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Insulin Resistance: Releasing the Brakes on Synovial Inflammation and Osteoarthritis?

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Emerging data link osteoarthritis (OA) with type 2 diabetes (T2DM) (1,2). As both are closely related to aging and obesity, it is no surprise that as our population has grown older and more obese incidences of both OA and T2DM have increased markedly. Previously, the association between OA and T2DM was considered correlative, with obesity thought to cause knee OA primarily by altering joint biomechanical loading and T2DM resulting largely from an imbalance in nutrient supply and demand leading to insulin resistance and pancreatic exhaustion. This perspective, though, is changing as the pathogenesis of obesity-associated OA is progressively considered more complex. For example, the increased incidence and severity of hand OA in obese persons has long suggested a systemic connection to obesity. Many studies now propose multiple pathways linking obesity and OA, including biomechanical, inflammatory, post-traumatic, genetic, and metabolic (3). In particular, there is growing evidence that diabetes increases OA risk even when controlling for obesity.

The diabetes-OA link arises from a number of key observations that highlight obesity-independent associations between OA and the metabolic syndrome (4). The metabolic syndrome, which has insulin resistance as its central feature, includes 3 or more of the following factors: hypertension, increased triglycerides, reduced HDL-cholesterol, increased waist circumference, and elevated fasting glucose. Increasing numbers of metabolic syndrome components predict an increased occurrence and progression of radiographic knee OA (5). Furthermore, a recent meta-analytic approach found a positive association between OA and T2DM with an odds ratio of 1.46 (95% CI: 1.08–1.96) for OA in T2DM populations (2). Interestingly, of those studies that adjusted for body mass index (BMI), a positive association between OA and T2DM was primarily observed in studies published since 2009.

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One potential explanation for this recent increase in BMI-adjusted odds is an increase in the prevalence of other metabolic syndrome factors that associate with T2DM and contribute to OA. In addition, an inflammatory contribution of diabetes to OA is supported by the observation that, in knee OA, persons with diabetes have more effusions and synovitis, which are independent of BMI (1).

In a report in this issue of *Arthritis & Rheumatology*, Hamada and colleagues present compelling data linking both synovial tumor necrosis factor alpha (TNF α) production and insulin resistance to OA pathology (6) (Figure 1). Although anti-TNF α therapies for OA have had limited success, the findings reported here suggest a causal role for TNF α in OA, specifically in obesity- and diabetes-associated OA. Using a high-fat diet mouse model of obesity and glucose intolerance, the authors showed that TNF α gene expression and protein levels were elevated in the synovium adjacent to osteophytes, an early pathogenic feature in this model. The authors further demonstrated the relevance of TNF α to the development of osteophytes in this model by replicating the experiments in TNF α knockout mice. The ablation of TNF α greatly diminished the high-fat diet-induced development of osteophytes and synovial hyperplasia. TNF α ablation also blunted the weight gain and glucose intolerance induced by a high-fat diet, suggesting potential local and systemic benefits of TNF α inhibition on joint remodeling and metabolic regulation. Indeed, in rheumatoid arthritis patients with high insulin resistance, anti-TNF therapy significantly improved β -cell function and insulin signaling (7).

TNF α was the first inflammatory molecule shown to be secreted from obese adipose tissue, thus igniting the burgeoning field of research on adipokines and obesity-associated inflammation. Since then, there has been a growing interest in identifying if and how obesity-associated inflammation contributes to OA. Here, Hamada and colleagues provide evidence that TNF α is elevated in the synovium of obese T2DM OA patients, but not in non-diabetic obese OA patients. In experiments using human fibroblast-like synoviocytes (FLS) obtained from non-diabetic patients undergoing joint replacement surgery, the authors showed that TNF α induced expression and secretion of OA-related proteinases, including ADAMTS4, MMP1, and MMP13. Furthermore, TNF α also induced the expression of OA-associated pro-inflammatory genes, such as IL-1 β , IL-6, and TNF α itself. Moreover, TNF α stimulated expression of the growth factor BMP2 in FLS cells; BMP2 has recently been shown to stimulate osteophyte formation (8).

The current work by Hamada and colleagues raises the question of how T2DM fits into the mosaic pattern of joint inflammation that characterizes OA. In an illuminating set of experiments, the authors provide evidence for a counter-regulatory role for insulin in synovial tissue inflammation and catabolism, linking insulin resistance to OA pathogenesis. Using immunohistochemistry, the authors demonstrated enriched insulin receptor expression in the synovium of mice and humans. Furthermore, in FLSs isolated from non-diabetic OA patients, insulin stimulation induced insulin receptor autophosphorylation and phosphorylation of Akt. However, in synovial tissue isolated from OA patients with T2DM, insulin-induced autophosphorylation of the insulin receptor and phosphorylation of Akt were significantly attenuated. Thus, these findings indicate that, like other insulin sensitive tissues (e.g., muscle, liver, and fat), synovium also develops insulin resistance in obese OA

patients with T2DM. This finding is significant because Hamada and colleagues report that insulin markedly reduced TNF α -stimulated production of MMP1, MMP13, and ADAMTS4 in non-diabetic human FLSs. Insulin also reduced TNF α -stimulated expression of BMP2 and IL-6. Interestingly, though, insulin did not reduce TNF α mediated expression of IL-1 β or TNF α itself. Overall, this work implicates insulin as a critical negative regulator of synovial inflammation and catabolism. Consequently, the development of synovial insulin resistance in obese individuals with T2DM would diminish the ability of insulin to suppress the production of inflammatory and catabolic mediators that promote OA.

Focusing on the role of insulin in regulating synovial inflammation and catabolism provides a new perspective on how insulin signaling contributes to the development and remodeling of diarthrodial joints. Much of the previous work on insulin action in joint tissues has centered on cartilage and bone where insulin acts as an anabolic agent, stimulating cellular differentiation, proliferation, and extracellular matrix production. Insulin also increases bone turnover by inducing osteoclastogenesis, and low-dose local insulin treatment promotes fracture healing in a rodent injury model (9). Conversely, impaired insulin signaling, such as that observed in chemically-induced and genetic models of type-1 diabetes, reduces the rate of bone synthesis and slows the rate of fracture healing. Providing local insulin delivery in these hypoinsulinemic diabetic models is sufficient to rescue fracture healing, indicating that the pathologic aspects of reduced insulin signaling are primarily local (10). Intriguingly, TNF α also appears to play a role in the delayed healing of bone fractures in diabetic animals. TNF α is elevated at the fracture repair site in streptozotocin-induced type 1 diabetic mice, and treatment with either insulin or a TNF α inhibitor rescues the rate of bone repair at least in part by reducing mesenchymal stem cell apoptosis and increasing proliferation (11). The extent to which insulin acts to suppress inflammation and promote repair in joint injury models independent of TNF α inhibition remains to be tested. The findings by Hamada and colleagues, though, support increased scrutiny of the synovium and in particular the interaction between macrophages and synovial fibroblasts.

While the work by Hamada and colleagues focused primarily on FLSs, they also showed that the number of synovial macrophages was increased in obese T2DM OA patients compared to obese non-diabetic OA controls. Other studies have also reported an increase in the number of activated synovial macrophages in OA, although a specific link to T2DM has not been previously reported. This preliminary finding raises a number of interesting questions regarding the pathogenesis of synovial insulin resistance and increased TNF α production. For one, are the two factors mechanistically linked? In skeletal muscle, TNF α causes serine phosphorylation of insulin receptor substrate-1, resulting in reduced insulin-stimulated signaling, less translocation of GLUT4 to the membrane, and impaired glucose uptake (12). Hamada and colleagues did not test the effect of TNF α on insulin signaling in either FLSs or synovial macrophages, and the temporal relationship between increased TNF α production and the development of insulin resistance also remains to be determined. The cellular source of synovial TNF α also remains to be established. Although activated synovial macrophages are one likely source, the complex interplay between synovial macrophages and FLSs in regulating inflammation (13) suggests that considerable challenges remain to identify the pathogenesis of synovial inflammation in chronic models of obesity and diabetes-associated OA.

Another important question is determining which cell types in the synovium develop insulin resistance in obese T2DM OA patients (Figure 1). Hamada and colleagues utilized synovial tissue homogenates to determine that T2DM was associated with impaired insulin signaling. However, with an increase in the number of synovial macrophages in these samples, the impaired insulin signaling could also be attributed to the macrophages, which express functional insulin receptors and have been previously reported to develop insulin resistance in the context of atherosclerosis (14). In that study, insulin resistant macrophages were shown to be more susceptible to lipid-mediated ER stress and apoptosis, suggesting a potential link to hyperlipidemia, another component of the metabolic syndrome and a feature of high-fat diet-induced obese mouse models of OA. The relative susceptibility of FLSs and synovial macrophages to developing insulin resistance remains to be determined. Identifying the cellular specificity and sequence of synovial insulin resistance in relationship to elevated inflammation and altered glucose and lipid metabolism is needed to more fully understand the causes and consequences of impaired insulin signaling in the development of OA.

Finally, a key issue that deserves further attention is the sex specificity of the association between diabetes and OA. As reviewed in the introduction by Hamada and colleagues, a number of studies have reported an association between diabetes and OA in men but not women. In particular, the work by Karvonen-Gutierrez and colleagues showed that HOMA-IR scores, which are derived from a model-based estimate of insulin resistance and β -cell function using fasting plasma insulin and glucose concentrations, were positively associated with osteophyte-defined knee OA in obese men but not women (15). In fact, HOMA-IR and OA odds ratios were 1.18 (95% CI: 1.15 – 1.22) for non-obese men and 1.34 (95% CI: 1.27 – 1.42) for obese men. In contrast, the odds ratios were marginally positive for non-obese women (1.04; 95% CI: 1.01 – 1.07) and were negative for obese women (0.88; 95% CI: 0.86 – 0.89) (15). The clinical sample sizes used by Hamada and colleagues to evaluate synovial insulin resistance in diabetic patients were too small to test for sex differences and were biased towards female patients in the non-diabetic group. Thus, whether or not a sex-dependent association between insulin resistance and osteophyte-defined knee OA is related to differences in synovial inflammation and insulin resistance remains to be tested.

While many questions remain, the current study strengthens the growing link between metabolic disorders and OA by highlighting the role of synovial inflammation and insulin resistance in obesity and T2DM. As a ‘whole-joint’ disease, OA-related pathologies occur in many joint tissues to various degrees and at different stages of disease. The work presented here implicates synovial inflammation, and in particular TNF α production, as an early-stage mediator of obesity- and diabetes-associated OA. The work also identifies insulin resistance as a potential key connection to understanding how conditions of the metabolic syndrome increase OA risk by sustaining joint inflammation. Furthermore, by extending the focus of a T2DM–OA link to FLSs and synovial macrophages, the study expands the list of cellular targets for metabolic-based OA therapies. If improving the insulin sensitivity of these synovial lining cells is sufficient to suppress the chronic production of OA inflammatory and catabolic mediators, this raises the possibility of exploring insulin-sensitizing therapies to slow the progression of OA in a patient population at high risk for total joint arthroplasty.

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Figure 1.

Type 2 diabetes mellitus (T2DM) mediates synovial inflammation and insulin resistance in the pathogenesis of osteoarthritis (OA). T2DM and other obesity-associated factors increase the production of synovial tumor necrosis factor alpha (TNFα). Synovial fibroblasts, also called fibroblast-like synoviocytes or FLSs, respond to TNFα by increasing the production of cytokines (IL-1β, IL-6, and TNFα), the growth factor BMP2, and proteinases (ADAMTS4, MMP1, and MMP13). These TNFα-derived factors, and in particular BMP2, are implicated in the development of osteophytes that form adjacent to inflamed synovium. In synovial fibroblasts isolated from non-diabetic OA patients, insulin inhibits the production of TNFα-derived cytokines, growth factors, and proteinases. However, T2DM OA patients, synovial insulin signaling is impaired, suggesting that the anti-inflammatory and anti-catabolic role of insulin is diminished in these patients. The role of TNFα in synovial insulin resistance as well as the effects on synovial fibroblasts versus macrophages remain to be determined.