DETECTION OF EARLY CHANGES IN BONE REMODELLING AS A CONSEQUENCE OF CARTILAGE ALTERATIONS IN A RAT MODEL FOR OSTEOARTHRITIS USING HIGH RESOLUTION MULTI PINHOLE SPECT/CT

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Introduction: Radionuclide bone scanning is a highly sensitive method for identifying degenerative changes as a consequence of osteoarthritis (OA) in patients. Due to low resolution, this imaging modality was not applicable for in-vivo monitoring of experimental OA in small animal models such as mice and rats. With the recent development of multi-pinhole single photon emission computed tomography (mph-SPECT) it is possible to monitor molecular processes in mice and rats at sub-millimetre resolution. If mph-SPECT is combined with μCT, exact skeletal anatomic information of the location of the SPECT tracers can be obtained. This would provide a new highly sensitive method for monitoring the effect of interventions on the OA disease process and generate knowledge about its aetiology. The aim of this study was to assess the capabilities of mph-SPECT/CT in detecting alterations in subchondral bone turnover as a consequence of cartilage degeneration.

Materials and Methods: We induced cartilage degeneration in the right knees of 18 male Wistar rats of 12 weeks of age by injection of 1 mg mono-iodoacetate (MIA)(MIA decreases the rate of glycolysis of the chondrocyt and thus diminishes proteoglycan and collagen production in the cartilage matrix). An equal amount of saline was administered to the left knees, which served as the control condition. The animals were scanned with a mph-SPECT/CT camera (nasonSpect, bioscan inc., 4 cameras, 4 apertures each containing 9 pinholes of 2,5 mm, resolution < 1mm, acquisition time 30 min.) at 2 (n=18), 14 (n=12) and 42 (n=6) days after induction of OA with MIA. 4 hours prior to mph-SPECT/CT scanning the animals were intra-venous injected with marker 185 mBq of radioactive technetium bound to methylenediphosphonate (99mTc-mdp) which incorporates into the newly formed bone (bone-scan). At each time-point 6 animals were sacrificed directly after scanning to evaluate the status of degeneration of the joint with histology by a safranin’O and a Goldner staining. Alterations in 99mTc-mdp uptake in the in the medial and lateral condyles were evaluated separately. The Wilcoxin signed rank test was used for statistical evaluation.

Results: At day 2 after MIA injection a 50% increase in subchondral bone turnover of the medial condyle was detected (MIA injected, (right medial condyle), vs. saline injected (left medial condyle)). At 14 and 42 days after MIA injection 99mTc-mdp uptake of the medial condyle increased even more to a 55, respectively 95 percent compared to the contra-lateral control condition. Histology showed no alterations in cartilage and bone 2 days post injection of MIA, though 14 and 42 days post injection, cartilage degeneration (safranin’O-staining) and bone alterations could be observed.

Discussion: For the first time the capabilities of high resolution mph-SPECT/CT for assessment of OA have been shown. The high resolution of the mph-SPECT/CT enabled us to separate the signal of the subchondral bone from the high signal intensity of the growth plate which is quite active in rats during almost their entire life span. Furthermore, mph-SPECT/CT could detect very early changes in bone turnover in the medial condyle (as early as two days post MIA injection), in which no clear alteration of the cartilage and bone could be detected by histology. Though at 14 and 42 days post injection of MIA, cartilage degeneration could be observed. These results suggest that early bone alterations can occur at a very early time-point in the OA process, since the MIA only has a short-term effect on the chondrocyte metabolism.

In conclusion, mph-SPECT/CT is a highly sensitive imaging modality for the assessment of OA in small animal models. In addition, mph-SPECT/CT provides the possibility to measure other molecules (e.g. VEGF, MMP), this makes mph-SPECT/CT a very valuable contribution to the OA small-animal imaging portfolio.

Acknowledgements: we thank the Dutch arthritis association for their financial support.

Fig. 1 Increase of bone remodeling activation of the lateral and medial condyle due to induction of OA.

Fig. 2. Image of a mph-SPECT/CT scan of both rat knees 2 days after MIA injection. In the right (MIA injected) knee there is an increase in bone turnover of the medial femoral condyle.