Metformin's Dual Actions on Articular Cartilage: Protection from Inflammatory Breakdown Versus Dose-Dependent Matrix Suppression

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INTRODUCTION: Metformin, a first-line drug for type 2 diabetes, has reported anti-inflammatory properties and is being explored as a potential disease-modifying agent for osteoarthritis (OA). We evaluated its direct effects on juvenile, healthy adult, and end-stage OA cartilage.

METHODS: Cartilage samples were harvested from OA knees after total knee arthroplasty (mean 65.2 yr; 6F/4M), healthy human cadaver knees (mean 37.5 yr, 2M), and juvenile bovine knees (1-2 mo). Samples were cultured with metformin (10 μM to 10 mM). Chondrocyte viability was quantified with Live/Dead™ staining. Matrix turnover was quantified with a click-chemistry assay that fluorescently tags newly synthesized glycosaminoglycans (GAG) and collagen. *Baseline viability and synthesis*: Explants were exposed to metformin alone for 7 days (bovine) or 10 days (human). Viability and matrix synthesis was measured at the end of the treatment period. *Inflammatory model*: In calf cartilage, matrix synthesis was measured following treatment with IL-1β (10 ng/mL) + metformin (10 mM or 100 μM) for 2 days. GAG loss was tracked for 10 days with IL-1β (1 ng/mL) + metformin (10 μM-10 mM).

RESULTS: *Baseline viability and synthesis*: 10 mM metformin decreased live cells in calf cartilage by ~40 % ($p < 0.01$), but 10 μM had no effect. Human OA cartilage had no loss of viability at either dose. Metformin alone had minimal impact on GAG synthesis but suppressed collagen synthesis at 10 mM in all three tissues (35-50 %, $p < 0.05$). A physiologic 10 μM dose lowered collagen synthesis by 25 % in healthy human cartilage ($p = 0.005$) but did not affect human OA tissue. *Inflammatory Model*: Metformin did not rescue IL-1β-suppressed matrix synthesis. IL-1β alone increased GAG loss six-fold versus control ($p < 0.001$). All doses of metformin significantly reduced this catabolic GAG loss ($p < 0.05$).

DISCUSSION AND CONCLUSION: Metformin prevented cytokine-driven cartilage degradation but impaired collagen anabolism in healthy tissue, even at low doses (10 μM). Human OA cartilage tolerated physiologic concentrations without cytotoxicity, suggesting a possible benefit in inflamed joints. Caution is warranted when extrapolating to young healthy cartilage, and dose optimization will be critical before clinical translation.