Bone 64 (2014) 65–74

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

Assessment of the healing process in distal radius fractures by high resolution peripheral quantitative computed tomography

Joost J.A. de Jong [a,b,*], Paul C. Willems [c,d], Jacobus J. Arts [c,d], Sandrine G.P. Bours [b], Peter R.G. Brink [e], Tineke A.C.M. van Geel [d,f], Martijn Poeze [a,e], Piet P. Geusens [b,d,g], Bert van Rietbergen [h], Joop P.W. van den Bergh [a,b,g,i]

[a] Research School NUTRIM, Maastricht University, The Netherlands
[b] Department of Rheumatology, Maastricht University Medical Center, The Netherlands
[c] Department of Orthopedics, Maastricht University Medical Center, The Netherlands
[d] Research school CAPHRI, Maastricht University, The Netherlands
[e] Department of Surgery, Maastricht University Medical Center, The Netherlands
[f] Department of General Practice, Maastricht University, The Netherlands
[g] Faculty of Medicine and Life Sciences, Hasselt University, Belgium
[h] Faculty of Biomedical Engineering, Eindhoven University of Technology, The Netherlands
[i] Department of Internal Medicine, Viecuri Medical Center Venlo, The Netherlands

ARTICLE INFO

Article history:
Received 11 July 2013
Revised 5 March 2014
Accepted 24 March 2014
Available online 2 April 2014

Edited by Michael Amling

Keywords:
Fracture healing
Distal radius
HR-pQCT

ABSTRACT

In clinical practice, fracture healing is evaluated by clinical judgment in combination with conventional radiography. Due to limited resolution, radiographs don't provide detailed information regarding the bone micro-architecture and bone strength. Recently, assessment of *in vivo* bone density, architectural and mechanical properties at the microscale became possible using high resolution peripheral quantitative computed tomography (HR-pQCT) in combination with micro finite element analysis (μFEA). So far, such techniques have been used mainly to study intact bone. The aim of this study was to explore whether these techniques can also be used to assess changes in bone density, micro-architecture and bone stiffness during fracture healing. Therefore, the fracture region in eighteen women, aged 50 years or older with a stable distal radius fracture, was scanned using HR-pQCT at 1–2 (baseline), 3–4, 6–8 and 12 weeks post-fracture. At 1–2 and 12 weeks post-fracture the distal radius at the contra-lateral side was also scanned as control. Standard bone density, micro-architectural and geometric parameters were calculated and bone stiffness in compression, torsion and bending was assessed using μFEA. A linear mixed effect model with time post-fracture as fixed effect was used to detect significant (p-value ≤ 0.05) changes from baseline. Wrist pain and function were scored using the patient-rated wrist evaluation (PRWE) questionnaire. Correlations between the bone parameters and the PRWE score were calculated by Spearman's correlation coefficient. At the fracture site, total and trabecular bone density increased by 11% and 20%, respectively, at 6–8 weeks, whereas cortical density was decreased by 4%. Trabecular thickness increased by 23–31% at 6–8 and 12 weeks and the intertrabecular area became blurred, indicating intertrabecular bone formation. Compared to baseline, calculated bone stiffness in compression, torsion and bending was increased by 31% after 12 weeks. A moderate negative correlation was found between the stiffness and the PRWE score. No changes were observed at the contra-lateral side. The results demonstrate that it is feasible to assess clinically relevant and significant longitudinal changes in bone density, micro-architecture and mechanical properties at the fracture region during the healing process of stable distal radius fractures using HR-pQCT.

Introduction

Fragility fractures of the distal radius are one of the most common fractures. The incidence is about 17% of all fractures [1]. Although not always acknowledged, the outcome of distal radius fractures is not uniformly good. Poor outcomes have been attributed to poor restoration of anatomy and secondary loss of reduction after an initially adequate reduction [2], leading to discomfort, loss of range of motion and/or soft tissue complaints [3–5].

It is expected that the addition of medication or supplements, such as vitamin D or calcium can improve the clinical outcome of distal radius fractures [6]. To monitor the process of fracture healing in patients, who either received supplemental medication or not, a method that is able to evaluate bone healing in detail is necessary. In clinical practice, fracture healing is evaluated by clinical judgment of the physician in combination with plain anteroposterior (AP) and lateral radiographs. However,

* Corresponding author at: Maastricht University Medical Center, Department of Rheumatology, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands.
E-mail address: joost.dejong@maastrichtuniversity.nl (J.J.A. de Jong).

http://dx.doi.org/10.1016/j.bone.2014.03.043
8756-3282/

these evaluations do not provide detailed information with regard to the healing process and consolidation of fractures on the level of cortical and trabecular bone micro-architecture.

Until recently, human bone micro-architecture could only be studied with bone biopsies, *i.e.* with 2D histomorphometry or 3D microCT, since imaging techniques that can provide sufficient resolution for bone structure *in vivo* were not available. Therefore, *in vivo* high resolution imaging studies on fracture healing were restricted to animals [7,8]. Classical QCT proved to be a successful estimator for the prediction of the mechanical stability of long bones [9], but was not sufficient to study fracture healing in the distal radius in patients because of insufficient resolution to visualize individual trabeculae [10].

With the development of a new low-dose radiation high resolution peripheral quantitative computed tomography (HR-pQCT) technique, *i.e.* XtremeCT, it is possible to assess *in vivo* bone density and architecture at the microscale [11–13]. Moreover, biomechanical properties of the bone can be calculated by micro finite element analysis (μFEA) based on such HR-pQCT images [11,14,15].

So far, these high resolution imaging techniques were mainly used to study micro-architectural changes due to aging [16,17], osteoporosis and other (bone) diseases [15,18,19] and the effect of different treatments [20–23]. These techniques, however, could be applied as well to analyze the process of bone healing after a distal radius fracture. Potentially, such analyses could provide a new tool to assess fracture consolidation based on bone morphology or μFEA derived mechanical parameters. In a recent study, Mueller et al. [24] investigated the feasibility of using these techniques to assess fracture healing *in vivo* and found an 18% increase in calculated stiffness over a period of 2 months. However, in that study biomaterials and plates were used to stabilize the fracture. The application of these techniques to fracture healing without any intervention, other than a standard cast, however, has not been demonstrated and it remains unclear to what extent the healing process can be captured by the standard morphological and mechanical parameters.

The objective of this study was, therefore, to explore the feasibility of HR-pQCT in combination with μFEA to assess longitudinal changes in bone density, micro-architecture and biomechanical parameters during the first 12 weeks of healing of conservatively treated distal radius fractures.

Materials and methods

Subjects

Twenty women aged 50 years or older with a stable distal radius fracture, which was immobilized by a cast, were included in this study. All patients were included at the departments of Orthopedics and Traumatology of the Maastricht University Medical Center, the Netherlands. The exclusion criteria were: a history of previous fractures at the fractured side; known systemic or metabolic disorders leading to progressive bone deterioration; use of glucocorticoids; presence of an active inflammatory disease; presence of an active or suspected infection; or malignancy in the last 12 months pre-fracture.

To assess changes in bone density, micro-architecture, geometry and biomechanics, all patients underwent HR-pQCT scanning of the fractured distal radius during 4 visits. The visits were scheduled 1–2 weeks post-fracture (baseline) and 3–4 weeks, 6–8 weeks and 12 weeks post-fracture. During the first and last visit, the radius at the contra-lateral side was scanned as well. The protocol (registration no. NTR3821) was approved by an independent Medical Ethics Committee, and all patients gave written informed consent prior to participation.

Scanning by HR-pQCT

During each visit, the fractured radius was imaged by HR-pQCT (XtremeCT, Scanco Medical AG, Switzerland) using clinical *in vivo* settings by the manufacturer (effective energy of 60 kVp, tube current of 900 μA and 100 ms integration time). The region of interest (Fig. 1) was based on AP and lateral radiographs of the fractured radius, in which the proximal edge of the lunate was used as reference. To make sure the complete fracture was scanned, the scan length was set to 18 mm. With an isotropic voxel size of 82 μm, each HR-pQCT measurement thus resulted in 220 parallel CT slices. The effective dose of each HR-pQCT measurement at the fracture side was less than 6 μSv. Because the patient's forearm was fixed in a cast, the forearm with the cast was placed in a custom cylindrical carbon holder with an inflatable cushion (Pearltec AG, Schlieren, Switzerland) to minimize patient motion. To scan the radius at the contra-lateral side, standard clinical *in vivo* settings by the manufacturer were used and resulted in one stack containing 110 parallel CT slices with an isotropic voxel size of 82 μm. The offset at the contra-lateral side was fixed for all patients and was chosen 9.5 mm from the proximal edge of the lunate. The volume between 9.5 and 18.5 mm from the lunate was thus scanned at the contra-lateral side. The same holder as for the fractured forearm was used to fix the contra-lateral side.

Each scan was checked for motion-induced image artifacts and was quality graded by the operator according to the manufacturer's guidelines and as described by Pialat et al. [25]. In case such artifacts occurred and thus resulted in images of insufficient quality, *i.e.* grade 4 or 5, the scan was repeated.

Evaluation of bone density, micro-architecture and geometry

The HR-pQCT images were evaluated using the standard patient evaluation protocol provided by the manufacturer, which has been described earlier in detail [26]. In short, the cortical and trabecular regions were separated first using a semi-automated contouring scheme in which the periosteal boundary surface of the radius was derived [27]. After contouring, a Laplace–Hamming filter (epsilon 0.5 and cut-off frequency 0.4) followed by normalization (range 0–1000) and global thresholding (threshold 400), was used in order to extract the voxels that represented mineralized bone and to create the segmented images. The used values were default values specified by the manufacturer and these are consistently used for all HR-pQCT scanners.

The following bone density parameters were calculated from the images: volumetric bone mineral density [mgHA/cm^3] was assessed for the total region (Dtot) and the trabecular (Dtrab) and cortical region (Dcort) separately.

The micro-architectural parameters that were used in this study were: the trabecular number (Tb.N) [1/mm], thickness (Tb.Th) [μm] and separation (Tb.Sp) [μm], which are all determined using a 3D ridge extraction method [28] and standard morphological relations. Bone geometry was expressed by the cortical thickness (Ct.Th) [mm], which is calculated by dividing the cortical volume by the outer cortical surface, and the cortical perimeter (Ct.Pm) [mm], which is the average outer perimeter of the cortex.

μFE analysis

With the standard approach for μFE analyses as used in most earlier studies, segmented images are used to create a representative μFE model of the bone's micro-architecture by converting each voxel that represents bone tissue into a brick element of the same size. Material properties then are chosen constant for all bone tissue [16], or varied only between cortical and trabecular bone tissue [15]. Whereas this approach has been well validated and successfully applied in clinical studies, its application to fractured bone is not trivial. The use of segmented images clearly limits the models to only represent the mineralized phase. In particular in the early stages of fracture healing this approach is expected to be inaccurate because it does not account for newly formed low mineralized bone. In an earlier study, Shefelbine et al. [8] therefore introduced a more sophisticated approach that can