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QUANTITATIVE ASSESSMENT OF BONE REMODELLING AND OSTEOPHYTOGENESIS IN MURINE OSTEOARTHRITIS

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BACKGROUND

Subchondral bone (Sb) remodelling and osteophyte growth are widely recognised hallmarks of knee osteoarthritis (OA), although their contribution to the disease is not fully understood. Murine models, for their amenability to genetic studies, have been instrumental to identify key pathways modulating OA and are becoming essential tools to discover new therapeutic targets. The interaction between bone and cartilage is not understood, with genetically chondroprotected mice further complicating this relationship as they still show prominent osteophytogenesis irrespective of cartilage damage.

AIM

To use 3D automated image analysis methods to characterize quantitatively Sb remodelling and osteophytogenesis during the progression of murine OA.

METHODS

Murine OA model. Six groups of C57BL/6J mice (10-week old, n=6) underwent surgical destabilisation of the medial meniscus (DMM) in right knee joints and were euthanized 1, 2, 4, 8, 12 and 20-weeks post-operatively.
Imaging. Dissected tibiae were imaged using µCT (Skyscan 1172, 5µm/pixel) and reconstructions were analysed by an automated software (Matlab), which maps subchondral bone plate (Sb.Pl.) and trabecular bone (Tb) compartments in the medial (MTP) and lateral tibial plateau (LTP) load-bearings and computes thickness (Sb.Pl.Th) and volume fraction (Tb BV/TV). Whole tibial epiphysis and osteophytes were segmented and their volume was computed. A group of naïve C57BL/6J animals (n=6) was used to set a healthy baseline for all the measurements. Results were evaluated comparing operated side (DMM) vs. contralateral (CTRL) over time (*p ≤ 0.05, DMM vs. CTRL).

3D AUTOMATED MICROSTRUCTURAL ANALYSIS

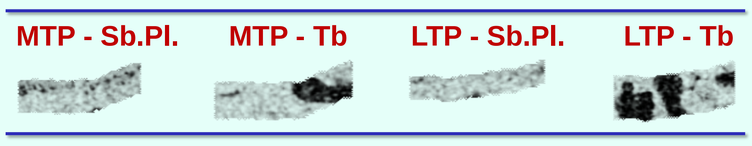
Sb.Pl and Tb compartmentalization is based on a threshold criterion (**cortical bone volume fraction > 90%**):

(1) Unprocessed µCT image of mouse tibia (middle coronal plane)

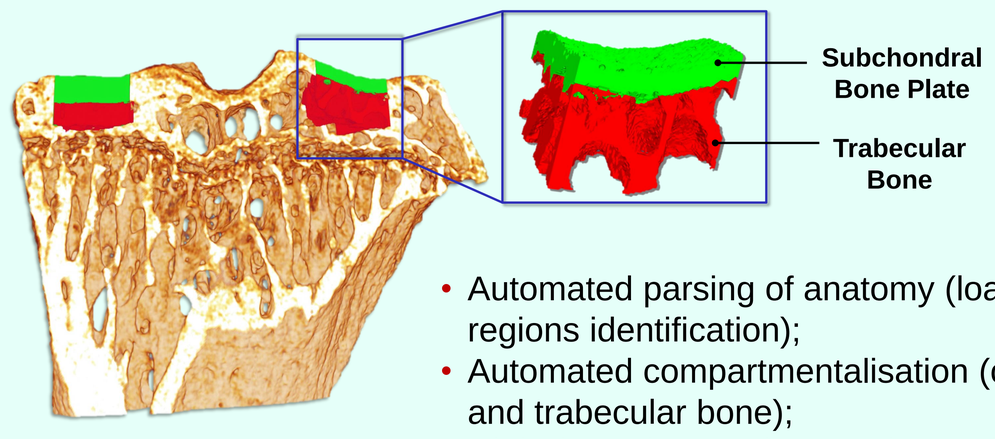
(2) Binarization and segmentation

(3) Generation of 4 masks to partition subchondral bone volume

(4) Volumes of interest enclosed in the masks



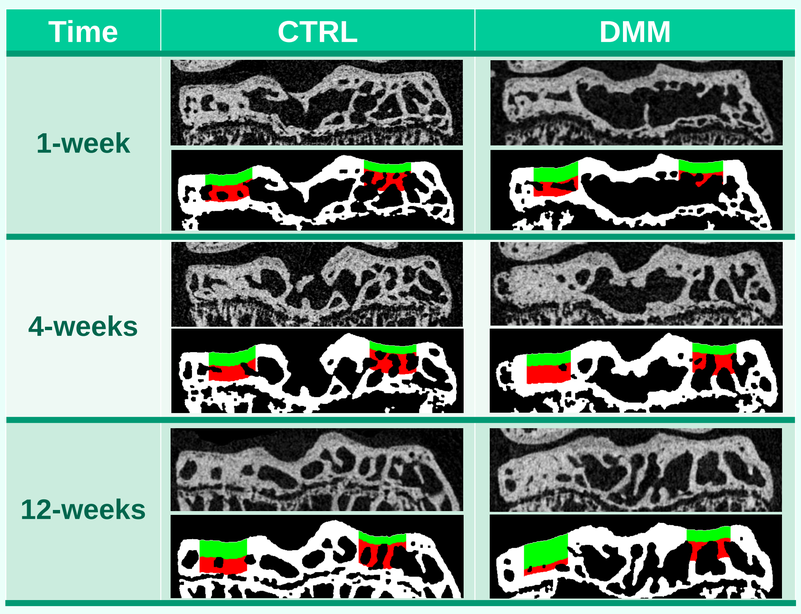
Novel ex-vivo µCT imaging method for 3D assessment of subchondral bone remodelling in the mouse model of OA



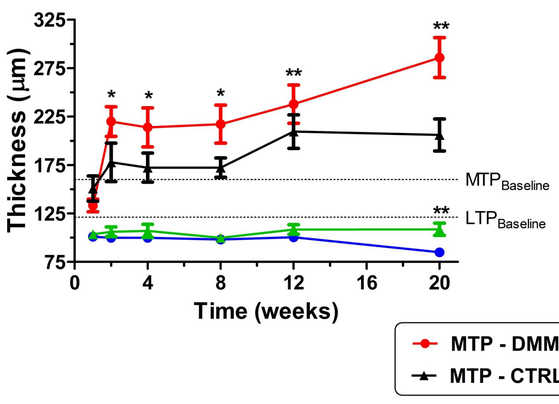
- Automated parsing of anatomy (load-bearing regions identification);
- Automated compartmentalisation (cortical and trabecular bone);
- High-throughput, robust and quantitative.

RESULTS

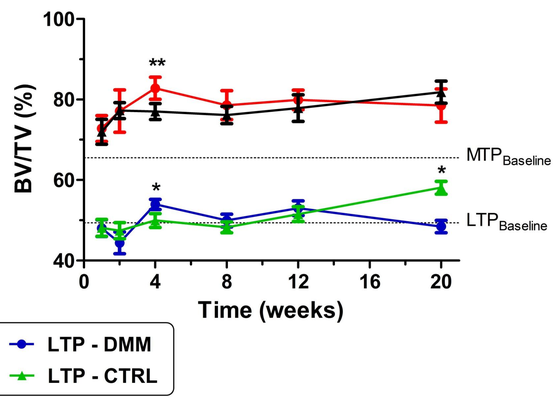
TEMPORAL CHANGES IN SUBCHONDRAL BONE STRUCTURE

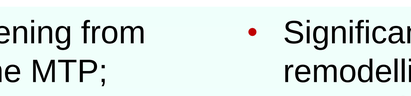


Subchondral Bone Plate Thickness



Trabecular Bone Volume Fraction

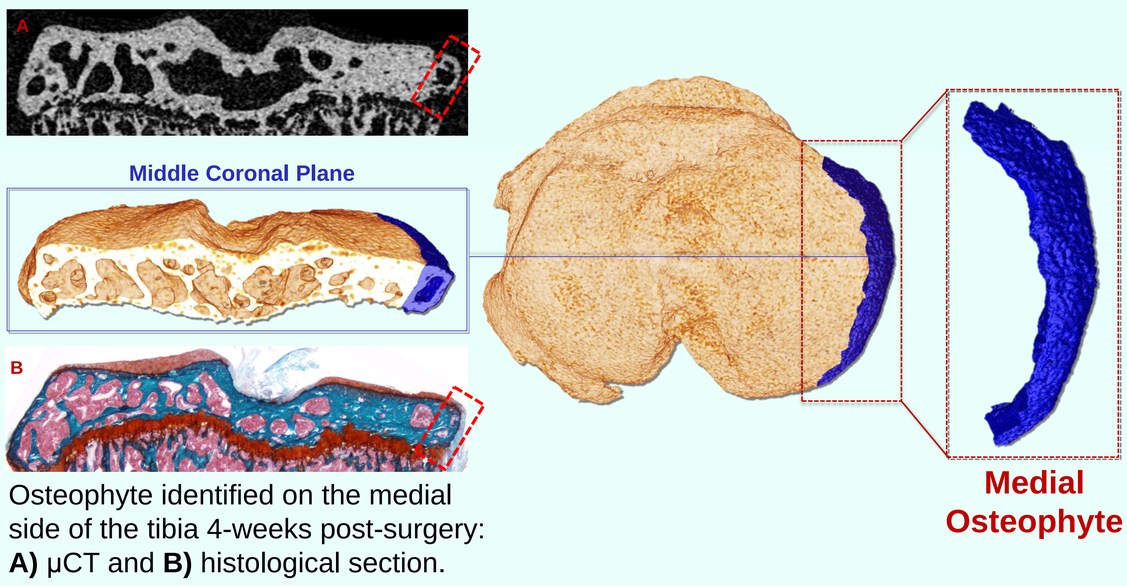




- Progressive Sb.Pl thickening from 2-wks post-surgery in the MTP;
- Bone dynamics observed also in the CTRL (non operated) knee;
- No changes in LTP.
- Significant trabecular remodelling from 4-wks post-surgery in the MTP;
- Medial osteophytes observed from 4-wks onwards.

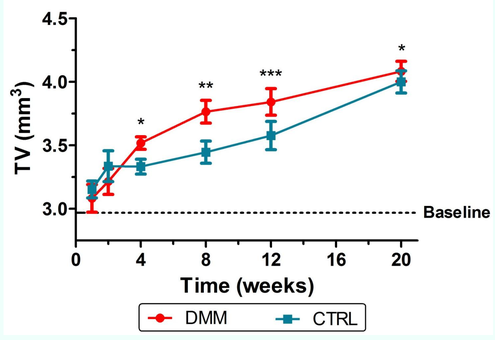
OSTEOPHYTOGENESIS ASSESSMENT

Osteophytogenesis is characterized by new bone formation in the margins of the joint leading to an overall epiphyseal expansion. In the DMM model, osteophytes can be clearly identified on the medial side of the tibia.



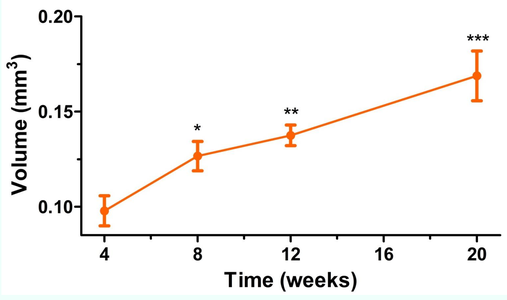
Osteophyte identified on the medial side of the tibia 4-weeks post-surgery: **A)** µCT and **B)** histological section.

Whole Epiphysis Volume



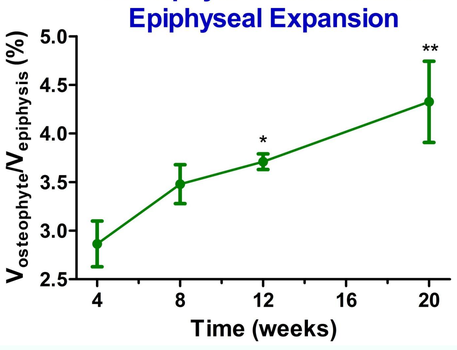
- Osteophytogenesis can be detected by measuring the volume (TV) of the whole epiphysis. Increased from 4-wks.
- Osteophyte volume contributes ~3% for whole epiphyseal volume at 4-wks and up to 4% at 20-wks post-surgery;
- Additional shape modelling might contributed to the remaining epiphyseal expansion (6% increased at 4-wks in DMM compared to CTRL).

Medial Osteophyte Volume



- Osteophyte volume increases over time (mineralised phase).

Osteophyte Contribution to Epiphyseal Expansion



CONCLUSIONS

- High-resolution µCT can been used to assess quantitatively bone micro-architecture in the tibial epiphysis;
- Automated (hence quantitative) image analysis identified Sb.Pl. thickening, Tb sclerosis and osteophyte growth, from early stages in the DMM mouse model of OA;
- The proposed method significantly increases throughput and sensitivity in the assessment of subchondral bone remodelling in murine OA.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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