Introduction: A worldwide epidemic of obesity and associated type 2 diabetes, in part due to the consumption of a high-fat Western diet, has resulted in an increased incidence of osteoarthritis (OA) in both weight bearing and non-weight bearing joints. Over 50% of diabetics have some form of arthritis. In the U.S., 52.1% of patients receiving knee replacements in 2005 were obese. In Canada, 87% were either obese or overweight. A morbidly obese patient is 33 times more likely to require knee replacement than an individual of normal body mass. Despite these statistics, current knowledge does not adequately explain the relative contribution of higher body mass versus the metabolic dysfunction in obesity to OA. To begin to address this question, an animal model was used to test the hypothesis that high fat diet-induced obesity and associated insulin resistance accelerate the progression of osteoarthritis following meniscal/ligamentous injury (MLI).

Methods: C57BL/6 mice were placed on a high fat (60% kcal) or low fat (10% kcal) diet at 4 wk of age (Open Source Diets, Research Diets Inc.). After 8 wk on diet, the medial collateral ligament of the right hind limb was severed and a segment of the medial meniscus detached and excised. The contralateral limb was sham-operated and represented the experimental control. Progression of OA was assessed by uCT (vivaCT 40, Scanco Medical) and histologic analysis at 1, 2, 3, and 4 mo. post surgery. Body weight and fasting blood glucose levels were also monitored. The University of Rochester Committee on Animal Resources approved all protocols.

Results: The high fat diet resulted in a 29% increase in body weight over lean controls at the time of MLI (8 wk) with a progressive increase in weight to the 3 mo. time point (Figure 1). Average fasting blood glucose levels never rose above 120 mg/dL in the lean mouse group at any time point while average fasting blood glucose levels were never lower than 180 mg/dL in mice on the high fat diet.

Quantitative microCT analysis of the periaricular region at the 3 and 4 mo. time points following MLI showed increased bone volume relative to sham-treated controls, but no difference was observed between dietary treatments. 3D uCT, however, revealed a more progressive meniscal calcification in the high fat diet group (Figure 2).

Analysis of the metaphyseal region of the femur in the high fat diet-treated mice. This was also associated with decreases in trabecular number and increases in trabecular spacing.

Discussion: The high fat diet protocol used in this study produced obesity and hyperglycemia in mice that is characteristic of type 2 diabetes. This metabolic dysfunction was associated with both decreased trabecular bone volume and accelerated progression of OA following MLI. The loss of trabecular bone on the high fat diet was selective because cortical bone density and volume were unaffected. MicroCT analysis demonstrated a marked increase in ossification of the injured meniscus in the obese mice, suggesting increased chondrocyte hypertrophy, consistent with injury-induced joint degeneration. Histologic analysis demonstrated degradation of articular cartilage in response to MLI. In the high fat fed group, this degradation was more pronounced with increased fibrillation, clefing, and eburnation. Articular chondrocyte cloning was also more prevalent in the high fat fed group. Collectively, these data indicate that OA progression is accelerated in the obese/type 2 diabetic mouse model. While the mechanism(s) by which the metabolic dysfunction of obesity and type 2 diabetes contributes to these effects requires further investigation, these results demonstrate a detrimental effect of the high fat Western diet on the progression of OA.

### Results

<table>
<thead>
<tr>
<th>Time Post Surgery</th>
<th>Lean</th>
<th>High Fat Diet</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
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<td>20</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>120</td>
</tr>
</tbody>
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### Figure 1. Weight gain as a function of diet.

C57BL/6 mice were placed on either a high fat (60% kcal) diet or lean (10% kcal) diet as described in the Methods section. Body weight was measured monthly for the duration of the experiment. Results are presented as mean ±SE with n=5.

### Figure 2. 3D uCT images of the mouse knee joint 4 mo. after MLI.

A and B are anterior and posterior views from a mouse on a lean diet. C and D are comparable views from a mouse on the high fat diet.

### Figure 3. Decreased bone volume in association with a high fat diet.

MicroCT analysis was utilized to quantify bone volume in the metaphyseal region of the femur. Measurements were made at 3 and 4 mo. in lean and high fat diet mice in sham and injured limbs. Results are presented as mean ±SE with n=5.

### Figure 4. Osteoarthritic changes in knee joints following MLI.

Surgically injured knees at the 2 mo. time point revealed increased fibrillation, clefing, and decreased proteoglycan staining in response to MLI. These changes were more pronounced in the high fat diet group (Figure 4).