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ACCELERATED METACARPAL BONE MINERAL DENSITY LOSS IS ASSOCIATED WITH RADIOGRAPHIC PROGRESSIVE HAND OSTEOARTHRITIS

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ABSTRACT

Objective. To study the association between metacarpal bone mineral density (BMD) loss and progressive hand osteoarthritis (OA) over 2 years.

Methods. Using the Kellgren-Lawrence (KL) grading scale and the Osteoarthritis Research Society International (OARSI) atlas, standardised hand radiographs of 181 patients with primary OA at multiple sites (mean age 60 years, 80% females, mean body mass index 27 kg/m²) were assessed for hand OA at baseline (KL ≥ 2 in ≥ 2 hand joints) and progressive hand OA over 2 years (≥ 1 point increase in total osteophyte and joint space narrowing score in patients with hand OA at baseline). Changes in BMD were measured over 2 years in metacarpals 2-4 by digital X-ray radiogrammetry. Accelerated BMD loss was defined as loss of >3 mg/cm²/year. Logistic regression analyses were performed to assess the associations between BMD loss and progressive hand OA.

Results. The baseline prevalence of hand OA was 68% and, after 2 years, 32% of these patients had progressive hand OA. Accelerated BMD loss was present in 79% of the patients with progressive hand OA compared to 60% and 57% of the patients with non-progressive hand OA and no hand OA, respectively. BMD loss was independently associated with progressive hand OA compared to non-progressive hand OA with a RR (95%CI) of 2.1 (1.1 to 4.3).

Conclusion. Accelerated metacarpal BMD loss is associated with progressive hand OA over a period of 2 years, knowledge of common mechanisms may lead to development of therapeutic interventions for hand OA.

INTRODUCTION

Osteoarthritis (OA) is a heterogeneous disease characterised by degradation of articular cartilage, changes in subchondral bone and osteophyte formation at the joint margins leading to joint failure. The disease has a major impact on the patient by increased morbidity and mortality and on society by high health care costs.¹

The pathogenesis of OA is incompletely understood, but thought to be multifactorial involving degenerative, biomechanical, metabolic, hormonal and genetic factors.² Within OA, hand OA seems to be a separate subset of the disease compared to knee and hip OA with differences in genetic factors, pathogenesis and disease course.³ Increasing evidence supports the involvement of local and low-grade systemic inflammation in the pathogenesis of OA, especially in the hands. With sensitive imaging modalities, inflammatory signs such as synovitis in interphalangeal joints in the hand is frequently seen in patients with OA.⁴⁻⁶ In patients with OA, increased levels of pro-inflammatory cytokines in synovial fluid^{7,8} and of high sensitive C-reactive protein (hsCRP) in peripheral blood are found.^{9,10}

Experimental animal studies have provided substantial evidence suggesting that inflammatory activity plays an important role in the pathogenesis of osteoporosis or bone mineral density (BMD) loss.¹¹ In health subjects, levels of inflammatory markers, such as interleukin 1 β and interleukin 6, tumour necrosis factor α and hsCRP, are associated with, and predictive for, changes in BMD over time.¹²⁻¹⁴ In patients with rheumatoid arthritis, measurement of localised BMD loss over time has been shown to be associated with radiographic progression over time and to be sensitive to indicate inflammatory bone involvement.^{15,16} In patients with OA, the level of BMD loss and the relation to the development or progression of OA is less clear. In contrast to data of cross-sectional studies¹⁷⁻²¹, longitudinal data on the relation between BMD and OA are limited. Two studies investigating changes in BMD in OA showed generalised BMD loss over time in hand, hip and knee OA.^{22,23} Only one study investigated both BMD and OA parameters longitudinally, showing that generalised BMD loss was associated with progressive knee OA.²⁴ To our knowledge, no data exists on the association between localised BMD loss and progressive OA in the hands.

We hypothesised that accelerated localised BMD loss might be present in hand OA and associated with disease progression, as a marker for an inflammatory pathway of the disease. Therefore, we investigated the relationship between changes in BMD at the metacarpals and radiographic progression of hand OA over a period of 2 years.

PATIENTS AND METHODS

Study design and patient selection

Patients were selected from the Genetics ARthrosis and Progression (GARP) cohort.²⁵ The cohort comprises 192 Caucasian sibling pairs with symptomatic primary OA, defined according to the American College of Rheumatology criteria, at multiple sites in the hands or in at least two of the following joint sites: hand, knee, hip or spine (cervical and lumbar).²⁶⁻²⁸ Patients with secondary OA (congenital or developmental diseases, bone dysplasia, local factors such as severe scoliosis and hypermobility,

metabolic diseases, intra-articular fractures, inflammatory joint diseases and other bone disease such as Paget disease and osteochondritis), patients with familial syndromes with a Mendelian inheritance pattern and patients with a shortened life expectancy were excluded. The medical ethics committee of the Leiden University Medical Center approved the study protocol and all patients gave written informed consent prior to participation in the study.

Of the original 192 sibling pairs, 105 pairs with at least one subject with symptomatic hip or knee OA were included in the 2-year follow-up study.²⁹ These 210 patients were eligible for the present study.

Radiographic assessment of hand OA

Standardised analogue radiographs of both hands (dorsal-volar) were obtained in a single center by the same experienced radiographer at baseline and after 2 years.

To assess the presence of hand OA, baseline hand radiographs (distal interphalangeal joints, proximal interphalangeal joints, first interphalangeal joints and first carpometacarpal joints) were scored by a single experienced reader using the Kellgren-Lawrence (KL) grading scale (0-4 for each joint).³⁰ This is a five-point scoring system with ascending severity based on the presence of osteophytes, joint space narrowing (JSN), sclerosis and degenerative cyst formation. Hand OA was defined as KL score of ≥ 2 in at least 2 hand joints.

To assess OA progression, baseline and 2-year hand radiographs were scored in pairs for osteophytes and JSN by consensus opinion of two experienced readers, blinded for patient characteristics and time sequence, using the Osteoarthritis Research Society International (OARSI) atlas (0-3 per joint for each feature).³¹ In case of disagreement the lower, more conservative score, was recorded. Progressive hand OA was defined as an increase in the total osteophyte and JSN score of at least 1 point over 2 years in patients with hand OA at baseline.

Intrareader reliability for the assessment of the prevalence and progression of hand OA, both dichotomous variables, expressed by kappa coefficients based on a random selection of 10% of the radiographs, was 1.0 for both assessments.

Metacarpal BMD measurements

Analogue radiographs of both hands were digitised by a high-resolution 300 DPI scanner (Canon Vidar VXR-12 plus, Canon Inc., Tokyo, Japan) and analysed under blinded conditions using the digital X-ray radiogrammetry (DXR) online from the Pronosco X-posure system (Sectra, Linköping, Sweden).

DXR is a computerised version of the traditional technique of radiogrammetry originally proposed by Barnett and Nordin to estimate bone strength with radiological assessed cortical bone thickness.³² The digitised hand radiograph was subjected to a number of image processing algorithms where the three regions of interests around the narrowest part of the second, third and fourth metacarpal joints were automatically identified and, subsequently, the outer and the inner cortical edges of the included cortical bone parts were found.³² The BMD estimate is defined as: $BMD = c \times VPA \times (1-p)$, where c is a constant, VPA is volume per area and p is

porosity. DXR can measure changes in BMD with high precision and has a smallest detectable differences ranging from 1.2 to 2.8 mg/cm².³³ DXR measurements are highly correlated with dual energy x-ray absorptiometry (DEXA) measurements at the hip and forearm, with correlation coefficients of 0.7 and 0.9, respectively.³³

Both hands were measured using the DXR method and the mean was used for the analyses to avoid bias regarding dominant and non-dominant hands and to achieve better precision. Accelerated metacarpal BMD loss was defined as BMD loss of >3 mg/cm²/year, equal to standard error of the DXR technique.³⁴

Demographic variables

Demographic variables, including age, sex, weight, length, smoking status and the use of hormone replacement therapy (HRT), bisphosphonates, and calcium and vitamin D supplements were collected by standardised questionnaires.

hsCRP measurement

hsCRP was measured in serum using an ultrasensitive immunonephelometry method on a BNA Behring nephelometer (N latex CRP mono; Behringwerke AG, Marburg, Germany).

Statistical analysis

Analyses were performed using SPSS, version 17 (SPSS, Chicago, Illinois, USA) and Stata, version 8.0 (Stata, College station, Texas, USA). The association between BMD loss and progressive hand OA were tested by Mann-Whitney and chi-squared tests. The p-values derived by multiple comparison tests were corrected by the step-down Bonferroni-Holmes adjustment. To determine the independent associations between BMD loss and progressive hand OA, multivariable logistic regression analyses were performed adjusted for age, sex, postmenopausal status, body mass index (BMI), family effect, smoking status, use of HRT, bisphosphonates, calcium and vitamin D supplements and BMD scores at baseline.

Odds ratios (ORs) and corresponding 95% confidence intervals (95%CI) were transformed to relative risks (RR) with 95%CI using the approximation formula described by Zhang and Yu, since ORs for common outcomes in a fixed cohort are not good approximations of RRs.³⁵

RESULTS

Patient characteristics

In 17 of the 210 patients eligible for the present study, 2-year hand radiographs were missing. In addition, of 12 patients baseline or 2-year BMD could not be analysed due to improper positioning of the hands and artifacts in regions of interest. Hence, 181 patients were included in the present study. There were no significant differences in baseline characteristics between the 181 patients included in the current study and the 29 patients who were not included (data not shown).

Baseline demographic, OA and osteoporosis related characteristics are shown in table 1. The mean age was 60 years and 80% were women, of which the majority were postmenopausal. At baseline, 123 patients (68%) had hand OA, defined as at least two

hand joints with KL ≥ 2 . The mean (SD) metacarpal BMD was 0.57 (0.07) g/cm². Patients with non-progressive hand OA during the 2-year study period were significantly older and more often postmenopausal at baseline than patients with no hand OA and progressive hand OA (table 1). Patients with no hand OA during the study period had significantly higher metacarpal BMD at baseline than patients with hand OA. There were no other significant differences in baseline characteristics between patients with no hand OA and non-progressive hand OA and progressive hand OA (table 1).

Changes in hand OA and BMD after 2 years

Of the 123 patients with hand OA at baseline, 39 patients (32%) had progressive hand OA, defined as at least 1 point increase in total osteophyte and JSN score over 2 years, while 84 patients (68%) had non-progressive hand OA. Of the women, 31 (31%) had progressive hand OA compared to 8 men (35%) (p=0.918).

In the total population, the median (IQR) metacarpal BMD change after 2 years was -9.9 (-17.6 to -3.1) mg/cm² which was -1.7% (-3.2% to -0.6%) of baseline BMD. On the individual level, 114 (63%) of the 181 patients had accelerated BMD loss, that is more than -6 mg/cm² over 2 years. Women had more BMD loss than men (table 2).

Progressive versus non-progressive versus no hand OA and BMD loss

Cumulative probability plots are shown in figure 1 categorised for no hand OA and non-progressive hand OA and progressive hand OA over 2 years. Patients with progressive

Table 1. Demographic, osteoarthritis (OA) and osteoporosis related baseline characteristics of the total study population and patients with no, non-progressive and progressive hand OA during the 2-year study period.

	Study population (n=181)	No hand OA (n=58)	Non-progressive hand OA (n=84)	Progressive hand OA (n=39)	Overall p-value
Demographic and OA related					
Age, years, mean (SD)	60 (7)	59 (7)	62 (7)	58 (6)	0.001
Women, no. (%)	145 (80)	45 (78)	69 (82)	31 (79)	0.8
Postmenopausal, no. (%)	133 (92)	38 (84)	69 (100)	26 (84)	0.003
BMI, kg/m ² , mean (SD)	27 (4)	27 (4)	26 (3)	26 (3)	0.2
Current smokers, no. (%)	33 (18)	14 (24)	15 (18)	4 (10)	0.2
hsCRP, mg/l, median (IQR)	1.8 (1.1-4.4)	2.0 (1.1-5.0)	1.7 (1.0-3.9)	1.8 (1.0-4.0)	0.4
Hand OA, no. (%)	123 (68)				
Osteoporosis related					
Metacarpal BMD, mean (SD)	0.57 (0.07)	0.60 (0.06)	0.58 (0.08)	0.57 (0.06)	0.027
HRT use, no. (%)	25 (14)	9 (20)	11 (16)	5 (16)	0.8
Bisphosphonates, no. (%)	6 (3)	2 (4)	3 (4)	1 (3)	1.0
Calcium supplements, no. (%)	5 (3)	2 (4)	3 (4)	0	0.5
Vitamin D supplements, no. (%)	3 (2)	0	2 (2)	1 (3)	0.5

Abbreviations: BMI: body mass index; BMD: bone mineral density; hsCRP: high sensitive C-reactive protein; HRT: hormone replacement therapy.

hand OA had higher BMD loss over 2 years than patients with non-progressive hand OA and patients without hand OA (table 3). There were no significant differences in BMD loss over 2 years between patients with non-progressive hand OA and no hand OA (table 3). Accelerated BMD loss occurred in 31/39 patients (79%) with progressive hand OA compared to 50/84 patients (60%) with non-progressive hand OA and 33/58 patients (57%) with no hand OA (table 4). In multivariable analysis, accelerated BMD loss was independently associated with progressive hand OA compared to non-progressive hand OA over 2 years with a RR (95%CI) of 2.1 (1.1 to 4.3) (table 4). This association with BMD loss concerned both osteophyte and JSN progression equally over 2 years (data not shown). Accelerated BMD loss was also independently associated

Table 2. Median (IQR) changes in metacarpal bone mineral density (BMD) and number (%) of patients with accelerated BMD loss in the total population and in women and men separately over 2 years.

	Total population (n=181)	Women (n=145)	Men (n=36)	p-value
BMD change, mg/cm ²	-9.9 (-17.6 to -3.1)	-10.0 (-18.4 to -3.9)	-6.9 (-11.9 to -0.4)	0.029
BMD change, % baseline BMD	-1.7 (-3.2 to -0.6)	-3.4 (-1.9 to -0.7)	-1.1 (-2.0 to -0.1)	0.009
Accelerated BMD loss	114 (63)	94 (65)	20 (56)	0.302

Accelerated BMD loss is defined as more than -6 mg/cm²

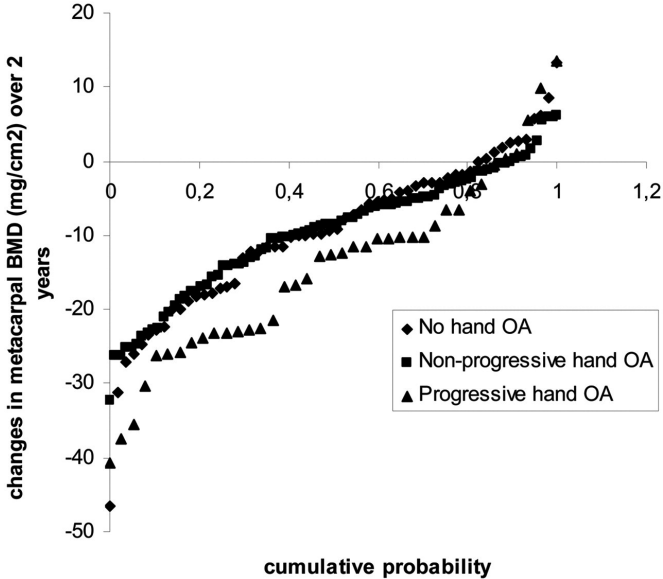


Figure 1. Cumulative probability for no hand osteoarthritis (OA) and non-progressive and progressive hand OA over 2 years with changes in bone mineral density (BMD), in mg/cm², on the y-axis.

Table 3. Median (IQR) changes in metacarpal bone mineral density (BMD) in patients with progressive hand osteoarthritis (OA), non-progressive hand OA and no hand OA over 2 years.

	Progressive hand OA group 1 (n=39)	Non-progressive hand OA group 2 (n=84)	No hand OA group 3 (n=58)
BMD change, mg/cm ²	-12.6 (-23.3 to -6.5)	-8.5 (-15.1 to -3.2)	-9.2 (-17.4 to -2.2)
p-value overall		0.025	
p-value 1 vs 2*		0.033	
p-value 1 vs 3*		0.040	
p-value 2 vs 3*		0.858	
BMD change, % baseline BMD	-2.2 (-4.1 to -1.4)	-1.4 (-2.9 to -0.6)	-1.4 (-3.1 to -0.4)
p-value overall		0.032	
p-value 1 vs 2*		0.045	
p-value 1 vs 3*		0.042	
p-value 2 vs 3*		0.604	

*p-values are corrected for multiple testing by the step-down Bonferroni-Holmes adjustment.

Table 4. Associations between progressive hand osteoarthritis (OA), non-progressive hand OA and no hand OA and accelerated metacarpal bone mineral density (BMD) loss over 2 years.

	Progressive hand OA	Non-progressive hand OA	p-value	Crude RR (95% CI)	Adjusted RR (95% CI)*
Accelerated BMD loss	31	50	0.030	2.0 (1.1 to 4.0)	2.1 (1.1 to 4.3)
Non-accelerated BMD loss	8	34		1	1

	Non-progressive hand OA	No hand OA	p-value	Crude RR (95% CI)	Adjusted RR (95% CI)*
Accelerated BMD loss	50	33	0.755	1.1 (0.8 to 1.3)	0.9 (0.6 to 1.2)
Non-accelerated BMD loss	34	25		1	1

*Adjusted for age, sex, postmenopausal status, BMI, family effect, smoking status, the use of hormone replacement therapy, bisphosphonates, calcium and vitamin D supplements and BMD scores at baseline.

with progressive hand OA over 2 years in comparison with no hand OA (data not shown). There was no association between accelerated BMD and non-progressive hand OA (table 4).

Association between hsCRP at baseline and BMD loss after 2 years

There was no correlation between hsCRP at baseline and metacarpal BMD loss after 2 years (data not shown). Furthermore, at an individual level, patients with high hsCRP at baseline did not have more BMD loss than patients with low hsCRP at baseline (data not shown).

DISCUSSION

As far as we know, this is the first study evaluating localised BMD loss in relation to radiographic progression of hand OA. We have shown that accelerated metacarpal BMD loss is associated with radiographic progression of hand OA over a period of 2 years.

Our results are in line with the data of Sowers et al., who showed that cortical bone loss over 23 years, estimated by a semiobjective method on plain radiographs, was associated with progressive hand OA in female patients.³⁶

There are several explanations for the association between accelerated BMD loss and progressive hand osteoarthritic joint damage in the hands. First, inflammatory activity may drive both processes. Previous studies have suggested that BMD loss is partially a result of circulating inflammatory factors in healthy subjects.¹¹⁻¹⁴ In rheumatoid arthritis, localised hand BMD loss has even been proposed as an outcome measure owing to the predictive value of inflammatory activity.³⁷ The finding that there were no differences in BMD changes over 2 years in patients with non-progressive hand OA compared to patients with no hand OA supports the role of inflammation in active, progressive OA only. However, it is also possible that there are two disease entities, namely, inflammatory and non-inflammatory subtypes of OA. Inflammatory OA might be defined as OA in the presence of subchondral erosions. A small proportion of our population had erosive hand OA (12%).³⁸ Sensitivity analysis showed the same effects in those with and without erosive OA. However, this may be owing to the small number of patients with erosive OA. Subanalyses did not show any association or correlation between hsCRP at baseline and metacarpal BMD loss over 2 years. Unfortunately, we had no data on changes in hsCRP during the study period. In order to unravel the possible inflammatory pathways of OA more research is needed on inflammatory activity in OA.

Second, other pathways driving both bone processes, such as estrogen deficiency, low BMI and familial factors, might explain accelerated BMD loss in patients with progressive hand OA. However, sensitivity analysis adjusted for age, sex, postmenopausal status, BMI, family effects and use of HRT showed unchanged associations and risk estimates.

Third, physical activity or immobility of hands with more severe OA might result in lower localized BMD in these hands. Subanalyses in which we additionally adjusted for functional limitations and pain, measured by the Health Assessment Questionnaire (HAQ) or Australian/Canadian OA Hand Index (AUSCAN), as surrogate for immobility, revealed no changes in associations.

Fourth, data on calcium intake and serum vitamin D levels were missing and therefore their effect on BMD loss and OA progression are unknown. On the other hand, the use of antiresorptive agents (calcium and vitamin D supplement and bisphosphonate use) was very low in the total population and there were no significant differences between the subgroups.

Our study has some limitations. First, since hand OA is a heterogeneous disease with entities varying from mild disease to erosive, destructive hand OA, our conclusions might not be relevant for all entities of hand OA. Second, BMD was measured by DXR. Generally DEXA is considered the gold standard for measuring BMD. However, DXR

and DEXA BMD measurements are highly correlated. Furthermore, DXR can detect changes in BMD with high precision and seems to identify patients with OA with low BMD better than quantitative ultrasound.^{33,34,39} DXR measures bone loss in the metacarpals, enabling assessment of local effects in the hands such as inflammation, without measuring the extra bone formation by osteophytes which can lead to 'false' high BMD measurements. Third, although there was a clear association between hand OA progression and BMD loss, 60% of patients with non-progressive hand OA had accelerated bone loss. This may be owing to the high proportion of females or advanced age of our population or because mild progressive hand OA is not traceable on radiographs with the methods used during the relatively short follow-up period of 2 years. Fourth, the rate of incident hand OA in this study is unknown. Therefore associations between accelerated metacarpal BMD loss and the development of new hand OA during the study period could not be investigated. Fifth, the degree of osteoporosis might have influenced the readers scoring the radiographs for OA. However, at the time of the radiographic assessment the readers were unaware of the objective of this study. And finally, data on physical activity or immobility of the hands were unavailable in our study.

In summary, we showed that accelerated metacarpal BMD loss is associated with progressive hand OA, suggesting that localised BMD loss and radiographic progression of hand OA share common pathophysiological pathways. Further research is needed to understand these mechanisms in order to develop possible therapeutic interventions for OA.

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