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A comparative analysis of articular bone in large cohort of patients with chronic inflammatory diseases of the joints, the gut and the skin

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ABSTRACT

Chronic inflammatory diseases are associated with bone loss. While the occurrence of systemic bone loss is well described in chronic inflammatory diseases, the impact of these conditions on articular bone has not been systematically investigated. Recent refinements in high-resolution CT assessment of the joints now allow the accurate measure of articular bone composition. In this study 476 subjects comprising healthy individuals and patients with anticitrullinated protein antibody (ACPA)-positive rheumatoid arthritis (RA), ACPA-negative RA, Crohn's disease (CD), ulcerative colitis (UC), psoriasis (PsO) and psoriatic arthritis (PsA) were subjected to high-resolution quantitative computed tomography (HR-pQCT) of the hand. Metacarpal heads were assessed for total, trabecular and cortical volumetric bone mineral density (vBMD). Only ACPA + RA, but not the remaining inflammatory diseases (ACPA − RA, CD, UC, PsO, PsA) showed significant ($p < 0.001$) loss of articular bone affecting both the trabecular and the cortical compartments. Age and body mass index were also associated with articular bone changes, the former with lower, the latter with higher articular bone mass. In multivariate models, presence of ACPA + RA was an independent factor for articular bone loss. Among chronic inflammatory diseases ACPA + RA is the most potent precipitator for articular bone loss pointing out the role of autoimmunity in the development of articular bone disease in the context of chronic inflammatory disease.

1. Introduction

Joints are central anatomical structures affected in chronic inflammatory disease. Next to rheumatoid arthritis (RA), which represents a prototype of an inflammatory joint disease, also inflammatory diseases of the skin, such as psoriasis, and the bowel, such as Crohn's disease, can affect the musculoskeletal system. The burden of bone disease among various forms of chronic inflammatory disease may vary substantially. Changes of the bone architecture in the joints may provide a clue for their cumulative exposure to inflammation. Hence, bone adjacent to the joints can be seen as a sentinel for the intensity and the time skeletal tissue has been exposed to an inflammatory environment. This concept is based on the negative influence of inflammation on bone, which is manifested by the increased rate of osteoporosis in inflammatory disease [1–3].

Accurate measurement of intra-articular bone is challenging. Traditionally, bone density in the peripheral skeleton has been assessed by dual energy X-ray absorptiometry (DXA), and sometimes also digital X-ray radiogrammetry (DXR) was used. Whereas DXA needs two X-ray beams with different energy levels to estimate square bone density [4, 5], DXR uses a single anterior-posterior conventional radiograph of the hand [6]. DXR evaluates cortical bone and square bone density in the diaphysis of the metacarpal bones, hence usually localized distant from the joints [7]. DXR has been successfully used for longitudinal analysis of hand bone loss in patients with RA [8–12]. In contrast to DXR, DXA is used to determine the BMD of the whole hand [4, 5, 13–15] and also to

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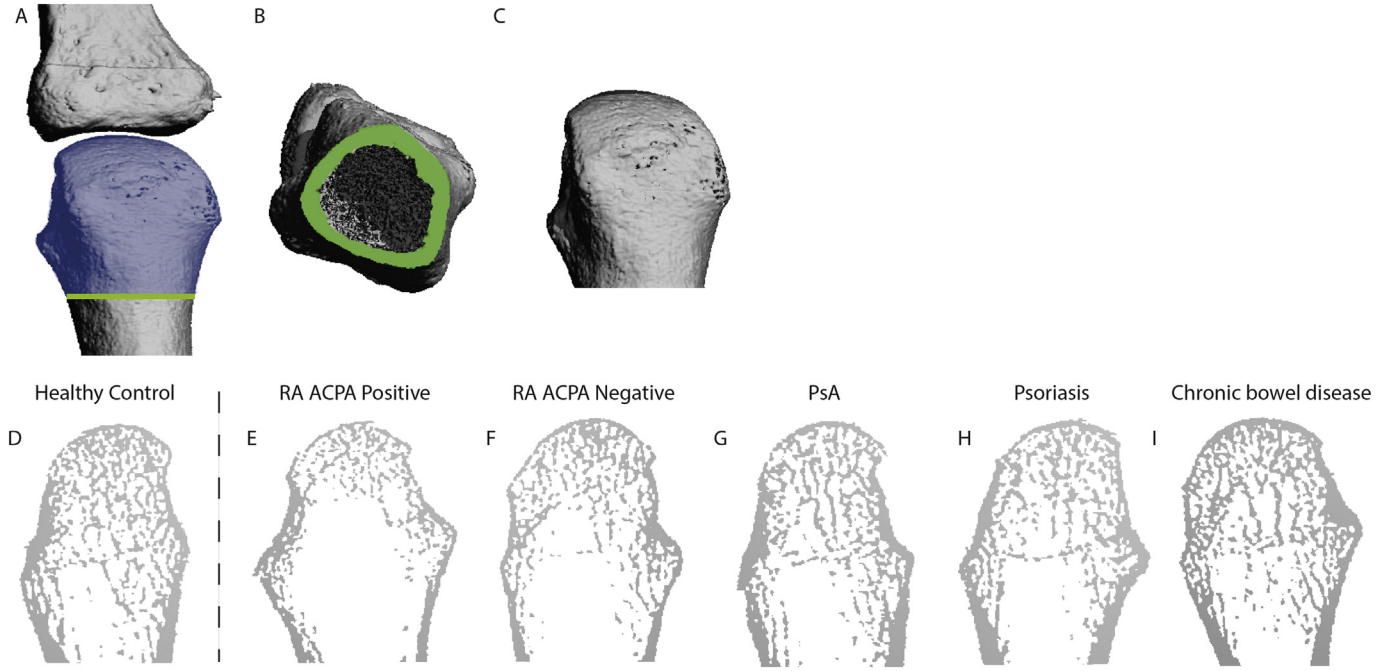

Fig. 1. Articular bone composition in chronic inflammatory diseases. (A–C) Depiction of the HR-pQCT measurement method applied in the study, showing the metacarpophalangeal joint with the region of interest being marked in blue (A) reflecting articular area, which ends at a typical triangular-shaped area of the bone (green marking, A, B). The subsequent segmented metacarpal head was used for bone mineral density evaluation (C). (D–I) HR-pQCT images of articular bone composition in healthy controls and the various chronic inflammatory diseases. Pictures show representative metacarpal heads (D) healthy controls, (E) anti-citrullinated protein antibody positive rheumatoid arthritis (ACPA + RA), (F) anti-citrullinated protein antibody negative rheumatoid arthritis (ACPA − RA), (G) psoriatic arthritis (PsA), (H) psoriasis, (I) chronic inflammatory bowel disease. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

approximate the BMD on the joint level with varying results in rheumatoid arthritis [16–18]. Both techniques, however, do not allow three-dimensional assessment of bone composition in the cortical and trabecular bone compartments [19]. This is a limitation since inflammatory processes in the joints are characterized by various degree of cortical and trabecular bone changes, the latter often associated with bone marrow inflammation, which is well known from magnetic resonance imaging (MRI) studies [20–22]. High-resolution peripheral quantitative computed tomography (HR-pQCT) allows quantitative analysis of peripheral bone using 82 μm voxel size. This allows to exactly determine bone mass and architecture of cortical and trabecular bone. Originally this technique was used to evaluate bone composition of the radius or the tibia in humans [23, 24]. During the last years HR-pQCT has also been used for the detection of local bone damage such as trabecular bone loss evaluation of bone erosions and osteophytes in rheumatoid arthritis [25–27] and psoriatic arthritis [28, 29]. Recently, we developed a method on how to exactly measure intra-articular bone composition of the joints, hence providing a tool to assess bone structure of joints in a larger population [27]. In this study we aimed to measure intra-articular bone composition in the several different chronic inflammatory diseases and compare them to healthy controls. Diseases investigated include anti-cyclic citrullinated peptide antibodies (ACPA) positive (+) RA, ACPA negative (−) RA, Crohn's disease (CD), ulcerative colitis (UC), psoriasis (PsO), psoriatic arthritis (PsA) and healthy controls (HC). We also aimed to identify the clinical factors that are associated with articular bone loss.

2. Methods

2.1. Patients and healthy controls

Healthy controls and patients were part of the Erlangen Imaging Cohort (ERIC), which prospectively assesses articular and peri-articular bone composition in healthy individuals and patients with inflammatory arthritis [27]. All participants were recruited at the Department of Internal Medicine 3 of the University of Erlangen-Nuremberg and were clinically examined by an experienced rheumatologist (AK, DS, JH). Participants provided written informed consent. The study was conducted upon approval of the ethical committee of the University Clinic of Erlangen and with the authorization of the National Radiation Safety Agency. HRpQCT investigation of the peripheral joints is part of routine clinical evaluation of patients with systemic inflammatory diseases in our institution replacing conventional radiography for two reasons: (i) lower radiation exposure and (ii) more precise detection of structural changes in HR-pQCT than conventional radiography. RA patients had to fulfill the ACR/EULAR classifications criteria 2010 of RA [30]. PsA patients had to fulfill the CASPAR [31] classification criteria. PsO patients were referred from the Dermatology Clinic with the diagnosis of plaque psoriasis according to the assessment by an experienced dermatologist (MS). PsO patients were meticulously assessed for musculoskeletal disease and had to fail CASPAR criteria. Patients with CD and UC were referred from the Department of Internal Medicine 1 (Gastroenterology). The diagnosis of CD or UC was done by the gastroenterologist (RA, SH, MFN) and was based on specific clinical symptoms together with colonoscopy-proven macro- and microscopic features of either CD or UC. Characteristics of healthy controls (HC) has already been described elsewhere [27]. Briefly, HC had to have [1] no presence or history of chronic joint pain/swelling, [2] no presence of systemic diseases, [3] no documented osteopenia/osteoporosis, [4] no present or past use of bisphosphonates or prednisolone and [5] no positivity for ACPA or rheumatoid factor (RF). In all patients and in HC, demographic characteristics such as age, sex, body mass index (BMI), as well as smoking status were collected. Presence of chronic kidney disease and diabetes mellitus were recorded.