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ARTICLE

Does osteoporosis cause pain even without a fracture? An observational study

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ABSTRACT

Introduction/background: Osteoporotic fractures are usually painful. However, data on whether osteoporosis without fracture causes pain are insufficient. This study aims to determine whether osteoporosis without fracture is the cause of pain.

Methodology: Patients aged over 18 years who visited the Physical Medicine and Rehabilitation outpatient clinic of a tertiary university hospital for dual-energy X-ray absorptiometry scan and were suitable for dual-energy X-ray absorptiometry scan without a history of fracture were included in the study. Patients with a history of fractures or those with fracture/fracture sequelae on X-rays were excluded. The cervical, lumbar, and thoracic spine and general body pains of the patients were questioned and dual-energy X-ray absorptiometry results were recorded.

Results: The study was conducted with 139 patients. Lumbar bone mineral density and T score values of the patients were found to be negatively correlated with the numerical rating scale levels of the cervical, thoracic, lumbar spine, and general body pain. Hip total bone mineral density and T score values were also negatively correlated with numerical rating scale scores of the lumbar and thoracic spine and general body pain. When the patients were divided into two groups as those with and without osteoporosis, it was found that the cervical, lumbar, thoracic spine, and general body pain numerical rating scale levels of the patients with osteoporosis were significantly higher than the group without osteoporosis.

Conclusion: The results of this study showed that osteoporosis might be associated with pain even though there is no fracture.

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Osteoporosis; fracture; neck pain; low back pain; back pain; pain

Introduction

Osteoporosis is a common condition characterized by low bone strength, deterioration of bone microarchitecture, and decreased bone mass (Coughlan and Dockery 2014). Decreased oestrogen, increased osteoclastic activity, and age-related changes in vitamin D and calcium metabolism have been blamed for the pathophysiology of osteoporosis (Tella and Gallagher 2014). Osteoporosis is a common public health problem and the most common bone disease. The elderly population is increasing rapidly all over the world; therefore, osteoporosis seems likely to become more prevalent in the future (Lane 2006).

Although there are various diagnostic criteria for osteoporosis, the most commonly used criterion is a T-score of −2.5 or less in the total hip, femoral neck, or lumbar spine in the bone mineral density (BMD) test (Siris et al. 2014). Dual-energy X-ray absorptiometry (DEXA) is the gold standard for the non-invasive measurement of BMD. Manufacturers' software calculates the T-score using BMD. The T-score is a value expressed as the standard deviation of BMD and is derived by comparing it to a young gender-matched population at peak bone mass (Carey and Delaney 2010). Osteoporosis consists of two categories, primary, and secondary. Primary osteoporosis is more common and includes two subtypes, postmenopausal osteoporosis (type I), and senile osteoporosis (type II). Secondary osteoporosis is due to a clearly identifiable aetiological cause, such as drug use and endocrine diseases. Type I is characterized by increased bone turnover due to the loss of oestrogen and androgen and a predominant loss of trabecular bone. Type II osteoporosis is caused by systemic ageing and loss of stem cell precursors. In type II osteoporosis, there is a predominant loss of cortical bone (Dobbs et al. 1999). Medical treatments such as bisphosphonates, denosumab, hormone replacement therapies, and teriparatide can be used in treatment (Qaseem et al. 2017). Various genetic, nutritional, behavioural, clinical, and medical risk factors for osteoporosis have been identified (Lane 2006).

More than 1.5 million new osteoporotic fractures are detected each year in the United States (Lane 2006). Twenty percent of patients who develop a hip fracture die within the first year. In addition, osteoporotic fractures are a cause of morbidity. Some patients require hospitalization.

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Worsening of functional capabilities and quality of life may occur in patients after an osteoporotic fracture (Lane 2006; Nazrun et al. 2014); 30–50% of the global population over the age of 50 is affected by osteoporotic vertebral fractures (Choi et al. 2020). Vertebral fractures can cause shortening of stature, kyphosis, and back pain. Nociceptive and/or neuropathic pain inevitably occurs in patients with fractures (Mattia et al. 2016; Moretti et al. 2022), but it is still a question of interest whether osteoporosis causes pain in patients who have not yet developed any fractures.

There is increased osteoclast activation in osteoporosis. The acidic microenvironment created by osteoclasts causes an increase in pain and neural sensitivity *via* peripheral sensory neurons (Vellucci et al. 2018).

It has been reported that there are fibres responsible for sensory innervation reaching the dorsal root ganglion from the cancellous bone, and there are mediators such as calcitonin gene-related peptide (CGRP) responsible for pain transmission in these fibres (Ohtori, Inoue, Koshi, Ito, Watanabe, et al. 2007; Ohtori, Inoue, Koshi, Ito, Yamashita, et al. 2007). These findings suggest that diseases such as osteoporosis without fracture, which affect the cancellous bone in the vertebral body, may cause pain.

We could not find any studies on whether osteoporosis is a cause of pain independent of fractures. This study aims to investigate the relationship between osteoporosis without fracture and pain, or in other words, to examine whether osteoporosis is associated with pain independent of fracture.

Material and method

The study protocol was approved by the local Ethics Committee of Kırşehir Ahi Evran University Faculty of Medicine (No:2020-09/60). The study was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

Patients over 18 years who presented to Kırşehir Ahi Evran University Hospital Physical Medicine and Rehabilitation outpatient clinic for DEXA scan and were suitable for DEXA scan, without a history of fractures and a diagnosis/cause of secondary osteoporosis were included in the study. The patients' age, height, weight, sex, and osteoporosis medications used were recorded. Femoral neck, hip total, and lumbar spine BMD and T scores were recorded from current DEXA results. The same DEXA device was used for all patients (DMS stratos DR, Mauguio, France). Full spine radiographs (anterior-posterior and lateral) were taken for all patients. Patients with vertebral fractures on radiographs were excluded. The following were determined as exclusion criteria: (1) History of osteoporotic fracture; (2) History of pelvic or spinal fracture; (3) Those with imaging compatible with compression fracture or sequela on thoracolumbar X-ray, wedging of the vertebrae, or other types of fractures; (4) active infection; (5) malignancy; (6) severe trauma within the last 6 months; (7) patients with Functional Ambulation Classification (FAC) stage 0 for at least 12 weeks;(8) long-term use of corticosteroids (>1 month) (Mundell et al. 2017); (9) inflammatory rheumatic diseases; (10) patients reporting radicular pain, neurogenic claudication clinic, history of disc herniation; (11) patients with >50 degrees thoracic kyphosis, spinal stenosis, scoliosis findings on their radiographs; and (12) having at least one cause of secondary osteoporosis.

Cervical, lumbar, and thoracic spine pain and general body pains of the patients were questioned by a physiatrist who was unaware of the bone densitometry results of the patients. The level of pain was recorded separately using a numerical rating scale (NRS). NRS is a frequently used scale to evaluate the pain levels of patients. Patients rate their pain from 0 to 10; where 10 points means the most severe pain. The Turkish validity and reliability of NRS have been demonstrated (Hjermstad et al. 2011; Akad et al. 2013).

Statistical analysis

Statistical analyses of the study data were performed using the Statistical Package for the Social Sciences for Windows version 22.0 software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp., USA). The normality assumption was tested using the Kolmogorov-Smirnov. It was found that the data were normally distributed. Explanatory statistics of the variables are given as mean ± standard deviation. The assumption of homogeneity of variances was tested using the Levene test. One-way analysis of variance (ANOVA) and the independent t-test were used for univariate analyses of the variables in the study. Relationships between variables were examined using Pearson correlation coefficients. In all statistical analyses, cases with a P-value below 0.05 were interpreted as statistically significant. The sample size was not calculated before the study because there was no study using the same method. Power analysis was performed after the participants were included in the study. The G*Power 3.1.9.7 program was used for the post-hoc power analysis of the study. With this program, the power of the study was calculated as 89.11%, with $\alpha = 0.05$ and effect size $d = 0.5$.

Results

One hundred eighty-four patients were evaluated for inclusion in the study. Six patients did not want to be included in the study. Thirty-nine patients were excluded because they had at least one of the exclusion criteria (e.g., osteoporotic fracture, cancer). The study was conducted with a total of 139 patients. The age, gender distribution, body mass index (BMI) values, use of antiresorptive drugs, and bone densitometry parameters of the participants are given in Table 1. None of the patients were receiving hormone replacement therapy.

The lumbar BMD and T score values of the patients were negatively correlated with cervical, lumbar, and thoracic spine pain and general body pain NRS levels. Hip total BMD and T score values were also found to be significantly negatively correlated with the lumbar, thoracic spine, and general body pain NRS scores (Tables 2 and 3).

When the patients were divided into two groups as those with and without osteoporosis, the cervical, lumbar, thoracic

spine pain, and general body pain NRS levels of the patients with osteoporosis were found to be significantly higher than the group without osteoporosis (Table 4). Fifty-six patients were with osteoporosis, and 83 patients were without osteoporosis.

Discussion

In this study, it was determined that osteoporosis was associated with pain independent of fractures. The most feared consequence of osteoporosis, which is a common public health problem, is fractures (Lane 2006; Clynes et al. 2020). Pain in osteoporotic fractures is typically localized to the fracture site and is severe. It is more common in the lumbar, lower or middle thoracic spine region and the severe pain usually subsides within a few weeks or months (Lamichhane 2005). In addition, vertebral deformities and spinopelvic alignment disorders caused by vertebral fractures are associated with increased pain and disability in the chronic period (Langella et al. 2021). Osteoporotic fractures and their sequelae are associated with pain, but data on whether osteoporosis without fractures is associated with pain are insufficient.

Ohtori et al. found that risedronate given for four months in patients with osteoporosis without chronic or acute vertebral fractures decreased low back pain, and urine and serum N-terminal telopeptide of type I collagen (NTx) levels. Improvement of low back pain was associated with a decrease in urinary and serum NTx. Thus, the authors argued that osteoporosis-related bone resorption may cause low back pain despite the absence of vertebral fractures (Ohtori et al. 2010). Moretti et al. demonstrated the effectiveness of denosumab in reducing pain in patients with vertebral fractures. Moretti et al. reported that denosumab reduces pain by inhibiting the RANK/RANKL pathway, providing negative modulation of nuclear factor-kappa B and reducing osteoclast-mediated acidification (Moretti et al. 2019). Considering these mechanisms, denosumab may also have a pain-reducing effect in patients with osteoporosis without a fracture. Further studies on this subject are needed.

Drugs that suppress osteoclast activity have shown analgesic effects. However, romosozumab, a monoclonal antibody developed against sclerostin, is in the anabolic osteoporosis drug group and low back pain is one of the

Table 1. Participants' age, gender distribution, BMI values, use of antiresorptive drugs, pain levels, and bone densitometry parameters.

	Mean
Sex	
Male	6 (4.3%)
Female	133 (95.7%)
Age (mean ± SD)	62.98 ± 8.72
BMI (mean ± SD)	28.88 ± 4.38
Lumbar spine BMD, g/cm^2 (mean ± SD)	0.850 ± 0.147
Lumbar spine T score (mean ± SD)	−1.92 ± 1.22
Femoral neck BMD, g/cm^2 (mean ± SD)	0.801 ± 0.130
Femoral neck T score (mean ± SD)	−0.87 ± 1.08
Total hip BMD, g/cm^2 (mean ± SD)	0.918 ± 0.132
Total hip T score (mean ± SD)	−0.75 ± 0.93
Number of patients who used antiresorptive	38 (27%)
Number of patients who did not use antiresorptive	101 (73%)
Lumbar spine NRS (mean ± SD)	3.64 ± 2.69
Cervical spine NRS (mean ± SD)	2.90 ± 2.49
Thoracic spine NRS (mean ± SD)	2.95 ± 2.69
General body pain NRS (mean ± SD)	2.64 ± 2.44

Note: BMI: body mass index; SD: standard deviation; BMD: bone mineral density; NRS: numerical rating scale.

Table 2. Correlations of cervical, lumbar, thoracic spine pain and general body pain of all participants with hip total, femoral neck, lumbar spine BMD, and T scores.

		Lumbar spine BMD	Lumbar spine T score	Femoral neck BMD	Femoral neck T score	Total hip BMD	Total hip T score
Lumbar spine NRS	*r*	−0.191[a]	−0.210[a]	−0.088	−0.084	−0.193[a]	−0.181[a]
	p Value	.024	.013	.303	.326	.023	.033
Cervical spine NRS	*r*	−0.189[a]	−0.194[a]	0.058	0.047	−0.114	−0.140
	p Value	.026	.022	.498	.583	.180	.100
Thoracic spine NRS	*r*	−0.204[a]	−0.211[a]	−0.037	−0.057	−0.220[b]	−0.263[b]
	p Value	.016	.013	.668	.507	.009	.002
General body pain NRS	*r*	−0.276[b]	−0.267[b]	−0.090	−0.086	−0.205[a]	−0.220[b]
	p Value	.001	.001	.293	.315	.016	.009

Note: r: Pearson correlation coefficient; NRS: numerical rating scale; BMD: bone mineral density.
[a]Correlation is significant at the 0.05 level (two-tailed).
[b]Correlation is significant at the 0.01 level (two-tailed).

Table 3. Correlations of cervical, lumbar, thoracic spine pain and general body pain in patients with osteoporosis with hip total, femoral neck, lumbar spine BMD, and T scores.

		Lumbar spine BMD	Lumbar spine T score	Femoral neck BMD	Femoral neck T score	Total hip BMD	Total hip T score
Lumbar spine NRS	*r*	−0.301[a]	−0.418[b]	−0.140	−0.139	−0.301[a]	−0.329[a]
	p Value	.024	.001	.304	.307	.024	.013
Cervical spine NRS	*r*	−0.251	−0.355[b]	−0.033	−0.104	−0.225	−0.300[a]
	p Value	.063	.007	.809	.446	.095	.025
Thoracic spine NRS	*r*	−0.307[a]	−0.445[b]	−0.098	−0.145	−0.322[a]	−0.386[b]
	p Value	.021	.001	.472	.286	.015	.003
General body pain NRS	*r*	−0.434[b]	−0.505[b]	−0.096	−0.122	−0.294[a]	−0.342[b]
	p Value	.001	.000	.480	.369	.028	.010

Note: r: Pearson correlation coefficient; NRS: numerical rating scale; BMD: bone mineral density.
[a]Correlation is significant at the 0.05 level (two-tailed).
[b]Correlation is significant at the 0.01 level (two-tailed).

Table 4. Demographic and clinical characteristics of participants with and without osteoporosis.

		With osteoporosis ($n = 56$)	Without osteoporosis ($n = 83$)	p Value
BMI		28.32 ± 3.92	29.27 ± 4.64	.212
Age		64.32 ± 7.66	62.07 ± 9.30	.136
Sex	Female	95%	96%	.623
	Male	5%	4%	
Lumbar spine NRS		4.25 ± 2.66	3.23 ± 2.65	**.028***
Cervical spine NRS		3.64 ± 2.46	2.40 ± 2.39	**.003***
Thoracic spine NRS		3.95 ± 2.94	2.28 ± 2.30	**.001***
General Body pain NRS		3.34 ± 2.45	2.17 ± 2.33	**.005***

Note: NRS: numerical rating scale; BMI: body mass index.

common side effects of romosozumab (10.5%). In addition, one of the most common side effects of abaloparatide, another new-generation anabolic osteoporosis drug that acts on osteoblasts, is low back pain (Iolascon et al. 2020). These results support the idea that osteoclasts rather than osteoblasts are effective in pain in osteoporosis.

Iwamoto et al. in their study with 40 postmenopausal female patients aged 60–86 years with osteoporosis without any vertebral fracture in the lumbar spine, reported that oral administration of etidronate 200 mg daily for two weeks every three months significantly reduced back pain and urinary NTX levels. It was found that daily administration of alfacalcidol 1 Ig daily in addition to etidronate significantly increased lumbar BMD (Iwamoto et al. 2003).

Pappagallo et al. reported a significant reduction in pain with intravenous pamidronate in patients with chronic mechanical spinal pain without vertebral fractures (Pappagallo et al. 2003). In studies detecting the positive effects of bisphosphonates on pain in patients without vertebral fractures, the authors generally claim that this positive effect is due to the inhibition of osteoclasts by bisphosphonates. In the view of these authors, bisphosphonates counterbalance the increase in pain-related cytokines and neuropeptides secreted by osteoclasts in bone tissue (Iwamoto et al. 2003; Pappagallo et al. 2003; Ohtori et al. 2010).

Sawicki et al. in their retrospective study with postmenopausal women with osteoporosis, found that patients with vertebral compression fractures (NRS: 6.14) had significantly more back pain than patients without fractures (NRS: 4.33) (Sawicki et al. 2021). However, we could not find a study comparing the pain level of patients with osteoporosis without fractures and those without osteoporosis.

In the present study, the mean lumbar spine pain NRS level was 4.25 and the mean thoracic spine pain NRS level was 3.95 in patients with osteoporosis without fractures. These scores were close to the back pain values (4.33) in patients with osteoporosis without fracture in the study of Sawicki et al. The results of the current study suggest that the idea that 'osteoporosis is asymptomatic unless there is a fracture' should be reconsidered.

If a more comprehensive pain scale such as the Brief Pain Inventory, McGill Pain Scale, Leeds Assessment of Neuropathic Symptoms and Signs Scale, and Pain DETECT Questionnaire had been used in this study to assess pain, it would have been more appropriate in terms of multidimensional assessment of pain (Migliore et al. 2021).

Osteoporosis is a disease characterized by changes in the microarchitecture of bone tissue and decreased bone mass, leading to increased bone fragility (Heuchemer et al. 2020). The balance between osteoblasts and osteoclasts in bone is under the influence of many genetic and local factors. In osteoporosis, this balance is disturbed in favour of osteoclasts (Yin et al. 2019). Osteoclasts degrade bone minerals by forming an acidic microenvironment around them with H+-ATPase. This acidic microenvironment activates TRPV1 channels in peripheral sensory neurons. Peripheral bone nociceptors are activated by TRPV1 receptors. Thus, there is an increase in pain and neural sensitivity. In addition, neural TRPV1 activation induces the release of substances such as substance P and CGRP (Vellucci et al. 2018). Cytokines, sensory innervation, and neuropeptides play an important role in bone pain. Nerve proliferation has been detected in the endplates and vertebral bodies in patients with reduced disc height and severe back pain. In these nerves, immunoreactivity was observed with neuropeptides that provide pain transmission, such as CGRP and substance P (Brown et al. 1997; Ohtori et al. 2010). In addition, CGRP-immunoreactive fibres involved in pain have been found in the bone, periosteum, and bone marrow of mice and rats (Ahmed et al. 1993; Mach et al. 2002; Ohtori et al. 2010). Taken together, the increase of pain-related neuropeptides released by osteoclasts in osteoporosis seems to be one of the possible mechanisms related to the increase in pain in osteoporosis without fracture. Another hypothesis regarding the causes of pain in patients with osteoporosis without fractures is microfractures (Silverman et al. 2005). Therefore, increased microfractures are another possible mechanism that may explain the increased pain in patients with osteoporosis compared with individuals without osteoporosis, despite the absence of visible fractures (Silverman et al. 2005).

Another possible mechanism to explain the results of this study may be that patients with pain reduce their physical activity to avoid pain. Physical activity is known to protect against osteoporosis, and immobility creates a predisposition to osteoporosis.(Benedetti et al. 2018) Patients with pain may be predisposed to osteoporosis if they reduce their physical activities to avoid pain.

Our study had some limitations. There was no long-term follow-up. Functional evaluation was not performed. Some of the participants with osteoporosis were receiving antiresorptive treatments. Although studies have shown that bisphosphonates reduce pain, and higher pain levels were detected in the osteoporosis group in this study, the antiresorptive intake of some patients in the osteoporosis group may have partially hindered the standardization of the groups. One of the limitations of the study is that pain was

evaluated only with NRS instead of a multidimensional pain assessment scale. The lack of blood or urinary bone turnover markers was another limitation of the study. In addition, the participants' lifestyles, physical activities, calcium intakes, and the fact that 25(OH)D vitamins in circulation were not included in the evaluation are also limitations of this study. The lack of spinal magnetic resonance imaging (MRI) in the participants is one of the limitations of this study, although this was the same for both groups and spinal MRI findings were not always clinically correlated. Despite these limitations, we think that this study is valuable because it is the first to compare patients with and without osteoporosis in terms of pain among individuals without any fractures. Moreover, our study shows that, contrary to popular belief, osteoporosis may cause pain even if there are no fractures.

Conclusion

The results of this study suggest that bone resorption in osteoporosis may be associated with pain, even in the absence of fracture.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available from the corresponding author (Mehmet Okçu) upon reasonable request.

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