Mineral Density Of Subchondral Bone May Be Quantitatively Evaluated Using A Clinical Cone Beam Computed Tomography Scanner

Mikael J. Turunen, PhD¹, Juha Töyräs, PhD¹, Harri Kokkonen, PhD², Jukka S. Jurvelin, Ph.D.¹.
¹University of Eastern Finland, Kuopio, Finland, ²Kuopio University Hospital, Kuopio, Finland.


Introduction:
Cone beam computed tomography (CBCT), a clinical technique with high imaging resolution, has been widely used in dentistry [1]. Recently, contrast agent enhanced CBCT (CE-CBCT) was applied successfully for clinical diagnostics of articular cartilage (Fig. 1) [2-3]. As an X-ray technique, CE-CBCT may also provide a tool for early detection of osteochondral lesions. During joint CT-scanning all soft tissues are simultaneously imaged. As restrictions from the cone beam geometry can prevent accurate quantitative analyses [1], bone integrity has rarely been evaluated [4-5]. However, quantitative information about the articular cartilage and bone would be beneficial e.g. for diagnostics of osteoarthritis (OA).
We aimed to clarify feasibility of CBCT for measurement of mineral density (BMD) in subchondral, trabecular and cortical bone. Therefore, in this study, we created hydroxyapatite (HA) phantoms which could be used for in vivo evaluation of BMD using CBCT. Further, we validated the phantoms for BMD measurements at four different regions in human distal femur.
Methods:

Phantoms: Five phantoms with different densities (250, 500, 750, 1000 and 1250 mg/cm$^3$) were created by mixing synthetic hydroxyapatite powder (reagent grade, Sigma-Aldrich Inc., St Louis, MO) with epoxy in 2 ml Eppendorf tubes. Additionally, one similar tube with only epoxy was created. After the mixing, the tubes were set into programmable rotator-mixer (Grant Bio PTR-30, Keison Products, Chelmsford, UK) and were let to congeal for 72 hours in room temperature to prevent gravitation driven deposition. Subsequently, the tubes were exposed to 100 °C for 12 hours to finalize the solidification. The tubes were cut open and the ends of the phantoms were flattened with a saw. The dimensions of the cylindrical shaped phantoms were measured and the volumes were calculated (1.71 ± 0.06 cm$^3$). A micro-CT scanner (Skyscan, 1172. Aartselaar, Belgium) was used to visually ensure the uniformity of the phantoms.

Calibration: The volumetric BMDs (vBMD [g/cm$^3$]) of the HA phantoms were determined using dual energy x-ray absorptiometry (DEXA, GE Healthcare Lunar iDXA, Madison, WI). The resulting bone mineral content was normalized with the volume to determine the vBMD of each phantom. Furthermore, the HA phantoms were imaged using a clinical CT (Siemens Somatom Definition Edge, Siemens, Germany) and a CBCT scanner (Verity, Planmed Oy, Helsinki, Finland) together with a commercial K$_2$HPO$_4$-based CT calibration phantom, developed for hip and spine analysis (Mindways Software Inc., Kiel, Germany). The CT measurements were conducted using total scanning time of 10 s, 3
different tube voltages (120, 100, 70 kV) and 80 mAs with a voxel size of 300 x 300 x 500 µm$^3$.
Correspondingly the CBCT measurements were conducted using tube voltages of 96, 90, 84 kV and
current of 12 mA with a voxel size of 200 x 200 x 200 µm$^3$.

**BMD determination**: Ten frozen human distal femora were imaged with a clinical CT and CBCT scanner
together with the commercial phantom and the HA phantoms. The same measurement settings were
used for calibration, but using only the highest tube voltages. A custom made elastic band with small
individual pockets for the HA phantoms was designed for clinical use and was wrapped around the
femur for clinical use. Four volumes of interest (VOIs) were segmented from the image-stacks using
Mimics (v12.3, Materialise, Leuven, Belgium): cortical bone (shaft), trabecular bone (medial condyle,
cylindrical area), subchondral plate and subchondral trabecular bone (lateral condyle). From each
image-stack, the average gray-scale values of the phantoms and the segmented bone VOIs were
calculated. The BMDs of different VOIs were determined using calibration curve based on the phantom
measurements. All data (calibration and BMD determination) were analyzed with MATLAB (R2012b,
MathWorks, Inc., MA).

**Statistics**: Linear correlations (Pearson) between the bone BMD values determined against both
phantoms and between modalities were calculated. Wilcoxon signed ranks test was used to compare
the calibration curves and bone BMD values determined with both phantom and modalities. All
statistical analyses were performed using SPSS (IBM SPSS, v. 21, Armonk, NY).

**Results**: The calibration curves of the HA phantoms are shown in Fig. 2. Compared to the DEXA, BMDs of HA
phantom, as determined using the commercial phantom with a CT scanner, yielded slightly lower values
(not significant). The values determined with the CBCT scanner were higher ($p < 0.05$ for every tube
voltage).
BMD values in distal femora were determined using the DEXA calibration curve for the HA phantoms. The vBMDs [g/cm³] in the VOIs of cortical shaft, trabecular bone, subchondral bone and subchondral plate using CBCT with HA phantom were 1.2 ± 0.1, 0.23 ± 0.05, 0.42 ± 0.10 and 0.73 ± 0.08, respectively. Using the CBCT with the commercial phantom the respective vBMDs were 1.5 ± 0.1, 0.34 ± 0.04, 0.56 ± 0.10 and 0.93 ± 0.07. The correlation between the bone BMDs determined with both phantoms was significant using both modalities (CT: $R^2 > 0.999$, $p < 0.001$; CBCT: $R^2 = 0.992$, $p < 0.001$, Fig. 3a,b). The correlations between the modalities were also significant (HA: $R^2 = 0.951$, $p < 0.001$; Commercial: $R^2 = 0.959$, $p < 0.001$, Fig. 3c,d). Overall, with both modalities the BMD values determined using the HA phantoms were lower ($p < 0.001$) than the ones determined with commercial phantom. Furthermore, BMD values determined with the clinical CBCT were lower than the values from clinical CT ($p < 0.001$).
Discussion:
This study demonstrates the potential of quantitative analysis of human bone density using a clinical CBCT scanner. The results indicate that the BMD values might not be directly comparable between different instruments. However, due to highly linear calibration curves, CBCT imaging coupled with applicable phantoms can enable quantitative detection of changes in bone density. The present CBCT technique could indicate the differences in mineral density (g/cm$^3$) of cortical, trabecular and subchondral bone. Especially in diagnostics of OA and knee injuries, quantitative and qualitative information on subchondral bone could improve understanding on its role in cartilage degeneration. In this study, a clinically applicable band allowing easy localization of the HA phantoms around the knee (or other limb) was designed and tested with cadaver joints. As a limitation of this study, effects of soft tissue were not evaluated since dissected bone samples were used. For further validation, forthcoming in vivo measurements using the present protocol will reveal the clinical applicability of CE-CBCT for quantitative diagnostics of articular cartilage [2-3] and subchondral bone.

Significance:
This study demonstrates the potential of quantitative analysis of human bone density using a clinical CBCT scanner.

ORS 2015 Annual Meeting
Poster No: 1093