OSTEOARTHRITIS

The influence of obesity on OA—does size matter or is metabolic dysfunction more important?

Obesity is on the increase worldwide, and is associated not only with type 2 diabetes mellitus, but also osteoarthritis (OA). New data published in *Arthritis Research & Therapy* support the theory that the metabolic dysfunction that occurs with obesity can increase OA progression and might even have a greater influence on the disease than body weight.

Robert Mooney and colleagues at the University of Rochester, USA, put C57BL/6 mice on a high-fat diet either 8 weeks before or directly after surgical induction of meniscal–ligamentous knee injury. OA progression was monitored during the 4 months after surgery.

Prior to surgery, mice fed a high-fat diet were obese (becoming more so after injury) and diabetic. Although mice transferred to a high-fat diet after surgery gained more weight than controls fed only a low-fat diet, they had normal body mass upon injury and did not become markedly obese; however, the switch in diet did lead to development of hyperglycemia indicative of a dysmetabolic state, which at 3 months after injury approached that of mice on the long-term high-fat regime.

Histological analysis of the injured knee joints at monthly time points revealed increased fibrillation and clefting, and reduced cartilage area in mice fed a high-fat diet—with cartilage loss almost exposing subchondral bone in some cases—compared with control animals. Furthermore, microCT analysis revealed increased meniscal calcification and osteophyte formation in the knee joint.

Interestingly, changes in cartilage, bone volume and OA severity were similar in mice fed a high-fat diet before or only after surgery, and thus were independent of body weight. These data suggest that “the acceleration of the OA seen in type 2 diabetic mice was mostly associated with metabolic dysfunction, given that the effect was seen in mice that were diabetic but not yet obese,” explains Mooney.

Alcian Blue-stained sagittal sections of knees 3 months after severing the right medial collateral ligament and excising a segment of the medial meniscus demonstrate more pronounced osteoarthritic changes in mice fed a high-fat diet (top; magnification 100×). 3D reconstructions of knee joints from microCT scans reveals increased calcification of the meniscus and osteophyte formation (arrows) in mice fed a high-fat diet at 4 months post-injury (bottom). Provided courtesy of R. A. Mooney.

“This fits with what we know about human OA, in that obesity is linked with progression, whereas weight alone does not seem to be,” adds Richard Aspden, Professor of Orthopedic Science at the University of Aberdeen, UK, commenting on this work. “The literature seems to indicate that obesity is a risk factor for progression due to its proinflammatory consequences rather than its effect on joint loading,” he continues.

Indeed, Mooney and co-workers plan to use this model system to investigate the role of inflammation in OA-associated with obesity and/or diabetes. They will also test the potential of therapy used in diabetes to restore metabolic function and inhibit progression of OA. In addition, Aspden suggests that “it would be interesting to repeat this study in the DBA mouse, which for

some reasons seems to be resistant to OA.” In fact, Mooney *et al.* noted with interest the resistance of DBA mice to metabolic changes upon high-fat feeding. Whether metabolic dysfunction affects development of OA in the absence of injury also requires clarification.

“Our line of research may eventually lead to the recognition of OA as a prominent secondary complication of the diabetic metabolic state,” concludes Michael Zuscik, a co-author of the paper.

David Killock

Original article Mooney, R. A. *et al.* High fat diet accelerates progression of osteoarthritis following meniscal/ligamentous injury. *Arthritis Res. Ther.* **13**, R198 (2011)

Further reading Aspden, R. M. Obesity punches above its weight in osteoarthritis. *Nat. Rev. Rheumatol.* **7**, 65–68 (2011)