SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

The applicability of quantitative CT in the study of inflammatory bone loss

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Head of the **Examination Committee**:	Árpád Illés, MD, PhD, DSc
Members of the Examination Committee:	Attila Jakab, MD, PhD
	Anikó Maráz, MD, PhD

The Examination takes place at Meeting Room of Bldg. B, Department of Internal Medicine, Faculty of Medicine, University of Debrecen
11:30, 03 March 2025

Head of the **Defense Committee**:	Árpád Illés, MD, PhD, DSc
Reviewers:	Zoltán Griger, MD, PhD
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Members of the Defense Committee:	Attila Jakab, MD, PhD
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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen
13:00, 03 March 2025

1. Introduction

Rheumatoid arthritis (RA) and ankylosing spondylitis (SPA) are associated with generalized osteoporosis (OP) and local inflammatory bone resorption and/or formation. The main molecular pathways responsible for inflammatory bone resorption include pro-inflammatory cytokines (tumor necrosis factor α [TNF-α], interleukin 1 [IL-1], IL-6, IL-17) and Receptor Activator Nuclear Factor κB (RANK)- They include the RANK ligand (RANKL) system. TNF-α is of particular importance in this respect. TNF-α also triggers osteoclast function directly. product indirectly causes bone breakdown, as it stimulates the production of Dickkopf-1 (DKK-1) and sclerostin (SOST). DKK-1 and SOST inhibit the Wingless protein (Wnt)-β-catenin pathway, thereby inhibiting osteoblasts from bone formation. Indirect evidence of the effect of TNF-α and other cytokines is that in clinical studies, TNF-α blockers inhibited bone destruction and reduced radiological progression in RA and, to a lesser extent, in SPA. In addition to the effect on local bone metabolism, anti-TNF therapies also affect the development and progression of generalized OP in RA and SPA. Improvement in bone status may be related to suppression of systemic inflammation and disease activity in these arthritis.

A characteristic feature of RA is local osteoporosis in the bones of the hand. In RA, bone mineral density (BMD) of the hand correlates with vertebral and hip BMD and generalized OP. In addition, OP of the bones of the hand is associated with the development of small joint erosions. BMD of the hand predicts later joint damage.

60-70% of patients with RA and SPA have generalized bone loss in the lumbar (L) vertebrae and/or the femoral neck. In both pathologies, the risk of vertebral and hip fractures increases. In addition to traditional risk factors (e.g. female gender, postmenopausal status, low vitamin D level, physical inactivity), systemic inflammation and the above-mentioned inflammatory mediators are involved.

BMD is traditionally measured by dual-energy X-ray absorptiometry (DXA). Quantitative computer tomography (QCT) is a tool suitable for the separate examination of the microarchitecture of bone and its various components, such as cortical and trabecular bone. While DXA is suitable for determining areal BMD and Trabecular Bone Score (TBS), QCT can measure volumetric BMD. QCT is commonly used to assess the bone density of the L vertebrae and the pelvis. Peripheral QCT determines the bone status of the limbs (forearm, lower leg).

Relatively few studies have been conducted in which RA patients were examined with QCT. Felder et al. investigated the effect of corticosteroids (CS) on cortical and trabecular bone in postmenopausal women with RA using QCT. Saario et al reported the adverse effect of CS on trabecular bone in RA. Eser et al found abnormal bone geometry in RA during QCT examination. Finally, Zhu et al. assessed the relationship between bone density and microarchitecture comparing axial and peripheral regions. In their study, the L vertebrae and femoral neck were measured with DXA, while the distal radius and the head of the second metacarpal were measured with peripheral QCT. Some examinations with QCT were also performed in SPA, which also confirmed the inflammatory bone loss in this pathology.

2. Objectives

The work presented in these theses contains the results of three studies. In the following chapters, we always do the 1st, 2nd and 3rd tests one by one didactically.

In the first cross-sectional study (hereinafter study 1), RA patients were examined with peripheral QCT. Cortical and trabecular BMD and beam attenuation values were compared with L vertebra and femoral neck BMD values determined by DXA. We correlated the QCT data with demographic data, disease activity, acute phase proteins and autoantibodies. Our aim was to determine the value of QCT compared to DXA in the assessment of bone density and bone structure in RA patients, and to determine the possible effects of autoimmunity (e.g. anti-citrullinated protein antibodies; ACPA) on bone properties.

In study 2, knowing the role of TNF-α in local and generalized bone loss, we analyzed the bone effects of biological therapy in a prospective setting in RA and SPA. For this purpose, we assembled a mixed patient cohort of RA and SPA patients. We assessed QCT BMD in patients receiving biologic therapy before starting treatment and after one year of treatment. To the best of our knowledge, our study is the first to prospectively assess the effects of one year of anti-TNF treatment on the bone status of RA and SPA patients. This study also included QCT, DXA examinations, as well as disease activity and bone biomarker data.

Study 3 is part of a larger collaborative work. In collaboration with the colleagues of the Hungarian Geological and Geophysical Institute (MFGI; currently the Hungarian Mining and Geological Service) in Budapest, we use laser-based geological-geophysical methods (laser-induced plasma spectroscopy; LIPS) to investigate the composition of bones, with particular attention to inorganic components and trace elements. Part of this extensive study was a comparative analysis in which we compared the LIPS and QCT tests on cattle bones. Only my QCT results were included in this dissertation.

3. Research subjects and methods

3.1. Examination 1

3.1.1. Patients

A total of 57 RA female patients (average age: 52.2±14.2 [23-76] years; average disease duration: 13.2±7.9 [1-40] years) who received regular care at the Rheumatology Clinic of the University of Debrecen Clinical Center (DEKK) were continuously selected. into our study (Table 1). All patients had moderate disease activity during the study: the mean value of DAS28 was 4.22±0.99 [1.76-4.72]. None of the patients had a history of bone fractures or other chronic diseases. The average cumulative CS dose taken by the patients was 2.8 grams. Although 72% of patients were taking CS by the time of QCT and DXA examination, only 3 patients received ≤10 mg of CS per day at the time of the study. A total of 48 patients received methotrexate (MTX; 10-20 mg/week) and 23 patients were treated with targeted therapy. A total of 32 age-matched healthy female hospital workers or visitors (average age: 50.6±13.8 [25-63] years) formed the control group (Table 1). Regarding the average age, there was no significant difference between patients and controls (p=0.068). The members of the control group also had no bone disease, previous bone fracture or other chronic disease. The study was approved by the Research Ethics Committee of the Health Science Council (authorization number: 14804-2/2011/EKU) and was carried out in accordance with the Declaration of Helsinki. All subjects gave their informed consent to participate in the study.

3.1.2. QCT and DXA examinations

L vertebrae (L2-L4) and femoral neck BMD were assessed by DXA (Lunar DPX-L; GE Healthcare UK, Chalfont, United Kingdom) according to a standard protocol. Area BMD is expressed in mg/cm2.

A single-slice QCT examination of the ultradistal region of the dominant forearm was performed using a Stratec XCT-2000 device (Stratec Medizintechnik GmbH, Pforzheim, Germany) (Figure 1). In the distal 4% of the length of the radius, there is mainly trabecular bone. QCT can differentiate between cortical and trabecular bone. Total, trabecular and cortical BMD values are given by QCT in mg/cm3 units. A pixel size of 0.59 mm was used for imaging. Data analysis was performed using XCT6.00B software (Stratec Medizintechnik GmbH, Pforzheim, Germany).

3.1.3. Laboratory tests and disease activity

Serum C-reactive protein (CRP; mg/l) was measured by quantitative nephelometry (Cobas Mira Plus-Roche Diagnostics, Basel, Switzerland) using CRP reagent (Dialab, Wiener Neudorf, Austria). Anti-CCP autoantibodies were detected in serum using the second-generation Immunoscan-RA CCP2 ELISA test (Euro Diagnostica, Arnhem, The Netherlands). The assays were performed according to the manufacturer's instructions. A concentration greater than 50 U/ml was considered positive.

RA disease activity was calculated using the DAS28 calculator.

3.1.4. Statistical analysis

The statistical analysis was performed with SPSS 20.0 (IBM, Armonk, NY, USA) statistical software. Descriptive data of normally distributed variables were expressed as mean value ± standard deviation (SD). Statistical analysis was performed using an independent two-sample t-test. The correlation between variables was determined using Pearson correlation analysis for normally distributed samples, otherwise Spearman correlation analysis. We calculated the R values of these correlations, and values of $p < 0.05$ were considered significant. General Linear Model (GLM) analysis of variance (ANOVA) was performed to determine independent predictors.

3.2. Examination 2

3.2.1. Patients

A total of 40 patients with inflammatory joint disease (24 RA and 16 axial SPA) - selected for the start of anti-TNF therapy, but not selected for any previous cardiovascular event, and osteoporosis (T-score < -2.5) - were included in the study. These patients were continuously included in the study at the DEKK Rheumatology Clinic. The patient characteristics of the total (RA+SPA) and the RA and SPA cohorts separately are shown in Table 2. The entire cohort consisted of 24 female and 16 male patients, their average age at the time of the examination was 51.5±13.6 (24-77) years, while the average age at the time of diagnosis was 42.1±13.5 (17-58) years volt. The average disease duration was 8.3±7.8 (1-44) years. Patients with active disease were included in the study before starting biological therapy. At baseline, the average DAS28 value of RA patients was 4.92±1.12, while the average BASDAI value of SPA patients was 5.66±1.33. The patients had not previously received biological therapy. At baseline, all patients started anti-TNF therapy and continued this treatment for one year.

The clinical condition assessments were performed at baseline and after 12 months of therapy. Of the 24 RA patients, 14 patients received 50 mg etanercept (ETN) weekly and 10 received 200 mg certolizumab pegol (CZP) biweekly by subcutaneous (SC) injection. A total of 12 RA patients receiving ETN and 8 treated with CZP also received MTX in combination with biological therapy. The other patients were treated with anti-TNF monotherapy. All 16 SPA patients received weekly 50 mg ETN monotherapy SC. A total of 8 patients with RA and 1 with SPA were taking low-dose (<6 mg/day) methylprednisolone. The study was approved by the Research Ethics Committee of the Health Science Council (authorization number: 14804-2/2011/EKU) and was carried out in accordance with the Declaration of Helsinki. All subjects gave their informed consent to participate in the study.

3.2.2. Clinical condition assessment

First of all, a detailed medical history was taken. Data on OP and bone fractures were also recorded from each patient. An additional clinical assessment, including a physical examination, was performed at admission and after 12 months of therapy.

3.2.3. QCT and DXA examinations

The tests are carried out exactly according to 3.1.2. as described in chapter

3.2.4. Laboratory tests and disease activity

The tests are carried out exactly according to 3.1.3. as described in chapter

3.2.5. Bone biomarkers

Serum calcium (Ca; Roche Diagnostics; normal value: 2.1-2.6 mmol/l) and phosphate (P; Roche Diagnostics; normal value: 0.8-1.45 mmol/l); parathyroid hormone (PTH; Roche Diagnostics; normal value: 1.6-6.9 pmol/l); total 25-hydroxy-vitamin D3 (VITD; DiaSorin; normal value: ≥75 nmol/l); osteocalcin (OC; Roche Diagnostics; normal value: <41 µg/l), procollagen 1 N-propeptide (P1NP; Roche Diagnostics; normal value: <75 µg/l), C-terminal collagen telopeptide (CTX; Roche Diagnostics; normal value: < 0.57 µg/l), osteoprotegerin (OPG; Biomedica; median: 2.7 pmol/l); SOST (Biomedica; median: 24.14 pmol/l), DKK-1 (Biomedica; median: 36 pmol/l), soluble RANKL (Ampli-sRANKL; Biomedica; median: 0.14 pmol/l) and cathepsin K (CATHK; Biomedica; median: 8.7 pmol/l) values were determined with the ELISA method at baseline and after 12 months of treatment.

3.2.6. Statistical analysis

The statistical analysis was performed with the SPSS 20.0 (IBM, Armonk, NY, USA) statistical software. Descriptive data of normally distributed variables were expressed as mean value ± SD. The distribution of continuous variables was evaluated with the Kolmogorov-Smirnov test. All bone-specific variables show a normal distribution. An independent and two-sample t-test was used to evaluate the difference between two groups. A $\chi 2$ test or Fisher's exact test was used to compare the nominal variables. Correlations (R value) were determined by Pearson analysis. Univariate and multivariate regression analyzes were used to examine the relationships between QCT-determined BMD (independent variable) and other clinical, laboratory, and DXA parameters (independent variables). In doing so, we determined the standardized linear coefficients β showing the correlations between the two parameters. The regression coefficient B (+95% CI) indicates independent relationships between the dependent and independent variables during the changes. Repeated-measures analysis of variance (RM-ANOVA) was used to investigate factors influencing the 12-month change in QCT BMD. In this analysis, the partial $\eta 2$ is the indicator of the degree of effect, taking into account the value of 0.01, a value of 0.01 indicates a small effect, a value of 0.06 indicates a medium effect, while a value of 0.14 indicates a high degree of effect. In all studies, $p<0.05$ was considered significant.

3.3. Examination 3

3.3.1. Bovine bone samples

A total of 5 male bovine tibia (B1-B5) bone samples were used. The organic materials (meat and marrow) were removed from the bones first mechanically and then by boiling in 1% hydrogen peroxide water. The bones were cut into slices with a diamond saw, and then thin polished bone slices were prepared. Polishing was done in dry conditions. First, one side of the slice was polished and glue was applied to the microscope slides. Then we carefully polished the other side as well.

3.3.2. QCT studies

The tests are carried out exactly according to 3.1.2. was performed as described in chapter 1, similar to the human bone. Volumetric BMD was expressed in mg/cm3.

3.3.3. LIPS studies

Since the LIPS results are not part of the dissertation, the method will not be described in detail. We refer to the original announcement.

3.3.4. Statistical analysis

The statistical analysis was performed with SPSS 20.0 (IBM, Armonk, NY, USA) statistical software. Correlations were determined using Pearson analysis. In the study, a value of $p < 0.05$ was considered significant.

4. Results

4.1. Examination 1

4.1.1. Measurement of bone density by QCT and DXA in RA patients and controls

During the peripheral QCT measurement, BMD and attenuation were measured in the ultradistal region of the dominant forearm in 57 RA patients and 32 healthy controls. Total BMD determined by QCT (310.4±79.7 mg/cm3 vs 354.0±54.1 mg/cm3; p=0.007) and attenuation (0.37±0.05 1/cm vs 0, 40±0.03 1/cm; p=0.001); trabecular BMD (157.6±57.0 mg/cm3 vs 193.8±48.7 mg/cm3; p=0.005) and attenuation (0.28±0.03 1/cm vs 0.32±0, 04 1/cm; p<0.001); and cortical BMD (434.3±115.8 mg/cm3 vs 492.5±64.0 mg/cm3; p=0.006) and attenuation (0.44±0.07 1/cm vs 0.47±0.04 1/cm; p=0.004) was significantly lower in RA compared to controls.

Regarding DXA, both L2-L4 vertebral BMD (RA: 0.665±0.120 g/cm2; control: 0.888±0.108 g/cm2; p<0.001) and T-score (RA: -2.29±0.98; control : -0.49±0.90; p<0.001), both femoral neck BMD (RA: 0.758±0.121 g/cm2; control: 0.897±0.100 g/cm2; p<0.001) and T-score (RA: - 1.54±1.00; control: -0.41±0.84; p<0.001) was significantly lower in RA than in controls.

4.1.2. Correlations between bone density values and clinical and laboratory data in RA

Within the RA patient population, age was inversely correlated with QCT-measured total BMD (R=-0.465, p<0.001) and attenuation (R=-0.464, p<0.001); with trabecular BMD (R=-0.404, p=0.002) and attenuation (R=-0.407, p=0.002); and with cortical BMD (R=-0.432, p=0.001) and attenuation (R=-0.431, p=0.001) (Table 3). Disease duration did not show any correlation with any QCT parameter.

The total and trabecular BMD determined by QCT showed a significant correlation with the L2-L4 vertebral BMD measured by DXA (R=0.280, p=0.033 and R=0.335, p=0.010) and the femoral neck BMD values (R= 0.362, p=0.005 and R=0.342, p=0.009) (Table 3). Cortical BMD measured by QCT was significantly correlated with DXA femoral neck BMD (R=0.329, p=0.012), but not with L2-L4 BMD.

Similarly, total and trabecular attenuation determined by QCT were significantly correlated with L2-L4 vertebral BMD measured by DXA (R=0.280, p=0.033 and R=0.334, p=0.010, respectively) and femoral neck BMD (R=0.362, p=0.005 and R=0.342, p=0.009) (Table 2). Cortical attenuation was significantly correlated with femoral neck BMD (R=0.328, p=0.012) but not with L2-L4 BMD.

The structure and composition of trabecular and cortical bone differ from each other, so we also compared the QCT parameters of the two types of bone. Overall, trabecular BMD and attenuation as well as cortical BMD and attenuation were significantly correlated with each other in both RA patients and controls.

Through a detailed GLM ANOVA analysis, we determined the independent effect of age (>52 years) and RA disease duration, as well as the combination of the two, on the various QCT and DXA parameters. Both total and cortical QCT BMD and attenuation were significantly affected by age, disease duration, and their combination. In contrast, only disease duration was associated with trabecular BMD and attenuation. Regarding DXA, age or duration of RA influenced L2-L4 BMD and T-score, as well as femoral neck BMD and T-score.

Among disease activity and laboratory markers, ACPA (anti-CCP) positive (≥50 U/ml) vs negative (<50 U/ml) patients differed significantly in trabecular BMD measured by QCT (p=0.036) and attenuation (p=0.035) (Table 6). In this regard, the two groups did not differ in terms of total and cortical BMD and attenuation.

4.2. Examination 2

4.2.1. Osteoporosis and osteopenia among patients

Two of the RA patients had OP (T-score < -2.5) and 12 had osteopenia (T-score < -1) at L2-L4 vertebrae as determined by DXA. In the femoral neck region, one patient had OP and 11 had

osteopenia. In the SPA subgroup, one patient had L2-L4 vertebrae and one femoral neck OP, and 2 patients had L2-L4 and 5 femoral neck osteopenia. A total of 7 RA and 6 SPA patients had a history of bone fracture. In the entire RA+SPA cohort, 3 patients had L2-L4 and two patients had femoral neck OP, while 14 patients had L2-L4 and 16 had femoral neck osteopenia. A total of 13 patients had a previous fracture.

4.2.2. Effect of anti-TNF therapy on volumetric BMD

In the entire cohort, as well as separately in the RA or SPA patients, no further bone loss was observed by peripheral QCT examination after one year of ETN or CZP treatment. In the entire cohort, total volume BMD (336.7±71.8 vs 340.9±75.3 mg/cm3; p=0.669), trabecular BMD (241.1±117.6 vs 258.0±123, 0 mg/cm3; p=0.283) and cortical BMD (426.3±110.1 vs 415.1±111.9 mg/cm3; p=0.591) did not change significantly after 12 months of treatment compared to baseline. In the RA subgroup, total volume BMD (319.9±66.3 vs 318.3±62.9 mg/cm3; p=0.828), trabecular BMD (199.4±79.2 vs 213.9±76, 8 mg/cm3; p=0.362) and cortical BMD (412.5±111.0 vs 391.6±95.6 mg/cm3; p=0.296) also did not change significantly during the one-year period. Finally, we observed a similar pattern in SPA patients. Total volume BMD (361.8±74.4 vs 374.8±81.4 mg/cm3; p=0.561), trabecular BMD (303.6±141.0 vs 324.1±150.0 mg/ cm3; p=0.528) and cortical BMD (456.3±107.1 vs 466.5±131.6 mg/cm3; p=0.845) also did not change during one year of anti-TNF treatment. Since BMD is known to decrease in both RA and SPA without treatment, these results suggested that TNF inhibitor treatment slowed or stopped further bone loss. It is also worth noting that the total, trabecular and cortical BMD values were significantly higher both at baseline and after 12 months of treatment in SPA than in RA ($p<0.05$).

4.2.3. Correlations between volumetric BMD and other clinical, laboratory and DXA parameters

Total, trabecular, and cortical volumetric BMD values determined by QCT at baseline and after 12 months of anti-TNF therapy were variably correlated with disease activity, BMD measured by DXA, and bone markers. In the RA+SPA mixed cohort, either DAS28 (RA) or BASDAI

(SPA) data were considered as disease activity markers. In the simple Pearson correlation analysis, using Bonferroni correction - to exclude the effects of multiple comparisons - baseline DAS28/BASDAI was inversely correlated with baseline trabecular BMD (p=0.015) and 12-month cortical BMD (p=0.005). Disease activity did not correlate with baseline total and cortical and 12-month total volumetric BMD. In addition, QCT values did not correlate with CRP. Similar data were obtained separately in the RA and SPA subgroups.

Regarding the correlations between QCT and DXA, the total, trabecular and cortical volume BMD values at baseline or after 12 months of treatment showed varying correlations with the regional BMD values measured by DXA at baseline and after 12 months of treatment at the L2-L4 vertebrae and femoral neck with the total RA in the +SPA cohort. Similar correlations were also observed in the RA subgroup, but not in the SPA subgroup. Thus, in general, volumetric BMD determined by QCT is positively correlated with areal BMD measured by DXA, both in the total RA+SPA cohort and in the RA group.

Regarding bone laboratory biomarkers, in the entire cohort, baseline trabecular volume BMD correlated with CTX measured after 12 months (p=0.011). In the RA subgroup, baseline SOST, while in the SPA subgroup, sRANKL at baseline and after 12 months showed variable correlation with BMD values measured by QCT.

4.2.4. Independent determinants of volumetric BMD

In the entire cohort, baseline disease activity (DAS28/BASDAI; p=0.030) was an independent inverse predictor of total volumetric BMD after 12 months of treatment, according to univariate regression analysis. Independent negative predictors of cortical BMD at 12 months were DAS28/BASDAI (p=0.005) and cathepsin K (p=0.025) at baseline, and cathepsin K at 12 months (p=0.033). Multivariate analysis of variance confirmed the inverse correlation of total (p=0.030) and cortical BMD (p=0.012) with baseline disease activity at 12 months. If RA and SPA patients are taken separately, baseline 25-hydroxy-vitamin D3 level was positively correlated with trabecular BMD after 12 months of treatment in both univariate and multivariate analysis (p=0.005). We did not find similar correlations in SPA. Based on these, baseline disease activity, cathepsin K or 25-hydroxy-vitamin D3 levels can be associated with the outcome of BMD measured by QCT after one year of treatment.

Finally, a GLM RM-ANOVA was performed to assess determinants of volumetric BMD changes over the 12-month treatment period. In the entire RA+SPA cohort, the change in trabecular BMD between baseline and 12 months of treatment was determined by anti-TNF treatment together with higher baseline 25-hydroxy-vitamin D3 levels (p=0.031). Similarly, TNF inhibition and lower cathepsin K levels jointly determined cortical BMD changes over the one-year period (p=0.006). Similarly, baseline 25-hydroxy-D3 vitamin or cathepsin K in RA, while baseline sRANKL in SPA may influence the effect of one year of anti-TNF treatment on changes in volumetric BMD (Table 9). All this means that the bone effect of anti-TNF treatment is more favorable if there is a higher 25-hydroxy-vitamin D3 or a lower level of cathepsin K or sRANKL at the start of the therapy.

4.3. Examination 3

4.3.1. Comparison of bovine bone BMD determined by QCT and "geological BMD" measured by the LIPS method

Bovine bone samples (B1-B5) were analyzed by QCT prior to slicing for LIPS testing. The attenuation (weakening) coefficient determined by QCT can be one of the best determinants of the structure of the changed bone tissue. First, we compared BMD and beam attenuation measured by QCT, and there was a significant correlation between these two parameters. Afterwards, the bone density determined by LIPS and QCT was compared. A significant correlation was found between BMD measured with QCT and LIPS.

5. Discussion

5.1. Examination 1

In RA, local joint erosions and secondary generalized OP can develop. In the area of the hand, a correlation between OP developing in the bones and juxtaarticular, marginal erosions was shown, suggesting the role of common pathogenetic factors. Among the bone density testing methods, DXA is suitable for measuring 2-dimensional, territorial, while QCT is suitable for measuring 3-dimensional, volumetric BMD. QCT can differentiate between trabecular and cortical bone.

In the present study, we assessed bone BMD and beam attenuation in RA patients and healthy controls using forearm QCT, and compared these results with those provided by DXA. During the QCT examination of RA patients, we found significantly lower total, trabecular and cortical BMD, as well as lower attenuation compared to controls. We also confirmed that significantly lower L2-4 vertebral and femoral neck BMD and T-score values are related to RA disease.

In an early RA study, Felder et al reported that CS treatment had a small effect on trabecular bone and no effect on cortical bone. Saario et al. measured the L vertebrae of 57 RA patients with QCT. Cumulative CS dose and functional impairment were inversely related to L BMD. Eser et al. reported on the abnormal bone geometry of the metacarpal axis in RA patients. In our present study, only a very small part of the RA patients received CS treatment, so the mentioned reports are not very relevant from our point of view.

Zhu and mtasi performed the only comparative study available to us, where lumbar and hip DXA and distal radius and second metacarpal head QCT were performed on 100 RA female patients. A moderate correlation was found between areal BMD determined by DXA and volumetric BMD determined by QCT. The authors did not examine the correlations of densitometric values with age, disease duration, disease activity and other laboratory markers. Zhu et al. did not include a control group in their study. In our present study, total and cortical QCT BMD and attenuation showed a significant correlation with age, disease duration and their combinations. In contrast, trabecular BMD and attenuation showed a correlation only with the

existence of the disease, not with age. These new observations show that age mainly affects cortical bone, whereas OP involving trabecular bone may be related to both trabecular and cortical bone. In addition, L and femoral neck DXA BMD and T-score values in the present study were related to age or duration of RA, but not to their combination. Thus, the combined effect of age and the underlying disease can be determined more with QCT, less with DXA. This may be an additional advantage of QCT over DXA.

Ours was the first study to assess the relationship between RA-related autoimmunity and bone metabolism. In our QCT study, anti-CCP seropositive patients had significantly lower trabecular BMD and attenuation compared to seronegative patients. There was no difference in cortical bone. These results indicate that RA-associated autoimmunity and its consequences affect trabecular rather than cortical bone.

Comparing the two methods that determine areal and volumetric BMD, total, trabecular and cortical BMD and attenuation values determined by QCT were all significantly correlated with L and/or femoral neck BMD values measured by DXA. Furthermore, QCT cortical BMD and attenuation only correlated with femoral neck DXA BMD, but not with L spine BMD, indicating a closer relationship of cortical bone to the femoral neck compared to the vertebral column. Finally, trabecular and cortical QCT BMD and attenuation correlated with each other in both RA patients and controls

The strength of our study is that we were among the first to investigate the applicability of QCT in bone loss associated with RA, compared with DXA, clinical and laboratory parameters. It is also important that in our study we compared RA patients free of other chronic diseases to a healthy control group, and we compared the two methods using QCT and DXA on the same individuals. The limitations of the study may be the relatively small number of patients and controls, as well as the cross-sectional nature.

In summary, both DXA and QCT may be suitable methods for assessing OP in RA patients. There can be a significant correlation between areal BMD determined by DXA and volumetric BMD determined by QCT. Both trabecular and cortical OP can be determined with forearm QCT in RA patients. Age and RA disease duration were independent factors for OP, both measured by QCT and DXA. In addition, trabecular OP is more related to an underlying autoimmune disease, while cortical OP may be more age-related. Further studies with a large number of patients are necessary to determine the exact place of QCT in everyday rheumatology practice.

5.2. Examination 2

To the best of our knowledge, this is the first study that analyzed the effects of one-year anti-TNF biological treatment on the bone status of RA and SPA patients in a complex manner, including QCT, DXA examinations and other clinical and bone markers. There was no progression of bone loss during treatment, meaning that TNF-α blockade likely slowed bone loss. Although there was no control group in our study, we know that without adequate treatment, continuous bone loss occurs in both RA and SPA. The correlations we found confirm the primary role of underlying disease activity and systemic inflammation in the development of local and generalized OP. This is in line with the European Association of Rheumatology Association (EULAR) and treat-to-target recommendations in the treatment of RA and SPA. These recommendations also emphasize that, in order to protect bones, it is essential to target the underlying disease, suppress inflammation and achieve clinical remission.

TNF-α plays a role in the pathogenesis of inflammatory bone loss, and anti-TNF biologics can halt generalized bone loss in arthritis. However, bone loss in the forearm near the wrist has not been investigated in RA and SPA patients receiving biological treatment. Previously, in the same cohort, no additional bone loss was detected in RA and SPA during the 12 months of ETN and CZP treatment using DXA. DXA determines areal BMD. QCT examination of the forearm can be of added value to assess the state of the bone in inflammatory rheumatic diseases. QCT measures volumetric BMD and examines bone condition separately in trabecular and cortical bone. Feehan et al developed a customized protocol for assessing the bone quality of the metacarpal head and body and the distal radius by QCT. Felder et al used QCT to study the bone effects of CS in RA patients. Caparbo et al and Devogelaer et al confirmed by QCT that SPA is associated with inflammatory bone loss. Korkosz et al. also measured the condition of the spine in SPA with QCT, but they could not prove any relationship between localized bone formation and generalized bone loss even with a 10-year follow-up.

In our present study, during the volumetric BMD assessment with QCT, we found that no additional volumetric bone loss occurs in patients with RA and SPA during one year of anti-TNF therapy. Very few publications have been published on the effect of targeted therapy on volumetric BMD. Shimizu et al. investigated the effect of 3 months of anti-TNF treatment on bone microstructural changes. This cohort included 27 RA patients treated with anti-TNF

biologics and 10 with MTX. The authors analyzed the number and volume of erosions using high-resolution QCT (HR-QCT). They found that TNF inhibition can slow down the erosion process. Changes in the number of erosions were related to changes in disease activity. This 3-month study was shorter than ours and did not include DXA and laboratory tests. In addition to denosumab (anti-RANKL antibody) therapy, Yue et al. observed a reduction in bone erosion formation by HR-QCT examination.

Regarding the comparison between QCT and DXA, Zhu et al looked for a relationship between bone density and microarchitecture. In their study, they compared hands, peripheral regions, and the spine. The L vertebrae and the femoral neck were studied with DXA, and the distal radius and head of the second metacarpal with QCT. In our previous study (see Study 1), total, trabecular, and cortical BMD were lower in RA patients compared to controls. ACPA seropositivity was associated with lower trabecular BMD. In this study, we found no correlation between seropositivity and volumetric BMD, although study 2 included different RA patients than study 1. This cohort also included SPA patients. In addition, the patients in the present study had significant disease activity and were awaiting biological therapy, while this was not the case in our previous study. Correlation analysis showed that areal BMD determined by DXA could correlate with volumetric BMD determined by QCT. In the present study, we found a multiple correlation between volumetric BMD determined by QCT and areal BMD measured by DXA, both in the entire cohort and in the RA subgroup. Not only did we find correlations at one point in time, but we also found that baseline volumetric and areal BMD can also determine volumetric and areal BMD after one year of anti-TNF therapy.

Regarding disease characteristics and bone biomarkers, Aschenberg et al. performed a HR-QCT study together with clinical and bone marker studies. Interestingly, only the duration of the disease was related to the development of erosions detectable by HR-QCT, not any bone biomarker. This is probably because erosions can take several years to develop, and the follow-up time was relatively short. In the present study, baseline disease activity (DAS28/BASDAI) was inversely correlated with baseline trabecular BMD determined by QCT and with total and cortical BMD after one year of treatment. Univariate and multivariate regression analysis also confirmed that baseline disease activity was an independent predictor of total and cortical volumetric BMD at 12 months. This is in line with the results of Shimizu et al., which confirmed a correlation between the number of erosions detected by HR-QCT and the change in disease activity after 3 months of anti-TNF therapy. The data are also exciting because in our present study the bone resorption markers cathepsin K and sRANKL were negatively correlated, while

the bone formation markers and the 25-hydroxy-vitamin D3 level were positively correlated with volumetric BMD at different time points. Since our QCT measurements were performed close to the wrist, the above-mentioned bone biomarkers in combination with systemic inflammation may also play a role in the formation of erosions examined by others with HR-QCT.

Based on the GLM RM-ANOVA analysis, it seems that biological therapy in combination with a higher baseline 25-hydroxy-vitamin D3 level exerts its beneficial effect on trabecular volume BMD. In other words, initial high vitamin D levels may enhance the beneficial effects of anti-TNF treatment on bone. Similarly, 12 months of TNF inhibition combined with lower cathepsin K levels at baseline may induce a favorable change in cortical BMD. We previously found that anti-TNF therapy reduces cathepsin K production in RA and SPA. In our patients with SPA, the initial lower sRANKL level increased the beneficial effect of biological therapy on total and cortical BMD. In the literature, we did not find any information about the role played by the RANKL level in the outcome of SPA. Overall, one year of anti-TNF treatment and baseline lower disease activity, cathepsin K and sRANKL and higher 25-hidroxy-vitamin D3 levels are co-determinants of changes in volumetric BMD over time in RA and SPA.

Our results also suggest that there may be differences between RA and SPA regarding the effects of biological treatment on bone. In our study, it was not easy to separate the two diseases due to the relatively low number of patients, but we could nevertheless draw some conclusions. Overall, volumetric BMD in all compartments (total, trabecular, cortical) was higher in SPA than RA both at baseline and after one year of anti-TNF treatment. Of course, SPA patients are younger than RA patients, but other factors may play a role in the observed differences. In addition, volumetric BMD values in RA showed a correlation with disease activity and BMD values measured by DXA, but not in SPA. All of this suggests that disease activity associated with systemic inflammation may lead to more pronounced bone loss in RA patients compared to SPAs. Regarding the bone markers, volumetric BMD changes were more related to 25-hydroxy-vitamin D3 and cathepsin K in RA, and sRANKL in SPA.

The strength of our present study is that, for the first time, we examined the change in volumetric BMD measured by QCT in RA and SPA patients undergoing anti-TNF treatment. We know from previous studies that generalized bone loss - away from joints, such as the spine - can be inhibited with anti-TNF agents. However, we have now also shown that all this can be stopped in the immediate vicinity of the joints (wrist/hand). We also tried to clarify the mechanism. The one-year increase in volumetric BMD was most pronounced in patients with

very low DAS28/BASDAI. In addition, we found that the most favorable volumetric BMD changes were observed in patients with low bone resorption markers (cathepsin K, sRANKL) before treatment. Limitations of the study include the relatively low number of patients with RA and SPA. We did not have access to the HR-QCT technique, so we used a standard QCT technique.

In conclusion, peripheral QCT may be suitable for determining volumetric BMD in different parts of the radius (trabecular and cortical compartments). The present QCT and our previous DXA studies in the same cohort (13) confirmed that biological therapy can stop generalized bone loss. Volumetric and areal BMD values correlate with each other, indicating the value of both QCT and DXA to assess bone status in inflammatory diseases. We also identified baseline parameters such as disease activity, cathepsin K, 25-hydroxyvitamin D3, and sRANKL that could predict the temporal effect of one year of anti-TNF therapy on volumetric BMD. The pre-treatment levels of cathepsin K and 25-hydroxy-vitamin D3 can be associated with the changes occurring in the cortical and trabecular bone compartments. Further larger clinical trials are needed to determine the value of QCT in following bone status changes in arthritis patients treated with targeted therapy.

5.3. Examination 3

As mentioned, this study was part of a larger collaborative work. The big project basically dealt with LIPS applied in geology. In this sub-investigation, QCT was compared with the LIPS technique during the examination of bovine leg bones. We found a correlation between BMD measured with QCT and attenuation, as well as BMD measured with QCT and LIPS, on beef bone samples. Since there was no previous study of a similar nature, we could not compare our results with the literature.

6. Summary

Introduction. Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are associated with general and focal osteoporosis. In addition to DXA, which determines areal bone density (BMD), peripheral quantitative computed tomography (QCT) also detects volumetric BMD. QCT can also differentiate between total, trabecular and cortical BMD.

Examination 1. We compared DXA and QCT in RA patients and healthy controls. BMD of a total of 57 RA patients and 32 age-matched healthy controls was determined by DXA. QCT examinations were performed in the ultradistal region of the forearm. Densitometric data were correlated with age, disease duration, disease activity, serum CRP and anti-CCP level. Areal BMD determined by DXA correlated with volumetric bone density measured by QCT. In addition, trabecular osteoporosis was associated with RA, while cortical osteoporosis was more correlated with age.

Examination 2. In this study, volumetric and areal BMD were measured by forearm QCT and DXA, in addition to laboratory biomarkers, in patients with RA and SPA who received one year of anti-TNF therapy. A total of 40 RA and SPA patients treated with etanercept (ETN) or certolizumab pegol (CZP) were followed for one year. We performed measurements of volumetric and areal BMD, parathyroid hormone (PTH), osteocalcin, RANKL, 25-hydroxyvitamin D (VITD), P1NP, CTX, sclerostin (SOST), Dickkopf 1 (DKK-1) and cathepsin K (CATHK). Volumetric BMD measured by QCT did not change during one year of anti-TNF treatment. Disease activity, CATHK, RANKL and VITD were associated with the effect of anti-TNF treatment on QCT BMD changes. RA and SPA differed in this regard.

Examination 3. We performed laser-induced plasma spectroscopy (LIPS) and QCT tests on cattle bone samples to assess the bone structure and mineral content. The LIPS results are not part of this dissertation. We found that the attenuation coefficient determined by QCT can be one of the best determinants of the altered bone tissue structure. We compared the attenuation coefficient measured by QCT and total BMD and found a significant correlation between these two parameters. We also compared BMD measured with LIPS and QCT techniques and found a significant correlation between the two types of BMD measurements.

Conclusions. QCT and DXA may be suitable for examining bone metabolism in inflammatory joint diseases. The advantage of QCT is that this method can detect bone changes in different bone compartments. In addition, QCT can be useful in examining inflammatory bone changes, structural abnormalities, and the effect of targeted therapies on bone.

7. Conclusions, new findings

Ours was the first study to assess the relationship between RA-related autoimmunity and bone metabolism. In our QCT study, anti-CCP seropositive patients had significantly lower trabecular BMD and attenuation compared to seronegative patients. There was no difference in cortical bone. These results indicate that RA-associated autoimmunity and its consequences affect trabecular rather than cortical bone.

The strength of our study is that we were among the first to investigate the applicability of QCT in bone loss associated with RA, compared with DXA, clinical and laboratory parameters. It is also important that in our study we compared RA patients free of other chronic diseases to a healthy control group, and we compared the two methods using QCT and DXA on the same individuals.

For the first time, we examined the change in volumetric BMD measured by QCT in RA and SPA patients undergoing anti-TNF treatment. We know from previous studies that generalized bone loss - away from joints, such as the spine - can be inhibited with anti-TNF drugs. However, we have now also shown that all this can be stopped in the immediate vicinity of the joints (wrist/hand). We also tried to clarify the mechanism. The one-year increase in volumetric BMD was most pronounced in patients with very low DAS28/BASDAI. In addition, we found that the most favorable volumetric BMD changes were observed in patients with low bone resorption markers (cathepsin K, sRANKL) before treatment.

The present QCT and our previous DXA studies in the same cohort confirmed that biological therapy can stop generalized bone loss. Volumetric and areal BMD values correlate with each other, indicating the value of both QCT and DXA to assess bone status in inflammatory diseases. We also identified baseline parameters such as disease activity, cathepsin K, 25-hydroxyvitamin D3, and sRANKL that could predict the temporal effect of one year of anti-TNF therapy on volumetric BMD. The pre-treatment levels of cathepsin K and 25-hydroxy-vitamin D3 can be associated with the changes occurring in the cortical and trabecular bone compartments.

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List of publications related to the dissertation

1. **Juhász, B.**, Gulyás, K., Horváth, Á., Végh, E., Karancsiné Pusztai, A., Szentpétery, Á., Pethő, Z., Bodnár, N., Hamar, A. B., Bodoki, L., Bhattoa, H. P., Szekanecz, É., Hódosi, K., Domján, A., Szamosi, S., Horváth, C., Szántó, S., Szűcs, G., Raterman, H. G., Lems, W. F., FitzGerald, O., Szekanecz, Z.: Peripheral quantitative computed tomography in the assessment of bone mineral density in anti-TNF-treated rheumatoid arthritis and ankylosing spondylitis patients. *BMC Musculoskelet. Disord. 22* (1), 1-9, 2021.
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