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Original article

Remaining local subclinical joint inflammation is associated with deteriorated metacarpeal head bone microarchitecture in rheumatoid arthritis patients low disease activity

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ABSTRACT

Objectives: Bone alterations at the subchondral level during rheumatoid arthritis (RA) remain under investigation. It remains unknown whether subchondral bone damage might still occur in RA patients in clinical remission, which could then infer suggesting that even minor subclinical inflammatory changes in the joint can induce local bone loss.
Methods: Thirty-two RA patients treated with biological disease-modifying anti-rheumatic drugs (bDMARDs) with low disease activity since at least 6 months and having erosion on the second or third metacarpeal head were enrolled in this pilot cross-sectional study. They were divided in two groups according to local inflammation assessed by Doppler-ultrasound exam surrounding the site of erosion. Cortical and trabecular parameters of the metacarpeal head were then assessed by high-resolution peripheral quantitative computed tomography (HR-pQCT) and compared in both groups.
Results: Twenty and twelve RA patients were enrolled in the "Doppler positive erosion" (DE+) group and Doppler negative erosion (DE−) group, respectively. No difference was observed in their clinical or biological RA characteristics. Both cortical density and thickness were similar among groups. Within the trabecular network, while no difference in bone volume was observed, trabecular density as well as trabecular number were decreased ($P<0.001$ and $P<0.05$ respectively), whereas trabecular separation and distribution of trabecular separation were increased in DE+ compared to DE− ($P<0.05$).
Conclusion: In RA patients in low disease activity under bDMARDs, persistence of local inflammation was associated with alteration of the trabecular compartment. Trabecular density was the most strongly altered parameter and could be a candidate to assess drug effect on periarticular bone damage.

1. Introduction

Rheumatoid arthritis (RA) is a chronic joint inflammatory disease associated with both periarticular and generalized bone loss starting at early stage of the disease [1]. RA patients develop marginal erosions which can lead to irreversible structural and functional joint impairment. In affected joints, hands and particularly metacarpophalangeal (MCP) joints are among the earliest sites susceptible to RA-related bone damage, probably due to anatomic and biomechanical factors [2]. To date, conventional X-rays have been considered as a gold standard tool to assess RA structural joint damage. Despite a high specificity for erosion detection at hand sites, its sensitivity is low to detect early erosions or changes. Imaging such as magnetic resonance imaging (MRI), ultrasound (US) or computed tomography (CT) have been investigated in order to improve visualization of early changes and monitoring disease progression [3,4]. High-resolution peripheral quantitative CT (HR-pQCT) is an *in vivo* non-invasive device assessing bone microarchitecture parameters and volumetric bone mineral density (vBMD) in both cortical and trabecular compartments. With its high spatial resolution of 80 μm and a very low radiation exposure, HR-pQCT provides evaluation of fracture risk independently of areal BMD assessed by dual X-ray absorptiometry (DXA) [5]. Recently, studies have shown the ability of HR-pQCT to assess bone microarchitecture at the hand [6], with the detection and

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quantification of periarticular bone lesions, such as erosions [7,8], osteophytes [9], and joint space narrowing [10] in RA patients.

In particular, HRpQCT analysis revealed a strong bone loss at 2nd and 3rd metacarpal heads (MH2 and MH3) of the dominant hand in early stage of RA mainly in the trabecular bone compartment [11]. Furthermore, cortical bone porosity was observed at the same sites in patients with detectable serum levels of anti-citrullinated protein antibodies (ACPA) prior to RA onset [12]. Biological disease-modifying anti-rheumatic drugs (bDMARDs) have strongly improved RA management outcome in terms of clinical improvement and joint damage blockage [13]. However, it remains unknown whether subchondral bone damage might still occur in RA patients in clinical remission [14], which could then infer suggesting that even minor subclinical inflammatory changes in the joint can induce local bone loss. Indeed, some studies have shown a discrepancy between clinical remission and persistence of synovitis detected by Power Doppler US (PDUS) or by MRI suggesting a situation at risk for joint damage progression [3,15]. To date, no association has been reported between residual local joint inflammation and bone microarchitecture impairment. We focused on MH localized inside the joint MH [16]. So, the aim of our study was to compare bone microstructure of metacarpal heads using HR-pQCT in RA patients with low disease activity, according to the persistence or not of local inflammation assessed by US exam.

2. Methods

2.1. Patients

For this pilot cross-sectional study, 32 RA patients fulfilling ACR/EULAR 2010 criteria were enrolled from May 2013 to January 2016. All patients were treated with bDMARDs with a low disease activity (DAS28 < 3.2) since at least 6 months with stable glucocorticoid dose for 3 months equal or below 5 mg per day of prednisone and at least one erosion at the MH2 or MH3 detected by US exam. Exclusion criteria were pregnancy or breastfeeding, comorbidity altering bone metabolism including treatment with zoledronic acid or denosumab. The protocol was conducted in accordance with de Declaration of Helsinki and was approved by the local ethics committee. All subjects gave written informed consent before enrolment. Demographic and clinical RA features were recorded.

2.2. Imaging procedure

To detect erosion and assess joint inflammation on MCP2 or MCP3, a linear multifrequency probe with a MyLab 60 ultrasound device (Esaote Medical SAS, Saint-Germain-en-Laye, France) was used. Bone erosion was defined as changes in the bone surface of the area adjacent to the joint as a defect in the bone surface in 2 planes. Patients were split in two groups according to the presence or not of local inflammation assessed by PDUS at the joint with erosion with semi quantitative US grading system previously described. “Doppler positive erosion” (DE +) group was defined by the grade 2 or 3 and “doppler negative erosion” (DE−) group by the grade 0 and 1at the MCP2 or MCP3 with the assessed erosion with a good reproducibility [17].

Volumetric BMD and microarchitecture parameters were evaluated by HR-pQCT (XtremeCT, Scanco Medical AG, Bassersdorf, Switzerland) at the MH2 or MH3with erosion detected by US exam. Hand of participant was fixed in a ‘thermoformed’ hand splint. A dorsopalmar scout-view X-ray image was obtained to define the region of interest (ROI) including the MHs. Scans were performed using the manufacturer’s standard patient settings for image acquisition (60 kVp, 1000 μA, 100 ms integration time, 1536 × 1536 reconstruction matrix) in accordance with protocol from the Study GrouP for XTrEme-CT in Rheumatoid Arthritis (SPECTRA) collaboration [18] with an effective dose around 3 μSv per measurement.

On the MH (2 or 3) with assessed erosion, followed bone density parameters were measured as previously described [11]: bone volume per total volume (BV/TV, %), BMD (in mg hydroxyapatite [HA]/cm^3), structural parameters (such as trabecular number (Tb.N, millimeter^{-1}), and cortical parameters (cortical thickness, mm)). Trabecular thickness (Tb.Th, mm), and spacing (Tb.Sp, mm) were derived from BV/TV and Tb.N analogous to standard bone histomorphometry. The standard deviation of 1/Tb.N (Tb.Sp*SD) was used to reflect heterogeneity of the trabecular network. The number of slices on assessed MH was 92. Reproducibility of MH assessments by HR-pQCT was already reported in our hands [11].

2.3. Statistical analysis

Due to a small number of subjects, demographic characteristics, biological data, and microarchitecture of MH were compared between DE+ and DE− groups or according to ACPA status by using non-parameter tests (Mann–Whitney test and χ^2 test). The statistical significance level was set at 0.05 and all data were analysed using GraphPad Prism 5.0 (GraphPad software, Inc, San Diego, CA, USA).

2.4. Role of the funding source

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3. Results

3.1. Demographic characteristics

Thirty-two RA patients were included in the study. They shared the main characteristics of RA patients treated with bDMARDs. Twelve were enrolled in the DE+ group and 20 in the DE-group (Table 1). Age, height, weight, BMI, disease duration, disease activity, serological status, inflammatory biomarkers, glucocorticoid dose, and bisphosphonate treatment were similar in both groups. ACPA was present in 10 (83%) and 14 (66%) patients in the DE+ and DE− groups, respectively (non significant, NS). Methotrexate was used in 16/20 patients (80%) in DE− group vs. 7/12 (58.3%) patients in DE + group (NS).

3.2. Comparison of vBMD and bone microarchitecture at MH

Cortical parameters Dcort and C.Th were similar in both groups (Table 2). In the trabecular compartment, while BV/TV and Tb.Th were not different, Dtrab and Tb.N were significantly lower in the DE+ group compared to the DE− group ($P < 0.001$ and $P < 0.05$, respectively). Furthermore, Tb.Sp and Tb.Sp*SD were higher in DE+ group than in DE− group ($P < 0.05$ for both). However, no differences were observed according to ACPA status. In the subset of ACPA positive patients, Tb.N, and Tb.Sp*SD were still lower in DE+ compared to DE- ($P < 0.05$ for both.

4. Discussion

Persistence of local inflammatory despite a clinical low RA disease activity may have deleterious effects on subchondral bone microarchitecture and such observations could potentially modify evaluation procedure as well as treatment management of the disease. In this study, using HRpQCT, we investigated for the first time bone microstructure changes related to local inflammation

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