EXTENDED REPORT

Bone mineral density in patients with hand osteoarthritis compared to population controls and patients with rheumatoid arthritis

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Objectives: Several studies have revealed increased bone mineral density (BMD) in patients with knee or hip osteoarthritis, but few studies have addressed this issue in hand osteoarthritis (HOA). The aims of this study were to compare BMD levels and frequency of osteoporosis between female patients with HOA, rheumatoid arthritis (RA) and controls aged 50–70 years, and to explore possible relationships between BMD and disease characteristics in patients with HOA.

Methods: 190 HOA and 194 RA patients were recruited from the respective disease registers in Oslo, and 122 controls were selected from the population register of Oslo. All participants underwent BMD measurements of femoral neck, total hip and lumbar spine (dual-energy *x* ray absorptiometry), interview, clinical joint examination and completed self-reported questionnaires.

Results: Age-, weight- and height-adjusted BMD values were significantly higher in HOA versus RA and controls, the latter only significant for femoral neck and lumbar spine. The frequency of osteoporosis was not significantly different between HOA and controls, but significantly lower in HOA versus RA. Adjusted BMD values did not differ between HOA patients with and without knee OA, and significant associations between BMD levels and symptom duration or disease measures were not observed.

Conclusion: HOA patients have a higher BMD than population-based controls, and this seems not to be limited to patients with involvement of larger joints. The lack of correlation between BMD and disease duration or severity does not support the hypothesis that higher BMD is a consequence of the disease itself.

Osteoporosis is recognised as a frequent complication to rheumatoid arthritis (RA).[1] Osteoarthritis (OA) is the most frequent rheumatic joint disease, and contrary to the situation in RA, several studies have revealed increased bone mineral density (BMD) in patients with knee or hip OA, even if the results have not been consistent in all studies.[2–10] The hand is a frequent site of peripheral joint involvement in OA. However, a limited number of studies have addressed the issue of osteoporosis in hand osteoarthritis (HOA), and the results from these few studies have been inconsistent regarding levels of BMD compared with controls.[8–15]

OA has generally been considered as a cartilage disease characterised by slow progressive degeneration of articular cartilage due to ''wear and tear'' mechanisms. However, there is increasing evidence that abnormalities in the subchondral bone and systemic factors may contribute to the pathophysiological process. Studies of subchondral bone have revealed alterations in microstructure including increased BMD. This local increase in BMD in OA joints may be a consequence of reduced shock absorption in joints with degenerated cartilage,[5] or on the contrary, thickening and stiffening of the subchondral bone with increased BMD may lead to development of OA.[16] However, elevated BMD levels at sites remote from the arthritic process cannot be explained by local biomechanical factors, and the question of whether primary OA rather is a systemic bone disease has been raised.[17] Systemic changes in subchondral bone could be explained by genetic factors, hormonal influences, vitamin D concentrations, growth factors or activity of bone-forming cells.[15 18–21] Better knowledge about the relationship between BMD and HOA may contribute to the understanding of the pathogenesis of OA.

Disease registers of patients with RA[22] and HOA[23] have been established in the city of Oslo. We have previously compared BMD levels in a cohort of RA patients from the Oslo RA Register (ORAR) and healthy controls.[24] The current study was designed to compare levels of BMD and the frequency of osteoporosis between patients with HOA, RA and controls. A second aim was to explore possible relationships between BMD levels and disease characteristics in patients with HOA.

MATERIAL AND METHODS

Study design

This cross-sectional study compared levels of BMD and the prevalence of osteoporosis and osteopenia between three groups of females; 190 patients with HOA, 194 patients with RA, and 122 population controls, all aged 50–70 years. The patients with HOA and RA were recruited from the respective disease registers in Oslo. All participants underwent BMD measurements in femoral neck, total hip and lumbar spine. Demographic and clinical variables were obtained partly by self-reported questionnaires and partly by interview and clinical joint examination performed by study nurses and rheumatologists.[23 24]

HOA patients

The inclusion criteria for the HOA patients for this study were clinical HOA, female sex, age between 50 and 70 years, and absence of other rheumatic diseases such as RA, psoriatic arthritis, systemic connective diseases, and spondyloarthropathies. The mean symptom duration was 10.7 years. The 190 patients with HOA had a wide spectrum of joint manifestations ranging from isolated carpo-metacarpal OA to generalised

Abbreviations: ACR, American College of Rheumatology; AUSCAN, Australian/Canadian OA hand index; BMD, bone mineral density; HOA, hand osteoarthritis; MHAQ, Modified Health Assessment Questionnaire; OA, osteoarthritis; RA, rheumatoid arthritis; VAS, visual analogue scale

erosive OA. The American College of Rheumatology (ACR) classification criteria for HOA were fulfilled by 159 (83.7%) patients, and 31 (16.3%) had clinical HOA, that is bony enlargement of a number of finger joints less than required to fulfil the classification criteria.[25] A total of 112 patients (58.9%) also fulfilled the clinical ACR criteria for knee OA.[26] Radiographic OA abnormalities (Kellgren and Lawrence grade 2 or more) of the finger joints were observed in 176 (92.6%) patients.[27]

RA patients

The RA patients were recruited from the ORAR, which includes patients with residential address in Oslo and with diagnosis of RA according to the American College of Rheumatology 1987 revised classification criteria.[28] This validated register, with a completeness of around 85%, contains both mild and severe cases that are suggested to be representative of the total RA population in the county.[29] The inclusion criteria for the current study were female sex, disease duration of at least 2 years, age between 50 and 70 years, and absence of clinical HOA. The mean disease duration since fulfilment of the ACR classification criteria was 18.8 years, 59.3% were rheumatoid factor positive, and 50.0 and 36.3% of the RA patients were current and previous users of DMARDs, respectively.

Control population

The control population was selected from the population register of Oslo. It consisted of 122 females aged between 50 and 70 years, and absence of clinical signs of HOA or other rheumatic diseases including RA, psoriatic arthritis, systemic connective diseases and spondyloarthropathies. They were originally recruited for a comparative analysis with RA patients,[24] and the original number of 249 patients was decreased to 122 after excluding patients with HOA.

BMD measurements

All participants underwent BMD measurements at the hip (total hip and femoral neck) and the lumbar spine L2–L4 (anterior–posterior view) by the same dual-energy *x* ray absorptiometry equipment (Lunar Expert, Madison, WI). In agreement with the WHO criteria, osteopenia (low bone mass) was defined as a T score between -1 and -2.5 and osteoporosis as a T score $\leqslant -2.5$.[30]

Clinical and self-reported health status

Demographic and clinical variables were obtained partly by self-report questionnaires and partly by interview and clinical joint examination by study nurses or rheumatologists. The patients completed several self-report health status questionnaires, including the Australian/Canadian OA hand index (AUSCAN), the Modified Health Assessment Questionnaire (MHAQ), scores for pain, fatigue and global disease activity on visual analogue scales (VAS), and the Short-Form 36 (SF-36) Health Survey (table 1).[23 31 32] Interviews concerning medications and medical disorders were performed by study nurses.

Statistical analysis

Statistical analyses were carried out using SPSS, version 12.0. BMD values were compared between the three groups with adjustment for age, height and weight (ANCOVA). Post-hoc two-group comparisons were performed when overall 3-group comparisons were significant ($p<0.05$). We also compared BMD across HOA patients with and without additional knee OA with adjustment for age, height and weight (ANCOVA). Chi-square tests were used to explore differences in proportions of osteoporosis across patients with HOA, RA and controls. Relationships between BMD and disease characteristics were explored with Pearson's correlation analyses.

RESULTS

Demographic and clinical variables

Demographic and clinical characteristics of the three groups are shown in table 1. There were no significant differences in age, height or age of menopause, but significant differences in weight ($p = 0.008$) and BMI ($p = 0.002$). There were also significant differences in smoking habits ($p = 0.02$) with the highest prevalence of current and previous smokers in RA patients and lowest in HOA patients. The proportion of patients with current or previous use of oestrogens was highest in HOA patients and lowest in controls ($p<0.001$). The use of corticosteroids and medications to prevent and treat osteoporosis like bisphosphonates, calcium and vitamin D was significantly higher in RA patients compared with HOA patients and controls. Oestrogens, corticosteroids and calcium were used more frequently in HOA patients versus controls ($p<0.05$).

HOA patients reported significantly worse health status across all instruments compared with controls. Differences between HOA and RA patients were mostly non-significant. However, HOA patients reported significantly more bodily pain and reduced mental health measured by SF-36 but significantly better physical functioning and lower MHAQ score compared with RA patients.

BMD values in patients with HOA, RA and controls

Adjusted BMD values differed at all measurement sites between patients with HOA, RA and controls ($p<0.001$). Two-group comparisons revealed significantly higher BMD in HOA patients versus controls, but only borderline significant at the total hip ($p = 0.06$) (table 2).

Frequency of osteoporosis

The frequency of osteoporosis (T score $\leqslant -2.5$) differed significantly across the three groups. Two-group comparison of HOA patients and controls revealed no significant differences, whereas the prevalence in RA patients was significantly higher than in HOA patients and controls (two-group comparisons) (data of RA versus controls not shown). The proportions with either osteoporosis or osteopenia (T score <-1) were lower in HOA patients compared with controls at all measurement sites, but only significant at total hip (table 3).

BMD in HOA patients with and without additional knee OA

Age-, weight- and height-adjusted BMD values did not differ between HOA patients with ($n = 112$) and without ($n = 78$) additional knee OA (clinical ACR classification criteria)[26] (table 4). The same pattern was revealed when comparing BMD values in patients with and without additional hip OA (ACR classification criteria)[33] (data not shown).

Correlation between BMD and symptom duration and levels of health status in patients with HOA

There were no significant correlations between BMD levels and symptom duration and health status measures (pain, stiffness, physical function and fatigue) (table 5). Correlations with SF-36 scores were also non-significant (data not shown).

DISCUSSION

This 3-group study demonstrates that BMD is increased in patients with HOA compared with controls. This finding is in agreement with a couple of previous studies.[14 15] However, negative associations between HOA and BMD at axial sites have also been found,[8 13] and two longitudinal studies did not find any associations between HOA and bone mass at appendicular sites.[11 12]

These contradicting results in axial BMD measurements may partly be due to radiographic versus clinical definition of HOA,

Table 1 Demographic and clinical variables (mean (SD) for continuous variables, % for counts)

	HOA (n = 190)	RA (n = 194)	Controls (n = 122)
Demographic variables			
Age (years)	61.6 (5.6)	60.9 (5.9)	60.2 (5.4)
Height (cm)	165.3 (6.3)	165.5 (5.9)	165.1 (6.3)
Weight (kg)	71.0 (13.2)	67.0 (12.3)	69.5 (11.5)
BMI (kg/m^2)	25.9 (4.4)	24.5 (4.3)	25.5 (4.0)
Age of menopause (years)	49.0 (5.1)	48.7 (6.1)	49.4 (6.2)
Smoking: Non/previous/current smoker	49.2/26.5/24.3	33.2/34.8/32.1	40.0/26.7/33.3
Oestrogens: Never/previous/current user	26.8/30.0/43.2	36.3/15.8/47.9	46.3/20.7/33.1
Corticosteroid: Never/previous/current user	76.6/20.2/3.2	28.9/24.6/46.5	92.6/6.6/0.8
Bisphosphonates: Never/previous/current user	95.3/1.1/3.7	86.8/3.2/10.1	97.5/–/2.5
Calcitonin: Never/previous/current user	99.5/0.5/–	95.7/3.2/1.1	99.2/0.8/–
Calcium: Never/previous/current user	61.8/14.5/23.7	25.8/12.9/61.3	74.6/4.9/20.5
Vitamin D: Never/previous/current user	27.1/11.7/61.2	19.3/8.6/72.2	38.0/6.6/55.4
Disease variables			
MHAQ	1.50 (0.41)	1.64 (0.54)	1.05 (0.17)
VAS Pain	39.5 (22.6)	36.3 (23.5)	8.9 (15.5)
VAS Fatigue	45.8 (30.2)	48.9 (28.8)	18.4 (23.3)
SF-36 Physical	57.6 (23.4)	48.5 (23.9)	83.1 (20.9)
SF-36 Role limitations due to physical problems	33.2 (40.2)	30.3 (36.8)	79.0 (34.6)
SF-36 Bodily pain	39.6 (18.7)	44.1 (20.8)	72.3 (27.8)
SF-36 General health	51.5 (22.8)	47.8 (22.4)	71.2 (22.7)
SF-36 Vitality/energy	40.0 (22.2)	43.5 (20.2)	60.5 (20.9)
SF-36 Social functioning	67.4 (25.7)	69.3 (27.0)	82.8 (20.4)
SF-36 Role limitations due to emotional problems	56.6 (40.9)	54.7 (40.5)	81.5 (34.3)
SF-36 Mental health	68.2 (20.3)	73.4 (19.2)	79.5 (14.4)

where hand radiographs tend to overdiagnose OA.[13] In most studies, HOA is defined radiographically according to the Kellgren–Lawrence scale.[27] However, another study of women with clinical HOA according to the ACR clinical classification criteria demonstrated significantly lower BMD levels in HOA compared with controls in contrast to the findings in our study.[13] Other factors that may contribute to the conflicting results are erosive versus non-erosive HOA, multijoint versus isolated HOA, hormonal influences or misdiagnosis of HOA.[13 34]

Previous studies of subchondral bone in OA joints have hypothesised that repair of microfractures caused by repetitive impact loading of the joints may cause local thickening and stiffening of subchondral bone, and that this stiffer bone reflected by higher BMD is less deformable leading to increased mechanical stress with degeneration and loss of articular cartilage.[16] An alternative hypothesis is that increased BMD may be due to reduced shock absorption as a consequence of OA or because of biomechanical factors with a dual effect on both joint cartilage and BMD.[5] However, local biomechanical changes cannot account for elevated BMD at sites remote from the osteoarthritic process as observed in this study.

Our demonstration of elevated BMD levels at axial sites supports the hypothesis that increases in BMD and subsequent development of OA at other sites are due to systemic intrinsic variations in bone structure, quality and metabolism rather than a consequence of local mechanical conditions.[35–38] The role of systemic factors is also supported by the similar levels of BMD across patients with and without additional knee OA. Further, the lack of correlation between BMD and disease duration and health status measures support the hypothesis that increased BMD precedes the development of OA, rather than being a consequence of the disease itself.

Several systemic factors have been studied in relation to development of increased BMD, including genetic factors, ovarian hormone levels, vitamin D concentrations, growth factors and activity of bone forming cells, but the results are conflicting.[15 18–21] The generalised increase in BMD in patients with OA may be due to common genetic factors shared by OA and high peak bone mass.[39 40] Several genes involved in the regulation of BMD, like those coding for the vitamin D receptor, the oestrogen receptor, collagen type IIaI and the insulin-growth factor, have been implicated in OA, but the findings are not consistent.[41–48] The protective role of oestrogen in bone loss is well known, suggesting a potential association between levels of oestrogen and development of OA. However, the majority of epidemiological studies in which women on HRT are compared with women not on HRT suggest that HRT protects against the occurrence of radiographic OA. In our study, the use of oestrogen-replacement therapy was highest in HOA patients and may contribute to the observed higher BMD. The contribution of oestrogen to the pathogenesis of OA still needs clarification.[49]

Smoking is a well-known risk factor of osteoporosis. The lower prevalence of current or previous smokers in HOA patients may contribute to increased levels of BMD compared with controls.

In other rheumatic diseases such as RA, inflammation is the principal pathogenic factor. The inflammatory component in the pathogenesis of OA is unclear, although inflammatory and

Table 2 Mean (SEM) BMD values (g/cm^2) adjusted for age, weight and height across patients with HOA, RA and control individuals (analysis of covariance, ANCOVA)

	HOA	RA	Controls	p value overall	p value HOA vs RA	p value HOA vs controls
Femoral neck	0.926 (0.010)	0.836 (0.010)	0.892 (0.012)	<0.001	<0.001	0.03
Total hip	0.953 (0.009)	0.869 (0.009)	0.925 (0.012)	<0.001	<0.001	0.06
L2–L4	1.203 (0.015)	1.088 (0.015)	1.131 (0.018)	<0.001	<0.001	0.002

Table 3 Proportions of patients (%) with osteoporosis at the femoral neck, total hip, and lumbar spine

	HOA	RA	Controls	p value overall	p value HOA vs RA	p value HOA vs controls
T score ⩽ −2.5						
Femoral neck	3.3	15.3	2.5	<0.001	<0.001	0.70
Total hip	3.8	14.2	2.5	<0.001	0.001	0.53
L2–L4	7.4	19.4	10.7	0.002	0.001	0.30
T score < −1.0						
Femoral neck	32.2	62.3	42.5	<0.001	<0.001	0.07
Total hip	29.0	57.4	40.0	<0.001	<0.001	0.05
L2–L4	32.1	53.4	38.0	<0.001	<0.001	0.29

autoimmune mechanisms have previously been suggested to contribute to the pathogenesis of erosive OA. A recent placebo-controlled study showed that a combination of low-dose prednisolone and dipyridamol (CRX-102) was effective in HOA, and this finding supports the hypothesis that inflammation may contribute to the symptoms of HOA.[50] These results will most likely lead to further examinations of long-term corticosteroid treatment in HOA. The use of corticosteroids is recognised as a risk factor for osteoporosis.[51] Even if the current study and several others[14 15] indicate that BMD is higher in HOA than controls, awareness of osteoporosis is still needed in patients with HOA, especially since the fracture risk is not reduced.[51]

Fractures are the most important clinical end point in patients with osteoporosis. This study did not focus on fractures, but the study nurses asked the patients to self-report the number of previous vertebral and non-vertebral fractures. There was no significant difference in frequency of fractures after the age of 50 years between the three groups (p overall = 0.52). The proportion of patients who had experienced bone fracture after the age of 50 years was similar in HOA patients vs controls (17.7% versus 18.6%), but lower in HOA patients compared with RA patients (17.7% versus 22.3%). Other studies have demonstrated increased fracture risk in OA patients including patients with HOA, in spite of increased BMD.[52 53] These results suggest that clinicians should not consider OA patients at lower fracture risk compared with the general population, since falls and other unmeasured factors seem to cancel out the benefits of increased BMD.[52]

This is the first study which simultaneously compares BMD levels in cohorts of HOA and RA patients and controls of the same gender and group of age. All patients underwent BMD measurements with the same equipment and were examined clinically and with questionnaires and interviews in the same setting. However, there are several limitations of this study. Because of the cross-sectional study design, the exact relation between increased levels of BMD and development of OA cannot be determined. The selection of the HOA patients was based on clinical symptoms and signs with risk of misdiagnosis, and without differing between erosive and non-erosive HOA. Only 83.7% of the HOA patients fulfilled the ACR clinical criteria, but analyses showed no significant differences in BMD values between HOA patients with and without fulfilment of the ACR criteria. In addition, the presence of osteophytes in patients with lumbar osteoarthritis may contribute to over-estimation of lumbar spine BMD measurements in the anteroposterior position,[54] and the difference in BMD values in this study between HOA patients and controls was more pronounced in lumbar spine (p = 0.002) than femoral neck (p = 0.03) and total hip (p = 0.06). The lack of a correlation between BMD levels and symptom severity may have been due to the use of clinical measures only addressing the patient's perspective. It is unclear whether more objective measures, like biomarkers and radiographic progression, may reflect disease activity more precisely.

There is increasing evidence that OA is not primarily a cartilage disease, but rather a result of disease in any of the tissues of the affected joint, including the subchondral bone, synovium, capsule, periarticular muscles, sensory nerve endings, meniscus (if present) or supporting ligaments.[17] In this article, we have focused on the importance of BMD. It has been assumed that increased BMD and stiffness of subchondral bone may cause joint breakdown by increasing stresses in the articular cartilage.[16] A recent study of high-resolution magnetic resonance imaging by Tan *et al*[55] focused on collateral ligaments in the pathogenesis of HOA, demonstrating structural changes in collateral ligaments in IP joints with apparently normal cartilage, indicating that this is the principal site of wear and tear in early disease. Further research on the pathogenesis of the failing organ, including the role of subchondral bone, is needed to make real progress in curing or preventing OA.[17]

In conclusion, this study demonstrates increased levels of BMD in patients with HOA compared with controls and also with patients with RA. Increased BMD levels at sites remote from the arthritic process and similar BMD levels across patients with and without knee OA suggest that systemic factors may contribute more than local biomechanical factors to the pathogenesis of OA. This hypothesis is further strengthened by the lack of associations between levels of BMD and symptom duration and severity.

Table 4 Mean values and p values of BMD (g/cm^2) after adjustment for age, weight and height (analysis of covariance, ANCOVA) in HOA patients with and without additional clinical knee osteoarthritis (OA)

	With knee OA	Without knee OA	p value
Femoral neck	0.944	0.948	0.97
Total hip	0.977	0.955	0.76
L2–L4	1.223	1.094	0.24

Table 5 Correlations between BMD and symptom duration, AUSCAN, MHAQ and VAS scores (Pearson's correlation coefficients (p values))

	BMD femoral neck	BMD total hip	BMD L2–L4
Symptom duration	−0.03 (0.70)	0.07 (0.42)	0.09 (0.27)
AUSCAN pain	0.08 (0.30)	0.12 (0.11)	0.06 (0.39)
AUSCAN stiffness	−0.08 (0.31)	−0.02 (0.82)	−0.06 (0.40)
AUSCAN physical	0.02 (0.81)	0.03 (0.72)	−0.02 (0.84)
MHAQ	0.05 (0.55)	0.03 (0.66)	0.13 (0.07)
VAS pain	0.12 (0.12)	0.09 (0.22)	0.13 (0.07)
VAS fatigue	−0.004 (0.96)	−0.02 (0.83)	−0.01 (0.92)
VAS activity	0.03 (0.67)	0.03 (0.70)	0.08 (0.29)

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