senescence. We have previously reported a significant reduction in the percentage of proliferating cells, but no significant change in the percentage of apoptosing cells, in tissue biopsies taken from tendinopathy patients seven weeks after local GC injection compared to in biopsies taken from the same patients immediately prior to injection. In the present study we found the percentage of p53-positive cells in tissue biopsies was significantly higher (p=0.03) post-GC injection compared to pre-GC injection. The percentage of p21-positive cells also tended to be higher (p=0.06) post-GC injection compared to pre-injection.

Conclusions: Results from this study demonstrate GCs activate the p53/p21 senescence-inducing pathway in vitro and provide compelling evidence that this pathway is also activated following local GC injection in vivo. The loss of normal cell functionality associated with senescence has been linked with disease and degeneration in a number of different tissues. Given the apparent irreversible nature of the senescent phenotype, GC-induced senescence is likely to have long-term detrimental consequences on tissue. The fact that we observed a marked increase in p53 expression seven weeks following GC injection supports the notion that the effects of local GC injection on tendon tissue are not transient. Senescence induction by GCs may exacerbate the underlying tissue pathology responsible for the pain for which the GCs were prescribed to treat.

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EFFECT OF LONG-TERM VOLUNTARY EXERCISE ON THE INDUCTION OF OSTEOARTHRITIS BY A VERY HIGH-FAT DIET IN AGED MICE

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Purpose: Short-term voluntary exercise protects against cartilage proteoglycan loss in young mice fed a very high-fat diet. Exercise also reduces the clustering of metabolic inflammatory markers and improves glucose metabolism without weight loss, suggesting a role for systemic metabolic factors in mediating obesity-associated knee OA. We hypothesized that despite an increase in joint loading, long-term exercise would protect against knee OA in aged mice fed a very high-fat diet by reducing age and diet-associated increases in weight and glucose intolerance.

Methods: Male C57BL/6J mice were fed either a control fat (CF; 10% kcal fat; n=21) or a very high fat (HF; 60% kcal fat; n=22) diet starting at 6 wks of age. At 26 wks, mice from each diet (n=9) were single-housed in cages with a running wheel until the end of the study at 52 wks of age. We compared joint loading between CF and HF fed mice using a custom force-instrumented running wheel. Body composition was quantified by DEXA and dissection of fat pads. Glucose tolerance testing was conducted at 24 and 48 wks. We evaluated OA pathology by MicroCT and histomorphometry. MicroCT was used to evaluate subchondral bone thickness and relative trabecular bone volume (BV/TV) in the medial and lateral tibial compartments. Stained sagittal knee sections were graded for cartilage OA severity using a modified Mankin scale (0-24), and anterior and posterior medial tibial osteophytes were graded using a semi-quantitative scale (0-3) by two blinded graders.

Results: Prior to exercise, body weight and body fat were increased 71% and 63%, respectively, with HF feeding. Voluntary running distance (7.1 vs. 2.7 km/day), speed (59 vs. 33 cm/s) and peak limb force (115 vs. 92 % bodyweight) were lower in HF fed animals (p<0.05). Exercise did not significantly decrease body weight or epididymal fat pad mass in HF animals, although weight and fat mass were reduced with exercise in CF animals (Fig. 1A, B). Glucose tolerance area under the curve (AUC) was greater in exercised but not sedentary HF fed animals compared to activity-matched dietary controls (Fig 1C). A HF diet increased cartilage OA scores in both activity groups (Fig. 2A, p=0.007), although there was no effect of exercise. There was, however, a trend for decreased osteophyte formation in exercised animals regardless of diet (Fig. 2B, p=0.05).

Conclusions: Contrary to our hypothesis, long-term voluntary wheel running exercise did not protect against HF diet-induced obesity, glucose intolerance, or OA severity in aged mice. Unlike short-term exercise in young HF-fed mice, mice that have already developed substantial diet-induced obesity show a decreased propensity for long-term voluntary wheel running exercise, which may contribute to the minimal activity-dependent changes with HF feeding in this study. Increased OA severity with long-term HF feeding was primarily due to increased cartilage degradation and proteoglycan loss and not due to increased osteophyte formation. Future work is needed to determine if systemic inflammatory markers are reduced with exercise in CF or HF fed animals to better understand the relationship between systemic metabolic inflammation and OA pathology.

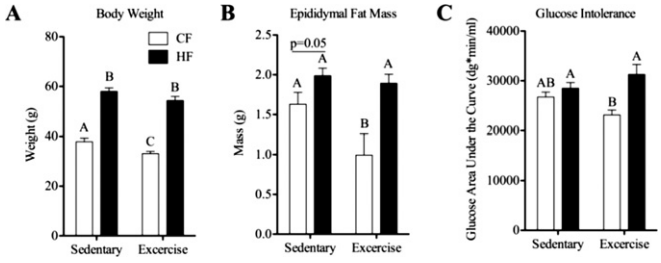

Figure 1. Effect of a HF diet and long-term exercise on body weight, epididymal fat mass, and glucose intolerance in 52-wk old mice. Bars sharing the same letters arc not significantly different from each other (p>0.05).

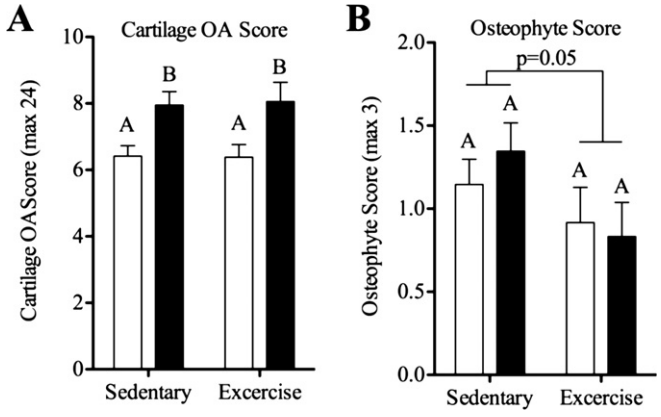

Figure 2. Effect of a HF diet (filled bars) and long-term exercise on OA severity in 52-wk old mice. Bars sharing the same letters are not significantly different from each other (p>0.05).

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EARLY RESPONSES OF JOINT TISSUES TO NONINVASIVE MOUSE KNEE INJURY PROVIDE POTENTIAL TARGETS FOR THERAPY

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Purpose: Joint trauma can lead to a spectrum of acute lesions, including articular cartilage degradation, ligament or meniscus tears, synovitis, and osteophyte formation, all potentially associated with osteoarthritis. The events induced by over loading of the knee are poorly defined. The goal of this study was to generate and validate a murine model of non-invasive knee joint trauma following controlled injurious compression in vivo.

Methods: Animals experienced normal locomotion, except during loading. Loading was applied non-invasively via axial compression of the mouse lower leg, with points of contact at the distal femur and foot. This results in compressive joint loading across the femoro-tibial joint. The right knee of mice was subjected to one of three peak forces (3, 6, 9 N) in axial compression for 60 cycles (0.3 sec of load/unload followed by 10 sec of rest) for 1 day and harvested at 5, 9 and 14 days post loading (n=3-5 for each time point). The left knee was not loaded and served as the contralateral control. Histological and immunohistochemical analyses were performed to evaluate pathologic features in posttraumatic joint tissues.