The effect of tetracyclines on human articular cartilage metabolism are dependent on the degree of osteoarticular alterations

J. Steinmeyer, J. Kordelle. Orthopaedic Research Laboratories, Dept. of Orthopaedic Surgery, University Hospital Giessen and Marburg, Giessen, GERMANY

Purpose: In search for potential new therapies in the treatment of osteoarthritis (OA), attention has focused also on tetracyclines and their ability to slow down the progression of OA. Several possible mechanisms have been proposed, including inhibition of the activity and expression of inducible nitric oxide synthase (iNOS) and matrix metalloproteinases (MMPs). Using normal bovine articular cartilage, minocycline, monencycline were found to have a stronger inhibitory effect on e.g. the expression of iNOS and MMP-1 than doxycycline.

In this line, the purpose of this in vitro study was to determine systematically whether tetracyclines (1) influence the synthesis and release of PGs, MMPs and PGE2 also from human OA cartilage, (2) are affected by the degree of OA alterations, (3) are different with respect to their individual ability to modulate cartilage metabolism, and (4) affect chondrocyte viability within human OA cartilage explants.

Methods: Full-thickness cartilage explants of the lateral compartment of the femoral condyles were taken from OA patients undergoing knee replacement surgery. 4-mm-diameter articular cartilage discs were obtained using a biopsy punch. The degree of OA changes of the femoral condyles was determined according to Collins. Explants from mild (Collins grade 0–1.5) or moderately (Collins grade 1.5–3) affected human OA condyles were cultured separately in supplemented Ham’s F12 media with media changes every 3–4 days. Explants were treated with 1, 10, 50 or 100 μM minocycline, doxycycline or tetracycline in the presence or absence of rec. human IL-1α (5 ng/ml). PG synthesis was determined by the incorporation of 35SSO4 during the final 18 h of the 11 days experiments whereas the content of PGs were quantitated with the DMMBS-assay. The viability of chondrocytes was assessed microscopically using fluorescein diacetate and propidium iodide. Nitrite levels in media were measured by using the Griess reaction. MMP-1, -8, and -13 as well as PGE2 were determined in media with ELISAs. Results were compared to untreated explants removed from the same joint. Each experimental condition was repeated five times using explants always obtained from 6 different patients (N = 6).

Results: The degree of OA alterations of explants can have a profound modulatory effect on the influence of tetracyclines on cartilage metabolism. Furthermore, doxycycline partly displayed a weaker pharmacological effect than minocycline, whereas tetracycline was found to have the lowest potential to change cartilage metabolism. The viability of explants was not affected by any of the drugs tested.

Conclusions: Our study indicate that the pharmacological efficacy of tetracyclines can be dependent on the clinical stage of OA. In addition, our findings indicate that minocycline possess a stronger potential than doxycycline to slow down cartilage destruction during OA.