CMBES/SCGB

2016 CMBEC39 Conference
Calgary AB
May 24–27, 2016

A NOVEL IN VIVO QUANTITATIVE ASSESSMENT OF THE KNEE USING HIGH RESOLUTION PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY

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INTRODUCTION

High resolution imaging of bone is an important research tool to assess the bone's 3D structure in detail. Using micro computed tomography scanners (μCT) allows for bone imaging with outstanding spatial resolution of less than 10μm isotropic voxel sizes, small enough to directly assess bone microarchitecture [1]. However, the small size of the field of view of such scanners limits the use to animal models or biopsies of human bone tissue. The latter is an invasive procedure, and only allows for the assessment of bone structure in the small sample [2].

Clinical CT scanners are designed for for *in vivo* assessment of human bone, however the limited spatial resolution does not allow for direct assessment of bone microarchitecture [3]. Recently, a new high resolution peripheral quantitative computed tomography (HR-pQCT) scanner was developed that is a novel μCT system designed to image human wrists (distal radius) and ankles (distal tibia) *in vivo* with spatial resolutions that allow for the assessment of bone microarchitecture at these sites [4]. Due to its non-invasive nature, this method allows for the longitudinal assessment of bone changes. HR-pQCT is typically limited to the most distal region of the wrist or ankle, but the 2nd generation of HR-pQCT scanners (XtremeCT2) is large enough to theoretically fit knees into the scanner and field of view.

The purpose of this study is to develop an imaging protocol and the required hardware to perform the first human *in vivo* HR-pQCT knee scans that allow for the assessment of bone microarchitecture. This includes the development of a knee brace that places and stabilizes the knee inside the field of view of the scanner as well as the analysis of the image data. The method will then be used to assess bone microarchitecture in the knees of individuals who have undergone anterior cruciate ligament (ACL) reconstruction.

METHODS

Subjects

Five individuals who underwent ACL reconstruction 6.5 (±0.45) years prior were imaged using HR-pQCT. At the time of scanning the participants were aged 20.9 to 43.1 years (M=31.7, SD±9.36), and included three males and two females. Four of the five participants were scanned at their left knees. The study was approved by the University of Calgary Conjoint Health Research Ethics Board (Ethics ID 20966).

Custom knee brace and participant positioning

To reduce motion during the HR-pQCT scans a custom carbon-fiber knee brace was developed (Figure 1) that stabilized the participant's knee centrally in the field of view of the scanner. An adjustable foot piece allowed for variable leg length while maintaining optimal knee positioning and reducing motion.

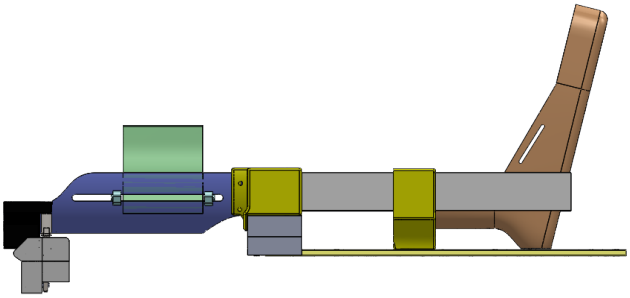

Figure 1: Schematic of the brace that positions the knee inside the field of view. The foot piece is adjustable by sliding along two bars to accommodate different leg lengths while still fitting the knee inside the field of view.

Participants sat in an upright position with the imaged knee in full extension placed inside the gantry of the HR-pQCT scanner. The contralateral limb was placed to the side.

Imaging parameters

All imaging was performed using the novel 2nd generation HR-pQCT (XtremeCT2, Scanco Medical, Brüttisellen, Switzerland) using a modified version of the standard imaging protocol (68kVp, 1470μA, 100ms integration time). The image stack measured 61.2mm around the knee joint space and was acquired at an isotropic voxel size of 60.7μm, resulting in 1008 axial slices with an image matrix size of 2304x2304. Approximately 4cm of the distal femur and 2cm of the proximal tibia were imaged (Figure 2). To accurately position the scanning region, the most distal point of the femoral condyles was identified as a landmark.

Data analysis

Data analysis was performed in three steps: image segmentation, region of interest (ROI) creation, and morphological bone parameter analysis within the defined ROIs.

During the segmentation step the periosteal and endosteal bone surfaces were identified using a modified version of the established dual thresholding method [5]. In short, after an initial manual segmentation of the distal femur and proximal tibia, the periosteal bone surface was identified using a global fixed threshold (320 mg HA/ccm) and morphological image operations. The resulting mask was applied to the original gray scale image and using a lower global threshold (450 mg HA/ccm) and morphological image operations, the endosteal bone surface is identified.

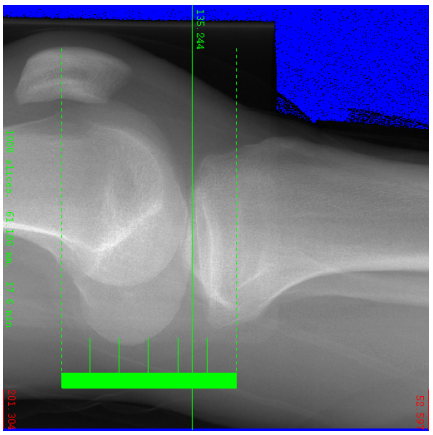

Figure 2: Imaging regions of the knee. The reference line (solid green line) is placed at the most distal point of the femoral condyle to position the scan region of 6 image stacks.

ROI definition followed similar analysis regions for quantitative CT knee previously described by Johnston et al [6]. In short, the bone morphology was analyzed at three depths (0-2.5mm, 2.5-5mm, 5-7.5mm) underneath the weight-bearing bone regions. The weight-bearing bone surface ROI was manually defined by the operator.

From the periosteal bone contour a surface model was created using a custom tool (blSurfaceViewer, C++, VTK 6.1), that served as a template to create participant-specific ROIs of the weight-bearing regions of both femur and tibia (Figure 3). Manually selected points outlining each ROI were processed using a custom algorithm (python 2.7.10, VTK 6.3.1). Underneath each weight-bearing surface three ROI were created using the depth definitions stated above (Figure 4). In addition to the three depth defined ROIs, a cortical bone ROI was defined as the space between the periosteal and endosteal bone contours within the manually selected weight-bearing region (Figure 4). Thus, for each knee 16 ROIs were defined, 8 per bone with 4 ROIs for both the lateral and medial compartment.

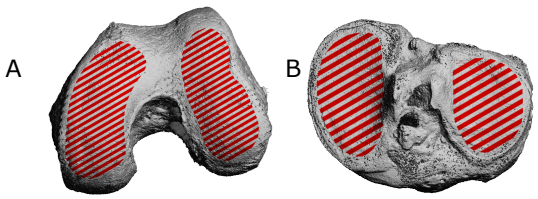

Figure 3: 3D volumetric rendering of the periosteal surface of the weight-bearing regions of the distal femur (A) and proximal tibia (B). In Red, the ROIs are depicted underneath of which the bone microarchitecture is analyzed.

Within each ROI bone morphology was evaluated using a standard analysis (IPL, Scanco Medical). Due to the high spatial resolution, direct thickness measurements were calculated using the sphere-filling approach [7]. The extracted cortical and trabecular bone microarchitectural parameters are summarized in Table 1.

Table 1: Bone morphological parameters calculated for each ROI and their units.

Parameter	Unit
Cortical bone mineral density	mg HA/cm^3
Cortical thickness	mm
Cortical porosity	%
Trabecular bone mineral density	mg HA/cm^3
Trabecular thickness	mm
Trabecular separation	mm
Trabecular number	1/mm
Bone Volume Fraction BV/TV	%

RESULTS

HR-pQCT scanning

All five participant-knees were successfully scanned using HR-pQCT. Due to physical scanner gantry size limitations, the maximal knee circumference that can be accommodated in the HR-pQCT's field of view is 42cm, and a maximal patella height of 52cm in standing participants allows positioning of the knee in the field of view. One subject had a patella that protruded slightly outside the field of view.

Each scan took approximately 25min to complete and resulted in 5GB of projection data. Splitting the projection data into 24 batches, the total reconstruction time was approximately 2.5h and resulted in 10GB grey scale image data for each knee. In cases when the reconstruction process is not divided into smaller batches, 13.3h reconstruction time is required. Estimated effective dose was 72μSv per knee scan.

The custom knee brace accurately positioned the knees in the center of the field of view. Motion observed over the duration of the scan was very low, and similar in magnitude as the shorter standard distal tibia HR-pQCT scans.

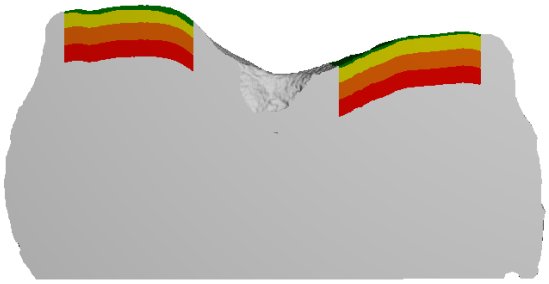

Figure 4: Coronal cut through a femur showing the different ROIs. In green: cortex; yellow: layer 1 (0-2.5mm); orange: layer 2 (2.5mm-5mm); red: layer 3 (5mm-7.5mm)

Bone morphology

The bone morphological analysis resulted in 76 measurements per knee. There were no statistically significant differences between the cortical ROIs of the lateral and medial compartment in either femur nor tibia in the five ACL reconstructed knees. Similarly, there were no statistically significant differences between the trabecular parameters when comparing trabecular bone parameters between layer 2 and 3 for a given compartment. With the exception of trabecular number and separation, trabecular parameters were significantly higher in layer 1 than in layer 2 indicating a change of bone morphology between these two layers.

DISCUSSION

This study demonstrated that it is possible to perform *in vivo* μCT scans on the human knee

using HR-pQCT with sufficiently high spatial resolution to directly assess the bone microarchitecture. This non-invasive imaging method allows for longitudinal assessment of bone microarchitecture in the human knee, which can be of interest for the investigation of injury or disease induced bone changes in the knee. While not well suited for clinical use due to long scanning times, HR-pQCT provides a unique opportunity to investigate bone changes in the knee and to learn about the effects of injury and changes related to surgical repair.

The size limitation of the gantry prevents large knees from being scanned (e.g. overweight or well muscled individuals). In addition, the long scan durations may result in discomfort for some people. On the other hand, the effective radiation dose is very low, and similar in magnitude to a standard DXA exam. The resulting dataset volumes require high computing power for post processing and data analysis.

The data analysis is complex. Due to the variability in the presented knees such as degree of osteophyte development and bone mineralization, currently the algorithm-based segmentations require manual corrections. ROI selection in this study was based on weight-bearing regions, but the rich image dataset allows for the selection of many other relevant ROIs. The final bone morphological analysis may result in an overwhelming amount of information about the underlying bone microarchitecture in the ROIs.

In the presented study, the cortical bone microarchitecture was similar between lateral and medial bone compartments of the ACL reconstructed knees. In the future, it will be interesting to compare the cortical bone parameters between the injured and the healthy contralateral knee to investigate injury-induced bone changes in the knee. Trabecular bone microarchitecture changed little between layers 2 and 3, and this raises the question whether the selected ROIs may be too large in depth (2.5mm each). But, because the sample size is small the variation in our data is large. Further work will be required to identify the optimal ROIs. Layers 1 and 2 demonstrated statistically significant changes in trabecular bone microarchitecture with depth, but it is important to keep in mind that in the presented ROI selection layer 1 also includes the cortical bone, which is more compact and dense compared to trabecular bone.

To summarize, this study demonstrated that it is possible to assess bone microarchitecture *in vivo* in the human knee using HR-pQCT. The scan results in low motion artifact, and results in unprecedented high-resolution datasets. This method provides a unique opportunity to assess bone changes *in vivo* to investigate the effect of injuries or diseases such as osteoarthritis on the human knee. It may be an important tool to develop effective interventions or treatments so that knee health can be maximized.

REFERENCES

[1] K. K. Nishiyama, G. M. Campbell, R. J. Klinck, and S. K. Boyd, "Reproducibility of bone micro-architecture measurements in rodents by in vivo micro-computed tomography is maximized with three-dimensional image registration," *Bone*, vol. 46, no. 1, pp. 155–161, 2010.

[2] P. Ruegsegger, B. Koller, and R. Muller, "A microtomographic system for the nondestructive evaluation of bone architecture," *Calcif. Tissue Int.*, vol. 58, no. 1, pp. 24–29, 1996.

[3] L. Gaalaas, L. Henn, P. R. Gaillard, M. Ahmad, and M. S. Islam, "Analysis of trabecular bone using site-specific fractal values calculated from cone beam CT images," *Oral Radiol.*, pp. 1–7, 2013.

[4] A. M. Cheung et al. "High-resolution peripheral quantitative computed tomography for the assessment of bone strength and structure: a review by the Canadian Bone Strength Working Group.," *Curr. Osteoporos. Rep.*, vol. 11, no. 2, pp. 136–46, Jun. 2013.

[5] H. R. Buie, G. M. Campbell, R. J. Klinck, J. a MacNeil, and S. K. Boyd, "Automatic segmentation of cortical and trabecular compartments based on a dual threshold technique for in vivo micro-CT bone analysis.," *Bone*, vol. 41, no. 4, pp. 505–15, Oct. 2007.

[6] J. D. Johnston, B. a Masri, and D. R. Wilson, "Computed tomography topographic mapping of subchondral density (CT-TOMASD) in osteoarthritic and normal knees: methodological development and preliminary findings.," *Osteoarthritis Cartilage*, vol. 17, no. 10, pp. 1319–26, Oct. 2009.

[7] T. Hildebrand and P. Rüegsegger, "A new method for the model-independent assessment of thickness in three-dimensional images," vol. 185, no. November 1995, pp. 67–75, 1997.