Aging Clinical and Experimental Research (2025) 37:199
https://doi.org/10.1007/s40520-025-03105-5

RESEARCH

Ultrasound- and clinical-defined disease activities are associated with altered bone microarchitecture and lower bone mineral density in patients with rheumatoid arthritis

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Received: 16 March 2025 / Accepted: 10 June 2025

Abstract

Background/aims We investigate if rheumatoid arthritis (RA) activity, defined clinically and with ultrasound, is associated with bone macro- and micro-architecture impairment on high-resolution peripheral quantitative computed tomography (HR-pQCT) and dual X-ray densitometry (DEXA).

Methods Disease activity was evaluated in 61 RA patients, with clinical indices and ultrasound (hands and wrists). Bone mineral density (BMD) and architecture were analyzed with HR-pQCT and DEXA.

Results Ultrasound RA disease activity parameters [synovitis, power doppler (PD)-positive joints, sum of positive power doppler signals and tenosynovitis] were associated with altered HR-pQCT bone density and structure at tibia or radius (trabecular volumetric BMD, trabecular bone volume fraction, trabecular thickness and cortical porosity). In addition, wrist ultrasound activity was specifically locally associated with impaired local bone microarchitecture at distal ipsilateral radius. Clinical and functional RA disease activity parameters (number of swollen joints, Health Assessment Questionnaire and disease activity score DAS28-CRP) were also correlated with HR-pQCT parameters (total and trabecular volumetric BMD, trabecular thickness and cortical thickness). At the hip, BMD correlated with VAS-fatigue and DAS28-ESR. The number of synovitis detected by ultrasound was higher when total hip T-score was lower than − 1.

Discussion Ultrasound and clinical disease activity parameters were associated with impaired HR-pQCT parameters (distal radius and tibia), with lower trabecular and cortical bone densities and impaired bone microarchitecture (organization of spans and cortical porosity). In addition to systemic contribution to bone impairment, a local correlation between wrist US activity and HR-pQCT at distal radius was observed.

Conclusion Patients with active RA, especially with US evaluation, are at higher risk for altered bone density and structure.

Keywords Rheumatoid arthritis · Disease activity · Ultrasound · High-resolution peripheral quantitative computed tomography

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease, in which the primary lesion corresponds to inflammation of the synovial membrane, characterized by hyperplasia, infiltration by immune cells, neo-angiogenesis and fibrosis [1]. With the advent of biologic treatments, the prognosis of RA has markedly improved, and more attention can be devoted to co-morbidities such as osteoporosis. Osteoporosis in RA is characterized by loss of peri-articular bone mass, around inflamed joints but also at distance, such as at the spine [2, 3, 4]. The pro-inflammatory cytokines as well as anti-citrullinated peptide antibodies (ACPA) are considered to be the

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Published online: 28 June 2025

main triggers for bone resorption through the induction of the receptor activator of NF-kB ligand (RANKL), thereby increasing the number of osteoclast precursors and stimulating their differentiation [5]. In addition, general risk factors such as corticosteroids, low vitamin D levels, postmenopausal status and sedentary lifestyle increase bone impairment in these patients.

The overall prevalence of osteoporosis in RA is around 20–30% at the spine and 7–26% et the hip [6]. As in general population, osteoporosis also leads to significant mortality in RA [7]. Regular evaluation of osteoporosis risk is part of the management of RA [8] and systematic dual X-ray densitometry (DEXA) is proposed [9]. Unfortunately, this screening remains largely insufficient [10] and it is therefore essential to help the practitioner to identify patients at higher risk of osteoporosis.

The objective of this study is to determine if RA disease activity is associated with an impairment in bone density or structure. We evaluated RA disease activity with clinical indices and systematic hands and wrists ultrasound (US), as US is more sensitive than clinical evaluation to detect synovitis and effusion [11]. Bone analyses included DEXA and HR-pQCT (high-resolution peripheral quantitative computed tomography) that currently allow to investigate bone structure in detail (bone geometry, bone density and microarchitecture) and to distinguish trabecular and cortical compartments.

Methods

Study design and patients

This cross-sectional study, approved by the ethics committee of our hospital (B70720108722), consisted of 61 patients fulfilling the American College of Rheumatology / European Alliance Against Rheumatism (ACR/EULAR) 2010 criteria for RA (inclusion criterion) [12] included from October 2018 to April 2021. Written informed consent was obtained from each patient. Disease activity was evaluated by US, questionnaire, clinical examination and blood analysis. Bone mineral density (BMD) and bone architecture were analyzed with DEXA and HR-pQCT. All joint assessments were performed on the same day by two independent investigators (one for the clinical evaluation, one for the US examination), blinded to the other results. Bone evaluations (DEXA and HR-pQCT) were performed if possible the same day, if not within a maximum delay of one month. The only exclusion criterion was pregnancy.

The patient (PtGA) and the physician (PGA) global assessments were determined using a visual analogue scale (VAS) (0–100 mm) as was patient fatigue. Patients also filled in the Health Assessment Questionnaire (HAQ) [13]. Disease activity was evaluated using disease activity scores (DAS) DAS28-CRP and DAS28-ESR [14], the simplified disease activity index (SDAI) [15] and the Clinical Disease Activity Index (CDAI) [16]. The number of tender and swollen joints was recorded. Blood analyses included vitamin D (ng/ml), parathyroid hormone (ng/L), rheumatoid factor, ACPAs, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Treatments [(conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), biological (b)DMARDs, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and anti-osteoporotic treatments] were recorded as well as age, gender, body mass index (BMI), history of fracture, active smoking and chronic alcohol consumption.

Ultrasound examination

Ultrasound evaluation was performed by a single experienced examiner (ChR) using a 9–15 MHz B-mode multifrequency transducer (Logiq 9, GE Healthcare, Milwaukee, WI, USA). A study in gray mode and power Doppler (PD) was carried out on 22 joints for each patient: wrists (radiocarpal and intercarpal), metacarpophalangeal (MCP) joints 1–5 and proximal interphalangeal (PIP) joints 1–5. The positioning of the patient and of the probe correspond to the EULAR recommendations [17]. Synovitis was classified according to OMERACT [18] (definition, measurement of grade from 0 to 3 in gray mode and in PD imaging) and US protocol was explained in detail in our previous article [19]. Wrist and hand tenosynovitis were documented in a binary way [20]. The following parameters were collected at the patient level: number of US-synovitis, sum of grade of the 22 joints (cumulative synovitis grade in gray score), the mean synovitis grade, cumulative synovitis thickness (mm), mean synovitis thickness (mm), number of joints with effusion, cumulative effusion grade, mean effusion grade, number of PD-positive joints, cumulative PD grade, presence or absence of hand or wrist tenosynovitis. An exemplative US scan with effusion, synovitis, PD activity and tenosynovitis is shown on Fig. 1.

DEXA procedure

All the examinations were performed on the same Discovery A DEXA system (Hologic, Bedford, MA, USA). Lumbar spine (L1-L4), total hip and femoral neck were analyzed. For total hip and femoral neck, the left side was analyzed except when prosthetic material was present. Bone mineral density (BMD) and T-scores were reported for these three sites. T-score values were considered as normal if > -1, osteopenic if ≤ -1 and > -2.5 and osteoporotic if ≤ -2.5.

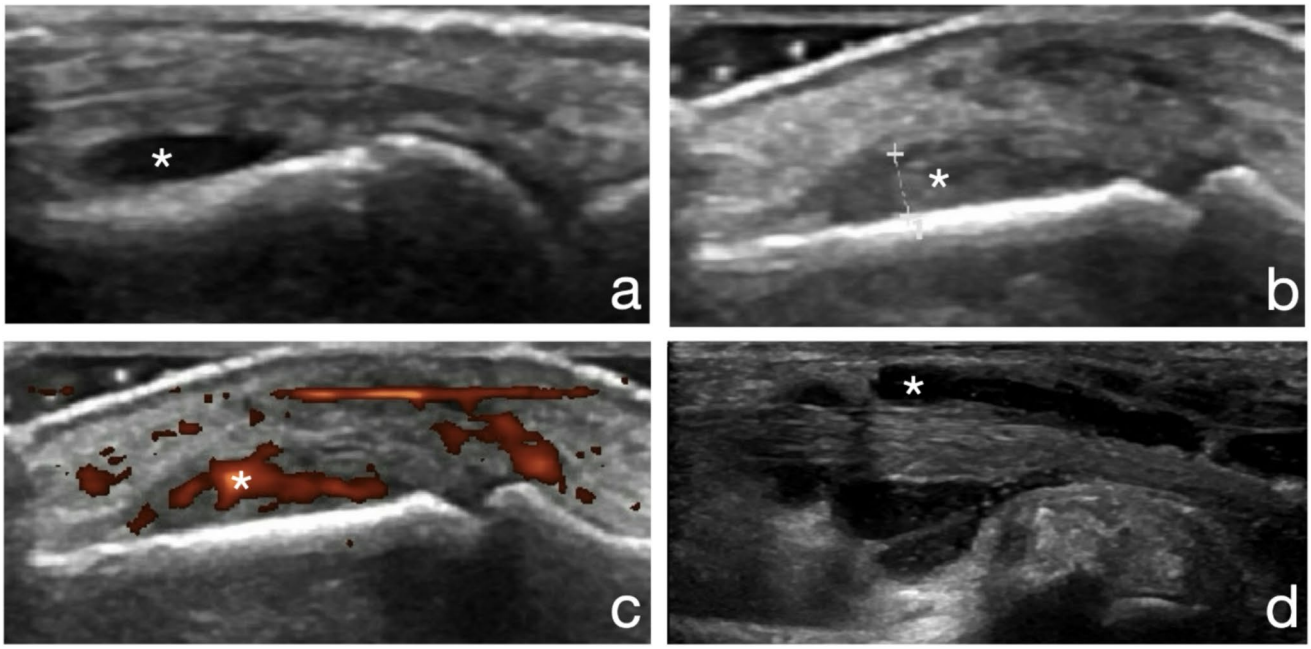

Fig. 1 Exemplative US scan with effusion, synovitis, power doppler activity and tenosynovitis. (**a**). Metacarpophalangeal joint with effusion in the dorsal recess (longitudinal view). (**b**). Proximal interphalangeal joint with synovitis (longitudinal view). (**c**). Power-doppler activity on this proximal interphalangeal joint (longitudinal view). (**d**). Tenosynovitis of the common flexors of the fingers (longitudinal view)

Standardization procedures were performed according to the International Society for Clinical Densitometry. Daily quality control with phantom was performed to ensure that these values were located at maximum +/− 1.5% of the mean value of calibration. About the parameters of the DEXA (Hologic, Bedford, MA, USA), the total bone mineral density (BMD) coefficient of variation (CV) was 1.0%. FRAX score was also calculated for each patient with national references tables (https://www.sheffield.ac.uk/FRAX/tool.aspx?lang=fr).

HR-pQCT procedure

Second generation HR-pQCT scanner (XtremeCT II, Scanco Medical AG, Bruttisellen, Switzerland) was performed at the non-dominant distal radius and controlateral tibia, as described in literature [21]. Subjects were positioned with their wrists and ankles immobilized in a carbon-fiber cast provided by the manufacturer. The reference line was set manually at the end plates of distal radius and tibia, and measurements were carried out 9 mm and 22 mm proximal to the reference lines, respectively. The standard mode (68kVp, 1462 µA, 100 W) was used and, for each site, 168 slices were acquired and analyzed. All scans were completed by a trained technologist according to the manufacturer's protocol.

For each scan, the following parameters were determined: total volumetric bone mineral density (Tt.vBMD); trabecular volumetric bone density (Tb.vBMD); meta Tb.vBMD (40% of Tb area) (Tb.Meta.vBMD); inner Tb.vBMD (60% of Tb area) (Tb.Inn.vBMD); cortical volumetric density (Ct.vBMD); trabecular bone volume fraction (BV/TV); trabecular number (Tb.N); trabecular thickness (Tb.Th); trabecular separation (Tb.Sp); inhomogeneity of the network (Tb.1/N.SD); cortical thickness (Ct.Th); cortical porosity (Ct.Po) and cortical pore diameter (Ct.Po.Dm).

Statistical analysis

Results are presented as mean ± standard deviation (SD) or as median for continuous variables and as frequency tables for qualitative variables. Linear and logistic regression models investigated the relationship between bone measurements and demographic / therapeutic / biological data or disease activity (estimate and standard error, SE). All the demographic, therapeutic, biological and US data described above were used for analysis. A univariate analysis was first performed (data not shown in the article). A multivariate analysis with stepwise selection was applied on the variables with a $p<0.1$ in univariate analysis. Comparisons of HR-pQCT and disease activity characteristics between patients that needed (or not) an anti-osteoporotic treatment were done by Student t-test. The results were considered significant at the uncertainty level of 5% ($p<0.05$). Calculations were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Results

Demographic, ultrasound and bone parameters

The 61 RA patients included (44 women; 17 men) had a median age of 61 (27–81) years and median disease duration of 7 (0–30) years. Rheumatoid factor and ACPA were positive in 67 and 69%, respectively. Forty (66%) subjects were taking csDMARDs; 32 (53%) bDMARDs and 26 (43%) daily oral methylprednisolone. The median (min-max) dose of methylprednisolone was 1 (0–8) mg. 8 (13%) patients were under anti-osteoporotic treatment at the time of the analysis. Mean BMI was 27.0 ± 5.2 kg/m^2. 18 (30%) were active smokers. Physical examination, disease activity and US evaluation are shown in Table 1.

Osteoporosis (at least one of the three sites) was identified in 14% of patients. At each anatomical location, osteoporosis was identified in 12.3% at the lumbar spine, 5.2% at the femoral neck and 3.4% at the total hip. BMD and T-scores are shown in the Supplementary Table 1. HR-pQCT tibia and radius results are shown in the Supplementary Table 2.

Relationship between RA disease activity parameters and bone parameters (HR-pQCT)

Multivariate analysis was performed to look for relationships between HR-pQCT and disease characteristics. The estimates and SE of the multivariate models are displayed in Table 2. First, several significant associations were found between clinical disease activity, at the patient level, and bone density or structure (Table 2, in white): the number of swollen joints was negatively associated with total volumetric BMD (Tt.vBMD) and with trabecular BMD (Tb.Meta. BMD) at tibia site. HAQ was also negatively associated with Tt.vBMD and with the cortical thickness (Ct.Th). In contrast, HAQ was negatively associated with the cortical pore diameter (Ct.Po.Dm) at tibia site. The global disease activity estimated by the DAS28-CRP score was negatively associated with the trabecular thickness (Tb.Th) at tibia and radius sites and with trabecular BMD (Tb.Meta.BMD) at radius site.

We further looked for associations between US disease activity parameters and bone density or structure (Table 2, in grey) and also demonstrated association between US

Table 1 Clinical and ultrasound characteristics of the RA patient population. N: number; SD: standard deviation; VAS: visual analogue scale; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS: disease activity score; CDAI: clinical disease activity index; SDAI: simplified disease activity index; PD: power doppler

Variable (per patient)	n	Mean ± SD or n (%)	Variable (per patient)	N	Mean ± SD or Number (%)
Subjective evaluation of disease activity			Ultrasound characteristics		
Patient global assessment - VAS (mm)	61	48.6 ± 27.8	Number of joints with synovitis	61	3.1 ± 4.5
Physician global assessment - VAS (mm)	61	23.1 ± 24. 7	Cumulative synovitis grade	61	5.4 ± 9.4
Health Assessment Questionnaire (/60)	61	16.6 ± 11.8	Mean synovitis grade	61	0.24 ± 0.43
Blood inflammatory parameters			Cumulative synovial thickness (mm)	61	7.01 ± 11.5
CRP (mg/L)	61	7.3 ± 15.9	Mean synovial thickness (mm)	61	0.32 ± 0.52
ESR (mm/h)	59	17.2 ± 16.0	Number of joints with effusion	61	1.0 ± 1.7
Clinical examination			Cumulative effusion grade	61	1.3 ± 2.5
Number of swollen joints / patient	61	3.2 ± 4.4	Mean effusion grade	61	0.06 ± 0.12
Number of tender joints / patient	61	5.7 ± 6.3	Number of PD positive joint	61	0.25 ± 0.70
DAS28-CRP	61	3.61 ± 1.38	Cumulative PD grade	61	0.43 ± 1.50
Remission		14 (23.0)	Mean PD grade	61	0.019 ± 0.068
Low activity		12 (19.7)	Tenosynovitis	61	
Moderate activity		27 (44.3)	No		48 (78.7)
High activity		8 (13.1)	Yes		13 (21.3)
DAS28-ESR	59	3.82 ± 1.36			
Remission		12 (20.3)			
Low activity		9 (15.3)			
Moderate activity		27 (45.8)			
High activity		11 (18.6)			
CDAI	61	16.0 ± 13.7			
Remission		9 (14.8)			
Low activity		18 (29.5)			
Moderate activity		16 (26.2)			
High activity		18 (29.5)			
SDAI	61	16.7 ± 14.0			
Remission		10 (16.4)			
Low activity		19 (31.1)			
Moderate activity		19 (31.1)			
High activity		13 (21.3)			

Table 2 Relationship between bone evaluation by HR-pQCT and RA evaluation, at tibia and radius. Only statistically significant associations ($p<0.05$) of the multivariate linear models are shown. Lines in white correspond to parameters reflecting disease activity. Lines in Gray correspond to US parameters. HR-pQCT: high-resolution peripheral quantitative computed tomography; tt.vbmd: total volumetric bone mineral density; tb.vbmd: trabecular volumetric bone mineral density; ct.vbmd: cortical volumetric density; BV/TV: trabecular bone volume fraction; tb.n: trabecular number; tb.th: trabecular thickness; tb.sp: trabecular separation; tb.1/n.sd: inhomogeneity of the network; ct.th: cortical thickness; ct.po: cortical porosity; ct.po.dm: cortical pore diameter; RA: rheumatoid arthritis; HAQ: health assessment questionnaire; US: ultrasound; DAS: disease activity score; CRP: C-reactive protein; PD: power doppler; SE: standard error

HR-pQCT parameters	RA characteristics	Estimate (SE)	P-value	RA characteristics	Estimate (SE)	P-value
	TIBIA			RADIUS		
Tt.vBMD	Number of swollen joints	-3.26 (1.58)	0.045	/		
	HAQ	-1.10 (0.51)	0.037			
Tb.vBMD	Number of US synovitis	-2.66 (0.95)	0.0072	/		
Tb.Meta.vBMD	Number of swollen joints	-2.44 (1.05)	0.0236	DAS28-CRP	-6.30 (2.90)	0.034
Tb.Inn.VBMD	Number of US synovitis	-2.59 (0.98)	0.0108	/		
Ct.vBMD				/		
BV/TV	Number of US synovitis	-0.0038 (0.0012)	0.0031	/		
Tb.N	/			/		
Tb.Th	DAS28-CRP	-0.0070 (0.0022)	0.0023	DAS28-CRP	-0.0023 (0.00096)	0.023
				US tenosynovitis	-0.0072 (0.0031)	0.026
Ct.Th	HAQ	-0.0074 (0.0029)	0.013	/		
Ct.Po	Sum of US PD-positive joints	0.0061 (0.0011)	<.0001	/		
Ct.Po.Dm	HAQ	-0.0013 (0.00038)	0.0013	/		
	Number of US PD-positive joints	0.015 (0.0060)	0.015			

activity and HR-pQCT parameters. The number of US synovitis was negatively associated with trabecular volumetric BMD (Tb.vBMD) and with the trabecular bone volume fraction (BV/TV) at tibia site. The presence of hand tenosynovitis detected by US was negatively associated with the trabeculation (Tb.Th). Concerning US PD parameters, the number of US PD-positive joints was positively associated with the cortical porosity diameter (Ct.Po.Dm) and the sum of US-positive PD signals was positively associated with the cortical porosity (Ct.Po), both at tibia site.

Lastly, in order to evaluate a more local correlation between disease activity and bone parameters, we specifically studied US and clinical activity of the non-dominant wrist, on the same side as the radius analysis with HR-pQCT. Wrist US synovitis was negatively associated with radius trabecular bone parameters: Tb.Inn.vBMD [Estimate (SE): -20.1 (7.63), $p=0.012$], BV/TV [-0.02 (0.0098), $p=0.044$] and Tb.N [-0.12 (0.057), $p=0.046$]. There were also associations with cortical parameters: wrist effusion was associated with Ct.vBMD [-23.0 (4.85), $p<0.0001$] and wrist PD was positively associated with radius cortical porosity (Ct.Po.Dm) [0.05 (0.20), $p=0.019$]. No relationship was found between HR-pQCT of the non-dominant side and number of clinically tender or swollen joints.

Relationship between RA disease activity parameters and bone parameters (DEXA)

With regard to clinical disease activity (Table 3, *in white*), femoral neck BMD was negatively associated with VAS fatigue while total hip BMD was negatively associated with DAS28-ESR. Disease duration was higher for patients with a femoral neck T-score lower than −1. As for US activity *(*Table 3, *in grey)* the number of synovitis detected was higher when total hip T-score was lower than −1. We also observed several significant associations with demographic and anamnestic data (data not shown): lower total hip/femoral neck BMD associated with female gender; lower femoral neck BMD associated with lower BMI; higher history of fracture when total hip T-score <-1.

Correlations between demographic, therapeutic and biological data and bone parameters are not displayed in this article. In brief (data not shown), as expected, BMI and male gender were positively associated with several bone density and structure parameters, while relationships were negative for age and history of fracture. Corticosteroid use was negatively associated with tibia trabecular volumetric BMD [Estimate (SE): -17.01 (8,31), $p=0,046$] and with higher rate of "any T-score lower than −1" [OR: 24,28 (3,20–184,35)]. bDMARD use was associated with lower trabecular vBMD [Estimate (SE): -13.22 (6,48), $p=0,047$]

Table 3 Relationship between bone evaluation by DEXA and RA evaluation. Only statistically significant associations ($p<0.05$) of the multivariate models are displayed. Lines in grey correspond to parameters reflecting disease activity. Lines in Gray correspond to US parameters. BMD: bone mineral density; RA: rheumatoid arthritis; SE: standard error; ESR: erythrocyte sedimentation rate; DAS: disease activity score; US: ultrasound; VAS: visual analogue scale

DEXA parameters	RA characteristics	Estimate (SE)	P-value
L1L4 BMD	VAS fatigue	-0.0019 (0.0007)	0.010
L1L4 T-score < -1	VAS fatigue	0.024 (0.011)	0.028
L1L4 T-score < -2.5	/		
Total hip BMD	DAS28-ESR	-0.023 (0.011)	0.046
Total hip T-score < -1	Number of US synovitis	0.32 (0.12)	0.0083
Total hip T-score < -2.5	/		
Femoral neck BMD	VAS fatigue	-0.0015 (0.00057)	0.012
Femoral neck T-score < -1	Disease duration	0.11 (0.046)	0.016
Femoral neck T-score < -2.5	/		

Linear regression models were used for BMD and logistic regression models were used for T-score cut-off.

and lower bone volume ratio (BV/TV) [Estimate (SE): -0.02 (0.009), $p=0,03$], while we did not find any significant relation between csDMARDs and bone parameters in multivariate analysis.

Disease activity among patients that should be treated according to ESCEO/IOF osteoporosis treatment guidelines

Among the 61 RA patients, 47 were considered to be in the field of ESCEO/IOF 2020 osteoporosis guidelines [22] (used for postmenopausal woman or men > 50 years). If we retrospectively applied these recommendations for osteoporosis treatment, 12 (26%) of patients should have been treated. As expected, these patients exhibited lower total hip and femoral neck BMD, higher FRAX index, higher FRAX-TBS index and more previous fractures ($p=0.0028$, $p=0.034$, $p=0.003$, $p=0.015$ and $p<0.0001$ respectively). HR-pQCT identified that these patients had lower tibia total volume densities (Tt.vBMD, $p=0.036$), lower trabecular volume densities (Tb.Meta.vBMD, $p=0.035$) and lower cortical thickness (Ct.Th, $p=0.023$). Of interest, US evaluation demonstrated in these 12 patients more synovitis ($p=0.0087$), a higher mean synovitis grade ($p=0.016$) and a higher mean synovial thickness ($p=0.04$) than in the 35 patients not requiring osteoporosis treatment. Clinical disease activity was also higher in this subgroup that needed a treatment: number of swollen joints ($p=0.0029$), number of tender joints ($p=0.0010$), VAS physician ($p=0.0048$), VAS fatigue ($p=0.036$), DAS28-CRP ($p=0.0048$), CDAI ($p=0.0007$) and SDAI ($p=0.0011$) were significantly higher in the subgroup identified by ESCEO/IOF.

Discussion

Our study shows that, in RA patients, US and clinical disease activity have a systemic influence not only on bone mineral density (as has been previously shown) but also on bone microarchitecture, both in trabecular and in cortical bone, and that this influence on bone microarchitecture is independent of glucocorticoid treatment or demographic data such as BMI or age.

US joint activity, especially PD activity, is strongly associated with structural progression. We first demonstrate that RA disease activity evaluated by US (number of US synovitis, number of PD-positive joints, sum of the US-positive PD signals and tenosynovitis) is negatively associated with volumetric bone density and bone structure studied with HR-pQCT. This association relates both to the trabecular (trabecular volumetric BMD, trabecular bone volume fraction, trabecular thickness) and the cortical compartments (cortical porosity). In addition, we also underlined that clinical evaluation of RA disease activity (number of swollen joints, HAQ and DAS28-CRP) is negatively associated with bone microarchitecture, both for trabecular and cortical parameters (total volumetric BMD, trabecular BMD, trabecular thickness and cortical thickness). These negative correlations were mainly present at the tibial localization, rather than at the radius. Patients with a high disease activity have lower volumetric BMD and bone microarchitecture.

In addition to the evaluation of the systemic disease activity, we also studied the local correlation between RA disease activity at the wrist and local bone microarchitecture at distal ipsilateral radius using HR-pQCT. We observed that wrist disease activity as evaluated by US (synovitis, effusion and PD) was associated with impaired local bone

microarchitecture specifically at distal ipsilateral radius, indicating also a more local influence. This local influence had repercussions on both trabecular and cortical components. Meanwhile, we did not find any significant correlation between RA activity of the wrist evaluated clinically and bone microarchitecture at the wrist.

Several studies previously demonstrated that RA patients have impaired bone microarchitecture compared to controls, with both trabecular and cortical alteration: these studies concerned juxta-articular bones of hands (such as peri-articular metacarpeal bone) [23, 24] but also distal radius and tibia [2, 21, 25, 26], the reference sites for HR-pQCT analysis in osteoporosis. Micro-architecture abnormalities are also correlated with fracture in RA population [3, 21]. However, data about correlations between bone microarchitecture and disease activity are limited in RA. To the best of our knowledge, this is the first study to correlate US disease activity with bone microarchitecture at distal radius and tibia sites, studied with HR-pQCT. Both synovitis in gray scale mode, PD and the presence of tenosynovitis were associated with impaired bone parameters. If we specifically look at correlations between wrist and local bone micro-architecture, effusion was also a significant element (while we found no correlation with clinical nor biological parameters for this localization). About clinico-biological evaluation, Jin et al. previously observed in 2021 a link between clinical disease activity factors (DAS-28 and HAQ) and trabecular (Tb.N) and cortical (Ct.vBMD and Ct.Th) microarchitecture impairment, but this link was restricted to the radius [21]. In 2014, Zhu et al. also demonstrated a link between DAS28, ESR and IL-6 levels in blood with radius microarchitecture, but distal tibia was not analyzed [25]. Wang et al. also demonstrated that wrist BMD significantly correlated with disease duration and systemic disease activity [27], in favor of a systemic influence, while Ben Abdelghani et al. found a significant correlation between the BMD of the wrist and the wrist synovitis, in favor of a local influence [28]. Of interest, Chen et al. demonstrated that persistent synovitis at the wrist was associated with total hip bone loss, highlighting that long-standing synovitis can also be associated with demineralization at other sites [29]. Furthermore, Kong et al. demonstrated that sub-clinical joint inflammation (i.e. joint inflammation assessed by US, in patients seeming under clinical remission) was associated with alteration of the trabecular bone compartment studied with HR-pQCT [30]. Even though this study was restricted to the evaluation of the local peri-articular subchondral bone, and did not evaluate the more distant site as we did, it provides a strong argument for the US to assess RA disease activity.

Our study underlines that links between clinical and US evaluation and bone microarchitecture was also (and mainly) present for tibial localization. In our study, RA disease duration was not associated with any HR-pQCT parameter and we only observed an association with femoral neck demineralization. In contrast, disease duration was previously described as associated with altered trabecular and cortical microarchitecture at radius [2, 21, 25] and tibia [21] sites.

In contrast to HR-pQCT, DEXA showed limited correlations with disease activity. We only identified significant links between BMD and VAS-fatigue or DAS28-ESR and between the number of US synovitis and total hip demineralization. In addition, the coefficient correlation between BMD obtained with DEXA and several HR-pQCT parameters is low, and the correlations never concerned the cortical compartment (data not shown).

The observation that US and clinical disease activity was associated with bone parameters was lastly confirmed by our analysis of the RA patients that needed an osteoporotic treatment according to international guidelines. If we retrospectively applied to our cohort the ESCEO/IOF osteoporosis treatment guidelines [22], that are mainly based on FRAX and BMD with DEXA, these guidelines identified a patient population characterized by impaired HR-pQCT parameters and higher US and clinical disease activity, indicating that following osteoporosis guidelines treatment effectively led to treat patients with higher disease activity. Lastly, even if not the initial scope of our article, we observed in the multivariate analysis that patients under bDMARDs had worst trabecular architecture, which could be the reflection of a higher disease activity, either present or past, needing immunosuppressive treatment intensification.

Our study has several limitations. First, the relatively small number of patients must be underlined. One single well-trained and experienced observer (Ch. R) made all the US evaluations by herself and on the same US machine, but the intra-observer variability was not assessed before the beginning of the study. Another limitation is the absence of systematic hand X-ray to look for bone erosions (Perez et al. recently demonstrated in pre-menopausal RA patients that bone erosions are associated with cortical fragility at the distal radius and tibia [26], but Kocijan et al. found no association between bone erosions and radius microarchitecture [2]). Synovitis was also only assessed by US; MRI could have been an alternative to assess synovitis, but it is less easily available and cannot be performed in everyday rheumatological practice as US can. Lastly, our study is cross-sectional, and therefore mainly observational, with conclusions that may only represent the time of the observation.

In conclusion, disease activity in RA, assessed both clinically and through US, is associated with lower trabecular and cortical bone density and impaired trabecular and cortical bone microarchitecture. However, beyond this expected

systemic effect of inflammation, our study contributes novel findings by combining HR-pQCT, DEXA, and detailed US evaluation, demonstrating that US-detected joint inflammation is independently linked to impaired bone quality. Moreover, the observation of a site-specific association between wrist US activity and microstructural deterioration at the ipsilateral distal radius supports a localized inflammatory impact that cannot be captured by clinical examination alone. These findings underscore the utility of hand US, beyond disease activity monitoring, to identify RA patients at higher risk for osteoporosis-related damage.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40520-025-03105-5.

Acknowledgements This work was supported by academic funding from "Fonds Léon Fredericq", University of Liège, Belgium. "Fonds Léon Fredericq" had no implication in the acquisition or analyzing of the data.

Author contributions OM performed the bone analysis, analyzed the data and wrote the manuscript. ChR performed the US analysis, analyzed the data and wrote the manuscript. FC and CG collected and analyzed the data. LS realized the statistics analyses. MM et ClR designed the study and analyzed the data. All the authors revised the manuscript critically and approved the final manuscript for submission and publication. All authors take full responsibility for the integrity of the study and all parts of the finalmanuscript.

Data availability Full data are available under reasonnable request.

Declarations

Competing interests The authors declare no competing interests.

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