findings may occur together or individually. Axial pain usually starts in midlife (3). Spinal nerve root pathology and radicular syndromes may result from an acutely disturbing disc injury or from a more slowly developing and degenerative neural foraminal stenosis (4,5). Myelopathic symptoms usually start after spinal cord is injured due to spinal stenosis (6-8).

It has been reported that more than 80% of individuals experience neck pain and related disorders throughout their lifetimes, and 30-50% of the general adult population report neck pain annually (9,10). The prognosis of neck pain is favorable in most patients; however, 23% of individuals recovering from an episode of neck pain will experience another episode afterward (11). For most individuals, neck pain is a complicated biopsychosocial disorder with problematic psychosocial and physical symptoms. Neck pain is also associated with decreased health-related quality of life, decreased work productivity, restrictions in daily activities, and increased health care costs (10,12-14).

Nurses often exhibit non-ergonomic behaviors in their daily work. During work activities, they repeatedly take the unergonomic body postures, use the wrong grip associated with the lack of favorable conditions for optimal performance of work activities. Due to the large number of patients in the wards, nurses often try to access the patient bed from different sides and cannot freely access the space around the patient bed (15). In this respect, two main factors of postural control are important in a nurse's work and this significantly affects musculoskeletal overload from a biomechanical point of view. The first is the prolonged standing position that strains the neck spine muscles, which destabilizes the shoulder girdle and causes neck pain, movement restrictions, pain radiating to the upper extremities and even dizziness and visual disturbances (16,17). The second stereotype is the position of extreme trunk hyperflexion, which is an extremely overloaded position, especially when lifting and moving the patient, causing local lumbar and sacral pain or pain radiating to the lower extremity (18,19).

Until now, many studies have pointed out the unhealthy aspects of nurses' lifestyles (20-22). Among these reasons; nurses working in a certain service (23,24), working in shifts (25-27), inappropriate diet and eating habits (28,29), sedentary lifestyle and less physical activity (30,31), exposure to continuous occupational stress (32-35) and overworking and showing symptoms of burnout syndrome (36,37) and they often experience musculoskeletal pain caused by not following ergonomic guidelines (38,39).

In light of this data, the object of this study was to assess the presence of neck pain, which is one of the most common musculoskeletal disorders in healthcare workers, in terms of different working conditions, and to investigate the possible relationships of demographic and aggravating factors on neck pain.

Materials and Methods

Ethics committee approval was obtained with the decision of Ege University Ethics Committee dated 22.01.2020 and numbered 20-1.1T/46. Female nurses working in outpatient clinics, wards and intensive care units of our university hospital were included in this study. The interviews were carried out between February and July 2020 on nurses working in physical medicine and rehabilitation, gynecology and obstetrics, neurosurgery, ear nose and throat diseases, neurology, internal medicine, anesthesiology, pulmonology departments of our university hospital were included.

Inclusion Criteria

- Being a female nurse working at university hospital,
- Being working in the same unit for the past year.

Exclusion Criteria From the Study

- Diagnosis of a rheumatological, neurological, metabolic disease that may cause pain,
- History of cervical vertebral fracture,
- Cancer history,

The unit in which he worked has changed in less than 1 year.

Evaluation Parameters Used in the Study

Short form-36 (SF-36): The SF-36 questionnaire is a general health questionnaire that is a validated and reliable inventory aiming to test mental and physical health in the previous 12 months (39). Three different sub-scores were used in the present study from the SF-36 questionnaire: mental health score, physical health score and general health score. An individual's highest score on the SF-36 is 100 and higher scores indicate better health (40). Turkish validity and reliability were performed by Kocyigit in 1999 (41).

Visual pain scale (VAS): The VAS is a scale that has many different versions that can be used for all types of pain and is also recommended to be used in the determination of disease activity by the American Rheumatology Association (42). The VAS simply consists of a horizontal straight line of 100 mm, mostly from left to right when evaluating various characteristics such as pain level, level of health; graded from good to bad (43). In some studies, right-to-left, vertical or pictorial versions were also used, but it was concluded that the direction of the line axis did not significantly affect the measurement (44).

Evaluation of Patients

Nurses working in the previously mentioned units of university hospital were informed about the study, written consents were obtained from those who agreed to participate in the study and were evaluated with VAS and SF-36 by the relevant research assistant who carried out the study.

The sociodemographic and clinical characteristics of all patients, age, marital status, education and employment status, comorbidities and medical treatment they received were questioned and recorded in the case evaluation form.

Statistical Analysis

The sample size was calculated by power analysis and was determined as 124. Stratified sampling was done, Shapiro-Wilk test was applied to examine whether the data were normally distributed. Since the data were not normally distributed, non-parametric tests were used. Chi-square test was used to analyze the distribution of categorical data. Group ratio distribution of numerical data was evaluated with Mann-Whitney U test. The statistical significance limit was accepted as <0.05.

Results

The mean age of the nurses included in our study was 36.85 (+/-8.67), the mean age of the nurses who had neck pain in the last month was 36.15 (+/-7.9) and those who did not have neck pain in the last month. The mean age was found to be 37.83 (+/-9.65).

Neck Pain Findings of the Participants

While 72 (58.1%) of the participants had neck pain for the last month, 52 (41.9%) of the participants did not have neck pain.

Demographic Information of the Participants

When the distribution of the participants according to the units they work in is examined; 10 (8.1%) in the physical medicine and rehabilitation department, 14 (11.3%) in the obstetrics and gynecology department, 12 (9.7%) in the neurosurgery department, 9 (7%) in the ear nose and throat diseases department, 6 (4.8%) in the neurology department, 29 (23.4%) in the internal medicine department, 32 (25.8%) in the anesthesia and reanimation department and 12 (9.7%) in the pulmonary diseases department. The number of participants who kept the night watch was 89 (71%), and the number of participants who did not keep the night watch was 35 (29%). Neck pain started in 82 of the participants (66.1%) after they started their profession and in 42 (33.9%) neck pain started before they started their profession. The demographic and disease characteristics of the participants are summarized in Table 1.

Correlations

In our study, a significant negative correlation was found between age, working time in the unit, working time in the profession and the physical function subscale of the SF-36 scale ($p<0.05$). A negative correlation was found between the amount of weekly working hours and SF-36 physical role, SF-36 emotional role, SF-36 mental health, SF-36 social function, and SF-36 physical pain ($p<0.05$). A significant negative correlation was found between the time spent in front of the computer for one day and SF-36 physical function ($p<0.05$). There is a statistically significant relationship between the current pain duration and

Table 1. Demographic and disease characteristic of subjects

Age, median (minimum-maximum)	
With neck pain	36.15 (23-56)
Without neck pain	37.83 (25-62)
Marital status, n (%)	
Married	80 (64.5%)
Single	44 (35.5%)
Educational status, n (%)	
High school	1 (0.8%)
University	113 (91.1%)
Master's	8 (6.5%)
Doctorate	2 (1.6%)
Department n (%)	
Physical medicine and rehabilitation	10 (8.1%)
Obstetrics and gynecology	14 (11.3%)
Ear nose and throat	9 (7.3%)
Neurology	6 (4.8%)
Internal medicine	29 (23.4%)
Anesthesiology	32 (25.8%)
Pulmonology	12 (9.7%)
Neurosurgery	12 (9.7%)
Working duration in unit (years, mean)	
With neck pain	10.2
Without neck pain	10.9
Working duration in profession (years, mean)	
With neck pain	13.167
Without neck pain	15.269
Works in night shifts, n (%)	
Yes	89 (71%)
No	35 (29%)
Weekly working hours, mean	
With neck pain	42.51
Without neck pain	41.52
Exposure to stress at work, n (%)	
Low	7 (5.7%)
Moderate	71 (58.2%)
High	44 (36.1%)
Neck pain in the last month, n (%)	
Yes	72 (58.1%)
No	52 (41.9%)
Neck pain history, n (%)	
Yes	67 (54%)
No	57 (46%)
Neck pain started after current employment, n (%)	
Yes	82 (66.1%)
No	42 (33.9%)

the level of neck pain according to VAS (p<0.05). Different from the current pain duration, an additional negative correlation was found between neck pain level and SF-36 health change (p<0.05). The correlation analysis performed to investigate the relationship between the evaluated parameters is summarized in Table 2.

Table 1. Continued

Initiating factor, n (%)	
Heavy object lifting	39 (31.5%)
Computer usage	46 (37.1%)
Stress/sadness	50 (40.3%)
Other	21 (16.9%)
Feeling tired, n (%)	
Yes	114 (91.9%)
No	10 (8.1%)

Discussion

Musculoskeletal pain has immediate and long-term consequences for an individual (45). Nurses have reported increased back pain due to prolonged standing and working in certain positions for a long time and low back pain associated with their positions in certain tasks (46). Some reduction in the prevalence of neck and back pain among nurses has been achieved through education on safe patient care (47). However, there is not enough data on this subject. Therefore, in our study, we aimed to examine the

Table 2. Results of correlation analysis between different parameters, r

	Age	**Duration of working in the unit (years)**	**Occupation duration (years)**	**Weekly working hours**
Age	1	0.743**	0.965**	-0.173
Duration of employment in the unit (years)	0.743**	1	0.775**	-0.019
Duration of employment (years)	0.965**	0.775	1	-0.173
Weekly working hours	-0.173	-0.019	-0.173	1
Duration of time spent a day on the computer	-0.19	0.079	-0.012	0.037
Duration of pain (days)	-0.53	-0.016	-0.078	0.097
Level of neck pain (VAS)	-0.85	-0.040	-0.113	0.124
SF-36 physical functioning	-0.244**	-0.292**	-0.200*	-0.194*
SF-36 physical role	-0.025	-0.064	0.019	-0.181*
SF-36 emotional role	0.066	-0.025	0.087	-0.291**
SF-36 energy	-0.060	-0.025	-0.054	-0.090
SF-36 emotional well-being	0.105	0.074	0.138	-0.191*
SF-36 social functioning	0.081	-0.016	0.093	-0.353**
SF-36 pain	0.040	-0.005	0.073	-0.229*
SF-36 general health	0.000	-0.044	0.030	-0.157
SF-36 health change	-0.077	-0.082	-0.019	-0.081
	Duration of time spent a day at the computer	**Duration of current pain (days)**	**Level of neck pain (VAS)**	**SF-36 physical function**
Age	-0.14	-0.053	-0.085	-0.244**
Duration of employment in the unit (years)	0.079	-0.016	-0.040	-0.292**
Duration of employment (years)	-0.012	-0.078	-0.113	-0.200*
Weekly working hours	0.037	0.097	0.124	-0.194
Duration of time spent a day on the computer	1	0.163	0.163	-0.215*
Duration of pain (days)	0.163	1	0.804**	-0.345**
Level of neck pain (VAS)	0.163	0.804**	1	-0.478**
SF-36 physical functioning	-0.215*	-0.345**	-0.478	1
SF-36 physical role	-0.116	-0.359	-0.451	0.591*

Table 2. Continued

	Duration of time spent a day at the computer	Duration of current pain (days)	Level of neck pain (VAS)	SF-36 physical function
SF-36 emotional role	-0.113	-0.247	-0.289**	0.407**
SF 36 energy	-0.122	-0.205	-0.253	0.180*
SF 36 emotional well-being	-0.141	-0.253**	-0.381**	0.368**
SF-36 social functioning	-0.099	-0.432**	-0.564**	0.503**
SF-36 pain	-0.179*	-0.648**	-0.822**	0.530**
SF-36 general health	-0.060	-0.452**	-0.569**	0.530**
SF-36 health change	-0.090	-0.173	-0.296**	0.426**
	SF-36 physical role	**SF-36 emotional role**	**SF-36 energy/ fatigue**	**SF-36 emotional well-being**
Age	-0.025	0.066	-0.060	0.105
Duration of employment in the unit (years)	-0.064	-0.025	-0.025	0.074
Duration of employment (years)	0.019	0.087	-0.054	0.138
Weekly working hours	-0.181*	-0.291**	-0.090	-0.191*
Duration of time spent a day on the computer	-0.116	-0.113	-0.122	-0.141
Duration of pain (days)	-0.359**	-0.247**	-0.205*	-0.253**
Level of neck pain (VAS)	-0.451**	-0.289**	-0.253**	-0.381**
SF-36 physical functioning	0.591**	0.407**	0.180*	0.368**
SF-36 physical role	1	0.539**	0.189*	0.351**
SF-36 emotional role	0.539**	1	0.254**	0.370**
SF-36 energy	0.189*	0.254**	1	0.553**
SF-36 emotional well-being	0.351**	0.370**	0.553**	1
SF-36 social functioning	0.571**	0.584**	0.399**	0.515**
SF-36 pain	0.588**	0.442**	0.246**	0.407**
SF-36 general health	0.492**	0.377**	0.400**	0.490**
SF-36 health change	0.360**	0.280**	0.359**	0.325**

SF-36: Short form-36, VAS: Visual pain scale, r: Correlation coefficient, *p<0.05, **p<0.01

presence of neck pain in nurses working in a university hospital and the factors affecting this pain.

Psychological stress exacerbates physical stress and is associated with job loss (48,49). It has been found that female health workers with increased occupational psychological stress have worse mental health (50). Therefore, the mental health of a patient with musculoskeletal symptoms is an indicator of the tendency to report pain and seek treatment and is associated with frequent general practice visits (50). Moreover, depression has been associated with increased pain intensity (51).

In a study conducted in 2014, it was determined that the pain threshold of women was higher than that of men (52). In addition, in another study conducted in 2015, it was shown that there are many differences between the two sexes, such as the composition of muscle fibers and changes in contractile functions (53). For these reasons, unlike most studies in the literature, only female nurses were included in our study to ensure homogenization.

While the presence of pain in the last month was found to be 58.1% in our study, it was found to be 41.9% in a study by Gül et al. (54) that included 217 nurses. In a study by Kandemir et al. (55) involving 162 theatre nurses participated, the rate of neck pain in the last month was found to be 39.5%. In a study by Carugno et al. (56) involving 751 nurses in which physical and psychological risk factors for musculoskeletal diseases of nurses in Italy and Brazil were evaluated, the rate of neck pain in the last 1 month was found to be 46.4% for Italian nurses and 40.4% for Brazilian nurses. Freimann et al. (57) included 221 nurses, and the rate of neck pain in the last month was reported as 38.9%.

71% of the nurses in our study were on night shifts. No statistically significant correlation was found between night shift and neck pain in the last month. In a study by Gül et al. (54) the rate of

those who kept the night shift was determined as 64.5%. Çelik et al. (58) found a statistically significant relationship between nurses' night shift keeping rate of 70.3% and right forearm and bilateral knee pain in nurses who were on night shift. In our study, although a significant relationship was found in favor of neck pain, the number of night shifts was found to be similar to previous studies.

In our study, weightlifting was found to be 31.5% among the factors triggering neck pain. Çelik et al. (58) reported that 40.2% of the nurses complained of weightlifting and neck pain and a statistically significant relationship was found (p=0.037).

In our study, there is a statistically strong correlation between computer use and triggering neck pain (p=0.000). In our study, the rate of patients whose neck pain was triggered by computer use was 37.1% and the rate of neck pain in the last month of these patients was 52.8%. In a study by Gül et al. (54) 20.1% of nurses describe musculoskeletal pain triggered by computer use. In our study, as high as 95.8% of the nurses stated that their jobs were stressful and their pain was triggered by stress, a statistically significant correlation was found between the amount of stress and the presence of neck pain in the last month (p=0.004). Joslin et al. (59) in a study that included 34 nurses, 11 of 25 nurses with neck pain attributed neck pain to psychological stress.

When the units they worked at were compared, a statistically significant relationship was found in the neck pain of the participants for the last month (p=0.019). In our study, the rate of those with neck pain in the last one month was determined as 63% in intensive care nurses, while it was determined as 63.3% in ward nurses and 27.8% in outpatient nurses. Çelik et al. (58) in a cross-sectional study including 111 intensive care unit nurses, the prevalence of neck pain in intensive care unit nurses was found to be as high as 73.9%, similar to our study. While intensive care unit and ward nurses perform compelling tasks such as lifting patients, positioning, personal care, they are exposed to factors such as stress and wrong movement.

91.9% of the nurses participating in our study feel tired. 60.5% of the nurses who felt tired had neck pain in the last month. No statistically significant relationship was found between neck pain and fatigue in the last month. Çelik et al. (58) in a study, 85.6% of the nurses mostly felt tired. This value was similar to our study, but unlike our study, a statistically significant relationship was found between fatigue and neck pain. The difference here is; the inclusion of intensive care unit nurses in this study and the fact that the rate of neck pain was 73.9% significantly higher than the rate of 58.1% found in our study.

27.4% of the nurses who participated in our study had additional diseases. A statistically significant correlation was found between the presence of additional disease and the presence of pain in the last month (p=0.032). As an additional disease, thyroid diseases were seen in 11 nurses with neck pain in the last month and came to the fore as the most common comorbidity. They followed thyroid diseases as diabetes in 4 nurses, migraine in 3 nurses, and asthma in 2 nurses, respectively. Grimby-Ekman et al. (60), the prevalence of comorbidity in patients with musculoskeletal pain was found to be statistically significant. In their study, among the participants with pain, those with heart disease were 10%, those without pain had a heart disease rate of 6.7% (p<0.001), the percentage of those with pain but hypertension was 26.5% and those without pain had hypertension at 18.7% (p<0.001), the rate of those who have pain and diabetes at the same time was 7.3%, while the rate of those who did not have pain and had diabetes was 14.4% (p<0.001). Contrary to our study, in contrast to questioning the presence of additional diseases in this study, it is not certain whether they have additional diseases or not, as the presence of certain diseases (such as heart disease, hypertension, diabetes) is questioned as a yes/no dichotomous.

Among the nurses in our study, 20.8% of those who had neck pain in the last month were observed to be using medications for neck pain. Of those with neck pain in the past, 11 use oral non-steroidal anti-inflammatory drugs and 3 use myorelaxants. Gül et al. (54) found that the rate of using medication for neck pain among the nurses participating in the study was 38.2%. Contrary to our study, there was no assessment of pain severity in this study, so the difference between drug use may be due to the higher severity of pain in the study.

In our study, no statistically significant correlation was found with the level of education and the presence of neck pain in the last month. Kandemir et al. (55) similarly, no significant relationship was found between education level and presence of neck pain.

In our study, no statistical difference was found between marital status and neck pain in the last month.

SF-36 physical function score decreased with age, working time in the unit and increasing working time in the profession (p<0.01).

As the weekly working hours increase, SF-36; a statistically significant decrease was found in emotional role (p<0.01), mental health (p<0.05) scores.

In our study, a statistically significant decrease was found in the SF-36 physical function score as the number of hours of computer use increased (p<0.05). Joslin et al. (59) reported that 76% of nurses with neck pain (n=19) was affected by certain triggers. Ardahan and Simsek (61) found an increase in the rates of musculoskeletal pain in all regions in office workers after using a computer longer than 7 hours.

A statistically significant positive correlation was found between current pain duration and VAS value (p<0.01). Basakci Calik et al. (62), office workers whose pain lasts for more than 3 months have a higher pain score than those with acute pain.

SF-36 with current pain duration; physical function (p<0.01), energy/fatigue (p<0.05), mental health (p<0.01), social function (p<0.01) a statistically significant positive correlation was found in pain (p<0.01) and general health (p<0.01) scores.

Joslin et al. (59) compared nurses without neck pain to those with existing neck pain; lower mental health, physical function and total SF-36 scores were obtained.

The presence of neck pain in the past was found to be strongly associated with current neck pain (p=0.003). This is an expected result since it is possible to have a neck pathology in the past or to continue the habits that may adversely affect the ongoing pathological process.

Neck pain started in 66% of the nurses after they started their profession, and 79.3% of them had neck pain in the last month. The rate of the participants whose neck pain first appeared after the beginning of the nursing profession was 66% and the rate of the participants whose pain arose in the period before starting the nursing profession for the first time was determined as 34%. While only 9.7% of the participants who had a neck pain problem in the period before starting the nursing profession had neck pain for the last month, 90.3% of the participants who had neck pain for the first time after starting the profession had neck pain for the last month. A statistically strong correlation was found between the onset of pain after starting the profession and neck pain for the last month (p=0.000). Gül et al. (54) found the average age of onset of neck pain in nurses to be 25. Considering the age of nurses starting to work, it was found to be similar to our study.

The strength of our study is that all of the nurses participating in the study were selected from female nurses and thus, it was aimed to make a healthier comparison between the compared units by excluding possible anatomical and physiological differences between the two genders, such as possible pain threshold differences between male nurses and female nurses, and muscle mass/structure. Before starting to our study, the required number of participants was determined by performing a power analysis and the determined number of participants was included. This is one of the strengths of our work. Among the limitations of our study, the body mass index values of the nurses included in the evaluation, whether the participants do regular sports, the presence of habits such as smoking and alcohol use, and the absence of important issues in terms of neck pain such as family history of rheumatological disease can be counted.

Conclusion

Musculoskeletal diseases are more common in healthcare workers than in the normal population. In our study, in which 124 female nurses were included, the prevalence of neck pain in nurses working in a university hospital and related factors were investigated and its potential relationship with factors such as ergonomic conditions, night shift, stress and fatigue. In order to prevent neck pain, ergonomic work environment modifications such as adjusting computer monitors to the appropriate height, not staying in the same anatomical position for a long time should be encouraged and physical training should be given at regular intervals to protect them from musculoskeletal pain. Regular surveys should be conducted to monitor their health and preventive measures should be taken. Arrangements should be made and measures should be taken to make the work environment less stressful. More prospective studies are needed to evaluate the long-term effects of neck pain and the relationship between environmental and occupational regulations and response to treatment.

*This article was produced from the thesis of Dr. İsmail Keskin, which was named "Assessment of Prevalence of Neck Pain and Related Factors in Nurses Working in A University Hospital". It was successfully presented by him and was accepted by Ege University School of Medicine, Department of Physical Medicine and Rehabilitation in 4th March 2021.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained with the decision of Ege University Ethics Committee dated 22.01.2020 and numbered 20-1.1T/46.

Informed Consent: Nurses working in the previously mentioned units of university hospital were informed about the study, written consents were obtained from those who agreed to participate in the study.

Authorship Contributions

Surgical and Medical Practices: İ.K., E.Ç., E.Y.G., M.B., Y.K., Concept: İ.K., E.Ç., E.Y.G., M.B., Y.K., Design: İ.K., E.Ç., E.Y.G., M.B., Y.K., Data Collection or Processing: İ.K., E.Ç., E.Y.G., M.B., Y.K., Analysis or Interpretation: İ.K., E.Ç., E.Y.G., M.B., Y.K., Literature Search: İ.K., E.Ç., E.Y.G., M.B., Y.K., Writing: İ.K., E.Ç., E.Y.G., M.B., Y.K.

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

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

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Case Report / Olgu Sunumu

DOI: 10.4274/tod.galenos.2023.75317
Turk J Osteoporos 2024;30:64-7

Alendronate-associated Polyarticular Synovitis: A Case Report

Alendronat İlişkili Poliartiküler Sinovit: Olgu Sunumu

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Abstract

Osteoporosis is a commonly observed systemic metabolic disease characterized by a decrease in bone mineral density and an increased risk of fractures worldwide. Bisphosphonates are commonly preferred for its prevention and treatment. Among the side effects of bisphosphonates used orally and parenterally are gastrointestinal symptoms, musculoskeletal pains, flu-like syndrome, and an increase in acute-phase reactants. In this case report, a rare side effect observed during alendronate treatment, polyarticular synovitis, will be presented.
Keywords: Osteoporosis, synovitis, alendronate, bisphosphonate

Öz

Osteoporoz, dünya çapında yaygın olarak görülen, kemik mineral dansitesinde azalma ve kırık riskinde artış ile karakterize sistemik metabolik bir hastalıktır. Önlenmesi ve tedavisinde bifosfonatlar yaygın olarak tercih edilmektedir. Oral ve parenteral olarak kullanılan bifosfonatların yan etkileri arasında gastrointestinal semptomlar, kas iskelet sistemi ağrıları, flu-like sendrom, akut faz reaktanlarında artış bulunmaktadır. Bu olgu sunumunda, alendronat tedavisi sırasında nadir gözlenen bir yan etki olarak poliartiküler sinovit olgusu sunulacaktır.
Anahtar kelimeler: Osteoporoz, sinovit, alendronat, bifosfonat

Introduction

Osteoporosis is a common, systemic, metabolic disease that is a significant cause of morbidity and mortality in postmenopausal women and the elderly population (1). It is characterized by the deterioration of bone architecture and an increased risk of fractures (2). Fractures associated with osteoporosis are more likely to occur in the vertebrae and hips, and the prevalence of fractures in postmenopausal osteoporosis is quite high (3). Postmenopausal women are at risk of developing osteoporosis due to the known decrease in estrogen hormone levels, which limits bone resorption (4). Bisphosphonates are analogs of pyrophosphate with a high affinity for the bone mineral surface and are commonly used in the treatment of postmenopausal osteoporosis (5). They help increase bone mineral density (BMD) and reduce the risk of fractures by suppressing osteoclast activity and reducing bone resorption (6). Alendronate is among the oral bisphosphonates commonly used for the prevention (5 mg daily) and treatment (70 mg weekly or 10 mg daily) of postmenopausal osteoporosis. Alendronate and other oral bisphosphonates commonly cause gastrointestinal side effects (7). Additionally, muscle and joint pains can rarely occur (8). Intravenous bisphosphonate treatment can lead to a temporary acute-phase reaction in patients. Acute-phase reactions can rarely be observed after oral bisphosphonate treatment as well (9). Jaw osteonecrosis typically develops as a long-term side effect of high-dose intravenous bisphosphonate administration (10). In this case, a rare case of polyarticular synovitis that developed after the use of oral alendronate for postmenopausal osteoporosis treatment will be presented.

Case Report

A 62-year-old postmenopausal female patient presented to our clinic for an annual check-up. The informed consent form has been obtained from the patient. She had a medical history of hypertension and diabetes. Dual-energy X-ray absorptiometry (DEXA) and routine blood tests were requested. DEXA showed a lumbar spine BMD of 0.701 g/cm^2 (T-score: -3.2) and a femoral neck BMD of 0.605 g/cm^2 (T-score: -1.7). The patient was diagnosed with osteoporosis, and her blood tests revealed 25-hydroxyvitamin D level of 23.6 ng/mL, calcium level of 8.6 mg/dL, and C-reactive protein (CRP) of 6.6 mg/dL. She was started on weekly 70 mg alendronate, oral calcium (1 g/day), and vitamin D3 (880 IU/day) treatment.

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Received/Geliş Tarihi: 02.09.2023 **Accepted/Kabul Tarihi:** 06.11.2023

Twenty-four hours after starting treatment, she complained of weakness, fatigue, myalgia, subfebrile fever, swelling, and pain in the left ankle, as well as in the 2nd, 3rd, and 4th proximal interphalangeal and 2nd and 3rd distal interphalangeal joints of both hands (Figure 1). These joints were tender upon palpation, and joint movements were restricted due to pain. Blood tests at that time showed CRP of 11.6 mg/L, with a normal complete blood count. Symptomatic treatment with oral diclofenac sodium 75 mg/day was initiated. In the following days, the patient's symptoms improved, but after taking the second week's dose of alendronate 75 mg, her symptoms recurred on the 2nd day. Blood tests on the 9th day of alendronate treatment showed CRP of 25 mg/L, procalcitonin of 0.12 ng/mL, sedimentation rate of 22 mm, white blood cell (WBC) of 9.47, rheumatoid factor <10, antinuclear antibody indirect immunofluorescence assay 1/100 titer negative, and anti-cyclic citrullinated peptide antibody negative. Prednisolone 10 mg/day was added to diclofenac sodium as an adjunct treatment. On the 12th day, blood tests showed CRP of 62 mg/L, sedimentation rate of 43 mm, and WBC of 10.1. Since her symptoms did not improve, a bilateral hand, wrist, and left foot magnetic resonance imaging was performed. The foot imaging showed an increase in synovial fluid in the 1st metatarsophalangeal joint space, tenosynovitis around the peroneal muscle tendons, and focal bone marrow edema in the 2nd and 3rd metatarsal proximal metaphyses and intermediate and lateral cuneiform bones (Figure 2). The right wrist imaging revealed mild synovial fluid increase in the radiocarpal and intercarpal joint spaces, focal bone marrow edema in the lunate bone, subchondral edema areas near the proximal interphalangeal joints of the 1st, 2nd, and 4th fingers, and synovial fluid increase in the joint space. The left wrist imaging showed mild synovial fluid increase in the radiocarpal and intercarpal joint spaces, mild synovial fluid increase between the dorsal 1st and 2nd extensor tendons, and synovial fluid increase in the joint space between the 3rd and 4th fingers (Figure 3). The patient had no history of rheumatic diseases, and there were no findings suggestive of pyrophosphate arthropathy. Since her current symptoms were attributed to alendronate treatment and she had not experienced similar joint complaints or morning stiffness before, the treatment was discontinued. One week later, there was a significant improvement in her symptoms, and acute-phase reactants returned to normal. After three weeks, her symptoms had completely resolved. Follow-up blood tests one month later showed no pathological findings. The patient was prescribed denosumab treatment for osteoporosis, and she was followed up for eight months without recurrent arthritis symptoms. Therefore, rheumatological diagnoses were ruled out, and the polyarthritis that developed was considered a side effect of alendronate treatment.

Figure 1. Swelling in the proximal and distal interphalangeal joints and dorsum of the left foot

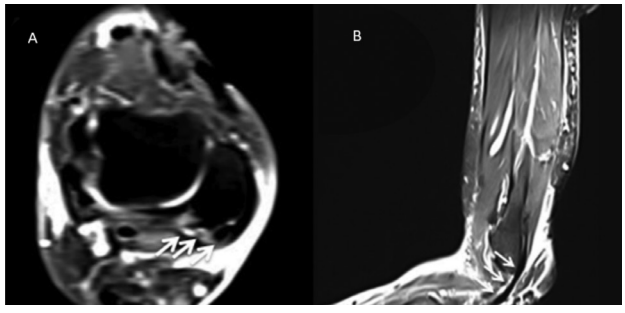

Figure 2. T2 weighted fat-sat axial (A) and sagittal (B) images show fluid increase in favor of tenosynovitis around peroneal tendons

Discussion

Bisphosphonates, synthetic pyrophosphate analogs, are potent inhibitors of osteoclastic bone resorption. They are successfully used in the prevention and treatment of osteoporosis and are well-tolerated (11). In the 1990s, it was discovered how bisphosphonates biochemically affect cells. Nitrogen-containing bisphosphonates (aminobisphosphonates) like alendronate, risedronate, ibandronate, and zoledronate inhibit the enzyme farnesyl pyrophosphate synthase, thereby suppressing osteoclast-mediated bone resorption. This enzyme is responsible for synthesizing farnesyl pyrophosphate from mevalonate and is a part of cholesterol biosynthesis. Reduced levels of farnesyl pyrophosphate prevent the prenylation of guanosine triphosphate binding proteins (such as ras, rab, rho), leading to dysfunction in osteoclasts. As a result, nitrogen-containing bisphosphonates, similar to statins, interfere with cholesterol biosynthesis (12). Nitrogen-free bisphosphonates (non-aminobisphosphonates) include etidronate and clodronate (13). Non-aminobisphosphonates inhibit the enzyme adenosine diphosphate/adenosine triphosphate (ATP) translocase, leading to the accumulation of non-hydrolyzed ATP analogs and, through

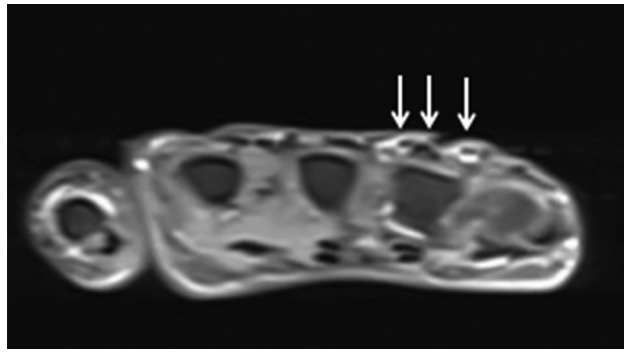

Figure 3. T2 weighted fat-sat coronal image shows fluid increase in favor of tenosynovitis around 3rd and 4th extansor tendons

this mechanism, inducing osteoclast apoptosis (14). Oral bisphosphonates most commonly cause upper gastrointestinal symptoms, including gastritis, esophagitis, and dyspepsia. One of the side effects seen in aminobisphosphonates is an acute-phase reaction characterized by fever, fatigue, an increase in erythrocyte sedimentation rate, CRP levels, myalgia, and arthralgia. This reaction is associated with the release of proinflammatory mediators and is more commonly observed after intravenous bisphosphonate therapy but can also rarely occur with oral bisphosphonate treatment (15).

Approximately 50-60% of the administered bisphosphonate is excreted unchanged through the kidneys. The use of non-steroidal anti-inflammatory drugs with potential nephrotoxicity, dehydration, and similar conditions can increase the risk of renal toxicity associated with intravenous bisphosphonates. Therefore, it is essential to ensure that the glomerular filtration rate is above 30 mL/min in patients starting intravenous bisphosphonate therapy (16). In the HORIZON study, atrial fibrillation was mentioned as one of the potential side effects of zoledronic acid treatment for the first time (17). However, subsequent studies have raised doubts about this association (18,19). Additionally, an association has been suggested between bisphosphonate use and conditions such as jaw osteonecrosis, esophageal cancer, and atypical femur fractures, although conclusive evidence has not been established (20). Bisphosphonate-associated synovitis was first reported in the literature in 2003 by the Uppsala Monitoring Centre with a case series of eight patients (21).

Gwynne Jones et al. (13) published a case series describing the development of synovitis in 7 postmenopausal osteoporosis patients who were treated with alendronate. In each of these cases, synovitis developed after alendronate treatment, similar to our case, and discontinuing the treatment led to the resolution of symptoms. Frederiksen et al. (22) reported a case presentation of a 62-year-old postmenopausal osteoporosis patient who developed polyarticular synovitis as a result of alendronate treatment. This patient continued to have residual synovitis despite low-dose prednisolone treatment during 14 months of follow-up. In a case reported by Gökkus et al. (23) in 2016, a postmenopausal osteoporosis patient developed polyarthritis starting on the 2nd day of alendronate treatment. Although more commonly seen with intravenous bisphosphonates, as in our case, this case also showed an increase in acute-phase reactants. Discontinuation of treatment resulted in the resolution of arthritis symptoms and the normalization of acute-phase reactants, similar to other cases and our case. When rheumatic diseases and potential etiologies like pyrophosphate arthropathy were excluded, the examined cases were considered as side effects of alendronate. Arthritis and synovitis are rarely observed among the side effects of bisphosphonates, and there are few cases reported in the literature. This case presentation aims to remind that although rare, bisphosphonate use can lead to the development of poly-synovitis and polyarthritis during the diagnosis and treatment process.

Ethics

Informed Consent: The informed consent form has been obtained from the patient.

Authorship Contributions

Concept: B.Ş. F.N.K., Design: B.Ş. F.N.K., Data Collection or Processing: B.Ş., Analysis or Interpretation: B.Ş. F.N.K., Literature Search: B.Ş., Writing: B.Ş.

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

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

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DOI: 10.4274/tod.galenos.2023.23281
Turk J Osteoporos 2024;30:68-9

An Osteoporotic Vertebral Fracture Case After Lumbar Sympathetic Ganglion Block

Lomber Sempatik Ganglion Bloğu Sonrası Gelişen Osteoporotik Vertebra Kırığı Olgusu

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Dear editor,

I would like to share my opinions about the publication "An Osteoporotic Vertebral Fracture Case After Lumbar Sympathetic Ganglion Block" (1). In this case report, a 66-year-old female patient diagnosed with lymphedema, cervical cancer, hypertension and osteoporosis (OP) is discussed. In this case, it was stated that the patient developed an osteoporotic vertebral fracture after lumbar sympathetic ganglion block (LSGB) performed due to persistent lymphedema (1).

As it is known, OP is an important clinical problem, especially in elderly women and men. As a result of increased bone fragility in OP, fractures may occur in many bones, especially the vertebrae. These fractures increase healthcare costs and negatively affect individuals' quality of life (2). From this perspective, we can say that fracture formation is one of the most important complications of OP. Topaloğlu and Erol (3) in their study evaluating the fracture risk in patients over the age of 65, they found that the bone mineral density of prediabetic patients was significantly lower than that of non-diabetic patients. However, fracture rates were found to be similar in both groups (3). When we look at this study, we can comment that bone mineral density measurement is not very sensitive in showing bone fragility. Mathew et al. detected a sacral insufficiency fracture in a 61-year-old female patient diagnosed with cervical cancer after cancer treatment without any steroid use and trauma. In this case, the patient applied with the complaint of severe back pain before treatment (4). In a study by Lee et al. (5), early diagnosis and treatment of gynecological cancers increased the treatment rate and survival rate of cancer patients; However, they emphasized that osteoporotic fractures not only reduce the quality of life of long-lived patients but also increase their mortality. This study suggests that the risk of bone density loss and OP in gynecological cancer should be recognized, prevented, and diagnosed early to reduce the incidence of osteoporotic fractures (5). In another study in the literature, Barron et al. (6) stated that bone mineral density, previous fractures, recent falls, physical functions, age, cognitive status and general health status are direct and/or indirect risk factors for possible osteoporotic fractures.

When we look at the literature in general, it is clear that there are many factors that increase the risk of osteoporotic fractures and that the risk of fracture cannot be predicted by bone mineral density measurement alone. In addition, treatments received in individuals with comorbid diseases such as cancer, decreased activity level, sarcopenia and many factors may increase the occurrence of osteoporotic fractures. In addition, high doses and long-term use of glucocorticoids lead to OP, especially in patients. Therefore, fracture risk assessment is recommended for all patients using long-term glucocorticoids (7).

When we look at the cases of osteoporotic fractures in the light of the literature, it is clear that it is difficult to establish a definitive relationship between osteoporotic fracture formation and LSGB. Because the cancer history of the patient in the current case is a significant risk for osteoporotic fracture. Apart from this, eating habits, sun exposure, sarcopenia and other risk factors should be questioned meticulously. In addition, the time between steroid injection and fracture formation is very close, and very high doses of steroids were not administered. In this respect, there is a possibility that the result obtained is coincidental.

I would like to thank the authors for their support to the literature. I think more cases and case series are needed to understand the existence of the relationship between LSGB and osteoporotic fracture. In this respect, it would be useful to look at patients receiving LSGB treatment from this perspective.

Keywords: Low back pain, lymphedema, osteoporotic fracture, sympathetic ganglion, steroids

Anahtar kelimeler: Bel ağrısı, lenfödem, osteoporotik kırık, sempatik ganglion, steroidler

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Received/Geliş Tarihi: 09.11.2023 **Accepted/Kabul Tarihi:** 21.12.2023

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

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

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