Bone mineral density loss in clinically suspect arthralgia is associated with subclinical inflammation and progression to clinical arthritis

Mangnus, L.; Steenbergen, H.W. van; Reijnierse, M.; Kalvesten, J.; Helm-Van Mil, A.H.M. van der

Scandinavian Journal of Rheumatology

ISSN: 0300-9742 (Print) 1502-7732 (Online) Journal homepage: https://www.tandfonline.com/loi/irhe20

Bone mineral density loss in clinically suspect arthralgia is associated with subclinical inflammation and progression to clinical arthritis

L Mangnus, HW van Steenbergen, M Reijnierse, J Kälvesten & AHM van der Helm-Van Mil

To cite this article: L Mangnus, HW van Steenbergen, M Reijnierse, J Kälvesten & AHM van der Helm-Van Mil (2017) Bone mineral density loss in clinically suspect arthralgia is associated with subclinical inflammation and progression to clinical arthritis, Scandinavian Journal of Rheumatology, 46:5, 364-368, DOI: 10.1080/03009742.2017.1299217

To link to this article: https://doi.org/10.1080/03009742.2017.1299217

Bone mineral density loss in clinically suspect arthralgia is associated with subclinical inflammation and progression to clinical arthritis

L Mangnus[1], HW van Steenbergen[1], M Reijnierse[2], J Kälvesten[3,4,5], AHM van der Helm-Van Mil[1]

[1]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands
[2]Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands
[3]Sectra AB, Linköping, Sweden
[4]Department of Medicine and Health Sciences, Section of Radiological Sciences. Faculty of Health Sciences, Linköping, Sweden
[5]Center for Medical Image Science and Visualization (CMIV), Linköping University, Linköping, Sweden

Objective: Peripheral bone mineral density (BMD) may be decreased in early rheumatoid arthritis (RA) but it is unknown whether BMD loss emerges before arthritis is clinically apparent. We aimed to study whether BMD loss occurs in patients with clinically suspect arthralgia (CSA), and whether it is associated with progression to clinical arthritis and magnetic resonance imaging (MRI)-detected subclinical inflammation.

Method: Patients with CSA had arthralgia for <1 year and were at risk of progressing to RA according to their rheumatologists. At baseline, a 1.5 T MRI was performed of unilateral metacarpophalangeal, wrist, and metatarsophalangeal joints, and scored on synovitis, bone marrow oedema, and tenosynovitis;. summing these features yielded the total MRI inflammation score. Digital X-ray radiogrammetry (DXR) was used to estimate BMD on two sequential conventional hand radiographs (mean interval between radiographs 4.4 months). The change in BMD was studied; BMD loss was defined as a decrease of ≥2.5 mg/cm^2/month. Patients were followed for arthritis development for a median of 18.4 months.

Results: In CSA patients (n = 108), change in BMD was negatively associated with age ($\beta = -0.03$, $p = 0.007$). BMD loss in CSA patients was associated with arthritis development [adjusted for age hazard ratio (HR) = 6.1, 95% confidence interval (CI) 1.7 to 21.4] and was most frequently estimated in the months before clinical arthritis development. The total MRI inflammation scores were associated with the change in BMD (adjusted for age $\beta = -0.05$, $p = 0.047$). The total MRI inflammation score and BMD loss were both independently associated with arthritis development (HR = 1.1, 95% CI 1.1 to 1.2, and HR = 4.6, 95% CI 1.2 to 17.2, respectively).

Conclusion: In CSA patients, severe BMD loss is associated with MRI-detectable subclinical inflammation and with progression to clinical arthritis.

Processes that underlie the development of rheumatoid arthritis (RA) are already active in the symptomatic phase before arthritis is clinically evident. In this phase, pro-inflammatory cytokines may be elevated, and auto-antibodies and subclinical inflammation may be present (1, 2). Whether bone metabolism is changed in the phase preceding clinical arthritis is less clear, but it has previously been reported that several biomarkers of bone and cartilage metabolism (cartilage oligomeric matrix protein, N-terminal telopeptide of type I procollagen, and osteoprotegerin) were altered (3, 4).

Lukas Mangnus, Department of Rheumatology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, the Netherlands. E-mail: l.mangnus@lumc.nl

Accepted 21 February 2017

Bone mineral density (BMD) loss of the hands (metacarpal bones II–IV) can be estimated with digital X-ray radiogrammetry (DXR) (5). Previous studies revealed that the association of radiographic progression with BMD estimated by DXR is stronger than that of BMD measured by dual-energy X-ray absorptiometry (DEXA) of periarticular metacarpal bones (6). BMD loss has been associated not only with radiographic progression in early RA (7), but also with RA development in patients presenting with undifferentiated arthritis (8).

Clinically suspect arthralgia (CSA) patients have no clinical arthritis and are at risk of progressing towards RA according to the rheumatologist (2, 10). This study aimed to address whether BMD loss is present in CSA and, if so, whether BMD loss is preferentially present in CSA patients who progress to clinically detectable arthritis. As MRI-detected subclinical inflammation in CSA has been strongly

DOI:10.1080/03009742.2017.1299217

associated with progression to RA (2, 11), the study also explored whether subclinical inflammation is associated with a decrease in BMD.

Method

Patients

Patients were included in the Leiden Clinically Suspect Arthralgia (CSA) cohort between April 2012 and August 2014. As described previously (10), this inception cohort was set up to study the symptomatic phase of RA before clinical arthritis emerges. Inclusion criteria were the presence of arthralgia of small joints for <1 year and an increased risk of progressing to RA according to the clinical expertise of the rheumatologists (2, 10). Patients were not included when clinically detectable arthritis was present or when another explanation for arthralgia was more likely. Patients had a visit at baseline and after 4, 12, and 24 months. If indicated, patients were seen in between visits to evaluate arthritis development. At all scheduled visits, a physical examination was performed, radiographs were made, and blood samples were obtained. MRI was performed at the baseline visit. Follow-up ended at 24 months, or earlier when clinical arthritis had developed. This outcome was verified in the medical files until 24 December 2014. The medical ethics committee of the Leiden University Medical Center approved this study. All patients provided written informed consent.

Digital X-ray radiogrammetry

Radiographs of both hands, taken in the posteroanterior position (at baseline and the first consecutive visit), were used to estimate BMD with DXR. In brief, DXR is an automated analysis of the cortical bone at the centres of metacarpal bones II–IV; this technique has been described in detail previously (5). The mean BMD change of both hands was calculated as the difference per month between the first two radiographs (mg/cm^2/month), as described previously (8, 9). BMD change was analysed as a continuous measure and was dichotomized, with a decrease in BMD of ≥2.5 mg/cm^2/month defined as BMD loss (8, 9).

MRI and scoring

At baseline, contrast-enhanced magnetic resonance images were made of unilateral metacarpophalangeal (MCP) 2–5 joints, wrist joints, and metatarsophalangeal (MTP) 1–5 joints, as described earlier (10). A detailed scan protocol is provided in the Supplementary methods. The more painful side was scanned or, in cases of equally severe symptoms on both sides, the dominant side. An ONI MSK extreme 1.5T extremity MRI scanner (GE, Wisconsin, USA) was used.

Inflammation [synovitis, bone marrow oedema (BMO) and tenosynovitis] was scored according to the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system (RAMRIS) (13, 14). Synovitis and BMO were scored in MCP, wrist, and MTP joints, and tenosynovitis was scored in the MCP and wrist joints. The total MRI inflammation score was calculated by summing the BMO, synovitis, and tenosynovitis scores of all scored joints. The mean MRI scores, performed by two trained independent readers (HWvS and LM) blinded for any clinical data, were used. For the total MRI inflammation score, the within-reader intraclass correlation coefficient (ICC) was 0.98 and 0.99, and the between-reader ICC was 0.96.

Analyses

The unpaired t-test, Mann–Whitney U test, and chi-squared test were used as appropriate. Univariable and multivariable linear regression models were used to study associations between inflammation and BMD change. Univariable and multivariable Cox proportional hazard regression analyses were used to determine associations with arthritis development. To prevent overfitting of the data, the multivariable Cox regression contained only age as an adjustment factor. Data were analysed using IBM SPSS statistics version 20 (IBM Corp., Armonk, NY, USA).

Results

Patients

In total, 162 patients were consecutively included in the CSA cohort. Of these, 116 patients had conventional radiographs taken at baseline and follow-up (mean time interval 4.4 months ± SD 1.3 months). Radiographs of eight patients could not be studied by DXR owing to different acquisition settings of the radiographs when the images were taken. Therefore, DXR results were obtained from 108 CSA patients in total. The 108 CSA patients who were studied and the 54 CSA patients who were excluded did not differ in their baseline characteristics (Table 1). The median follow-up of the studied patients was 18.6 months (interquartile range 14.4–25.0 months).

BMD change and age

A higher age was associated with a larger decrease in BMD (β = −0.03, p = 0.007) (Figure 1A). No statistically significant difference in BMD change was observed between genders (mean females = −0.18, males = 0.003, p = 0.60), rheumatoid factor (RF) status (mean RF-positive = −0.89, RF-negative = −0.079, p = 0.06), and anti-citrullinated protein antibody (ACPA) status (median ACPA-positive = −0.23, ACPA-negative = −0.09, p = 0.58).

Table 1. Baseline characteristics of included and excluded clinically suspect arthralgia (CSA) patients.

	CSA patients analysed (n = 108)	CSA patients excluded (n = 54)	p
Age (years), mean ± SD	44.5 ± 12.9	40.4 ± 12.3	0.057
Female, n (%)	81 (75)	39 (72)	0.70
TJC, median (IQR)*	5.0 (3.0–10.0)	5.5 (3.0–8.0)	0.92
CRP, median (IQR)	0.0 (0.0–4.6)	0.0 (0.0–4.3)	0.98
RF positive, n (%)	24 (22)	13 (24)	0.79
ACPA positive, n (%)	14 (13)	12 (22)	0.13
Total MRI inflammation, median (IQR)	2.0 (1.0–5.5)	2.0 (0.5–4.9)	0.43
Total synovitis score, median (IQR)	1.0 (0.0–2.5)	1.0 (0.0–2.8)	0.67
Total BMO score, median (IQR)	0.5 (0.0–1.5)	1.0 (0.0–1.5)	0.81
Total tenosynovitis score, median (IQR)	0.0 (0.0–2.0)	0.0 (0.0–1.0)	0.33

TJC, tender joint count; IQR, interquartile range; CRP, C-reactive protein; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody; MRI, magnetic resonance imaging; BMO, bone marrow oedema.

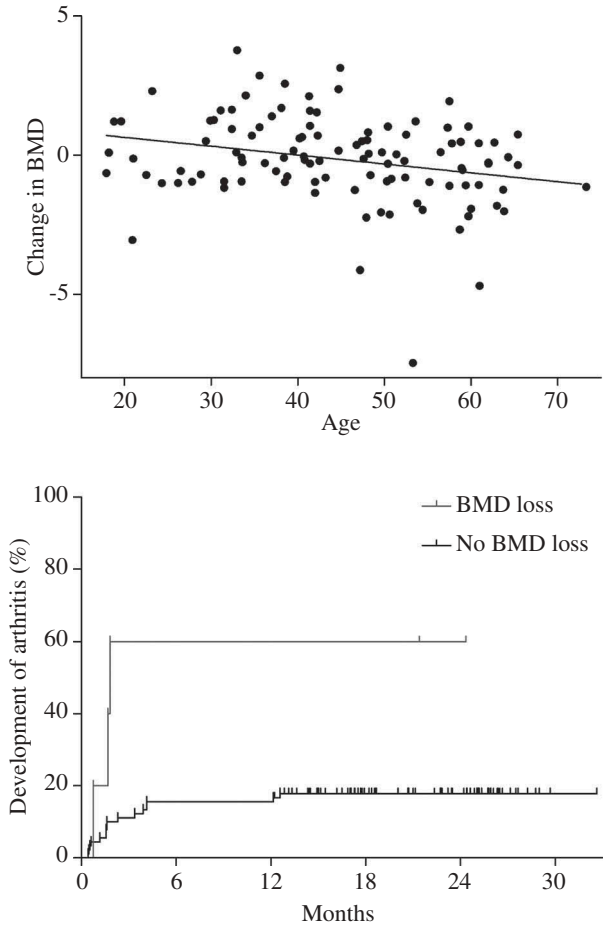

Figure 1. (A) Association between age and bone mineral density (BMD) decrease, and (B) the development of clinical arthritis in clinically suspect arthralgia (CSA) patients with and without increased BMD loss.

(A) The correlation coefficient of age with BMD loss was −0.03 (p = 0.007). (B) BMD loss was defined as a decrease in BMD of ≥2.5 mg/cm^2/month. The upward increase of the line indicates that patients had progressed to clinical arthritis. The vertical marks on the line indicate that a patient was censored, which indicates wich indicates the end of follow-up of that patient.

MRI-detected inflammation and BMD decrease

The total MRI inflammation score at baseline was associated with BMD decrease during the first months of follow-up (β = −0.07, p = 0.018) (Table 2); β = −0.07 indicates that for each point increase in total MRI inflammation, the BMD decreased by 0.07 mg/cm^2/month. The association remained after adjustment for age (β = −0.05, p = 0.047). Studying the MRI-detected inflammatory features separately revealed that synovitis and tenosynovitis scores were associated with BMD loss (β = −0.18, p = 0.008 and β = −0.19, p = 0.006, respectively), in contrast to the BMO score (β = −0.03, p = 0.63).

The association between BMD loss in one hand and MRI inflammation of the metacarpal bones of the same metacarpals was studied in a subanalysis (Supplementary Figure S1). This analysis revealed similar results to those presented above (see Supplementary Table S1).

BMD loss and progression to clinical arthritis

Twenty (19%) CSA patients developed clinically apparent arthritis after a median interval of 1.7 months (range 0.4–15.0 months), and 15 of these fulfilled the 1987 criteria for RA. BMD loss was present in five (4.6%) of the CSA patients, of whom three developed arthritis. BMD loss was more often present in CSA patients who progressed to clinically apparent arthritis than in CSA patients who did not progress [hazard ratio (HR) = 4.94, 95% confidence interval (CI) 1.44 to 16.97] (Figure 1B). After adjustment for age, the HR of BMD loss was 6.01 (95% CI 1.72 to 21.38) (Table 3). Furthermore, the association of BMD loss and arthritis development was independent of MRI inflammation (HR = 4.62, 95% CI 1.24 to 17.20) (Table 3).

Six patients converted to clinical arthritis 1 month after inclusion in the CSA cohort and these patients had the

Table 2. Association between magnetic resonance imaging (MRI)-detected inflammation at baseline and bone mineral density (BMD) decrease.

BMD		
	β (95% CI)	p
Univariable		
Total MRI inflammation score*	−0.07 (−0.12 to −0.01)	0.018
Total BMO score	−0.03 (−0.16 to 0.10)	0.63
Total synovitis score	−0.18 (−0.32 to −0.05)	0.008
Total tenosynovitis score	−0.19 (−0.32 to −0.05)	0.006
Multivariable		
Age	−0.03 (−0.05 to −0.01)	0.015
Total MRI inflammation score*	−0.05 (−0.11 to 0.00)	0.047

BMO, bone marrow oedema.
*The sum of all scored synovitis, BMO, and tenosynovitis in one hand and foot.

second radiograph taken 2–3 months after arthritis development. A sensitivity analysis excluding these patients revealed similar results (Supplementary Table S2).

Discussion

Studying patients with arthralgia at risk for RA can increase the understanding of the processes that are active in the earliest symptomatic phase of RA. In this light, this study evaluated BMD loss, estimated at the metacarpals using DXR. We observed that BMD loss was present in CSA, that BMD loss was more often present in the CSA patients who progressed to arthritis than in patients who did not progress, and that MRI-detected subclinical inflammation was associated with a decrease in BMD.

BMD loss was mostly estimated using radiographs taken in the months preceding the development of clinical arthritis. Therefore, our study mainly evaluated the last preclinical phase and does not allow conclusions on the presence of bone loss in earlier, asymptomatic, preclinical phases.

We showed that MRI-detected subclinical inflammation was associated with a decrease in BMD and that BMD loss was associated with arthritis development. A multivariable analysis showed that MRI-detected inflammation and BMD loss were both independently associated with progression to clinical arthritis, suggesting that both are markers of processes that are active in a very early phase of RA.

This study is the first to assess BMD loss in CSA patients. Only some of the CSA patients progressed to arthritis and most patients did not progress. This explains why the average decrease in BMD observed in this study is lower than previously reported in RA (8, 9,15).

The cut-off value for BMD loss that we used was suggested by the manufacturer and based on data from studies in RA; age was not included in this cut-off. A very recent study assessed variation in BMD in the general population and established age- and gender-adjusted reference values (14). Applying these cut-off values revealed that 46% (n = 50) of the CSA patients had BMD loss, but that BMD loss was equally present in CSA patients who did not progress to arthritis and in those who did progress (HR 0.99 (95% CI 0.41 to 2.38, p = 0.98). Hence, this did not increase the discriminative ability in the present population.

The most important limitation of this study is the sample size. A small proportion of patients progressed to clinical arthritis during the follow-up period and BMD loss was also infrequent. Further studies are therefore needed to confirm the present findings.

Table 3. Association between bone mineral density (BMD) loss and progression from clinically suspect arthralgia (CSA) to clinical arthritis in univariable and multivariable Cox regression analyses.

	HR (95% CI)	p
Univariable		
BMD loss*	4.94 (1.44 to 16.97)	0.011
Multivariable		
Model A		
BMD loss*	6.07 (1.72 to 21.38)	0.005
Age	0.97 (0.94 to 1.00)	0.076
Model B		
BMD loss*	4.62 (1.24 to 17.20)	0.023
Age	0.96 (0.93 to 0.99)	0.016
Total MRI inflammation score	1.12 (1.05 to 1.19)	<0.001

HR, hazard ratio; CI, confidence interval; MRI, magnetic resonance imaging.
*Defined as a decrease of ≥2.5 mg/cm^2/month.

Conclusion

Severe BMD loss is increased in CSA patients progressing to clinical arthritis and is associated with MRI-detectable subclinical inflammation.

Acknowledgements

The research leading to these results was funded by a Vidi grant from the Netherlands Organisation for Scientific Research, a grant from the Dutch Arthritis Foundation, and the EU euroTEAM.

References

1. van Steenbergen HW, Huizinga TW, van der Helm-Van Mil AH. The preclinical phase of rheumatoid arthritis: what is acknowledged and what needs to be assessed? Arthritis Rheum 2013;65:2219–32.
2. van Steenbergen HW, Mangnus L, Reijnierse M, Huizinga TW, van der Helm-Van Mil AH. Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis. Ann Rheum Dis 2016;75:1824–30.

3. Turesson C, Bergström U, Jacobsson LTH, Truedsson L, Berglund G, Saxne T. Increased cartilage turnover and circulating autoantibodies in different subsets before the clinical onset of rheumatoid arthritis. Ann Rheum Dis 2011;70:520–2.
4. Schaardenburg D, van, Nielen MMJ, Lems WF, Twisk JWR, Reesink HW, Stadt RJ, et al. Bone metabolism is altered in preclinical rheumatoid arthritis. Ann Rheum Dis 2011;70:1173–4.
5. Rosholm A, Hyldstrup L, Backsgaard L, Grunkin M, Thodberg HH. Estimation of bone mineral density by digital X-ray radiogrammetry: theoretical background and clinical testing. Osteoporos Int 2001;12:961–9.
6. Jensen T, Hansen M, Jensen KE, Pødenphant J, Hansen TM, Hyldstrup L. Comparison of dual X-ray absorptiometry (DXA), digital X-ray radiogrammetry (DXR), and conventional radiographs in the evaluation of osteoporosis and bone erosions in patients with rheumatoid arthritis. Scand J Rheumatol 2005;34:27–33.
7. Forslind K, Kälvesten J, Hafström I, Svensson B. Does digital X-ray radiogrammetry have a role in identifying patients at increased risk for joint destruction in early rheumatoid arthritis? Arthritis Res Ther 2012;14:R219.
8. de Rooy DP, Kälvesten J, Huizinga TW, van der Helm-Van Mil AH. Loss of metacarpal bone density predicts RA development in recent-onset arthritis. Rheumatology (Oxford) 2012;51:1037–41.
9. van Steenbergen HW, van der Helm-Van Mil AH. Clinical expertise and its accuracy in differentiating arthralgia patients at risk for rheumatoid arthritis from other patients presenting with joint symptoms. Rheumatology (Oxford) 2016;55:1140–1.
10. Østergaard M, Edmonds J, McQueen F, Peterfy C, Lassere M, Ejbjerg B, et al. An introduction to the EULAR–OMERACT rheumatoid arthritis MRI reference image atlas. Ann Rheum Dis 2005;64:i3–7.
11. Haavardsholm EA, Østergaard M, Ejbjerg BJ, Kvan NP, Kvien TK. Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study. Ann Rheum Dis 2007;66:1216–20.
12. van Steenbergen HW, Van Nies JA, Huizinga TW, Bloem JL, Reijnierse M, van der Helm-Van Mil AH. Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI. Ann Rheum Dis 2015;74:1225–32.
13. Bøyesen P, Hoff M, Ødegård S, Haugeberg G, Syversen SW, Gaarder PI, et al. Antibodies to cyclic citrullinated protein and erythrocyte sedimentation rate predict hand bone loss in patients with rheumatoid arthritis of short duration: a longitudinal study. Arthritis Res Ther 2009;11:R103.
14. Ørnbjerg LM, Østergaard M, Jensen T, Hyldstrup L, Bach-Mortensen P, Bøyesen P, et al. Establishment of age- and sex-adjusted reference data for hand bone mass and investigation of hand bone loss in patients with rheumatoid arthritis treated in clinical practice: an observational study from the DANBIO registry and the Copenhagen Osteoarthritis Study. Arthritis Res Ther 2016;18:53.

Supporting information

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1. Baseline characteristics of included and excluded CSA patients.
Supplementary Table S2. A sensitivity analysis.
Supplementary Figure S1. The association between BMD loss in one hand and MRI inflammation of metacarpal bones of the same metacarpals.
Supplementary Method.

Please note that the editors are not responsible for the content or functionality of any supplementary material supplied by the authors. Any queries should be directed to the corresponding author.