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Comprehensive Morphological Characterisation of Arthritis in Animal Models by Micro-Computed Tomography

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Introduction

Understanding the development of osteoarthritis (OA) and the subsequent establishment of efficacious treatment strategies have been confounded by the inability to visualise the condition of the cartilage and quantitatively assess and monitor pathological changes in time. Previous studies have demonstrated the potential of combining a contrast agent Hexabrix™ with microcomputed tomography (micro-CT) imaging in animal and human cartilage explants or disrupted joints. Hexabrix™ is a negatively-charged iodinated dimer which inversely correlates to the proteoglycan content of articular cartilage allowing quantitative assessment of cartilage quality [1].

Objective

The objective of this study was to develop a quantitative 3D imaging methodology for the measurement and analysis of intact knee joint tissues in a commonly-used animal model of OA by combining Hexabrix™ with micro-CT imaging.

Methods

The tibio-femoral joints from 11 rats were employed to establish the SOP for the scans that would distinguish between joint space, soft tissue and bone, figure 1. Various contrast agents were explored by either direct injection into the knee joint, to encourage diffusion into the cartilage or to fill the joint space, or by immersing the sample and staining the surrounding joint structures. Additionally, sample preparation and handling methods, including warming, massaging, flexion and ultrasonic vibration were explored to enhance flow through the joint space and improve distribution. Subsequently, the knee joints were scanned with micro-CT (μCT, 80, Scanco Medical, CH) at an isotropic voxel size of 10 μm. The outcome criterion was the clear distinction of structures inside the joint (i.e. cartilage, joint space and bone), figure 2a with the option of automated segmentation in the best case, figure 2b.

Results and Discussion

An SOP was established for optimal sample preparation, handling, stain and scan quality. The injected silicon-based contrast agent was able to fill the joint space and distinguish the synovial spaces separately from the cartilage and surrounding tissues, figure 3. Using massage and flexion of the joint after injection, a reproducible and even stain could be achieved. Following this, immersion of the sample overnight in Hexabrix™ and re-scanning, see figure 3, enabled not only the discrimination of the cartilage tissue for morphometric analysis, figure 4a & b, but also demonstrated the potential to correlate GAG content with the gradation of grey content in the stained tissue, figure 4c.

Conclusions and Outlook

The established protocol has great potential to provide a sensitive and reproducible technique for gathering 3D image data on both healthy and diseased animal models. The method is currently being tested against the histological gold standard, figure 5. In a next step this novel technique will be reproduced in rabbit and goat models with the goal of providing a preclinical tool for assessment of commonly-used animal models of OA. Additionally, more quantitative outcome criteria based on preclinical and clinical interests will be defined for a more comprehensive overview of the OA joint. These quantitative outcomes will include cartilage measures such as GAG content, volume, surface, surface roughness; joint measures such as curvature and morphometry, alignment angles and translation, joint space volume and thickness; bone measures such as subchondral cortical and trabecular bone morphometry, and number of osteophytes.

Reference


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