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Diabetes and osteoarthritis: an unhealthy relationship

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Abstract

Osteoarthritis and diabetes are common conditions that frequently coexist. As they have shared risk factors, this is unsurprising; however, there is interest in determining whether the association is causative. Patients with osteoarthritis are at increased risk of mortality, and this risk is exacerbated in those with walking disability. When making physical activity recommendations for patients with both diseases, the implications of mobility limitations must be considered. Although historically considered a disease of wear and tear, it is now known that osteoarthritis is not solely caused by mechanical damage to joints. Low-grade systemic inflammation caused by metabolic diseases could trigger or aggravate the disease. Furthermore, diabetes may influence the osteoarthritis process independently of other metabolic comorbidities. Human histology and animal model studies suggest hyperglycemia-induced accumulation of advanced glycosylation end products in the synovial tissue can induce endoplasmic reticulum stress and the release of proinflammatory mediators, resulting in chondrocyte degradation and promotion of osteoarthritis progression. The finding that systemic inflammation may be involved osteoarthritis has given rise to interest in repurposing drugs with systemic anti-inflammatory properties as disease modifying osteoarthritis therapeutics (injected intraarticularly). Trials of liraglutide in murine models of osteoarthritis have yielded promising results.

Key words: diabetes, glucagon-like peptide 1, inflammation, osteoarthritis

Introduction

Osteoarthritis is a leading cause of disability.[1] In 2020, it was estimated that, globally, >650 million individuals (aged ≥40 years) had knee osteoarthritis. In the past, osteoarthritis was considered not strictly a disease, but rather a consequence of wear and tear, with old age being the key risk factor for its development.[2] The well-known quote, attributed to the renowned British rheumatologist Dr William Copeman, 'osteoarthritis is to the joints what wrinkles are to the skin and white hairs to the scalp [paraphrased]', illustrates this view. The fact that obesity is also a key risk factor for osteoarthritis[3] was explained by an increased mechanical load causing exacerbation of joint damage. More recent research has led to a profound modification of this paradigm, and it is now known that osteoarthritis is not solely caused by mechanical damage to the joint.

Given that both osteoarthritis and type 2 diabetes are increasing in prevalence and have shared risk factors, including aging and obesity, it is unsurprising that the two diseases frequently coexist.[4] However, it has not yet been established whether there is a causal link between the two diseases. This report gives a brief overview of research into the relationship between these two diseases, the pathogenesis of osteoarthritis, and a possible treatment option for osteoarthritis.

The association between osteoarthritis and diabetes

Although it may not occur to the diabetologist to inquire, US data show that almost half of patients with diabetes also have arthritis.[4] According to a large meta-analysis, the risk of osteoarthritis is significantly higher in patients with diabetes than in the non-diabetic population (odds ratio 1.46; $P = 0.01$).[5] Similarly, the risk of diabetes in patients with osteoarthritis was found to be significantly higher than that in people without osteoarthritis (odd ratio 1.41; $P < 0.000001$). This association, of course, does not imply causality; one must also consider that there may be some bias, for example, obesity is a risk factor for both diseases, and weight-adjusted studies show mixed results regarding the association.[6] Furthermore, amongst patients with arthritis, it appears that those with diabetes have more severe joint pain than those without. An age-adjusted analysis of US National Health Interview Survey data (2002–2014) showed that, overall, 26.5% of arthritis patients reported having recently experienced severe joint pain (defined as ≥7 on a scale of 0–10), compared with 40.9% of those with both diabetes and arthritis.[7] This proportion was higher than in obese arthritic patients (31.7%). Several groups are currently investigating possible reasons for this increase in pain severity in patients with diabetes; however, that is beyond the scope of this report.

As we know, lifestyle changes, including increased physical activity, are important treatment goals for patients with diabetes and prediabetes.[8,9] In inactive patients with diabetes, the prevalence of osteoarthritis is 61.1%.[10] This relationship creates a vicious cycle: joint pain caused by osteoarthritis can lead to a decreased level of physical activity and its associated health benefits, and an increased chance of obesity, and thus a poorer diabetes prognosis. An analysis of US data from 2005 and 2007 showed that almost 30% of patients with arthritis and diabetes were inactive, compared with only ≈11% of people with neither condition.[9] Compared with the general population, patients with osteoarthritis have an increased risk of all-cause and cardiovascular mortality.[11] This risk is exacerbated in those with walking disability; in a study of >1000 patients with osteoarthritis, after a median of 14 years follow-up, those with walking disability had a significantly increased risk of mortality (adjusted hazard ratio [HR] 1.48; $P = 0.001$) and cardiovascular mortality (adjusted HR 1.72, $P = 0.002$). Additionally, as the severity of walking disability increased, so too did the risk of mortality ($P < 0.001$).[11] The implications of possible mobility limitations must be carefully considered during consultations with patients with diabetes, and it is possible to design non-weight-bearing exercise programs that fulfil activity recommendations.[8]

Pathophysiology of osteoarthritis: a brief overview

Imaging of an osteoarthritic joint will show cartilage destruction, subchondral bone that is more condensed than normal, and the formation of osteophytes.[12] The synovial membrane (which lines the joints) may also be inflamed. Briefly, cartilage degradation products are released into the synovial fluid, and recognized as 'nonself', leading to the release of inflammatory mediators.[13] Subsequent release of matrix metalloproteinases and other proteases leads to further cartilage degradation. Synovial membrane inflammation also contributes to osteophyte formation. In addition to localized inflammatory and mechanical factors, we now know that systemic factors can contribute to the joint degradation.[14] This realization materialized from the surprising results of studies (several years ago), in which overweight people were significantly more likely to have hand osteoarthritis than people of normal weight.[15] This finding challenged the paradigm that the increased

risk of osteoarthritis in obese individuals is due solely to increased mechanical loading on the joints,[14] and, as one would expect, prompted research into the possible involvement of adipokines.[16] Although beyond the scope of this report, there are now many experimental data supporting the hypothesis that cytokines released from adipose tissue can contribute to inflammation, cartilage degradation, and bone remodeling in osteoarthritis.

Metabolic syndrome and osteoarthritis

Numerous studies have investigated the relationship between osteoarthritis and metabolic factors. As an example, the Japanese ROAD (Research on Osteoarthritis Against Disability) cohort study followed 1384 individuals for 3 years, and assessed the occurrence or progression of knee osteoarthritis, relative to the number of components of metabolic syndrome (such as overweight, hypertension, dyslipidemia, impaired glucose tolerance) in each patient.[17] As the number of metabolic syndrome components a patient had increased, so too did the risk of knee osteoarthritis; compared with those with no components, the adjusted odds ratio for osteoarthritis occurrence was 2.33 for those with one component, 2.82 for two components ($P < 0.05$), and 9.83 ($P < 0.001$) for those with three or more components. Similarly, in those who had knee osteoarthritis at baseline, the odds ratio for disease progression was 1.38 for those with one component, 2.29 for two ($P < 0.001$), and 2.80 for three or more components ($P < 0.001$). These analyses were adjusted for numerous potential risk factors, including age, gender, smoking, alcohol consumption, physical activity, and history of knee injury. Thus, in addition to the mechanical impact of increased weight, and beyond the adipokine theory, there are data suggesting that each of these cardiometabolic factors may have direct or indirect systemic effects on the joint and the osteoarthritis process.

Impact of diabetes on the joints

Although we know there is an association between diabetes and arthritis, we are still in the early stages of investigating the possibility that diabetes may cause or aggravate osteoarthritis in some patients; therefore, data are limited. Our initial hypothesis was that diabetes-induced osteoarthritis may be a separate osteoarthritic phenotype.[18] More recently, we performed a simple experiment to investigate the consequence of diabetes in osteoarthritis, in which we compared the cartilage from diabetic and non-diabetic patients who were undergoing a total joint replacement due to late-stage osteoarthritis.[19] When exposed to a pro-inflammatory environment (interleukin [IL]-1β), the cartilage from diabetic patients secreted 2.7-fold more IL-6, and 3-fold more prostaglandin E_2 (PGE_2) than the non-diabetic cartilage (both $P < 0.05$). Further experiments showed that, compared with that from non-diabetic patients, osteoarthritis cartilage from diabetic patients showed significantly reduced levels of the protective antioxidant enzyme heme oxygenase-1 (HO-1), as well as of nuclear factor-erythroid 2-related factor-2 (Nrf-2, a transcription factor which regulates many cytoprotective responses and is involved in the HO-1 pathway).[20] Thus, it appears that antioxidative effects are less present in diabetic osteoarthritis cartilage.

A more recent paper investigated the role of hyperglycemia on synovial tissue from patients with osteoarthritis, and in a rat model of diabetes.[21] Examination of the synovial tissue from patients with both osteoarthritis and diabetes showed a more obvious inflammatory response, higher levels of endoplasmic reticulum stress (ERS), and an excess of advanced glycosylation end products (AGEs) compared with the tissue from nondiabetic patients with osteoarthritis. Similar results were observed in rat models, in which some of the diabetic rats had osteoarthritis induced by long-distance treadmill running. These findings represent another step towards an increased understanding of the link between diabetes and osteoarthritis, showing that hyperglycemia-induced accumulation of AGEs in the synovial tissue can induce ERS and the release of proinflammatory mediators, which, via communication between the synovial tissue and cartilage, can result in chondrocyte degradation and the promotion of osteoarthritis progression.

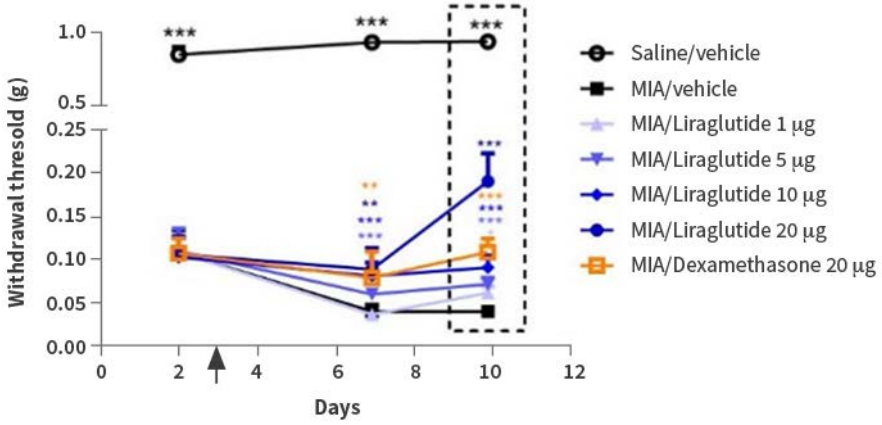
Osteoarthritis treatment

Although osteoarthritis is an extremely common and disabling disease, the only current treatment options are symptomatic drugs, which are often inadequate,[22] and total joint replacement. There has been significant interest in finding disease-modifying agents for osteoarthritis. The above-mentioned possibility that low-grade systemic inflammation in metabolic diseases may trigger and/or aggravate osteoarthritis, along with the possibility that hyperglycemia may increase responsiveness to this inflammation, has led to the investigation of the joint-localized effects of drugs known to reduce systemic inflammation.[22,23] Glucagon-like peptide 1 (GLP-1) receptor agonists, in addition to lowering glucose, have been shown

to have anti-inflammatory effects in numerous organs and cell types,[23,24] and our group has been researching the use of these agents in osteoarthritis.

GLP-1 receptors have been identified in chondrocytes and synovial membrane from patients with osteoarthritis, as well as the cartilage, synovial membrane, bone marrow and meniscus of healthy mice, suggesting a pleiotropic role of GLP-1 receptors in both healthy and arthritic joints.[22,23] We therefore tested the GLP-1 receptor agonist, liraglutide, in a murine osteoarthritis model. Given that osteoarthritis generally effects only one, or at least very few, joints, we hypothesized that intraarticular injection of the drug may be an effective method of providing treatment with reduced adverse effects. Our recently-published results show that this method of delivery in a murine model showed anti-catabolic activity, and thus may provide cartilage protection. This treatment also reduced synovitis, and had an analgesic effect that was as strong as dexamethasone, which is the standard of care of an osteoarthritis flare (**Figure 1**).[22] Based on these results, we will soon begin a phase 1 trial of intraarticular liraglutide in patients with osteoarthritis.

Figure 1: *Analgesic effect of liraglutide in a sodium monoiodoacetate (MIA) osteoarthritis mouse model. Mice knee joints were intraarticularly (IA) injected with 0.75 mg of MIA or saline on day 1. Liraglutide, dexamethasone, or vehicle were injected IA on day 3 and inflammation pain sensitivity was determined by the von Frey test on day 2 (for randomization), 7, and 10. Paw withdrawal threshold was assessed by von Frey filament stimulation on days 2, 7, and 10. Reproduced from Meurot et al., 2022,[22] under a Creative Commons Attribution 4.0 International License.*



Conclusion

Diabetes and osteoarthritis are common conditions that frequently coexist. Osteoarthritis is a leading cause of walking disability, which can deter patients from achieving physical activity goals, and thus contribute to the observed increased mortality, particularly cardiovascular mortality, in these patients. It is also possible that diabetes may influence the osteoarthritis process, independently of the other metabolic comorbidities such as obesity; although, future research into this possibility is required. Repurposing of antidiabetic drugs that have systemic anti-inflammatory properties is a novel option for future disease modifying osteoarthritis therapeutics, and promising results have been obtained in murine trials of intraarticular liraglutide.

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Disclosures: Francis Berenbaum is CEO of 4Moving Biotech, which is developing GLP1R analogues for treating osteoarthritis.

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