Calcif Tissue Int (2012) 91:343–355
DOI 10.1007/s00223-012-9644-z

ORIGINAL RESEARCH

Bone Density and Microarchitecture: Relationship Between Hand, Peripheral, and Axial Skeletal Sites Assessed by HR-pQCT and DXA in Rheumatoid Arthritis

Tracy Y. Zhu · James F. Griffith · Ling Qin · Vivian W. Y. Hung · Tsz-Ning Fong · Anthony W. Kwok · Ping-Chung Leung · Edmund K. Li · Lai-Shan Tam

Received: 31 May 2012 / Accepted: 2 August 2012 / Published online: 4 September 2012

Abstract We assessed the relationship of bone density and microarchitecture between hand, peripheral, and axial skeletal sites using high-resolution peripheral quantitative computed tomography (HR-pQCT) and dual-energy X-ray absorptiometry (DXA) in patients with rheumatoid arthritis (RA) and which factors influence these parameters. This was a cross-sectional study of 100 female patients (53.4 ± 9.3 years) with RA. HR-pQCT scans at distal radius and the second metacarpal head were performed to assess cortical and trabecular volumetric bone mineral density (vBMD) and microarchitecture. DXA scans at the hip, lumbar spine, and ultradistal radius were performed to assess areal BMD. There was significant correlation in vBMD and microarchitectural parameters between the second metacarpal head and distal radius ($r = 0.201-0.628$). Areal BMD at the axial skeleton was moderately associated with vBMD at the peripheral sites ($r = 0.354$–0.558). Factors related to disease severity/chronicity significantly correlated with vBMD and microarchitecture at the distal radius and the second metacarpal head. Factors related to disease activity were more likely to correlate with vBMD and microarchitecture at the second metacarpal head but not those at the distal radius. HR-pQCT is a promising technique that is capable of providing detailed quantitative assessment of disease-associated periarticular bone loss at both cortical and trabecular bone compartments in patients with RA. Future longitudinal studies will be needed to investigate whether assessment by HR-pQCT can be used as a marker of disease activity and a predictor of disease progression in RA.

Keywords Rheumatoid arthritis · Osteoporosis · HR-pQCT · DXA

The authors have stated that they have no conflict of interest.

T. Y. Zhu · E. K. Li · L.-S. Tam
Department of Medicine and Therapeutics,
The Chinese University of Hong Kong,
Shatin, Hong Kong, China

J. F. Griffith
Department of Imaging and Interventional Radiology,
The Chinese University of Hong Kong,
Shatin, Hong Kong, China

L. Qin · V. W. Y. Hung · T.-N. Fong
Department of Orthopedics and Traumatology,
The Chinese University of Hong Kong,
Shatin, Hong Kong, China

A. W. Kwok · P.-C. Leung
The Jockey Club Centre for Osteoporosis Care and Control,
The Chinese University of Hong Kong,
Shatin, Hong Kong, China

L.-S. Tam (✉)
Department of Medicine and Therapeutics, The Prince of Wales Hospital, 9/F Clinical Sciences Building, 30-32 Ngan Shing Street, Shatin, N.T., Hong Kong, China
e-mail: lstam@cuhk.edu.hk

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease associated with both periarticular and generalized bone loss. Periarticular bone loss in the hands and feet is an early sign of RA and a predictor of subsequent radiographic joint damage [1]. Accelerated generalized osteoporosis at the axial and appendicular skeleton is common in RA in both females and males and is an important determinant of fracture risk [2]. The overall prevalence of osteoporosis in RA is in the order of 20–30 % at the spine and 7–26 % at the hip [3].

Dual-energy X-ray absorptiometry (DXA) and digital X-ray radiogrammetry (DXR) are two techniques widely

used to assess generalized and periarticular bone loss, respectively. DXA measures integral areal BMD (DXA-BMD) of cortical and trabecular bone. DXR measures areal BMD (DXR-BMD) of the second to fourth metacarpals to quantify cortical bone density and thickness [4]. In patients with RA, a reduction in hand DXR-BMD correlates well with increasing disease activity and severity [5]. Early DXR-BMD reduction is associated with the development of joint damage for up to 20 years [6, 7]. Studies on the relationship between DXA-BMD of the hip or spine and disease activity or severity of RA found inconsistent results [8–11]. Only a few studies have investigated the relationship between generalized and periarticular bone loss in RA, with a significant correlation being found between hip or spine DXA-BMD and DXR-BMD of the hand [12, 13].

Neither standard DXA nor DXR provides information on bone microarchitecture, an important component of bone quality [14]. High-resolution peripheral quantitative computed tomography (HR-pQCT), yielding isotropic voxel imaging of 82 μm at a tolerable radiation dose (3 μSv), has recently become available for assessment of cortical and trabecular volumetric bone mineral density (vBMD) and microarchitecture at the peripheral skeleton (distal radius, distal tibia, and metacarpals). Cortical and trabecular volumetric density and microarchitectural parameters by HR-pQCT can, independently of DXA-BMD, discriminate postmenopausal women with and without osteoporotic fracture [15]. Good reproducibility of HR-pQCT volumetric measurements at the second and third metacarpal heads with recognizable deterioration in trabecular density and microarchitecture at these sites has been found in patients with RA [16].

Detailed examination of the relationship between hand and generalized bone loss may provide insight into shared mechanisms between these two types of bone loss in RA. The primary aims of this study were to investigate (1) whether vBMD and microarchitectural measurements at the distal radius were significantly associated with those at the second metacarpal head and (2) whether vBMD at the distal radius and the second metacarpal head were significantly associated with areal BMD (aBMD) at the hip, lumbar spine, and distal radius. A secondary aim was to determine the clinical factors which influence cortical and trabecular vBMD and microachitecture of the distal radius and second metacarpal head in patients with RA.

Methods

Patients

A consecutive sample of 100 Chinese female patients with a diagnosis of RA was recruited for this cross-sectional study from the outpatient rheumatology clinic at the Prince of Wales Hospital in Hong Kong between August and October 2011. All patients fulfilled the American College of Rheumatology (ACR) 1987 revised classification criteria for RA [17]. Patients were excluded if they (1) had a known metabolic disorder that could affect bone metabolism, such as severe renal impairment (defined as a creatinine clearance of < 30 mL/min), thyroid or parathyroid disease, or malignancy; (2) were receiving treatment that affects bone metabolism, including antiresorptive drugs, thyroid or parathyroid hormone, and hormonal replacement therapy; or (3) were pregnant or breast-feeding. Patients with current or past use of glucocorticoids or calcium and vitamin D were not excluded. The study protocol was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee, with all participants providing written informed consent.

Clinical Assessment

Clinical characteristics of the patients were assessed by interview and clinical examination. Demographics included age, body weight, body height, menstrual status, and smoking and drinking status. The fracture history of the patients and their first-degree relatives was recorded. Only low-trauma fracture, defined as trauma equivalent to a fall from less than or equal to standing height or a fracture arising from trauma which would not normally be expected to result in fracture, were recorded. History of falls and number of falls in the previous year were also recorded.

Clinical characteristics of RA were divided into those related to disease activity and disease severity/chronicity. Assessment of disease activity included the number of tender/swollen joints (0–28), visual analogue scale (VAS) for pain (0–10 = most pain), VAS for patient global assessment (0–10 = worst score), and VAS for physician global assessment (0–10 = worst score), Disease Activity Score in 28 Joints (DAS28), and C-reactive protein (CRP, mg/dL). Disease remission was determined using Boolean criteria [18]. A patient was considered to be in disease remission if scores on the number of tender or swollen joints, patient global assessment, and CRP were all ≤ 1. Assessment of disease severity/chronicity included disease duration since diagnosis, number of deformed joints, global functional status according to the ACR 1991 revised criteria [19], disability according to the disability index of Health Assessment Questionnaire (HAQ) (0–3 = most functional disability), and presence of radiographically apparent erosions on the hands and wrists.

History of use (current, previous, and never) of the following disease-modifying antirheumatic drugs (DMARDs) was recorded: methotrexate, sulfasalazine, hydroxychloroquine,

leflunomide, azathioprine, oral or intramuscular gold, and biologics. Variables related to the use of oral glucocorticoids included current or previous use, current dose, duration of use, and cumulative dose. We found three types of oral glucocorticoids, prednisolone, hydrocortisone (one current user, two previous users), and dexamethasone (two previous users), ever or currently used by the cohort. All doses of glucocorticoids were converted to equivalent doses of oral prednisolone using the following algorithm: 1 mg hydrocortisone = 0.25 mg prednisolone, 1 mg dexamethasone = 6.67 mg prednisolone. Use of calcium supplements, vitamin D supplements, or multivitamin supplements was also recorded.

DXA Assessment

aBMD of the hip (total hip and femoral neck), lumbar spine (L1–L4, anteroposterior view), and ultradistal radius was determined by a trained technician using the same DXA equipment (model Hologic Delphi W, Bedford, MA) in all patients. Results were expressed in grams per centimeter squared, and T scores were calculated with reference to local population norms [20].

HR-pQCT Assessment

vBMD and microarchitecture at the distal radius and second metacarpal bone of the nondominant hand were evaluated by 3D HR-pQCT (XtremeCT; Scanco Medical AG; Bassersdorf; Switzerland). The patient's forearm was immobilized in a carbon fiber cast fixed within the scanner gantry. A dorsopalmar projection image was obtained to define the tomographic scan region. For the distal radius, the scan commenced 9.5 mm proximal to the midradiocarpal articular margin and spanned proximally 9.02 mm in length, equivalent to 110 contiguous acquisitions of 82 μm thickness. At the second metacarpal bone, the scan region started at the distal end of the metacarpal head and spanned proximally 9.02 mm (110 slices). Image analysis for the distal radius and second metacarpal head was performed separately. The entire volume of interest was automatically separated into cortical and trabecular areas, thus yielding average bone density (Dtotal), trabecular bone density (Dtrab), and cortical bone density (Dcort) in milligrams of hydroxyapatite (HA) per centimeter cubed. Mean cortical thickness (Ct.Th, millimeters) was defined as the mean cortical volume divided by the outer bone surface. Trabecular bone volume fraction (BV/TV) was derived from trabecular density assuming fully mineralized bone to have a mineral density of 1.2 g HA/cm^3. To assess trabecular topology and orientation, 3D ridges (i.e., the center points of trabeculae) were identified, and the spacing between them was assessed three-dimensionally using distance-transformation methods [21]. Trabecular number (Tb.N, 1 mm) was defined as the inverse of the mean 3D ridge spacing. Trabecular thickness (Tb.Th, millimeter; Tb.Th = BV/TV/Tb.N) and spacing (Tb.Sp, millimeter; Tb.Sp = [1–BV/TV]/Tb.N) were derived from BV/TV and Tb.N analogous to standard bone histomorphometry. The standard deviation of 1/Tb.N (Tb.1/N.SD, millimeter) was used to reflect inhomogeneity of the trabecular network. At the distal radius, the short-term in vivo precision error of density measurements, expressed as the coefficient of variance (CV) was 0.7–1.5 %, while that for microarchitectural parameters was 0.9–4.4 % [22]. At the second metacarpal head, the CVs for density measurement were 0.7–1.8 %, while that for microarchitectural parameters was 3.3–12.5 % [16].

Statistical Analyses

Statistical analyses were performed using the Statistics Package for Social Sciences (SPSS for Windows, version 13.0; SPSS, Inc., Chicago, IL). Correlations between vBMD and microarchitectural parameters at the distal radius and those at the second metacarpal head were analyzed using Pearson's or Spearman's correlation depending on data distribution. The relationships between vBMD and microarchitectural parameters and demographic and clinical characteristics were examined using Pearson's correlation or the two-sample t test for normal continuous variables and Spearman's correlation or the Mann–Whitney U test for non-normal continuous variables. Variables with $p < 0.1$ in the univariate analyses were entered into linear regression (enter selection) with cortical and trabecular vBMD and microarchitectural parameters as the dependent outcomes. All hypotheses were two-tailed, and $p < 0.05$ was considered significant.

Results

Characteristics of the Cohort

Table 1 shows the demographic and clinical characteristics of the 100 Chinese patients included in the study. The cohort consisted of middle-aged females with a mean disease duration of 9.1 years. The majority (67 %) of the 100 patients were postmenopausal. Overall, the cohort had mild disease activity as evidenced by a mean DAS28 score of 3.7; a largely preserved functional status, with only 14 patients having ACR functional class III or above; and mild disability, with a median HAQ score of 0.38. Only six patients were classified as being in disease remission. Forty-nine patients had erosive disease at the wrists or hands. Of these, 32 patients had erosions at the hands and 35 patients had erosions at the wrists. Seven patients had joint replacement, three of whom had more than one joint

Table 1 Demographic and clinical characteristics of the 100 rheumatoid arthritis patients

Variable	All patients ($n = 100$)
Demographics	
Age (years)	53.4 ± 9.3
Body weight (kg)	54.1 ± 9.8
Body height (m)	1.6 ± 0.1
Postmenopausal (%)	67
Current smoker (%)	6
Current drinker (%)	29
Falls in the previous year (%)	22
Fracture, first degree relative (%)	10
Fracture, after age 25 (%)	7
Disease activity	
Number of tender joints (0–28)	1 (0–4)
Number of swollen joints (0–28)	1 (0–2.8)
Pain, VAS 0–10	4 (2–6)
Patient global assessment, VAS 0–10	4 (2–6)
Physician global assessment, VAS 0–10	1 (0.4–2.6)
CRP (mg/dL)	0.3 (0.1–0.7)
DAS28 score	3.7 ± 1.2
Boolean remission (%)	6
Disease severity/chronicity	
Disease duration (years)	9.1 ± 7.8
Number of deformed joints	0 (0–3.8)
ACR functional class III or above (%)	14
Health Assessment Questionnaire, 0–3	0.38 (0.13–1)
Erosive disease (%)	49
Treatment	
MTX current/previous/never user (%)	74/10/16
SSZ current/previous/never user (%)	19/37/44
HCQ current/previous/never user (%)	17/37/46
Leflunomide current/previous/never user (%)	22/18/60
Biologic current/previous/never user (%)	7/13/80
Oral glucocorticoids	
Current users (%)	19
Current dose (mg/day)[a]	5 (2.5–10)
Previous users (%)	30
Cumulative dose (g)[a]	1.3 (0.5–3.2)
Cumulative duration (months)[a]	10 (3.3–24.5)

Results are mean ± SD or median (interquartile range) unless otherwise indicated

VAS visual analogue scale, *CRP* C-reactive protein, *DAS28* Disease Activity Score in 28 Joints, *ACR* American College of Rheumatology, *MTX* methotrexate, *SSZ* sulfasalazine, *HCQ* hydroxychloroquine

[a] Cumulative dose/duration for current and previous users. Results were equivalent doses of oral prednisolone. Cumulative dose/duration for two previous users was not calculable due to lack of records

replacement. The majority (93 %) of the patients were currently on DMARDs, with 32 patients currently on more than one DMARDs. Methotrexate was the most commonly used DMARD, followed by leflunomide. Only seven patients were currently on biologics, including one on infliximab, two on adalimumab, and four on etanercept. The last use of oral glucocorticoids among the 30 previous users occurred at an average 6.3 years (median 4 years, range 1 month–20 years) prior to the study. Only 16 patients were currently on supplements of calcium or multivitamin, while 19 patients were currently on oral glucocorticoids.

Relationship Between vBMD and Microarchitectural Parameters at the Distal Radius and the Second Metacarpal Head

Significant correlations were found between vBMD and microarchitectural parameters at the distal radius and the second metacarpal head (Table 2). This included moderate correlation between total and trabecular, but not cortical, vBMD. Weak to moderate correlation was found between microarchitectural parameters at the distal radius and second metacarpal head, with the strongest correlation being for trabecular bone volume fraction and the weakest being for trabecular thickness.

Table 2 Correlations between vBMD and microarchitectural parameters at the distal radius and at the second metacarpal head

Variable	Correlation coefficient	*p*
Dtotal (mg HA/cm^3)	0.628	<0.0001
Dcort (mg HA/cm^3)	0.379	<0.0005
Dtrab (mg HA/cm^3)	0.564	<0.0001
Ct.Th (mm)	0.406	<0.0001
BV/TV	0.565	<0.0001
Tb.N (1/mm)	0.539	<0.0001
Tb.Th (mm)	0.201	0.045
Tb.Sp (mm)	0.410	<0.0001
Inhomogeneity (mm)	0.298	0.003

vBMD volumetric bone mineral density, *Dtotal* average bone density, *Dcort* cortical bone density, *Dtrab* trabecular bone density, *Ct.Th* cortical thickness, *BV/TV* trabecular bone volume fraction, *Tb.N* trabecular number, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, *inhomogeneity* the standard deviation of 1/trabecular number, *HA* hydroxyapatite

Relationship Between aBMD of the Hip, Lumbar Spine, and Ultradistal Radius with vBMD of the Distal Radius and Second Metacarpal Head

Seventeen (17 %) patients had osteoporosis (T score ≤ -2.5 at either the hip or lumbar spine) and low bone mass (T score <-1.0 but >-2.5 at either the hip or lumbar spine) was present in 37 patients. aBMD of the hip, lumbar spine, and ultradistal radius correlated moderately with vBMD measurements of the distal radius and metacarpal heads (Table 3). As expected, a strong correlation was observed between aBMD at the ultradistal radius and Dtotal at the distal radius ($r = 0.870$).

Factors Influencing Cortical and Trabecular vBMD and Microarchitectural Parameters at the Distal Radius in Patients with RA

Univariate analyses

Age had a significant negative correlation with nearly all vBMD and microarchitectural parameters at the distal radius (Table 4). Body weight and body height correlated positively with Dtrab and several trabecular microarchitectural parameters. Postmenopausal patients had significantly lower vBMD and inferior microarchitecture compared with premenopausal patients (Table 5). Smoking and drinking habit, fracture history, and fall in the previous year did not influence any vBMD and microarchitectural parameters at the distal radius (data not shown).

Several factors related to disease activity significantly correlated with at least one vBMD and microarchitectural parameters at the distal radius, though no consistent pattern was observed. Patient global assessment correlated with trabecular vBMD and microarchitecture (Dtrab and BV/TV), while DAS28 score and CRP level correlated with cortical vBMD and microarchitecture (Dcort and Ct.Th) (Table 4). Disease remission correlated with both trabecular and cortical vBMD and microarchitecture (Dtrab, Dcort, Ct.Th, BV/TV, and Tb.Th) (Table 5).

There was a more uniform correlation between clinical factors related to disease severity/chronicity and vBMD or microarchitectural parameters at the distal radius. Disease duration significantly correlated with trabecular vBMD and microarchitecture (Dtrab, BV/TV, Tb.N, and Tb.Sp), while the number of deformed joints correlated with both trabecular and cortical vBMD and trabecular microarchitecture (Dcort, Dtrab, and BV/TV) (Table 4). Patients with functional class III or with erosive disease had significantly lower trabecular vBMD and inferior trabecular microarchitecture compared to those with functional class I/II or those with nonerosive disease, respectively (Table 5).

Factors related to treatment, including use of DMARDs, number of current DMARDs, use of biologics, use of oral glucocorticoids, cumulative dose, and duration of oral glucocorticoids did not influence any vBMD and microarchitectural parameters at the distal radius.

Multivariate Analyses

In addition to demographics, factors independently associated with vBMD and microarchitectural parameters at the distal radius were mostly related to disease severity/chronicity (Table 6). Functional status and erosive disease were independent explanatory variables associated with trabecular vBMD and microarchitecture (Dtrab, BV/TV, Tb.N, and Tb.Sp), while the number of deformed joints was independently associated with cortical vBMD (Dcort). CRP level was the only factor related to disease activity that remained in the multivariate analyses and was shown to be independently associated with cortical vBMD (Dcort). No clinical factors were independently associated with Ct.Th, Tb.Th, or inhomogeneity of the trabecular network.

Table 3 Relationships between aBMD by DXA and vBMD by HR-pQCT

Variable	aBMD femoral neck	aBMD total hip	aBMD lumbar spine	aBMD ultradistal radius
Distal radius				
Dtotal (mg HA/cm^3)	0.549	0.546	0.550	0.870
Dcort (mg HA/cm^3)	0.413	0.447	0.382	0.629
Dtrab (mg HA/cm^3)	0.500	0.494	0.561	0.639
Second metacarpal head				
Dtotal (mg HA/cm^3)	0.427	0.500	0.570	0.610
Dcort (mg HA/cm^3)	0.436	0.475	0.541	0.528
Dtrab (mg HA/cm^3)	0.441	0.527	0.573	0.626

All correlation coefficients are significant (all $p < 0.0001$)

BMD bone mineral density, *DXA* dual-energy X-ray absorptiometry, *vBMD* volumetric BMD, *HR-pQCT* high-resolution peripheral quantitative computed tomography, *Dtotal* average bone density, *Dcort* cortical bone density, *Dtrab* trabecular bone density, *HA* hydroxyapatite

Table 4 Univariate analyses between continuous demographic and clinical variables and volumetric bone mineral density and microarchitecture at the distal radius and at the second metacarpal head

Variable	Demographics			Disease activity						Disease severity/chronicity		
	Age	Body weight	Body height	No. of tender joints	No. of swollen joints	Pain	Patient global assessment	CRP	DAS28 score	Disease duration	HAQ score	No. of deformed joints
Distal radius												
Dcort (mg HA/cm^3)	−0.426*	0.038	0.017	−0.034	−0.100	−0.07	−0.120	−0.369*	−0.215*	−0.199*	−0.168	−0.214*
Dtrab (mg HA/cm^3)	−0.305*	0.191	0.238*	0.052	−0.162	−0.185	−0.231*	−0.109	−0.020	−0.151	−0.061	−0.260*
Ct.Th (mm)	−0.391*	0.175	0.088	−0.037	−0.048	−0.054	−0.036	−0.200*	−0.163	−0.047	−0.091	−0.090
BV/TV	−0.306*	0.191	0.238*	0.052	−0.162	−0.185	−0.232*	−0.110	−0.020	−0.152	−0.065	−0.262*
Tb.N (1/mm)	−0.288*	0.339*	0.314*	0.111	−0.125	−0.104	−0.148	−0.066	0.071	−0.200*	−0.011	−0.196
Tb.Th (mm)	−0.172	−0.091	0.050	0.027	−0.085	−0.122	−0.170	−0.032	−0.087	−0.007	−0.031	−0.143
Tb.Sp (mm)	0.306*	−0.238*	−0.193	−0.105	0.132	0.118	0.171	0.077	−0.038	0.212*	0.018	0.213*
Inhomogeneity (mm)	0.279*	−0.181	−0.126	−0.102	0.137	0.053	0.138	0.071	0.009	0.145	0.032	0.188
Second metacarpal head												
Dcort (mg HA/cm^3)	−0.126	0.233*	0.024	−0.166	−0.217*	−0.244*	−0.167	−0.238*	−0.208*	−0.079	−0.291*	−0.178
Dtrab (mg HA/cm^3)	−0.273*	0.227*	0.048	−0.089	−0.139	−0.153	−0.183	−0.393*	−0.189	−0.291*	−0.193	−0.336*
Ct.Th (mm)	−0.063	0.181	−0.021	−0.17	−0.163	−0.254*	−0.18	−0.173	−0.208*	−0.013	−0.297*	−0.166
BV/TV	−0.274*	0.228*	0.048	−0.093	−0.144	−0.155	−0.185	−0.396*	−0.189	−0.291*	−0.194	−0.337*
Tb.N (1/mm)	−0.194	0.249*	0.137	0.091	−0.209*	−0.044	0.023	−0.246*	0	−0.303*	0.019	−0.311*
Tb.Th (mm)	−0.078	−0.006	−0.091	−0.214*	−0.021	−0.181	−0.244*	−0.176	−0.168	0	−0.272*	−0.081
Tb.Sp (mm)	0.250*	−0.243*	−0.129*	−0.055	0.230*	0.066	0.014	0.298*	0.048	0.356*	0.021	0.339*
Inhomogeneity (mm)	0.283*	−0.220*	−0.207*	−0.087	0.271*	0.040	0.048	0.248*	0.063	0.299*	0.006	0.240*

Results are presented as correlation coefficients. Physician global assessment did not associate with any vBMD or microarchitectural parameter (not shown in the table)

CRP C-reactive protein, *DAS28* Disease Activity Score in 28 Joints, *HAQ* Health Assessment Questionnaire, *Dtotal* average bone density, *Dcort* cortical bone density, *Dtrab* trabecular bone density, *Ct.Th* cortical thickness, *BV/TV* trabecular bone volume fraction, *Tb.N* trabecular number, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, *inhomogeneity* standard deviation of 1/trabecular number, *HA* hydroxyapatite

* $p < 0.05$

Table 5 Volumetric bone mineral density and microarchitecture at the distal radius and at the second metacarpal head of study subjects according to menstrual status, disease remission, functional status, and erosive disease

Variable	Demographics		Disease activity		Disease severity/chronicity			
	Premenopause ($n = 33$)	Postmenopause ($n = 67$)	Not in disease remission ($n = 94$)	In disease remission ($n = 6$)	ACR functional class I/II ($n = 86$)	ACR functional class III ($n = 14$)	Non-erosive disease ($n = 49$)	Erosive disease ($n = 49$)
Distal radius								
Dcort (mg HA/cm^3)	951 ± 48	884 ± 75*	902 ± 74	965 ± 62*	907 ± 74	899 ± 76	918 ± 66	893 ± 79
Dtrab (mg HA/cm^3)	134 ± 32	107 ± 45*	113 ± 42	161 ± 32*	120 ± 43	89 ± 37*	128 ± 40	102 ± 43*
Ct.Th. (mm)	1.02 ± 0.21	0.82 ± 0.21*	0.87 ± 0.23	1.07 ± 0.20*	0.89 ± 0.23	0.82 ± 0.23	0.87 ± 0.19	0.89 ± 0.26
BV/TV	0.11 ± 0.03	0.09 ± 0.04*	0.09 ± 0.04	0.13 ± 0.03*	0.10 ± 0.04	0.07 ± 0.03*	0.11 ± 0.03	0.09 ± 0.04*
Tb.N (1/mm)	1.52 ± 0.24	1.32 ± 0.41*	1.37 ± 0.38	1.65 ± 0.20	1.42 ± 0.35	1.17 ± 0.47*	1.47 ± 0.26	1.29 ± 0.44
Tb.Th (mm)	0.074 ± 0.01	0.066 ± 0.02*	0.07 ± 0.01	0.08 ± 0.02*	0.07 ± 0.02	0.07 ± 0.01	0.07 ± 0.02	0.07 ± 0.01
Tb.Sp (mm)	0.60 ± 0.11	0.81 ± 0.47*	0.75 ± 0.41	0.53 ± 0.06	0.70 ± 0.35	1.00 ± 0.59*	0.63 ± 0.14	0.86 ± 0.53*
Inhomogeneity (mm)	0.26 ± 0.06	0.43 ± 0.41*	0.38 ± 0.36	0.24 ± 0.03	0.33 ± 0.29	0.61 ± 0.55	0.28 ± 0.09	0.47 ± 0.47
Second metacarpal head								
Dcort (mg HA/cm^3)	548 ± 78	497 ± 76*	509 ± 78	591 ± 86*	520 ± 80	479 ± 73*	525 ± 76	500 ± 83
Dtrab (mg HA/cm^3)	222 ± 30	192 ± 41*	200 ± 40	231 ± 26	203 ± 40	193 ± 37	208 ± 38	193 ± 40
Ct.Th (mm)	0.19 ± 0.11	0.13 ± 0.08*	0.14 ± 0.09	0.23 ± 0.11*	0.15 ± 0.10	0.12 ± 0.07	0.15 ± 0.09	0.14 ± 0.10
BV/TV	0.18 ± 0.03	0.16 ± 0.03*	0.17 ± 0.03	0.19 ± 0.02	0.17 ± 0.03	0.16 ± 0.03	0.17 ± 0.03	0.16 ± 0.03
Tb.N (1/mm)	1.86 ± 0.27	1.77 ± 0.34	1.78 ± 0.32	2.03 ± 0.30	1.80 ± 0.32	1.82 ± 0.36	1.86 ± 0.31	1.73 ± 0.34
Tb.Th (mm)	0.10 ± 0.02	0.09 ± 0.02*	0.09 ± 0.02	0.10 ± 0.01	0.10 ± 0.02	0.09 ± 0.02	0.09 ± 0.02	0.09 ± 0.02
Tb.Sp (mm)	0.45 ± 0.07	0.50 ± 0.14*	0.49 ± 0.12	0.41 ± 0.07	0.48 ± 0.12	0.48 ± 0.11	0.46 ± 0.09	0.51 ± 0.14*
Inhomogeneity (mm)	0.26 ± 0.07	0.34 ± 0.19*	0.32 ± 0.17	0.23 ± 0.08	0.31 ± 0.17	0.34 ± 0.17	0.27 ± 0.10	0.36 ± 0.21

Between-group comparisons were by two-sample *t* test (Dcort, Dtrab, Ct.Th, BV/TV, Tb.N, and Tb.Th) or Mann–Whitney *U* test (Tb.Sp and inhomogeneity)

ACR American College of Rheumatology, *Dtotal* average bone density, *Dcort* cortical bone density, *Dtrab* trabecular bone density, *Ct.Th* cortical thickness, *BV/TV* trabecular bone volume fraction, *Tb.N* trabecular number, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, *inhomogeneity* standard deviation of 1/trabecular number, *HA* hydroxyapatite

* $p < 0.05$

Table 6 Final multivariate regression model showing coefficient (95 % confidence interval) of independent explanatory variables associated with volumetric bone mineral density and microarchitectural parameters at the distal radius

Variable	Dcort	Dtrab	Ct.Th	BV/TV	Tb.N	Tb.Th	Tb.Sp	Inhomogeneity
Demographics								
Age (per 1 year)	−2.9 (−4.3,−1.6)	−1.0 (−1.9,−0.1)			−0.01 (−0.02, −0.004)		0.01 (0.004, 0.02)	0.01 (0.003, 0.018)
Body weight (per 1 kg)					0.01 (0.005, 0.02)			
Postmenopausal			−0.2 (−0.3, −1.0)	−0.02 (−0.03, −0.002)				
Disease activity								
CRP (per 1 mg/dL)	−22 (−38, −6.5)							
Disease severity/chronicity								
ACR function III		−25 (−48, −0.8)		−0.02 (−0.04, −0.002)	−0.2 (−0.4, −0.002)		0.27 (0.06, 0.49)	
No. of deformed joints (per 1 joint)	−3.4 (−6.0, −0.9)							
Erosive disease		−20 (−36, −3.2)		−0.02 (−0.03, −0.003)			0.18 (0.03, 0.33)	
R^2	0.333	0.271	0.182	0.273	0.255	–	0.244	0.078

Dtotal average bone density, *Dcort* cortical bone density, *Dtrab* trabecular bone density, *Ct.Th* cortical thickness, *BV/TV* trabecular bone volume fraction, *Tb.N* trabecular number, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, *inhomogeneity* standard deviation of 1/trabecular number, *HA* hydroxyapatite, *CRP* C-reactive protein, *ACR* American College of Rheumatology

Factors Influencing Cortical and Trabecular vBMD and Microarchitectural Parameters at the Second Metacarpal Head in Patients with RA

Univariate Analyses

Menstrual status significantly correlated with all vBMD and microarchitectural parameters, except Tb.N, at the second metacarpal head (Table 5), while age only significantly correlated with trabecular vBMD and microarchitecture (Table 4). Body weight correlated with vBMD and trabecular microarchitecture, while body height correlated with Tb.Sp and inhomogeneity of the trabecular network (Table 4). Smoking and drinking habit, fracture history, and fall in the previous year did not influence any vBMD and microarchitectural parameters at the second metacarpal head (data not shown).

There was more extensive correlation between factors related to disease activity and vBMD and microarchitectural parameters at the second metacarpal head than at the distal radius. The number of tender joints and patient global assessment both significantly correlated with Tb.Th, while pain and DAS28 score significantly correlated with cortical vBMD and microarchitecture (Dcort and Ct.Th) (Table 4). The number of swollen joints and CRP level significantly correlated with both cortical and trabecular vBMD and microarchitecture (Table 4). Patients in disease remission had significantly higher cortical vBMD and Ct.Th values compared with those not in disease remission (Table 5).

There was also a uniform correlation between clinical factors related to disease severity/chronicity and vBMD or microarchitectural parameters at the second metacarpal head. Disease duration and the number of deformed joints significantly correlated with trabecular vBMD and microarchitecture (Dtrab, BV/TV, Tb.N, Tb.Sp, and inhomogeneity of trabecular network) (Table 4). HAQ score correlated with both cortical and trabecular vBMD and microarchitecture (Dcort, Ct.Th, and Tb.Th) (Table 4). Functional status and erosive disease did not influence any vBMD and microarchitectural parameters, except Dcort and Tb.Sp, respectively (Table 5).

Similar to the distal radius, factors related to treatment did not influence any vBMD and microarchitectural parameters at the second metacarpal head.

Multivariate Analyses

In addition to demographics, both factors related to disease activity and disease severity/chronicity were independently associated with vBMD and microarchitectural parameters at the second metacarpal head (Table 7). The number of swollen joints was an independent explanatory variable associated with cortical vBMD only (Dcort), while CRP level and the number of deformed joints independently associated with trabecular vBMD and microarchitectural parameters (Dtrab, BV/TV, Tb.N, Tb.Sp, and inhomogeneity of trabecular network). HAQ score independently associated with cortical vBMD and microarchitectural parameters (Dcort and Ct.Th) along with Tb.Th.

Discussion

This is the first study to investigate the relationship between vBMD and microarchitectural parameters of the distal radius and hand and to explore the influence of demographic and clinical factors on vBMD and microarchitectural parameters at these sites in patients with RA. Such a study is relevant to further our understanding of the pathogenesis of RA-associated osteoporosis and bone fragility.

Periarticular osteoporosis is an early and common feature of RA and could be the first disease-associated morphological change, preceding erosion or joint space narrowing. Innovative technology assessing periarticular bone loss would be helpful in identifying patients at risk of aggressive disease. The commonly used DXR-BMD has been shown to be a predictor of subsequent joint damage and to allow assessment of anti-inflammatory therapeutic effects [23]. But DXR assesses only the cortical compartment of bone, while periarticular osteoporosis in RA may stem also from the trabecular compartment [16]. HR-pQCT is capable of assessing vBMD and microarchitecture of both cortical and trabecular bone compartments. Our results showed that vBMD assessed by HR-pQCT significantly correlated with aBMD at the peripheral and central skeleton, and there were significant correlations between vBMD, microarchitectural parameters, and disease activity and severity parameters. These findings suggest that HR-pQCT might be a promising technique capable of providing detailed quantitative assessment of disease-associated periarticular bone loss at the distal radius and metacarpal head. Future longitudinal studies will be needed to investigate whether such assessment by HR-pQCT can be used as a marker of disease activity and a predictor of disease progression in RA.

aBMD at the axial skeletal moderately correlated with vBMD at the distal radius and hand. This is expected as DXA measures integral bone density (combined trabecular and cortical BMD) and is influenced by bone size, unlike vBMD. In addition, the proximity to sites of synovitis (hands and wrists) might influence the relationship between the axial and peripheral skeletal sites. This is particularly true for the metacarpal head since this site was in contact with the synovium of the metacarpophalangeal joint. In

Table 7 Final multivariate regression model showing coefficient (95 % confidence interval) of independent explanatory variables associated with volumetric bone mineral density and microarchitectural parameters at the second metacarpal head

Variable	Dcort	Dtrab	Ct.Th	BV/TV	Tb.N	Tb.Th	Tb. Sp	Inhomogeneity
Demographics								
Age (per 1 year)							0.003 (0, 0.005)	0.004 (0.001, 0.008)
Body weight (per 1 kg)	1.7 (0.3, 3.1)				0.006 (0, 0.012)		−0.002 (−0.004, 0)	
Postmenopausal	−39 (−70, −7)	−24 (−38, −10)	−0.05 (−0.09, −0.01)	−0.02 (−0.03, −0.01)				
Disease activity								
No. of swollen joints (per 1 joint)	−10 (−17, −2)							
CRP (per 1 mg/dL)		−13 (−22, −5)		−0.01 (−0.02, −0.004)			0.03 (0.01, 0.06)	
Disease severity/chronicity								
No. of deformed joints (per 1 joint)		−1.8 (−3.2, −0.5)		−0.002 (−0.003, 0)	−0.03 (−0.04, −0.02)		0.01 (0.006, 0.014)	0.01 (0.01, 0.02)
HAQ score (per 1 unit)	−53 (−82, −24)		−0.05 (−0.08, −0.02)			−0.008 (−0.015, −0.001)		
R^2	0.323	0.321	0.198	0.322	0.273	0.108	0.398	0.307

Dtotal average bone density, *Dcort* cortical bone density, *Dtrab* trabecular bone density, *Ct.Th* cortical thickness, *BV/TV* trabecular bone volume fraction, *Tb.N* trabecular number, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, *inhomogeneity* standard deviation of 1/trabecular number, *CRP* C-reactive protein, *HAQ* Health Assessment Questionnaire

contrast, the distal radius site was slightly (9.5 mm) removed from the wrist joint. We found a weak to moderate correlation of vBMD and microarchitectural parameters between the distal radius and the second metacarpal head. This can be explained by the difference in bone composition between the two sites. At the second metacarpal head, the bone composition is mainly trabecular, while at the distal radius, although there is an appreciable trabecular component, cortical bone tends to predominate [22]. In addition, erosion, which occurs more commonly at the second metacarpal head than at the scan region of the distal radius [24], might also weaken the relationship between these two sites since this affects cortical more than trabecular bone.

Clinical characteristics of RA contributed differently to vBMD and microarchitecture at the distal radius compared to the second metacarpal head. Factors related to disease severity/chronicity correlated well with vBMD and microarchitecture at both sites. This is in concordance with previous DXA and DXR studies showing decreased BMD at the spine, hip, or hand, in line with decreased ACR functional class, increased HAQ scores, and increased erosive disease [7, 25–27]. In contrast, factors related to disease activity correlated well with vBMD and microarchitecture at the second metacarpal head but much less so at the distal radius. This again is most likely the result of the second metacarpal head being influenced by synovitis in the adjacent metacarpophalangeal joint. Disease activity, as opposed to disease chronicity/severity, has not been shown to affect bone density at more distal sites [9, 26]. For a cross-sectional study, factors related to disease severity/chronicity could be an appropriate measure of past cumulative disease activity. An increased CRP level independently associated with reduced cortical vBMD in final multivariate regression analysis still supports a role for inflammation in the pathogenesis of generalized bone loss in RA [28, 29]. Furthermore, one clinical variable usually correlated with vBMD and/or microarchitecture of either the cortical or trabecular bone compartment. This indicates that improvement in an isolated clinical factor may not be sufficient to improve both cortical and trabecular bone density and microarchitecture. Aggressive anti-inflammatory therapies, capable of suppressing composite disease activity and halting progression to more advanced disease status, may likewise have the potential to preserve bone quality in RA.

We did not find any significant relationship between factors related to therapy and vBMD and microarchitecture at either the distal radius or hand in RA. In determining the net effect of therapy, particularly glucocorticoids, on bone density and quality in RA, one should bear in mind the dual effect of this therapy. While glucocorticoids will significantly inhibit bone formation, they also will suppress disease activity and restore functional capacity, which will reduce bone resorption. Several studies reported no or limited effect of oral glucocorticoids on generalized bone loss in RA [30, 31]. The overall use of glucocorticoids in our study cohort was low as reflected by a short duration of cumulative use and a relatively low cumulative dose. Ibanez et al. [32], in their 2-year study of 100 patients with early arthritis, concluded that use of oral glucocorticoids, as a "bridge therapy" in patients with severe disease, does not seem to significantly decrease aBMD at the femoral neck, total hip, or lumbar spine.

Our study has several limitations. First, although the reproducibility of HR-pQCT measures at the second metacarpal head was comparable to that at the distal radius [16], hand positioning and image analyses among patients with RA, especially among those with severe articular deformation, can be difficult compared to healthy subjects. Such difficulty may lead to obliquity of the scan plane at the second metacarpal head, which may be reflected in the only modest correlation between the distal radius and the second metacarpal head. Second, we used the built-in default analysis program to assess cortical bone at the second metacarpal head. This default analysis is based on a simple segmentation process, which may not perform optimally for moderately thin or porous cortices [33]. This could influence measurements of cortical bone at the second metacarpal head. A direct quantitative measure of cortical bone density and microarchitecture may provide a truer measurement of cortical parameters [34]. Third, we did not quantify erosive disease using radiological scoring in our cohort. A significant relationship between the level of bone erosion and vBMD and microarchitecture at the distal radius or the second metacarpal head may provide valuable clinical information using HR-pQCT to assess periarticular bone loss in RA. Fourth, our cohort may have overrepresented patients with mild and moderate disease because subjects were exclusively recruited from an outpatient clinic. Fifth, most of the correlations between individual clinical variables and vBMD and microarchitecture were weak and insignificant. This might be due to the small sample size of our study and the relatively large number of correlations being investigated. Hence, results from the multivariate regression analyses examining the independent explanatory variables might provide a more useful assessment of such correlations. Finally, the cross-sectional design does not allow a true cause–effect relationship between clinical characteristics and bone vBMD or microarchitecture to be established. A longitudinal study is needed to further determine the influence of disease activity on periarticular bone and investigate the sensitivity of HR-pQCT in detecting periarticular bone loss in RA. Our experience in this cross-sectional study will help with the design of such a prospective study.

In conclusion, among female patients with RA, vBMD and microarchitectural measures of the distal radius had a weak to moderate correlation with those at the second metacarpal head. A moderate correlation between aBMD in the axial skeleton and vBMD at the peripheral skeleton was also found. Disease activity affected density and microarchitectural parameters at the metacarpal head only, while parameters related to disease severity/chronicity of RA had an effect at both the distal radius and metacarpal head. Aggressive anti-inflammatory therapies, capable of suppressing composite disease activity and halting disease progression, could potentially be effective in preserving bone quality in RA. Our results show that HR-pQCT is a promising technique capable of providing quantitative assessment of hand bone loss in RA patients. Its usefulness in predicting disease progression and assessing the therapeutic effect in RA should be assessed in future longitudinal studies.

Acknowledgments The authors thank Dr. Arthur L. S. Lui, Providence Foundation, for the generous financial support of this study. The authors acknowledge Ms. Betty Au for her assistance in performing the DXA scans. The funder had no role in the study design, data collection, data analysis, and production of the manuscript. The authors independently interpreted the results and made the final decision to submit the manuscript for publication.

References

1. Forslind K, Boonen A, Albertsson K, Hafstrom I, Svensson B (2009) Hand bone loss measured by digital X-ray radiogrammetry is a predictor of joint damage in early rheumatoid arthritis. Scand J Rheumatol 38:431–438
2. Orstavik RE, Haugeberg G, Uhlig T, Falch JA, Halse JI, Hoiseth A, Lilleas F, Kvien TK (2003) Vertebral deformities in 229 female patients with rheumatoid arthritis: associations with clinical variables and bone mineral density. Arthritis Rheum 49:355–360
3. Roux C (2011) Osteoporosis in inflammatory joint diseases. Osteoporos Int 22:421–433
4. Böttcher J, Pfeil A, Petrovitch A, Schmidt M, Kramer A, Schäfer ML, Gajda M, Hein G, Wolf G, Kaiser WA (2006) Metacarpal index estimated by digital X-ray radiogrammetry as a tool for differentiating rheumatoid arthritis related periarticular osteopenia. Int J Biomed Sci 2:241–250
5. Bottcher J, Pfeil A, Rosholm A, Petrovitch A, Seidl BE, Malich A, Schafer ML, Kramer A, Mentzel HJ, Lehmann G, Hein G, Kaiser WA (2005) Digital X-ray radiogrammetry combined with semiautomated analysis of joint space widths as a new diagnostic approach in rheumatoid arthritis: a cross-sectional and longitudinal study. Arthritis Rheum 52:3850–3859
6. Kapetanovic MC, Lindqvist E, Algulin J, Jonsson K, Saxne T, Eberhardt K, Geborek P (2011) Early changes in bone mineral density measured by digital X-ray radiogrammetry predict up to 20 years radiological outcome in rheumatoid arthritis. Arthritis Res Ther 13:R31
7. Hoff M, Haugeberg G, Odegard S, Syversen S, Landewe R, van der Heijde D, Kvien TK (2009) Cortical hand bone loss after 1 year in early rheumatoid arthritis predicts radiographic hand joint damage at 5-year and 10-year follow-up. Ann Rheum Dis 68:324–329
8. Guler-Yuksel M, Bijsterbosch J, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Hulsmans HM, de Beus WM, Han KH, Breedveld FC, Dijkmans BA, Allaart CF, Lems WF (2008) Changes in bone mineral density in patients with recent onset, active rheumatoid arthritis. Ann Rheum Dis 67:823–828
9. Lodder MC, de Jong Z, Kostense PJ, Molenaar ET, Staal K, Voskuyl AE, Hazes JM, Dijkmans BA, Lems WF (2004) Bone mineral density in patients with rheumatoid arthritis: relation between disease severity and low bone mineral density. Ann Rheum Dis 63:1576–1580
10. Solomon DH, Finkelstein JS, Shadick N, LeBoff MS, Winalski CS, Stedman M, Glass R, Brookhart MA, Weinblatt ME, Gravallese EM (2009) The relationship between focal erosions and generalized osteoporosis in postmenopausal women with rheumatoid arthritis. Arthritis Rheum 60:1624–1631
11. Martin JC, Munro R, Campbell MK, Reid DM (1997) Effects of disease and corticosteroids on appendicular bone mass in postmenopausal women with rheumatoid arthritis: comparison with axial measurements. Br J Rheumatol 36:43–49
12. Rosholm A, Hyldstrup L, Backsgaard L, Grunkin M, Thodberg HH (2001) Estimation of bone mineral density by digital X-ray radiogrammetry: theoretical background and clinical testing. Osteoporos Int 12:961–969
13. Desai SP, Gravallese EM, Shadick NA, Glass R, Cui J, Frits M, Chibnik LB, Maher N, Weinblatt ME, Solomon DH (2010) Hand bone mineral density is associated with both total hip and lumbar spine bone mineral density in post-menopausal women with RA. Rheumatology (Oxford) 49:513–519
14. Fouque-Aubert A, Chapurlat R, Miossec P, Delmas PD (2010) A comparative review of the different techniques to assess hand bone damage in rheumatoid arthritis. Joint Bone Spine 77: 212–217
15. Sornay-Rendu E, Boutroy S, Munoz F, Delmas PD (2007) Alterations of cortical and trabecular architecture are associated with fractures in postmenopausal women, partially independent of decreased BMD measured by DXA: the OFELY study. J Bone Miner Res 22:425–433
16. Fouque-Aubert A, Boutroy S, Marotte H, Vilayphiou N, Bacchetta J, Miossec P, Delmas PD, Chapurlat RD (2010) Assessment of hand bone loss in rheumatoid arthritis by high-resolution peripheral quantitative CT. Ann Rheum Dis 69:1671–1676
17. Funovits J, Aletaha D, Bykerk V, Combe B, Dougados M, Emery P, Felson D, Hawker G, Hazes JM, Huizinga T, Kay J, Kvien TK, Smolen JS, Symmons D, Tak PP, Silman A (2010) The 2010 American College of Rheumatology/European League against Rheumatism classification criteria for rheumatoid arthritis: methodological report phase I. Ann Rheum Dis 69:1589–1595
18. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, Aletaha D, Allaart CF, Bathon J, Bombardieri S, Brooks P, Brown A, Matucci-Cerinic M, Choi H, Combe B, de Wit M, Dougados M, Emery P, Furst D, Gomez-Reino J, Hawker G, Keystone E, Khanna D, Kirwan J, Kvien TK, Landewe R, Listing J, Michaud K, Martin-Mola E, Montie P, Pincus T, Richards P, Siegel JN, Simon LS, Sokka T, Strand V, Tugwell P, Tyndall A, van der Heijde D, Verstappen S, White B, Wolfe F, Zink A, Boers M (2011) American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 63: 573–586
19. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F (1992) The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum 35:498–502
20. Lynn HS, Lau EM, Au B, Leung PC (2005) Bone mineral density reference norms for Hong Kong Chinese. Osteoporos Int 16: 1663–1668

21. Hildebrand T, Ruegsegger P (1997) A new method for the model-independent assessment of thickness in three-dimensional images. J Microsc 185:67–75
22. Boutroy S, Bouxsein ML, Munoz F, Delmas PD (2005) In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. J Clin Endocrinol Metab 90:6508–6515
23. Pfeil A, Haugeberg G, Hansch A, Renz DM, Lehmann G, Malich A, Wolf G, Bottcher J (2011) Value of digital X-ray radiogrammetry in the assessment of inflammatory bone loss in rheumatoid arthritis. Arthritis Care Res (Hoboken) 63:666–674
24. Stach CM, Bauerle M, Englbrecht M, Kronke G, Engelke K, Manger B, Schett G (2010) Periarticular bone structure in rheumatoid arthritis patients and healthy individuals assessed by high-resolution computed tomography. Arthritis Rheum 62:330–339
25. Laan RF, Buijs WC, Verbeek AL, Draad MP, Corstens FH, van de Putte LB, van Riel PL (1993) Bone mineral density in patients with recent onset rheumatoid arthritis: influence of disease activity and functional capacity. Ann Rheum Dis 52:21–26
26. Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK (2000) Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County Rheumatoid Arthritis Register. Arthritis Rheum 43:522–530
27. Hall GM, Spector TD, Griffin AJ, Jawad AS, Hall ML, Doyle DV (1993) The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. Arthritis Rheum 36:1510–1516
28. Gough AK, Lilley J, Eyre S, Holder RL, Emery P (1994) Generalised bone loss in patients with early rheumatoid arthritis. Lancet 344:23–27
29. Mazzantini M, Di Munno O, Incerti-Vecchi L, Pasero G (2000) Vertebral bone mineral density changes in female rheumatoid arthritis patients treated with low-dose methotrexate. Clin Exp Rheumatol 18:327–331
30. Felder M, Ruegsegger P (1991) Bone loss in patients with rheumatoid arthritis—effect of steroids measured by low dose quantitative computed tomography. Rheumatol Int 11:41–44
31. Desai SP, Solomon DH (2010) The use of glucocorticoids in rheumatoid arthritis—no "rational" approach yet. Arthritis Res Ther 12:127
32. Ibanez M, Ortiz AM, Castrejon I, Garcia-Vadillo JA, Carvajal I, Castaneda S, Gonzalez-Alvaro I (2010) A rational use of glucocorticoids in patients with early arthritis has a minimal impact on bone mass. Arthritis Res Ther 12:R50
33. Buie HR, Campbell GM, Klinck RJ, MacNeil JA, Boyd SK (2007) Automatic segmentation of cortical and trabecular compartments based on a dual threshold technique for in vivo micro-CT bone analysis. Bone 41:505–515
34. Burghardt AJ, Buie HR, Laib A, Majumdar S, Boyd SK (2010) Reproducibility of direct quantitative measures of cortical bone microarchitecture of the distal radius and tibia by HR-pQCT. Bone 47:519–528