

PROTOCOL FOR
THE CENTRAL DENMARK REGION COMMITTEE ON
HEALTH RESEARCH ETHICS

ADMINISTRATIVE INFORMATION

1 TITLE

RACTX – An observational study of bone erosion determination and progression in Rheumatoid Arthritis assessed by HR-pQCT and conventional X-ray.

2 TRIAL REGISTRATION

The trial is registered at Clinicaltrials.gov. This protocol is structured according to SPIRIT 2013 checklist.¹

3 PROTOCOL VERSION

Version 1.19.01.2018

4 ROLES AND RESPONSIBILITIES

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INTRODUCTION

5 BACKGROUND AND RATIONALE

Rheumatoid arthritis (RA) is the most common autoimmune joint disease, afflicting about 35,000 people in Denmark. Morbidity and mortality are significant and result in multiple joint destruction and disability and reduce life expectancy by ten years. Bone destruction (erosion) occurs in the early disease course and is seen in about half of patients at diagnosis². Early treatment with disease modifying anti-rheumatic drugs (DMARDs) in mono- or combination therapy in a treat-to-target regime improves prognosis³. In case of long-term disease remission without radiological progression, it may be considered to terminate biological DMARD therapy, but identifying patients with low risk of progression of bone erosion is not trivial. Bone erosion is usually considered an irreversible damage. Some studies show that regression of the radiographic erosion score may happen^{4,5}. However, bone formation may be prevalent in bone tissue of arthritic joints⁶. Bone resorption and formation are uncoupled in RA⁷; true healing may therefore not occur. Longitudinal assessment of these lesions with respect to repair is, however, scarce, and more sensitive methods than convention X-ray are needed.

Several factors are prognostic for the progressions of joint destruction, such as the presence of rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA), genetics, smoking, age and gender. Apart from the patient's risk profile, treatment escalation is based on the radiographic progression of joint erosions, disease activity score (DAS28-CRP) using the number of tender and swollen joints, acute phase reactants, and patient-reported outcomes. However, no prognostic factors exist that at an early stage can reliably predict the disease course at the individual level.

Bone erosion is present in approximately 40% of Danish RA patients already at diagnosis². Knowledge of what happens in the joints in the period up to the clinical diagnosis is sparse, and bone changes are particularly poorly described. Studies have demonstrated that ACPA may be present in patients for many years before diagnosis^{8,9}. Therefore, individuals with positive ACPA may be ideal candidates for prospectively studying the period before a clinical diagnosis can be established (pre-RA phase). A single study has demonstrated a shift in serum biomarkers in pre-RA patients, which may indicate that bone changes occur before clinical disease¹⁰. Another minor study found thinner and more porous cortical bone in the metacarpophalangeal joint (MCP joint) of individuals with positive ACPA, but no symptoms of rheumatoid arthritis¹¹. Our research group, however, has previously found no change in the cortical bone, but thinner trabecular bone in the MCP joint of individuals with positive ACPA compared with individuals with negatively ACPA¹².

The treat-to-target escalation algorithms for RA have reduced the amount of bone destruction that is allowed before treatment is instituted. The changes in the radiographic score during the first 2 years of the disease is less than 1% of the maximal radiographic score used for conventional X-ray examination^{13,14}. Therefore, more

sensitive imaging methods could be a valuable factor to prognosticate development of bone erosion and shift treatment towards a more personalised medicine approach.

The Danish multi-centre study on early RA (CIMESTRA) showed that bone marrow oedema as seen by magnetic resonance imaging (MRI) was a predictor of progression of joint destruction¹⁵. Bone marrow oedema is associated with inflammation¹⁶; and in experimental arthritis, bone resorption is prominent adjacent to inflammatory cells in the bone marrow⁶. Before the appearance of destructive bone erosion, a more diffuse loss of bone may occur¹², but this parameter is not included in the scoring system for conventional X-ray examination used in research and the clinic¹⁴.

Conventional X-ray examination is the gold standard for detecting progression of joint destruction, but even at moderate resolutions (voxel size 400×400×1000 microns), CT systems have higher sensitivity for detecting erosions than conventional X-ray and MRI¹⁷. Ultrasound is used in daily clinical practice for assessing joint effusion and synovitis, but observer dependence is prominent, and the specificity for bone erosions is low¹⁸. The *areal* bone mineral density (aBMD) measured by dual-energy X-ray absorptiometry (DXA), is used clinically in diagnosis and monitoring of osteoporosis. The aBMD by DXA is also a useful measure of disease activity and progression in RA, although, it is seldom used clinically^{19,20}. The DXA scan, however, has its disadvantages. Firstly, the bone mineral density by DXA is only a two-dimensional estimate of the bone loss. Secondly, the bone mineral density by DXA is systemic and not juxta-articular; and, finally, DXA gives no information of the bone's microarchitecture. The imaging method high-resolution peripheral quantitative computed tomography (HR-pQCT), however, has a high resolution with voxel size 82×82×82 microns. Still, scan time is short and radiation exposure low, equaling that of conventional X-ray. The HR-pQCT scanner has been used in osteoporosis research for measuring juxta-articular *volumetric* bone mineral density (vBMD) and bone microarchitecture²¹. Patients with RA have an increased risk of osteoporosis and fragility fractures²². Lately, the HR-pQCT-scanner has also been used for detecting erosions, bone loss and possible healing in RA joints²³⁻²⁸. The HR-pQCT has been shown to be a promising technique capable of providing a quantitative assessment of hand bone loss in RA patients²⁹. Further studies are needed, however, to examine the diagnostic and prognostic value of minimal erosions and loss of bone mineral density (BMD) as measured by HR-pQCT imaging.

6 OBJECTIVES

6.1 Perspectives

If the HR-pQCT imaging system turns out to be a reliable candidate for individual disease monitoring, it may establish a basis for precision medicine in the treatment of RA. The perspective is that appropriate immunosuppressive treatment can be initiated at an earlier stage to improve the prognosis for patients at

risk of developing severe bone destruction and disability and that the immunosuppressive treatment can be omitted or stopped in those patients not at risk, thus avoiding excessive health cost and patient adverse events.

6.2 Objectives

The overall objective of this observational study is to detect erosive changes in patients with RA and pre-RA earlier than conventional X-ray, using the new image diagnostic method HR-pQCT. Specifically, the following are investigated:

- The number, size and volume of bone erosions, determined by HR-pQCT imaging, compared with erosion score by conventional X-ray examination at baseline. In RA patients, pre-RA patients and healthy subjects.
- The number, size and volume of bone erosions, determined by HR-pQCT imaging, compared with erosion score by conventional X-ray examination at one-year follow-up. In RA patients, pre-RA patients and healthy subjects.
- The progression of number, size and volume of bone erosions, determined by HR-pQCT imaging, versus the progression in radiographic erosion score determined by conventional X-ray examination throughout the trial period. In RA patients, pre-RA patients and healthy subjects.
- Correlation between changes in radiographic erosion score, determined by conventional X-ray, throughout the trial period, and the mean disease activity, assessed by DAS28-CRP, HAQ and VAS, throughout the trial period, as well as serological markers for bone metabolism and inflammation (see 11.2) throughout the trial period. In RA patients, pre-RA patients and healthy subjects.
- Correlation between changes in radiographic erosion score, determined by conventional X-ray, and the mean disease activity, assessed by DAS28-CRP, HAQ and VAS, throughout the RA patients' entire disease duration.
- Correlation between change in number, size, and volume of erosions, determined by HR-pQCT imaging, throughout the trial period, and the mean disease activity, assessed by DAS28-CRP, HAQ and VAS, throughout the trial period, as well as serological markers for bone metabolism and inflammation (see 11.2) throughout the trial period. In RA patients, pre-RA patients and healthy subjects.
- Correlation between change in number, size, and volume of erosions, determined by HR-pQCT imaging, throughout the trial period, and the mean disease, assessed by DAS28-CRP, HAQ and VAS, throughout the RA patients' entire disease duration.

- The regression of the articular vBMD and bone architecture by HR-pQCT imaging throughout the trial period. In RA patients, pre-RA patients and healthy subjects.
- Correlation between articular vBMD by HR-pQCT imaging and systemic aBMD by DXA, at both baseline and one-year follow-up in patients with RA.
- Correlation between change in the articular vBMD, determined by HR-pQCT imaging, throughout the trial period, and the mean disease activity assessed by assessed by DAS28-CRP, HAQ and VAS, throughout the trial period, as well as biomarkers for bone metabolism and inflammation (see 11.2), throughout the trial period. In RA patients, pre-RA patients and healthy subjects.
- Correlation between change in the articular vBMD, determined by HR-pQCT imaging, throughout the trial period, and the mean disease activity, assessed by DAS28-CRP, HAQ and VAS, throughout the RA patients' entire disease duration.

6.3 Hypothesis

1. The progression of number, size and volume of bone erosions, determined by HR-pQCT imaging, throughout the trial period are higher in RA patients compared with pre-RA patients and healthy subjects.
2. The progression of the number, size and volume of bone erosions, determined by HR-pQCT imaging, throughout the trial period are correlated with a higher disease activity score, assessed by DAS28-CRP, HAQ and VAS, throughout the trial period in RA patients, pre-RA patients and healthy subjects.
3. The progression of the number, size and volume of bone erosions, determined by HR-pQCT, throughout the trial period are correlated with changes in biomarkers for bone metabolism and inflammation (see 11.2)
4. The progression in the radiographic erosion score throughout the trial period, determined by conventional X-ray, is higher in RA patients compared with pre-RA patients and healthy subjects.
5. The progression in the radiographic erosion score throughout the trial period, determined by conventional X-ray, is correlated with a higher disease activity score, assessed by DAS28-CRP, HAQ and VAS, throughout the trial period in RA patients, pre-RA patients and healthy subjects.
6. The progression in the radiographic erosion score throughout the trial period, determined by conventional X-ray, is correlated with changes in biomarkers for bone metabolism and inflammation (see 11.2)
7. The regression of articular vBMD and bone architecture throughout the trial, determined by HR-pQCT imaging, are higher in RA patients compared with pre-RA patients and healthy subjects.

8. The regression of articular vBMD and bone architecture throughout the trial, determined by HR-pQCT imaging, is correlated with a higher disease activity score, assessed by DAS28-CRP, HAQ and VAS, throughout the trial period in RA patients, pre-RA patients and healthy subjects.
9. The regression of articular vBMD and bone architecture throughout the trial, determined by HR-pQCT imaging, is correlated with changes in biomarkers for bone metabolism and inflammation (see 11.2)
10. The articular vBMD, determined by HR-pQCT imaging, correlates with the systemic aBMD, determined by DXA scan, in RA patients

METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

7 TRIAL DESIGN

The design of the trial is an observational study with three distinct groups. At the start of the trial period and at one-year of follow-up, the trial subject will have their hand X-rayed by conventional radiography, and their metacarpophalangeal (MCP) joint and wrist scanned by HR-pQCT-Imaging. The 28-joint Disease Activity Score (DAS28-CRP)³⁰, Health Assessment Questionnaire (HAQ)³¹, Visual analogue scale (VAS)-score for pain, fatigue and quality of life are performed to investigate the correlation between radiographic changes and disease activity. Blood samples are collected to investigate serological markers of bone metabolism and inflammation and the radiographic changes. The following groups are investigated:

RA patients: Patients with RA ≥ 5 years according to the ACR/EULAR 2010 classification criteria³² or the American Rheumatism Association 1987 revised criteria³³ are recruited from the outpatient clinic at the Department of Rheumatology, Aarhus University Hospital. Treatment will be adjusted according to the patient's need and according to national guidelines. (n=450)

Pre-RA patients: Patients with pre-RA, (joint pain, but now swelling and ACPA 3 times above the upper limit) are recruited from the outpatient clinic at the Department of Rheumatology, Aarhus University Hospital. (n=75)

Healthy subjects: Healthy age- and sex-matched Individuals are recruited, as a control group, by posting at libraries in Aarhus, Aarhus University, Aarhus University Hospital and postings on the websites www.forsogsperson.dk and www.Sundhed.dk. (N=100)

8 STUDY SETTING

Aarhus University Hospital, Department of Rheumatology. Nørrebrogade 44, 8000 Aarhus C, Denmark.

9 ELIGIBILITY CRITERIA

9.1 RA patients

Inclusion criteria

- Patients (> 18 years) with rheumatoid arthritis ≥ 5 years according to the ACR/EULAR (2010) classification criteria³² or American Rheumatism Association 1987 revised criteria³³ for the patients who were diagnosed before 2010.
- Patients who are receiving treatment on an outpatient basis.
- Ability and willingness to give written informed consent and to meet the requirements of the trial protocol.

Exclusion criteria

- Patients who have previously suffered trauma in the form of fracture or luxation of the hand are excluded.
- Evidence of active malignant disease.
- Hypo- or hyperthyroidism.
- Hypocalcaemia.
- Impaired renal function (eGFR <35ml/min).
- Pregnancy.

9.2 Pre-RA patients

Inclusion criteria

- Age over 18 years.
- ACPA 3 times the upper limit of the reference interval.
- Arthralgia.
- Ability and willingness to give written informed consent and to meet the requirements of the trial protocol.

Exclusion criteria

- Pregnancy.
- Swelling of joints. Verified by clinical ultrasound.
- Patients who have previously suffered trauma in the form of fracture or luxation of the hand are excluded.
- Evidence of malignant disease.
- Hypo- or hyperthyroidism.
- Hypocalcaemia.

- Impaired renal function (eGFR <35ml/min).
- Earlier or present rheumatological disease or bone metabolic disease.

9.3 Healthy subjects

Inclusion criteria

- Age over 18 years.
- No joint complaints.
- Ability and willingness to give written informed consent and to meet the requirements of the trial protocol.

Exclusion criteria

- Patients who have previously suffered trauma in the form of fracture or luxation of the hand are excluded.
- Evidence of malignant disease.
- Hypo- or hyperthyroidism.
- Hypocalcaemia.
- Impaired renal function (eGFR <35ml/min).
- Earlier or present rheumatological disease or bone metabolic disease.
- Positive anti-CCP.
- Pregnancy.

10 INTERVENTIONS

The study is an observational study. This study does not perform any Interventions on any of the groups.

11 OUTCOMES

11.1 Primary outcomes

- a) Changes in bone erosion number, size and volume by HR-pQCT-imaging from baseline to one-year follow-up, in the three groups.
- b) Change in radiographic erosion score from baseline to one-year follow-up, in the three groups.
- c) Changes in vBMD in cancellous and trabecular bone respectively from baseline to one-year follow-up by the HR-pQCT, in the three groups.
 - Average bone density (Dtotal).
 - Trabecular bone density (Dtrab).
 - Cortical bone density (Dcort) in milligrams of hydroxyapatite (HA) per centimetre cubed.

- Mean cortical thickness (Ct.Th, millimetres).
- Trabecular bone volume fraction (BV/TV).
- Trabecular number (Tb.N, 1 mm).
- Trabecular thickness (Tb.Th, millimetre).
- Trabecular spacing (Tb.Sp, millimetre).

11.2 Secondary outcomes

- d) aBMD in the lumbar spine, and the left hip by DXA, in RA patients
- e) Changes from baseline to one-year follow-up in the following serological markers of bone metabolism and inflammation, in the three groups:
- C-terminal telopeptide (CTX).
 - Procollagen type 1 N-terminal propeptide (P1NP).
 - Bone-specific alkaline phosphatase, (BAP).
 - Tumor necrosis factor-alfa (TNF- α).
 - RANK-Ligand (RANK-L).
 - Osteoprotegerin (OPG).
 - Osteocalcin (BGLAP).
 - Sclerostin(SCL).
 - Dickkopf-related protein 1 (Dkk-1).
 - Interleukins 1, 6, 15, 16, 17, 22, and 33 (IL-1, IL-6, IL-15, IL-16, IL-17, IL-22, and IL-33).
 - Chemokine ligand 11 (CCL11).
 - Chemokine (C-X-C) motif ligand (CXCL13).
 - C-reactive protein (CRP).
 - Tartrate-resistant acid phosphatase 5b (TRACP 5b).
- f) Clinical information.
- DAS28-CRP.
 - HAQ.
 - VAS-pain, fatigue and quality of life.

12 PARTICIPANT TIMELINE

Visit	1	2	3	4
Month	0	3	6	12
Information Meeting	X			
Informed consent	X			
Demography	X			
Inclusion/exclusion criteria	X			
Medical history	X			
Physical examination	X			X
HR-pQCT	X			X
DXA ¹	X			
DAS 28-CRP	X			X
X-Ray of hand	X			X
Blood samples ²	X	(X)	(X)	X

¹Only RA Patients without a recent DXA scan (< 2 years) will be referred to a DXA scan at the time of baseline.

²Blood samples at the 3rd and 6th month are only collected from RA and pre-RA Patients.

13 SAMPLE SIZE

Data on relevant study populations on which sample size can be calculated is not available. The planned population size is estimated based on the following. Statistical significance is 0.05. Sensitivity, specificity, positive and negative predictive values could be estimated in a group of only 17 patient using low-resolution CT⁴. Progression in the radiographic score is however much less sensitive. The changes in the radiographic score during the first two years of the disease is less than 1% of the maximal radiographic score used for conventional X-ray examinations^{13,14}. Therefore, a substantially higher number of patients are needed. Our study includes a study group of 450 patients with RA ≥ 5 years, and a group of 75 patient with pre-RA, not it medical treatment, where we expect a higher initial change in the articular bone. A group of 100 healthy individuals are included as a control group, which we assess, are sufficient.

14 RECRUITMENT

14.1 RA and pre-RA patients

Patients are recruited from the outpatient clinic at the Department of Rheumatology, Aarhus University Hospital. The Department of Rheumatology treats about 1400 patients with RA. In the present study, we include 450 patients with RA. Patients participating in the trial are subjected to the same procedures as their annual doctor's visit, which includes a physical examination, blood samples and questionnaires. At the annual doctor's visit, the patients are also examined with DXA scans and conventional X-ray according to clinical status. In this trial, the patients are also subjected to HR-pQCT imaging, at the start and one-year follow-up,

and extra blood samples at the 3rd and 6th month. We, therefore, do not expect any trouble with the recruitment of the patients, owing to the large patient population to recruit from, and because the patients only have to participate in a few additional procedures compared to their annual physical.

14.2 Healthy subjects

Healthy controls are recruited by posting at libraries in Aarhus, Aarhus University, Aarhus University Hospital, and postings on the website www.forogsperson.dk and www.sundhed.dk. Contact information in the form of the principal investigator's email address is listed on the postings. Interested subjects can subsequently contact the trial investigator for further information. The healthy subjects are compensated 500 DKK for the disadvantages that may be associated with the trial. The healthy subjects are compensated after their last examination at the one-year follow-up. In case of exclusion or absence, the healthy subjects do not receive compensation. In previous studies, our research group has, under similar trial settings, not experienced any problems with recruiting healthy subjects. We, therefore, do not expect problems with recruiting.

METHODS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS

15 DATA COLLECTION METHODS

15.1 HR-pQCT

All Patients will be scanned at baseline and one year after using the HR-pQCT scanner (Xtreme CT, Scanco Medical AG, Switzerland). The hand is scanned in a 2.7 cm long region corresponding to the 2. and 3. metacarpophalangeal joint, being the joints most commonly involved in RA³⁴. The wrist is scanned over a 0.9 cm long region starting at the most proximal joint surface of the radius. The number, size and volume of bone erosions are estimated. Structural parameters for cortical and trabecular bone are calculated.

15.2 Conventional X-ray

All patients will be examined at baseline and a year after with conventional X-ray using the standard dorsopalmar (PA) projection of the hands and wrist, a focus distance of 100-115 cm, and an exposure of 50-55 kV and 2-12 mAs. Erosions score is appraised by the Sharp-van-der-Heijde method¹⁴, among other methods. If a conventional X-ray of hand and wrist has been performed within the last three months or is scheduled in the three months following inclusion, this will be recorded as the baseline scan.

15.3 Blood samples

A research biobank for blood samples will be established for the project, with an expected start on the 1st of January 2018 and which expires d. 31st of December 2026. The standard set of blood samples are stored

nine years in the research biobank, three years for inclusion, one-year of follow-up, and the last five years for the analysis. The standard set of blood samples (see 11.2) is collected from all the RA and pre-RA patients at the beginning of the trial, at the 3rd month, at the 6th month, and after one-year. A total of 300 ml is collected throughout the experiment. The standard set of blood samples is collected from the healthy subjects at the beginning of the trial, and after one-year. A total of 150 ml is collected throughout the experiment.

The standard set of blood samples are collected by the Danish Reuma Biobank (DRB) under the regional Bio- and Genome Bank Denmark (RBGB). Immediately after sampling, blood samples are sent to the Molecular Medical Department (MOMA), AUH Skejby, where they are handled, registered and stored in DRB. Material for analysis in the project is then provided by DRB to the project's research biobank. At the end of the project period, nine years after the project start, the research biobank ceases. Excess material is requested to be transferred to a biobank for future research. Participants may withdraw any commitment to participate in the project, or for storage of the standard blood samples in RBGB at any time. If the participant only agrees to the research project, but not to RBGB, or if the consent to RBGB is withdrawn, the material in RBGB will be destroyed. The Central Denmark Region Committee on Health Research Ethics and Regional Data Protection Authorities are applied for permission before use of the standard set of blood samples from the for biobank for future research use in any ancillary studies.

15.4 Physical examination

The patients and healthy subjects are examined with a focus on their joints at the beginning of the trial and one-year later. The following twenty-eight joints, which also are included in DAS28-CRP are examined for swelling and tenderness: shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints and the knees. In addition, a general joint examination with a focus on remaining joints is made.

15.5 Recording of patient demography and clinical information

Demographic and clinical information is retrieved from the electronic patient journal (EPJ), which stores patient information indefinitely. The demographic and clinical information: Gender, age height, weight, duration of disease, menarche, menopause, pregnancies, births, medication, comorbidity, alcohol consumption, tobacco consumption, dietary calcium intake, which might not be obtainable from the journal, are retrieved directly from the patient in cooperation with the trial investigator. The following biomarkers are also extracted from EPJ: Creatinine, calcium ion (Ca^{+2}), potassium ion (K^{+}), magnesium ion (Mg^{+2}), rheumatoid factor (RF), anti-citrullinated protein antibodies (anti-CCP), 25-OH-vitamin D, parathyroid hormone (PTH).

From the clinical database DanBio under The Danish Clinical Registries (RKKP) the following information is extracted; 28-joint Disease Activity Score (DAS28-CRP), Health Assessment Questionnaire (HAQ), C-reactive protein (CRP) and Visual analogue scale (VAS)-score for pain, fatigue and quality of life.

15.6 DXA

Patients with RA, but without a recent DXA scan (<2 years) will be referred to a DXA scan according to clinical guidelines. Patients with osteoporosis, defined by a T-score <-2.5 according to DXA imaging, are treated according to National guidelines.

To ensure comparative results, the same machine is used for each participant at each scan. Lumbar spine anterior-posterior and left hip pictures are recorded following local guidelines. In brief, the lumbar spine is scanned with the patient positioned on his/her back, with legs bent 90 degrees at both hip and knee. Then, the subject is placed flat on his/her back, and the left leg is rotated inward and fixated to position the femoral neck for the total hip scan. BMD in g/cm² and Z- and T-scores are calculated using the built-in software.

15.7 Practical feasibility

In this study, cooperation with experienced and key persons in the relevant departments has been established, ensuring both recruitment of patients and subsequent imaging and blood sample. Our research group has initiated this line of clinical studies focusing on the early diagnosis of joint destruction in rheumatoid arthritis based on results from experimental arthritis^{6,12}. We have experience with HR-pQCT imaging from a previous PhD project^{35,36} and more than 300 scans of RA and pre-RA patients completed at Aarhus University Hospital. In addition, the first publication on the pre-RA patients has been published¹². Since 2013 our group has been participating in the international research group SPECTRA, which has recently become a Special Interest Group of the OMERACT initiative, an international initiative to improve outcome measurement in rheumatology²⁸. The Department of Rheumatology at Aarhus University Hospital is currently the only Danish department investigating HR-pQCT imaging in RA patient for precision medicine.

16 DATA MANAGEMENT

All of the data mentioned above are considered source data. HR-pQCT-scans, X-rays and demographic information are documented in Research Electronic Data Capture (REDCap). The clinical information is extracted from DanBio and stored in REDcap. The standard set of blood samples (see 11.2) are stored at RBGB. The remaining data can be retrieved using the patients' medical records, the electronic patient journal (EPJ), which stores patient information indefinitely. All data is anonymised, with the code of anonymisation stored separately.

17 STATISTICAL METHODS

A p-value < 0.05 will be considered significant when comparing two study groups, or the change from baseline to the one-year follow-up in the same group. Significant differences are calculated with either student's t-test if data is normally distributed. In case the data is not normally distributed the Mann–Whitney U test is used to calculate significant differences. Correlation is calculated with either Pearson correlation coefficient or Spearman's rank correlation coefficient. A p-value < 0.05 will be considered significant. The following comparison is made:

1. Δ erosion number, size and volume at baseline, determined by HR-pQCT imaging, in RA patients compared with pre-RA patients and healthy subjects.
2. Δ erosion number, size and volume at baseline, determined by HR-pQCT imaging, in pre-RA patients compared with healthy subjects.
3. Δ radiographic erosion score at baseline, determined by conventional X-ray, in RA patients compared with pre-RA patients and healthy subjects.
4. Δ radiographic erosion score at baseline, determined by conventional X-ray, in pre-RA patients compared with healthy subjects.
5. Δ erosion number, size and volume at one-year follow-up, determined by HR-pQCT imaging, in RA patients compared with pre-RA patients and healthy subjects.
6. Δ erosion number, size and volume at one-year follow-up, determined by HR-pQCT imaging, in pre-RA patients compared with healthy subjects.
7. Δ erosion number, size and volume, determined by HR-pQCT imaging, at baseline compared with one-year follow-up. In RA patients, pre-RA patients and healthy subjects.
8. Δ radiographic erosion score at one-year follow-up, determined by conventional X-ray, imaging in RA patients compared with pre-RA patients and healthy subjects.
9. Δ radiographic erosion score at one-year follow-up, determined by conventional X-ray, in pre-RA patients compared with healthy subjects.
10. Δ radiographic erosion score, determined by conventional X-ray, at baseline compared with one-year follow-up. In RA patients, pre-RA patients and healthy subjects.
11. Δ articular vBMD and bone architecture at baseline, determined by HR-pQCT imaging, in RA patients compared with pre-RA patients and healthy subjects.
12. Δ articular vBMD and bone architecture at baseline, determined by HR-pQCT imaging, in pre-RA patients compared with healthy subjects.

13. Δ articular vBMD and bone architecture at one-year follow-up, determined by HR-pQCT imaging, in RA patients compared with pre-RA patients and healthy subjects.
14. Δ articular vBMD and bone architecture at one-year follow-up, determined by HR-pQCT imaging, in pre-RA patients compared with healthy subjects.
15. Δ articular vBMD and bone architecture, determined by HR-pQCT imaging, at baseline compared with one-year follow-up. In RA patients, pre-RA patients and healthy subjects.
16. Δ values of the serological markers of bone metabolism and inflammation (*see 11.2*) between RA patients and pre-RA patients at baseline.
17. Δ values of the serological markers of bone metabolism and inflammation (*see 11.2*) between RA patients and healthy subjects at baseline.
18. Δ values of the serological markers of bone metabolism and inflammation (*see 11.2*) between pre-RA patients and healthy subjects at baseline.
19. Δ values of the serological markers of bone metabolism and inflammation (*see 11.2*) between baseline and one-year follow-up. In RA patients, pre-RA patients and healthy subjects.
20. Δ values of the serological markers of bone metabolism and inflammation (*see 11.2*) between RA patients and pre-RA patients at 3rd-month follow-up
21. Δ values of the serological markers of bone metabolism and inflammation (*see 11.2*) between RA patients and pre-RA patients at 6th-month follow-up
22. Δ values of the serological markers of bone metabolism and inflammation (*see 11.2*) between RA patients and pre-RA patients at one-year follow-up
23. Δ values of the serological markers of bone metabolism and inflammation (*see 11.2*) between RA patients and healthy subjects at one-year follow-up
24. Δ values of the serological markers of bone metabolism and inflammation (*see 11.2*) between pre-RA patients and healthy subjects at one-year follow-up
25. Correlation between Δ number, size and volume of bone erosions, determined by HR-pQCT imaging, and Δ values of the serological markers for bone metabolism and inflammation (*see 11.2*) throughout the trial period. In RA patients, pre-RA patients and healthy subjects.
26. Correlation between Δ radiographic erosion score, determined by conventional X-ray, and Δ values of the serological markers for bone metabolism and inflammation (*see 11.2*) throughout the trial period. In RA patients, pre-RA patients and healthy subjects.
27. Correlation between Δ number, size, and volume of erosions, determined by HR-pQCT imaging, throughout the trial period and the mean disease activity, assessed by DAS28-CRP, HAQ and VAS, throughout the RA patient's entire disease duration.

28. Correlation between Δ number, size, and volume of erosions, determined by HR-pQCT imaging, throughout the trial period, and the mean disease activity, assessed by DAS28-CRP, HAQ and VAS, throughout the trial period. In RA patients, pre-RA patients and healthy subjects
29. Correlation between Δ radiographic erosion score throughout the trial period, determined by conventional X-ray, and the mean disease activity, assessed by DAS28-CRP, HAQ and VAS, throughout the trial period. In RA patients, pre-RA patients and healthy subjects.
30. Correlation between Δ radiographic erosion score throughout the trial period, determined by conventional X-ray, and the mean disease activity, assessed by DAS28-CRP, HAQ and VAS, throughout the RA patient's entire disease duration.
31. Correlation between Δ articular vBMD and bone architecture, determined by HR-pQCT imaging, and Δ values of the serological markers for bone metabolism and inflammation (see 11.2) throughout the trial period. In RA patients, pre-RA patients and healthy subjects.
32. Correlation between Δ articular vBMD and bone architecture throughout the trial period, determined by HR-pQCT imaging, and the mean disease activity, assessed by DAS28-CRP, HAQ and VAS, throughout the RA patient's entire disease duration.
33. Correlation between systemic aBMD, determined by DXA scan, and articular vBMD, determined by HR-pQCT imaging, in RA patients.

ETHICS AND DISSEMINATION

18 RESEARCH ETHICS APPROVAL

In this scientific study, joint destruction in rheumatoid arthritis patients is investigated with a new medical Imaging modality (HR-pQCT). Furthermore, data from the annual monitoring of patients' disease from the Department of Rheumatology are included. One risk/disadvantage for the patients in this trial is to have their hand fixated in 3 minutes, and 8 minutes, otherwise, no discomfort is related to HR-pQCT. The total radiation dose of HR-pQCT in the study is less than 0.1 mSv, which is about the same as in conventional X-ray of hands. Each DXA scan gives a radiation dose of 0,01mSv. Background radiation in Denmark is three mSv a year. The total radiation in the study enhances the risk of cancer with 1/1.000.000 compared to the overall lifetime risk of 1/4, which is considered as insignificant. Slight pain associated with blood sampling may occur but is deemed acceptable. The risk of infection is estimated to be very low.

This trial does not benefit the individual patient with RA or pre-RA. The knowledge gained through the trial, however, will contribute with significant scientific information of importance to the future treatment of rheumatoid arthritis patients, and it is thus the investigator's opinion that the trial is relevant and ethical. It is estimated that potential risks for patients by participating in the experiment are insignificant.

Approval must be provided from The Central Denmark Region Committee on Health Research Ethics and Regional Data Protection Authorities before the recruitment of research subjects.

19 PROTOCOL AMENDMENTS

All Modifications to the protocol are reported to The Central Denmark Region Committee on Health Research Ethics and The Data Protection Authorities.

20 CONSENT OR ASSENT

20.1 RA and Pre-RA patients

Patients are recruited from the outpatient clinic at the Department of Rheumatology, Aarhus University Hospital. Information about the trial is given at an already scheduled appointment in the outpatient clinic or by sending written information to the patient. All information is provided by the trial investigator or by a person designated by the trial investigator. Patients who are interested in participating in the trial will be invited to a meeting with the trial investigator. Here, the patient will receive full oral and written information in uninterrupted surroundings and have the opportunity to ask questions. The patients are informed of their right to bring a friend or relative to the conversation beforehand and will be offered one week to consider their decision. The informed consent form is signed and dated by both the trial subject and the investigator. Subsequently, it is reviewed by the investigator for the correct date, readable name and signature. A copy of the signed informed consent is offered to the trial subject. The patient may, at any time and without giving a reason, withdraw his or her consent. Withdrawal of consent will not affect the further treatment of the patient.

20.2 Healthy subjects

Healthy subjects, interested in participating in the trial after seeing the postings are encouraged to contact the trial investigator. A meeting between the healthy subject and the trial investigator are scheduled. Here, the subject will receive full oral and written information in uninterrupted surroundings and have the opportunity to ask questions. The subject is informed of the right to bring a friend or relative to the conversation beforehand and will be offered one week to consider his or her decision. The subject may, at any time and without giving a reason, withdraw his or her consent. The informed consent form is signed and dated by both the trial subject and the investigator. Subsequently, it is reviewed by the investigator for the correct date, readable name and signature. A copy of the signed informed consent is offered to the trial subject. The subject may, at any time and without giving a reason, withdraw his or her consent. Withdrawal of consent will not affect the further treatment.

21 CONFIDENTIALITY

Information regarding previous medical history and treatment is gathered from the participants' medical records. All information is recorded in REDCap. The Law on the processing of personal data is followed. Patients informed written consent is collected before participation in the study. Patient information is protected accordance with the Danish law concerning the processing of personal data. Approval must be provided by the Data Protection Authorities. The scan results are deleted or submitted to the state archives at the end of the study.

22 DECLARATIONS OF INTEREST & FUNDING

Aarhus University has awarded a fully financed PhD fellowship which includes both PhD-scholarship (1.350.000 DKK) and PhD-fee (180.000 DKK) for the trial investigator.

The Novo Nordisk Foundation have donated 2.500.000 DKK for the conventional radiography and HR-pQCT-imaging.

The Danish Rheumatism Association have donated 140.000 DKK and "Fonden for lægevidenskabens fremme" have donated 40.000 DKK for which is earmarked for salary to a research nurse.

Aarhus University Hospital administers all funds for salaries and imaging. Financial contributors do not influence the study implementation or publication of results. There is a continuous search for funding from other funds. If such funding is granted, an amendment to the protocol will be submitted to The Central Denmark Region Committee on Health Research Ethics

23 ACCESS TO DATA

All source data will be accessible for Inspection by the Danish Health and Medicine Authority. All original informed consent forms and detailed records of medical disposition will be stored safely and destroyed after 15 years. Original data including laboratory data can be retrieved from the electronic medical records (EPJ). Investigator will ensure that direct access to all source data is available for Inspection by Danish Health and Medicines Authority and other authorities.

24 ANCILLARY AND POST-TRIAL CARE

The Patient Compensation Association covers patients who against all expectations, should be injured in the study.

25 DISSEMINATION POLICY

Positive, negative and inconclusive results will be published in high-ranking international peer-reviewed journals. We plan two publications related to the aims in *Annals of Rheumatic Diseases*, and 1 in *Arthritis & Rheumatology*. MD, PhD student Rasmus Klose Jensen will first author on all publications. Chief physician, Clinical Professor, PhD Ellen-Margrethe Hauge will be senior author. MD, PhD Kresten Krarup Keller, MD, PhD-student Anne-Birgitte Garm and Professor DMSc Bente Langdahl will be co-authors according to contributions. Authorship for other co-authors is awarded according to the Vancouver guidelines for authorship. This protocol will be published on ClinicalTrials.gov.

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