

Original article

Periarticular osteoporosis: a useful feature in the diagnosis of early rheumatoid arthritis? Reliability and validity in a cross-sectional diagnostic study using dual-energy X-ray absorptiometry

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Abstract

Objectives. To identify regions of interest (ROIs) relevant to periarticular osteoporosis in RA with low precision error and sufficient inter-rater reliability and to test diagnostic validity for RA.

Methods. Periarticular BMD was measured using dual-energy X-ray absorptiometry (DXA). Five ROIs were defined around MCP and/or PIP joints II–V, II–IV and mid-metacarpal to mid-phalangeal. They were evaluated for precision using the root mean square coefficient of variation (RMS-CV) and the intra-class correlation coefficient (ICC) for inter-reader reliability. To test validity, established RA patients ($n=25$) and early arthritis patients ($n=25$) were compared with healthy controls ($n=37$) matched on sex, age and menopausal status using paired *t*-tests, ROC curves and scatterplots.

Results. The RMS-CV was 0.45–1.07%. The ICC was 0.99. Mean BMDs of the five ROIs ranged from 0.321 to 0.372 g/cm² in established RA, from 0.321 to 0.382 g/cm² in early arthritis and from 0.342 to 0.401 g/cm² in healthy controls. Mean differences ranged from 0.012 to 0.032 g/cm² for established RA and from 0.023 to 0.033 g/cm² for early arthritis patients compared with matched controls, with $P < 0.05$ for ROIs 1–5 in early arthritis and the whole hand in established RA. ROC curves indicated low discriminative power, with an area under the curve (AUC) of 0.61–0.64, and scatterplots showed great overlap between BMD values of patients and controls.

Conclusions. Periarticular BMD measured with DXA seems not to be a useful diagnostic feature due to strong overlap of BMD values between healthy controls, established RA patients and early arthritis patients.

Key words: Rheumatoid arthritis, Bone, Epidemiology, Diagnostic imaging, Study design.

Introduction

Due to new drugs and tightly controlled medication strategies, patients have better disease outcome, especially if

treated in the early stages of the disease [1, 2]. The need for early identification of RA is recognized worldwide and resulted recently in new ACR/EULAR criteria for the classification of RA [3]. This new criteria set contains the domains joints, serology, disease duration and acute-phase reactants. Patients are classified as RA if their total score is ≥ 6 points out of 10. The classification criteria perform well as diagnostic criteria in early arthritis [4]. Despite the improved criteria set, diagnostic uncertainty can still remain in patients scoring < 6 points on the new criteria set.

To decrease the diagnostic uncertainty, there is a need for easy applicable and cheap imaging techniques. Early bone and cartilage changes, features of RA, could have

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Submitted 16 September 2010; revised version accepted 18 July 2011.

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added value in the diagnostic process. Currently, these are depicted using conventional radiography, a valid and reliable method but insensitive for early bone and cartilage changes [5]. An early feature of the disease is thought to be periarticular osteoporosis [6, 7]. It can be estimated using DXR, quantitative US, CT and dual-energy X-ray absorptiometry (DXA) [8]. DXA is regarded as the reference method in generalized osteoporosis [8]. It is a valid and reliable method to measure BMD and it is cheap and has low radiation doses making it a good candidate to reduce diagnostic uncertainty in patients at risk for RA.

One of the difficulties using DXA for measuring periarticular BMD is the definition of the region of interest (ROI). It is hypothesized that the areas closest to the joint surface are more prone to BMD loss early in the disease. Previous studies tried to measure BMD in very small areas just below the joint surface, but this resulted in large measurement error [6, 9–13]. BMD measured by DXA is sensitive to surface size because it is determined by bone mineral content per squared surface measure (square centimetres). With a smaller surface the impact of repositioning the hand is larger, and therefore bigger differences in BMD values occur when repeating the same measurement in a patient. To solve this, one could use a larger area like the whole hand surface, but the effect of localized periarticular osteoporosis will be diluted.

In this study, we aim to increase precision without losing the benefit of small ROIs. We, therefore, aim to (i) identify periarticular ROIs relevant to RA with a low precision error and sufficient inter-rater reliability; and (ii) to test the validity of these ROIs first by comparing extreme groups, i.e. healthy controls with patients with established RA, and secondly by comparing healthy controls with patients with early arthritis who can be regarded as patients who potentially have RA.

Methods

Precision/reliability

Precision and inter-reader reliability were assessed before using DXA in our patient sample. Five healthy adults were measured seven times to calculate the short-term precision [14]. The hand was repositioned for each measurement. To calculate the short-term precision of all ROIs and the whole hand, the formula for the root mean square coefficient of variation (RMS-CV) was used:

$$\sqrt{(\Sigma(CV^2))/\text{number of persons}}$$

To determine the inter-rater reliability, 20 patients were analysed on separate occasions by two readers (C.A. and W.J.vO.). The intra-class correlation coefficient (ICC; two way, agreement) was used to estimate inter-reader reliability of the ROIs and the whole hand measurement [15, 16].

Validity

Design

A cross-sectional, matched, case-control study was set up to assess the BMD values of periarticular regions of the hands in three groups: healthy controls, established RA and early arthritis patients. This design allowed both an extreme group comparison (healthy vs established RA) as well as evaluation among patients who would undergo the test in practice (early arthritis). If BMD values overlap in the extreme group comparison, the difference would probably not be large enough to use in daily practice where groups are not extreme. Also, an evaluation whether test results can be used to identify those with and without the target disease in practice can be done by testing in a group representative of those in whom the test will be applied. This is called a Phase 1 and Phase 2 diagnostic study; the first step to evaluate the discriminative properties of a test. It could provide data to merit the more elaborate and expensive Phase 3 diagnostic study, where the test is applied to a larger cohort of those patients that would be tested in practice [17].

Patients

Patients with established RA and a scheduled appointment in the rheumatology outpatient clinic were recruited between September 2006 and January 2008. Established RA was defined as patients with RA according to the 1987 ACR criteria existing for >1 year. This patient group was considered the extreme group for the extreme group comparison. For the evaluation of the test in those patients in whom it might be used in practice, early arthritis patients were recruited via the Rotterdam Early Arthritis CoHort (REACH) between September 2006 and October 2008. This ongoing, prospective, inception cohort study was set up in the greater Rotterdam area in July 2004. Patients were recruited either via the general practitioner (GP), or via outpatient rheumatology clinics at first consultation. Patients were included if they had at least one swollen joint or two or more joints with either pain or loss of movement with two or more of the following criteria: morning stiffness >1 h; unable to clench a fist in the morning; pain when shaking someone's hand; pins and needles in the fingers; difficulties wearing rings; difficulties wearing shoes; a family history of RA; unexplained fatigue lasting <1 year. Patients were excluded if their symptoms resulted from trauma or overuse, were >12 months, or if they were <16 years. Details of this cohort are reported elsewhere [18]. Early arthritis patients were eligible for current analysis if they had: (i) an intermediate or high probability ($\geq 33\%$) of having persistent disease according to the prediction model of Visser *et al.* [19]; (ii) arthritis of at least one of the hand joints by palpation (wrist, MCP and/or PIP joints); and (iii) were Caucasian. Patients were excluded if they ever had a fracture of the hands, had hip or hand prosthetics, if there was alcohol abuse or if they had comorbidity influencing bone metabolism, such as untreated thyroid disease.

Controls

Healthy controls were recruited to match patients on sex, age and menopausal status. The same exclusion criteria as described for patients were applied to controls. Controls were matched twice if they matched both patients in the established RA and early arthritis groups. For each patient and each control, informed consent (according to the Declaration of Helsinki) was obtained and this study was approved by the Medical Ethical Committee of Erasmus MC, Rotterdam.

Data collection

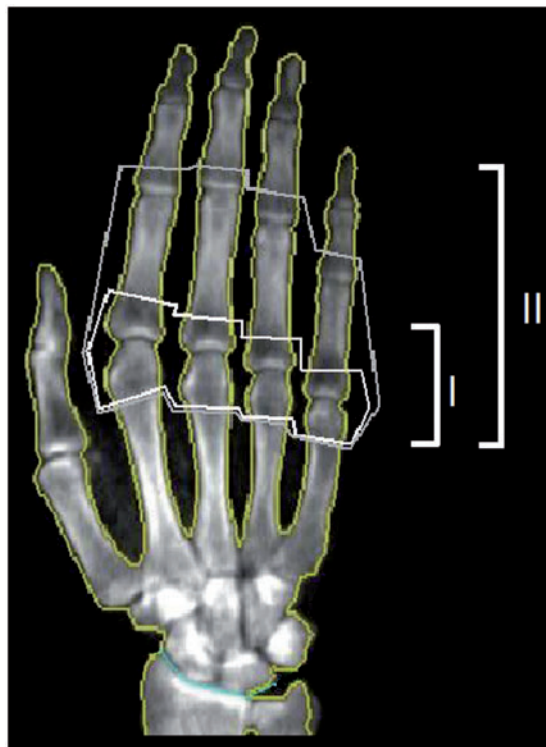
Data on risk factors for generalized osteoporosis was collected using a self-reported questionnaire. The questionnaire included medication, medical history and dietary intake of calcium. BMD of the hand, hip and lower spine were estimated using the Lunar Prodigy for DXA. Disease characteristics of patients were collected using chart data on disease duration, diagnosis, bone erosions, RF and anti-cyclic citrullinated peptide (anti-CCP).

BMD measurements of hand ROIs

The most affected hand of each patient was scanned. In case of equal involvement of both hands or no hand symptoms, the left hand was scanned. Both hands of each control were scanned and in the matched analysis the hand corresponding to the hand of the patient was chosen.

Hand BMD was assessed on the Lunar Prodigy using the hand software. The hand was placed flat on the table, with the fingers joined together. The hand was aligned using a laser light line through the styloid process of the ulna and metacarpal phalanx IV. The hand was scanned once (for 1 min and 3 s with a radiation dose of $2.0\mu\text{Gy}$). The ROIs and the whole hand were then analysed on a single scan. The whole hand analysis was done outlining all bones of the hands including the metacarpalia and excluding the ulna and radius using the standard analysis program in the Lunar Prodigy. ROIs were chosen in the most frequently affected joints in RA in the area close to the joint surface and a surface size sufficiently large to prevent large measurement errors. ROI 1 was drawn manually along the side of the bone from the end of the distal curvature of the proximal phalanx to the end of the proximal curvature of the metacarpal bone for the MCP digits II–V (Fig. 1). ROI 2 was drawn from the end of the distal curvature of the distal phalanx to the end of the proximal curvature of the metacarpal bone for the MCPs until the PIPs of digits II–V (Fig. 1). ROI 3 was drawn identical to ROI 1, but excluded digit V and ROI 4 was drawn identical to ROI 2 excluding digit V. Finally, ROI 5 was drawn alongside the bone from mid-carpal to the middle of the phalanges for MCP II–IV. All analyses for the ROIs were done using the custom analysis program in the Lunar Prodigy. The periarticular areas of ROI 1–4 enclosed the area around the joints and were delineated where the curvature of the cortical bone started.

Fig. 1 ROIs. ROI, shown in white region 1 (I) and in grey region 2 (II). Not shown: region 3–5. Regions 3 and 4 were similar, but included only phalanx II, III and IV, while region 5 included the larger area from mid-phalanx to mid-carpal.



Statistics

Simple descriptive analyses were used to compare characteristics of RA patients, early arthritis patients and the healthy controls. To evaluate patterns in BMD values of patients and controls, scatter plots were made. The paired *t*-test was used to evaluate the matched differences of the mean BMDs between cases and controls. Sensitivity and specificity for the different ROIs were calculated and shown in receiver operating characteristic (ROC) curves.

Results

Reliability

The precision expressed as RMS-CV of the ROIs and the whole hand varied from 0.74 to 1.07% for Reader 1 and from 0.45 to 0.81% for Reader 2. ROI 4 had the lowest RMS-CV in the RMS-CVs of both readers. The inter-reader reliability, as measured with an ICC (two-way agreement), was 0.99 for each of the ROIs and the whole hand measurements.

Validity

Subject characteristics

Twenty-five established RA and 25 early arthritis patients and 37 healthy controls were included. Demographic and

subject characteristics are described in Table 1. The mean age of menarche was 13 years for both patients and controls. Fifteen patients were post-menopausal, eight with established RA and seven with early arthritis. Four patients had thyroid disease, but all were euthyroid.

In the early arthritis group, 52% of the patients were diagnosed as RA ($n = 13$). DMARDs were used by all the established RA patients and 88% ($n = 22$) of the early arthritis patients. Use of steroids, calcium or vitamin D was highest in early arthritis patients, 52, 44 or 44%, respectively. In this group, the exposure to medication (DMARDs, steroids, calcium or vitamin D) was <2 weeks, as they were recruited for this study immediately after diagnosis.

BMD measurements

Unmatched BMD means are given per group for each ROI and the whole hand in Table 2. The mean BMDs of the different ROIs ranged from 0.321 to 0.372 g/cm² in the established RA group, from 0.321 to 0.382 g/cm² in the early arthritis group and from 0.342 to 0.401 g/cm² in the healthy controls. The mean differences for established RA compared with their matched controls ranged from 0.012 to 0.032 g/cm² and were only significant in the

whole hand measurement ($P < 0.05$). In the early arthritis patients, ROIs 1–5 showed significant differences with the matched controls (Table 3). The mean differences ranged from 0.023 to 0.033 g/cm² for these patients with their matched controls.

To illustrate patterns in BMD values of patients and controls, the rough data of ROI 1 were plotted in Fig. 2. The scatter plot showed that the BMD values for patients overlapped those of the controls. The other ROIs and separate plots for established RA and early arthritis showed similar patterns of overlap in values of patients and controls (data not shown).

To evaluate discriminative power of the different ROIs, ROC curves were made. One of the ROC curves is demonstrated in Fig. 3. It indicated low discriminative power, as did all other ROC curves. The corresponding area under the curve (AUC) for these ROC curves varied from 0.61 to 0.64.

Discussion

Despite high measurement precision of the ROIs defined in this study to evaluate periarticular BMD loss in the

TABLE 1 Characteristics of patients and controls

Characteristic	Established RA ($n = 25$)	Early arthritis ($n = 25$)	Controls ($n = 37$)
Age, mean (s.d.), years	53 (13)	52 (12)	52 (12)
Female, %	72	68	68
Height, mean (s.d.), cm	170 (7.6)	170 (8.9)	173 (8.5)
Weight, mean (s.d.), kg	78 (12.2)	74 (16.9)	76 (12.1)
BMI, mean (s.d.)	27 (5.2)	25 (5.5)	25 (2.8)
Thyroid disease, ^a n	0	4	0
Years since menopause, median (range)	11 (1–24) ($n = 8$)	11 (1–19) ($n = 7$)	8 (3–23) ($n = 11$)
Smoking current, %	8	32	13
Smoking past, %	70 (mv = 2)	53 (mv = 8)	53 (mv = 5)
Dietary calcium intake, median (range), mg/week	3770 (154–9901)	3718 (480–7264)	3666 (385–7612)
Disease characteristics			
Diagnosis			
RA, %	100	52	NA
Monoarthritis, %	NA	16	NA
Polyarthritis, %	NA	16	NA
PsA, %	NA	8	NA
SpA (unclassified), %	NA	4	NA
OA, %	NA	4	NA
Current DMARD use, %	100	88 ^b	NA
Current steroid use, %	4 ^b	52 ^b	NA
Current calcium medication, %	4	44 ^b	NA
Current vitamin D use, %	4	44 ^b	NA
Bone erosions, %	52	20	NA
Disease duration, median (range), months	57 (13–258) (mv = 1)	5 (0–18) (mv = 2)	NA
DAS-28, mean (s.d.)	2.79 (1.18) (mv = 4)	3.53 (1.27) (mv = 1)	NA
RF positive, %	56	48	NA
Anti-CCP positive, %	48 (mv = 2)	52	NA
ESR at baseline, median (range)	15 (1–38)	12 (2–75) (mv = 1)	NA
Sharp–van der Heijde score, median (range)	9 (0–92)	4 (0–44)	NA

^aPatients had either been hypothyroid in the past or had had a struma. ^bMedication was no longer than 2 weeks. mv: missing values on this specific item; NA: not applicable.

TABLE 2 BMD—unmatched mean (s.d.)

Region of interest	Established RA (n = 25)	Early arthritis (n = 25)	Controls (n = 37)
ROI 1, g/cm ²	0.321 (0.047)	0.321 (0.058)	0.342 (0.048)
ROI 2, g/cm ²	0.334 (0.044)	0.338 (0.057)	0.353 (0.046)
ROI 3, g/cm ²	0.334 (0.048)	0.334 (0.058)	0.358 (0.050)
ROI 4, g/cm ²	0.347 (0.047)	0.351 (0.058)	0.368 (0.047)
ROI 5, g/cm ²	0.372 (0.051)	0.382 (0.060)	0.401 (0.047)
Whole hand, g/cm ²	0.387 (0.048) (n = 24)	0.392 (0.062)	0.420 (0.050)
Lumbar spine, g/cm ²	0.953 (0.128) ^a	1.171 (0.160)	1.228 (0.146)
Hip, g/cm ²	0.966 (0.141) (n = 24)	0.939 (0.107)	1.003 (0.123) (n = 36)

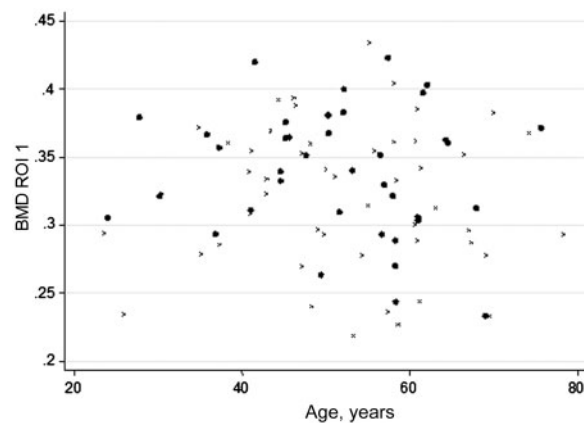
^aOne outlier was removed from the analysis of lumbar spine BMD.

TABLE 3 One sample *t*-test on matched differences between BMD patients and controls

Region of interest	Established RA (n = 25)	Early arthritis (n = 25)
ROI 1, mean diff. (s.d.), g/cm ²	-0.015 (0.061)	-0.028 (0.052)*
ROI 2, mean diff. (s.d.), g/cm ²	-0.012 (0.053)	-0.023 (0.054)*
ROI 3, mean diff. (s.d.), g/cm ²	-0.017 (0.066)	-0.033 (0.060)*
ROI 4, mean diff. (s.d.), g/cm ²	-0.016 (0.060)	-0.024 (0.057)*
ROI 5, mean diff. (s.d.), g/cm ²	-0.022 (0.062)	-0.026 (0.056)*
Whole hand, mean diff. (s.d.), g/cm ²	-0.032 (0.061) § (n = 24)	-0.021 (0.078)

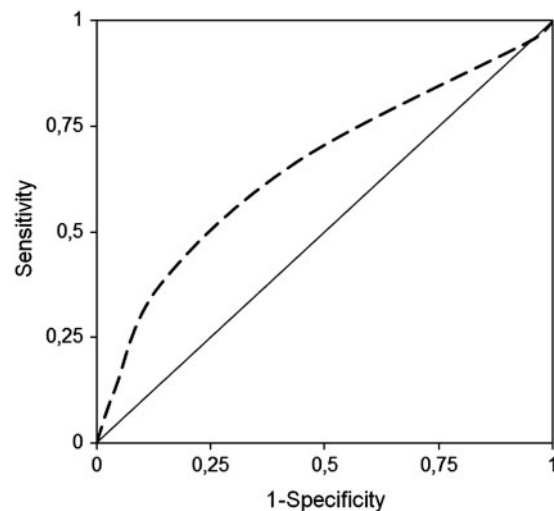
**P* < 0.05.

FIG. 2 Scatterplot of unmatched BMD values of ROI 1 for all patients (X) and controls (●).



hand, we could not demonstrate that unmatched BMD values distinguished between healthy controls and established RA or early arthritis. This means that simple application of hand DXA without correcting for age, sex and post-menopausal status is likely not to improve diagnostic certainty in patients at risk for RA, despite significant differences in periarticular BMD shown in matched analysis.

FIG. 3 ROC curve for ROI 1 in early arthritis (AUC = 0.62).



Previous studies have suggested that a decrease in periarticular BMD could have diagnostic value, based on significant differences between RA patients and healthy controls [6, 9, 20–22]. These studies did not evaluate the diagnostic properties of DXA using a specific cut-off. The average BMD values that were presented suggest that

also in these studies DXA would not discriminate between healthy controls and early arthritis or RA patients if a cut-off had been applied. However, determination of periarticular osteoporosis might still be used as a diagnostic tool. Two longitudinal studies with early arthritis patients who were later on diagnosed with RA showed BMD values at baseline comparable with those of the other diagnostic groups, while over time BMD decreased more rapidly for the patients later on diagnosed with RA compared with the other diagnostic groups [10, 12]. So it might be that the raw BMD value in itself does not have strong discriminatory properties, but its change over time might have.

Measuring early changes in BMD over time requires a very small measurement error to prove that the observed change is larger than the smallest detectable change. DXA is less likely a candidate instrument for this due to its precision error of 1%. Quantitative US (QUS) or digital X-ray radiogrammetry (DXR) might be better candidates, with measurement errors as low as 0.50% for QUS and 0.25% for DXR [23, 24]. Both have shown promising results in regard to predictive value for early diagnosis, with the more promising results for DXR [25, 26]. These small precision errors are sufficiently small to use these techniques in the diagnostic workup for RA if measured twice in a short period, for instance 3 months.

Another possibility of detecting RA early might be by measuring markers of bone damage instead of using imaging techniques. Measurement of the serum Receptor activator of nuclear factor kappa-B ligand/osteoprotegerin (RANKL/OPG) ratio might be a candidate approach. RANKL promotes bone damage through up-regulation of osteoclast formation and is increased in RA [27]. OPG decreases the effect of RANKL, but is down-regulated in RA. The RANKL/OPG ratio provides information on the severity of RA and on bone damage. It has shown promising results in predicting development of bone damage [28]. Therefore, measurement of serum RANKL/OPG ratio might also be valuable as a diagnostic tool for RA and it might also inform us on disease severity at the moment of diagnosis.

This study has certain strengths and weaknesses. Its strength is first that we included established RA as well as early arthritis patients, enabling us to evaluate BMD loss in an extreme group as well as patients who are likely to undergo the test in practice. This last patient set allows evaluation of BMD in a group including not only patients with RA but also those with arthritis due to other causes. This is an important step in the evaluation of a diagnostic test [17]. Secondly, we were able to reduce the precision error by creating sufficiently large periarticular ROIs, without the need to estimate the whole hand BMD. This increased our chance to pick up small differences in periarticular BMD early in the disease course.

Weaknesses of our study could be, first, our relatively small sample size, which may change the BMD estimates when replicating this study with a larger sample size. However, this design was intended to evaluate the need for a larger diagnostic study. As there was a great overlap of BMD values in both healthy and diseased individuals,

increasing the sample size would lead to more significant results, but the BMD values on an individual level would not change by enlarging the sample. Thus, it would still be difficult to use periarticular BMD as a diagnostic test based on DXA estimates, and therefore gathering a larger sample would not be cost-effective. Secondly, the DXA measurements might be influenced by the presence of synovitis. From measuring BMD in the spine, we know that inaccuracies up to 20% may occur due to obesity [29]. Synovitis creates a small increase in the amount of soft tissue around the joint that may affect the BMD assessments in a similar way as obesity does. However, to what extent is unknown. Thirdly, we did not correct for the presence of bone erosions. In case of bone erosions on the side of the joint, the area of eroded bone will not be picked up by the DXA. As DXA is a surface measure, this will not directly affect the BMD reading. We tested this hypothesis by randomly excluding portions of bone. BMD, however, remained the same (data not shown). If an erosion is more central in the bone, the erosion will be regarded as complete BMD loss by DXA in that particular area, and therefore decrease the periarticular BMD. This would only increase differences between BMD of patients vs controls, and therefore improve diagnostic power. This is not a problem in a diagnostic study, although it would be for an aetiological study.

In conclusion, periarticular BMD measured cross-sectionally with DXA is not a useful diagnostic feature to distinguish RA patients from healthy people, due to the wide distribution in BMD values. This resulted in strong overlap between healthy controls, established RA patients and early arthritis patients. This gives rise to a discussion about the use of periarticular osteoporosis, measured by DXA, as a diagnostic criterion for RA early in the disease course.

Rheumatology key messages

- Periarticular osteoporosis may be a diagnostic feature of early RA.
- Cross-sectional measurement with DXA cannot discriminate patients with early RA from healthy controls.
- Imaging techniques such as DXR and QUS need further assessment of their ability to diagnose RA.

Acknowledgements

We would like to thank F. Rivadeneira Ramirez, PhD, for his contribution in the set up of the DXA measurements.

Funding: This work was supported by Proctor and Gamble via an unrestricted grant enabling us to do the DXA scans. The study sponsor had no role in the study design, data collection, analysis, interpretation of data, the writing of the manuscript and on the decision to submit the manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

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