

## Original Article

# Clinical manifestations of osteoarthritis in osteoporotic and osteopenic postmenopausal women

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**Objective:** We investigated the frequency of clinical manifestations of osteoarthritis in women with low BMD. **Methods:** This prospective epidemiological study investigated the degree of osteoarthritic pain and functional disability in symptomatic joints of a randomly selected population of postmenopausal Greek women aged >45 years with osteoporosis or osteopenia. Degree of osteoarthritic impairment (none, mild, moderate or severe) was classified at the knee, hip, neck or hand using a site-specific internationally validated osteoarthritis questionnaire. **Results:** 3000 women were included with mean age of 66.7 years. Osteoporosis was more common than osteopenia. Mild osteoarthritic impairment was most prevalent. An inverse relationship between severity of osteoarthritic impairment and mean femoral neck T-score was observed, regardless of site. There was a significant difference in mean femoral neck T-score between patients with severe osteoarthritic impairment and those with no, mild, or moderate impairment. This was also observed when lumbar spine BMD results were pooled. **Conclusions:** Most postmenopausal women with low BMD suffer from osteoarthritic impairment, with an inverse association between severity of osteoarthritic impairment and mean femoral neck T-score. Mean lumbar spine or femoral neck T-scores of patients with severe osteoarthritic impairment were significantly lower than those of patients with less impairment.

**Keywords:** Osteoarthritis, Osteoporosis, Osteopenia, Postmenopausal Woman, Bone Mineral Density

**Introduction**

Osteoporosis and osteoarthritis are common diseases in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD) and microarchitectural disruption of bone tissue with consequent increases in bone fragility and fracture risk<sup>1</sup>. Osteoarthritis, by contrast, is the result of damage to articular cartilage caused by a complex interaction of genetic, metabolic, biochemical, and mechanical factors with secondary components of inflammation<sup>2,3</sup>. The pathological changes of osteoarthritis result in the interruption of the physiological equilibrium of the whole joint<sup>4</sup>. Both diseases are major public health

issues that affect the overall health and quality of life—pain, functional ability and physical fitness—of the elderly<sup>5,6</sup>.

Clinical experience shows that osteoporosis and osteoarthritis may coexist. The relationship between them remains unclear, though hereditary studies have established the presence of common genetic connections<sup>7-12</sup>. Dual-energy x-ray absorptiometry (DXA) studies have shown that patients with osteoarthritis have increased BMD and bone mineral content. Nevertheless, higher BMD does not translate into reduced risk of osteoporotic fracture because the structural benefits of reduced trabecular separation and increased number of trabeculae in the bone of osteoarthritic patients are counterbalanced by osteoarthritis-related factors like postural instability and muscle weakening<sup>7</sup>.

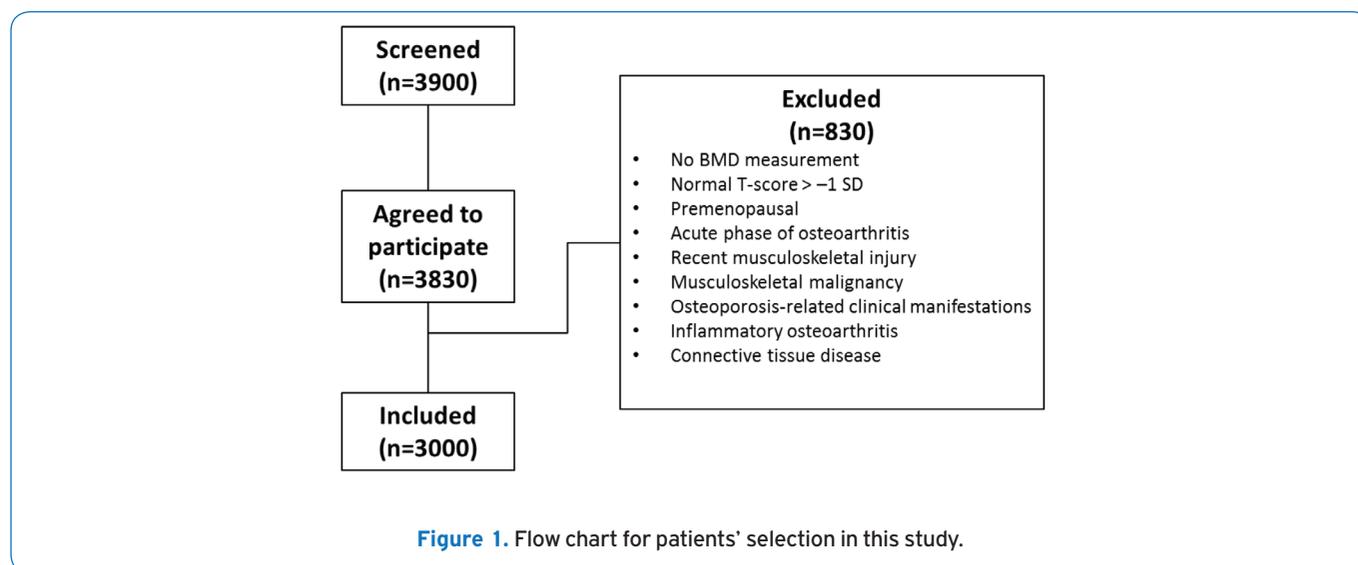
Currently, there is more epidemiological data on the incidence of osteoporosis in osteoarthritic patients than vice versa. Data on osteoporotic women with joint symptoms due to osteoarthritis are particularly sparse. In this study, we investigated the frequency and severity of clinical manifestations of osteoarthritis in women with osteopenia

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or osteoporosis to clarify the impact of osteoarthritis in postmenopausal women with low BMD.

## Material and methods

This prospective epidemiological study investigated the severity of osteoarthritic pain, discomfort and functional disability in symptomatic joints of a randomly selected population of postmenopausal women suffering from osteopenia or osteoporosis. Successive patients were selected by osteoporosis specialists, and recruitment took place at one of three participating centres in Greece: the Department of Rheumatology at Evangelismos District General Hospital in Athens, the Greek National Organization for Healthcare Services Provision, and a private osteoporosis practice. The study was conducted in accordance with the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

Postmenopausal women aged over 45 years who had undergone bone densitometry of the hip or lumbar spine with DXA and had BMD values consistent with osteoporosis (T-score  $\leq -2.5$  SD) or osteopenia (T-score -1 to -2.5 SD) were included<sup>1</sup>. Women with osteoporosis-related clinical manifestations (eg, new fractures or wrist fractures) were excluded, as were women suffering from inflammatory diseases of the musculoskeletal system or acute attacks of osteoarthritis. Patients receiving non-steroidal anti-inflammatory drugs over the short term were also excluded. All participants gave written informed consent.

Age, height, and weight were recorded. Based on T-score values, participants were categorised as osteopenic (T-score -1 to -2.5 SD) or osteoporotic (T-score  $\leq -2.5$  SD)<sup>1</sup>. Patients already receiving treatment for osteoporosis or another disease that could adversely affect bone mass (eg, inflammatory bowel disease) were allowed to continue this

treatment. All sites affected by osteoarthritis and the number of sites affected by osteoarthritis were documented. The degree of osteoarthritis-associated functional impairment at four anatomic sites was recorded by a rheumatologist or orthopaedist using an internationally recognized and validated osteoarthritis questionnaire<sup>13-16</sup>.

In the knee and hip joints, the Lequesne and Samson questionnaire was used to assess the presence of pain or discomfort, in relation to time of day or posture; maximum walking distance (in pain); and daily activities<sup>13</sup>. In the cervical spine, the Northwick Park Neck Pain Questionnaire was used to assess the degree to which neck pain affects daily life, in terms of pain intensity, sleep, numbness, duration, carrying, recreational activities, work, social activities and driving<sup>14,15</sup>. The Michigan Hand Outcomes Questionnaire contains six distinct scales to measure health outcomes in patients with chronic hand conditions: overall hand function; daily activities; pain; performance at work; aesthetics; and patient satisfaction with hand function<sup>16</sup>.

Functional impairment of the knee, hip, neck or hand was classified into one of four categories: no functional impairment; mild impairment; moderate impairment (requiring conservative drug therapy and physiotherapy); and severe impairment (requiring surgery with arthroplasty). The degree of impairment was assessed as follows: knee and hip (Lequesne and Samson score: 0, no disability; 1-7, mild; 8-13, moderate; and  $\geq 14$ , severe)<sup>13</sup>, neck (Northwick Park Neck Pain Questionnaire: 0-4, no disability; 5-14, mild; 15-24, moderate; and  $\geq 25$ , severe)<sup>14,15</sup>, and hands (Michigan Hand Outcomes Questionnaire: 0, no disability; 1-6, mild; 8-12, moderate; and  $\geq 12$ , severe)<sup>16</sup>. Osteoporosis and osteoarthritis treatments were documented.

## Statistical methods

Data were expressed as means  $\pm$  standard deviations for

**Table 1.** Characteristics of patients with low bone mineral density (n=3000) and clinical manifestations of osteoarthritis (OA) in this population. Data are presented as means±standard deviations or numbers and percentages. <sup>a</sup>n=1531. <sup>b</sup>n=1469. <sup>c</sup>osteopenia (T-score between -1 SD and -2.5 SD) and osteoporosis (T-score ≤ -2.5 SD) measured with dual-energy x-ray absorptiometry at femoral neck or lumbar spine. <sup>d</sup>anti-inflammatory therapy included non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, tramadol, and salicylate. Use of NSAIDs for more than 10 days was defined as regular use. <sup>e</sup>common analgesics included paracetamol, ibuprofen, naproxen and selective inhibitors of cyclo-oxygenase 2.

Characteristics of patients with low bone mineral density n=3000	
<b>Demographic characteristic</b>	
Age (years)	66.7±10.4
• No OA pain and disability <sup>a</sup>	65.5±10.8
• OA pain and disability <sup>b</sup>	68.0±9.7
Weight (kg)	65.4±10.5
• No OA pain and disability <sup>a</sup>	64.6±10.0
• OA pain and disability <sup>b</sup>	66.5±10.8
Height (cm)	157.6±6.1
• No OA pain and disability <sup>a</sup>	157.6±6.3
• OA pain and disability <sup>b</sup>	157.6±5.7
Body mass index (kg/m <sup>2</sup> )	26.4±4.2
• No OA pain and disability <sup>a</sup>	26.4±4.2
• OA pain and disability <sup>b</sup>	26.8±4.3
<b>Clinical characteristic</b>	
Osteoporosis <sup>c</sup>	1717 (57%)
• No OA pain and disability <sup>a</sup>	825 (54%)
• OA pain and disability <sup>b</sup>	892 (61%)
Osteopenia <sup>c</sup>	1283 (43%)
• No OA pain and disability <sup>a</sup>	706 (46%)
• OA pain and disability <sup>b</sup>	577 (39%)
<b>Sites affected by osteoarthritis</b>	
Lumbar spine	1226 (41%)
Knee	537 (18%)
Thoracic spine	505 (17%)
Cervical spine	445 (15%)
Hip	328 (11%)
Shoulder	267 (9%)
Hands	252 (8%)
Feet	109 (4%)
<b>Number of sites affected</b>	
1	870 (29%)
2	1230 (41%)
≥3	900 (30%)
<b>Previous osteoporosis medication</b>	
Alendronate	1080 (36%)
Denosumab	720 (24%)
Risedronate	540 (18%)
Strontium ranelate	330 (11%)
Ibandronate	210 (7%)
Raloxifene	90 (3%)
Teriparatide	60 (2%)
<b>Other medication</b>	
Occasional anti-inflammatory <sup>d</sup>	750 (25%)
Regular anti-inflammatory <sup>d</sup>	90 (3%)
Common analgesics <sup>e</sup>	1770 (59%)

continuous variables and as numbers and percentages for categorical data. The normality of continuous variables was analysed using a Kolmogorov-Smirnov test. In osteoporotic patients with osteoarthritic pain and functional disability, the percentages of mild, moderate and severe osteoarthritic pain and functional disability in the hip, knee, neck and hand were compared using a  $\chi^2$  test. The comparison of femoral neck and lumbar spine T-scores among the 4 osteoarthritic pain and functional disability categories (no, mild, moderate and severe) in the hip, knee, neck and hand, respectively, were performed using a one-way analysis of variance model. Post hoc analysis used the Bonferroni test, but where normality was violated the Kruskal-Wallis test or Mann-Whitney test were used. All tests were two-sided, with a p value <0.05 denoting statistical significance. All analyses were carried out using the SPSS v.17.00 statistical package (SPSS Inc., Chicago, Illinois, USA).

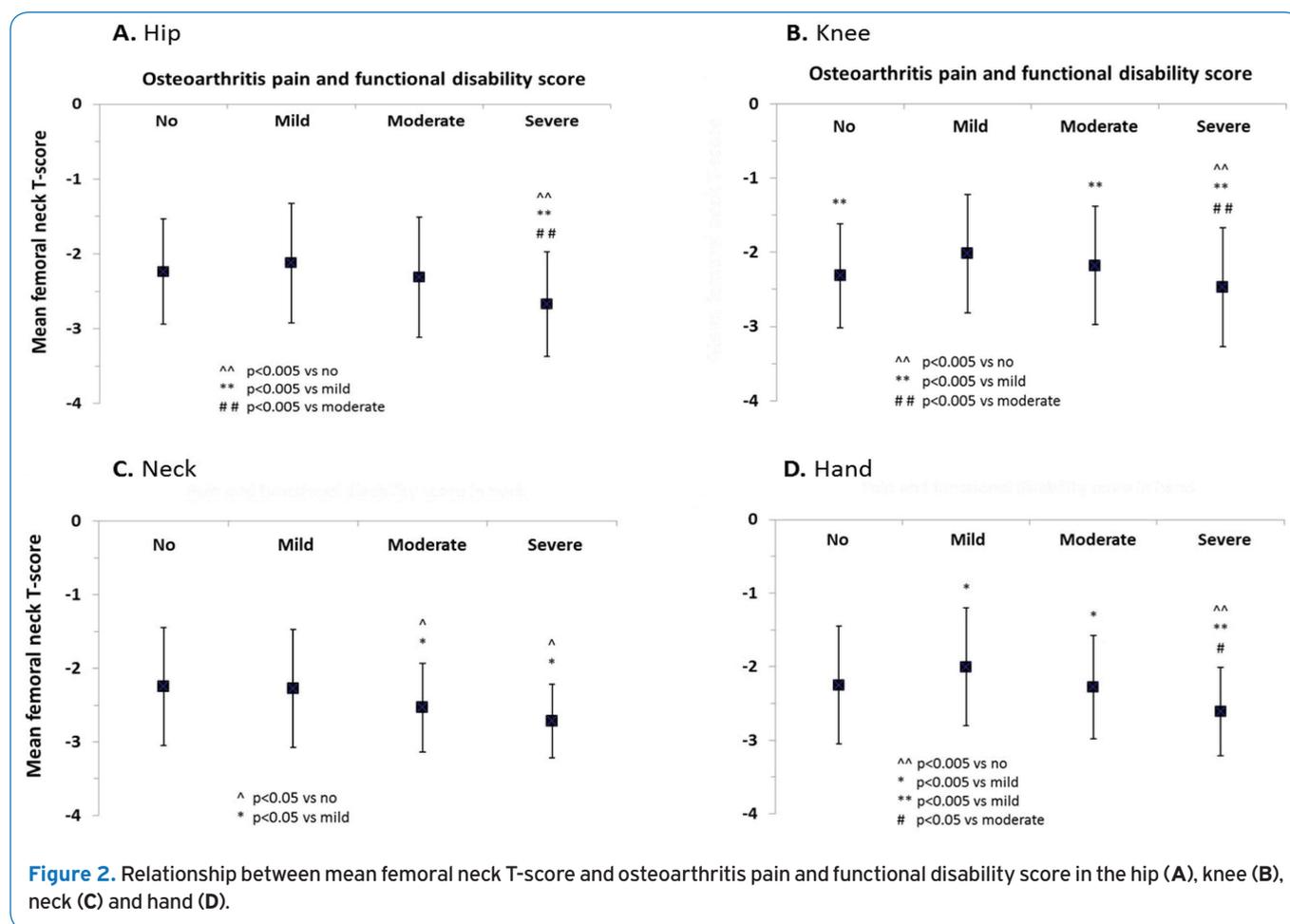
## Results

Of the 3900 women screened, 3830 agreed to participate and 3000 postmenopausal women with low BMD were included (Figure 1). The main reasons for exclusions were lack of dual-energy x-ray absorptiometry measurement, normal BMD (T-score >-1 SD) and premenopausal status. Mean age was 66.7±10.4 years and mean body mass index was 26.4±4.2 kg/m<sup>2</sup> (Table 1). Patients reporting osteoarthritic pain and disability (n=1469; 49%) were more likely to be older (68.0±9.7 versus 65.5±10.8 years) and to have osteoporosis (61% versus 54%) than those without osteoarthritic pain and disability (n=1531; 51%). Osteoporosis was more common than osteopenia (1717 vs 1283 patients; 57% vs 43%). Nearly three quarters (n=2190; 73%) of patients had received previous osteoporosis therapy, most often a bisphosphonate or denosumab. Most (n=2636; 88%) reported pain or functional disability affecting at least one anatomic site. In these patients, 9% were taking glucosamine sulphate and 2% were taking diacerein. Most patients were affected by osteoarthritis at two sites (n=1230 41%), notably at the lumbar spine, thoracic spine or knee, which together accounted for 62% of the 3669 painful sites reported.

Nearly two thirds (65%; n=2367) of the 3669 cases of osteoarthritic pain and functional disability occurred in the hip, knee, neck or hand. In these four locations, mild osteoarthritic pain and functional disability was the severity reported most often (n=977; 27%), followed by moderate (n=844; 23%) and then severe (n=546; 15%) osteoarthritic pain and functional disability. Osteoarthritic pain and functional disability was most commonly observed in the knee (n=853; 23%), followed by the neck (n=638; 17%), hip

**Table 2.** Osteoarthritic pain and functional disability at the hip, knee, neck and hand. Values are presented as numbers and percentages.

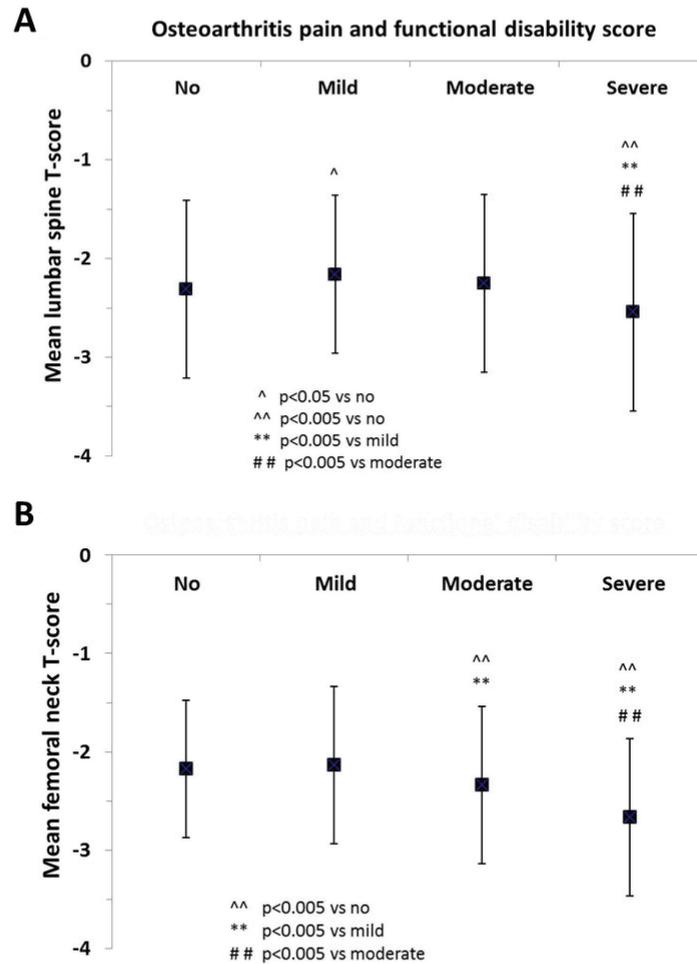
Site of pain/ disability	Osteoarthritic pain and functional disability				p-value
	Mild	Moderate	Severe	All	
Hip	97 (3%)	211 (6%)	190 (5%)	498 (14%)	p<0.05
Knee	239 (7%)	385 (10%)	229 (6%)	853 (23%)	p<0.05
Neck	526 (14%)	87 (2%)	25 (<1%)	638 (17%)	p<0.05
Hand	115 (3%)	161 (4%)	102 (3%)	378 (10%)	p<0.05
Total	977 (27%)	844 (23%)	546 (15%)	2367 (65%)	



(n=498; 14%) and hand (n=378; 10%) (Table 2). Moderate pain and functional disability was reported most frequently at the hip (n=211; 6%), knee (n=385; 10%) and hand (n=161; 4%), while at the neck mild pain and functional disability was most frequently reported (n=526; 14%).

In patients who had BMD measured at the femoral neck at one of these four sites (n=1339), there appeared to be an inverse relationship between worsening severity of osteoarthritic pain and functional disability and mean T-score

values at the hip, knee, neck and hand (Figure 2). When osteoarthritic pain and functional disability scores at these four sites were pooled, there was a significant difference in mean T-score between patients with severe osteoarthritic pain and disability and those with no, mild or moderate osteoarthritic pain and disability (all p<0.005) (Figure 3). This significant difference was also observed when the results at these four sites were pooled in patients who had BMD measured at the lumbar spine (n=1028) (Figure 3).



**Figure 3.** Relationship between mean lumbar spine T-score (A) and mean femoral neck (B) T-score and osteoarthritis pain and functional disability score.

## Discussion

Most postmenopausal women with low BMD suffered from osteoarthritic pain and disability at one or more anatomic sites. Many were likely to have taken a previous osteoporosis medication, but few were regular users of anti-inflammatory drugs despite the common presence of osteoarthritic pain and disability. In patients with osteoarthritic pain and functional disability, there appeared to be an inverse association between worsening osteoarthritic pain and functional disability score at the hip, knee, neck or hand and mean femoral neck T-score. When results from these four sites were pooled, the mean lumbar spine or femoral neck T-scores of patients with severe osteoarthritic pain and functional disability were significantly lower than those of patients with no, mild or moderate pain and functional disability. Overall, our findings underline the importance of the holistic management of musculoskeletal health in postmenopausal women with low BMD.

Consideration of the development of osteoarthritis is one

of the keys to understanding why osteoporosis may coexist more frequently with osteoarthritis than previously thought and why increased BMD in osteoarthritis may not reduce fracture risk<sup>8</sup>. In the early stages of osteoarthritis, osteoclastic activity increases with a possible resultant decrease in BMD and increase in comorbid osteoporosis. In later stages of osteoarthritis, however, compact bone thickens and sclerosis occurs, leading to increases in BMD. But although BMD increases, a reduction in bone mineralization and decrease in bone elasticity mean bone quality is compromised. Combined with postural instability and muscle weakening, it is perhaps not surprising that fracture risk may remain unchanged<sup>7</sup>.

In our study and contrary to the widely held belief that the prevalence of osteoarthritis and osteoporosis are inversely related<sup>7</sup>, the majority of osteopenic or osteoporotic women reported active clinical manifestations of osteoarthritis at one or more skeletal location. Women with osteoporosis were more likely to report osteoarthritis pain and disability than women with osteopenia.

Furthermore, the presence of osteoarthritis did not appear to confer protection against primary generalized osteoporosis. Patients reporting severe osteoarthritic pain and functional disability had significantly lower mean T-score values at the femoral neck or lumbar spine, compared with those reporting no, mild or moderate osteoarthritic pain and functional disability. The comparison of mean femoral neck T-scores between patients reporting severe and mild clinical manifestations of osteoarthritis, in particular, was significant at all skeletal sites.

At a molecular level, many chemical messengers and systems are common to both osteoarthritis and osteoporosis: for example, insulin-like growth factor 1, transforming growth factor  $\beta$ 1 and the OPG (osteoprotegerin)/RANK (receptor of nuclear factor kappa B)/RANK ligand system are involved in both diseases<sup>7,17-20</sup>. It might therefore be supposed that osteoporosis treatments may modulate osteoarthritis, and existing medical literature indicates that several osteoporosis treatments do indeed have an effect on osteoarthritis<sup>8</sup>. In humans, calcitonin has been shown to reduce markers of cartilage degradation, while bisphosphonates reduced osteophyte score, dorsal-lumbar disc space reduction score and symptoms of osteoarthritis. A meta-analysis of 13 bisphosphonate trials showed that osteoarthritic pain assessed by visual analogue scale improved in 8 trials, but bisphosphonates appeared to have little effect on osteoarthritic knee pain measured by Western Ontario and McMaster Universities Arthritis Index (WOMAC) score<sup>21</sup>. Treatment with strontium ranelate in patients with knee osteoarthritis in SEKOIA (Strontium ranelate Efficacy in Knee Osteoarthritis trial) led to both reduction in WOMAC knee pain and joint space narrowing<sup>22</sup>.

Our study has some limitations that need to be acknowledged. Treatment effect was not taken into account, as it was not a requirement that measurement of BMD and assessment of osteoarthritic pain and disability occurred at the same time. This may have impacted our results. The diagnosis of osteoarthritis in affected joints was not confirmed radiographically. Where multiple BMD measurements were available, the earliest one obtained (before osteoporosis treatment) was used. This avoided any impact of treatment on BMD recordings, which would have affected our results<sup>23,24</sup>.

## Conclusion

Osteoarthritis and osteoporosis can occur together in the same patient. Most postmenopausal women with low BMD appear to have some form of osteoarthritic impairment. In these patients, severity of osteoarthritic impairment at the hip, knee, neck or hand was inversely proportional to mean femoral neck T-score. After pooling, mean lumbar spine or femoral neck T-scores of patients with severe osteoarthritic impairment were significantly lower than those of patients with no, mild or moderate impairment.

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