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EDITORIAL

Diabetes – osteoarthritis and joint pain

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Osteoarthritis (OA) is a common musculoskeletal disability with a prevalence in the aged population (≥ 60 years old). Analysis of the data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) revealed an increase in the age standardized annual incidence rate of OA and of the years lived with disability from 1990 to 2017 by 8.2% and 9.6%, respectively.[1] OA has also been the topic of 16 articles published in 2020 in *Bone & Joint Research* (PubMed search: "Bone Joint Res" AND osteoarthritis AND 2020, February 2021). Besides the investigation of operation techniques and mortality rate, they also aimed to identify biomarkers, studied the pathomechanism, and developed or evaluated treatment options; the studies cited here are exemplary.[2-8] Even though some mentioned the influencing effect of comorbidities, none explicitly analyzed the association of diabetes mellitus (DM) and OA. Diabetic patients, however, are adversely affected by severe musculoskeletal problems such as bone fracture, joint pain, and OA.[9]

Courties and Sellam[10] showed that DM increases the progression and incidence of OA. A recent meta-analysis revealed that the increased BMI and weight of DM patients are not responsible for the association between DM and the development and presence of radiological and symptomatic OA.[11] Several diabetes-associated mechanisms are proposed to increase pathophysiological processes of OA. The assumption that DM can also initiate OA led to the concept of a diabetes-induced OA phenotype.[12] In this concept, Berenbaum[12] described three main mechanisms leading to degradation, inflammation, and destabilization of the joint structure, which induce and aggravate OA processes. Hyperglycaemia was considered: 1) as the main trigger of joint degradation by increasing the formation of advanced glycation endproducts (AGEs), which activates chondrocytes and synoviocytes to produce prodegradative and proinflammatory mediators; 2) to provoke a low-grade systemic inflammation that induces local joint inflammation, aggravating OA processes in various joint structures; and 3) to cause neuromuscular deficiencies, which destabilize the joint and worsen OA.

Several pathomechanisms therefore presumably contribute to the DM-induced aggravation of OA processes. Under high extracellular glucose concentrations, the ability to control glucose uptake by downregulation of glucose transporters is impaired in OA chondrocytes, resulting in accumulation of glucose and higher reactive oxygen species (ROS) production, which promote degenerative changes and facilitate the progression of OA.[13,14] Hyperglycaemia leads to the accumulation of AGEs in cells and tissues, inducing oxidative stress and proinflammatory conditions.[14,15] Zhang et al[16] analyzed the level of different AGEs in serum and synovial fluid of 84 patients with knee OA, including 46 with DM and 38 without DM. They found no significant difference in all analyzed AGEs in serum between DM and non-DM patients, but they could detect higher levels of methylglyoxal and free methylglyoxal-derived hydroimidazolone in the synovial fluid of OA-affected joints of DM patients.[16] They concluded that alterations in the phosphatidylcholine metabolism, leading to higher production of AGEs in OA-affected joints of DM patients, might be responsible for the observed association between OA and DM. Furthermore, AGEs induce inflammatory pathways in human OA chondrocytes via AGE receptor (RAGE) and toll-like receptor, and enhance the production and release of interleukin-6 (IL-6).[17] Laiguillon et al[18] also found an increased inflammatory response of OA cartilage from DM patients compared to non-DM patients. They detected a higher release of IL-6 and prostaglandin E_2 (PGE_2) after interleukin-1β (IL-1β) stimulation of OA

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cartilage from DM patients. Furthermore, diabetic OA patients have elevated levels of several matrix metalloproteinases, leading to increased degradation of cartilage.[19]

Only a few studies analyzed whether DM can really induce OA. To analyze this, animal experiments are used for ethical and practical reasons. Onur et al[20] performed an animal study to investigate whether DM can initiate OA: DM rats showed a mild global degeneration of cartilage in the knee joint, but no changes of the level of type II collagen. Since the DM rats had a higher body mass compared to the control rats in this study, the authors could not extrapolate whether the aspect of DM or higher body mass predominantly contribute to the osteoarthritic phenotype. Another study by Ribeiro et al[21] explored the impact of DM on experimentally induced OA. Ten weeks after surgical induction of OA, DM mice exhibited increased cartilage damage and inflammation of the synovial tissue, which was reduced by activation of autophagy. Surprisingly, the histological scores of cartilage damage and synovial inflammation showed no differences between DM mice and control mice without experimentally induced OA.[21]

Additionally, diabetic OA patients experienced more severe osteoarthritic joint pain, especially for knee and erosive hand OA.[22-24] The review by Eitner et al[25] summarized several mechanisms which are generally involved in OA pain, including local pathological processes, neuronal alterations of pain processing, and systemic factors such as DM and high BMI. The specific mechanism by which DM induces or increases OA pain is under discussion. DM can induce a low-grade systemic inflammation, which can alter local joint processes leading to increased joint pain. Indirect effects are also conceivable. The higher BMI of DM patients could lead to a higher mechanical stress on joint structures. Weiss's study[26] showed that patients with a higher BMI experience more intense OA pain. The innate immune system is also an important factor influencing OA pain by production of algogenic factors, which amplify the activation of sensory neurones.[27] This neuroimmune crosstalk occurs in the joint tissue, but also in the dorsal root ganglia and spinal cord.[27] Further, methylglyoxal, which is increased in the synovial fluid of DM patients,[16] can directly enhance the excitability of nociceptive neurones.[28] In recent years, only a few studies have investigated the association between DM and OA pain, revealing that diabetic OA patients have stronger local inflammation in the OA-affected joints with pronounced synovitis and higher concentration of the pro-inflammatory cytokine IL-6 in the synovial fluid compared with non-diabetic OA patients.[23,24] The grade of synovitis was associated with the level of OA pain.[24] Furthermore, increased IL-6 level can sensitize joint nociceptors for other stimuli.[29] A recently published study of a large patient cohort revealed that increased OA pain is a specific feature of DM, and not only a result of increased OA progression or higher BMI.[30] Thus, systemic, local, and neuronal processes are impaired in OA patients with DM, which have an influence on pain mechanisms in OA joints.

In summary, the presented studies showed that DM is an important factor that aggravates OA processes and OA pain. Since the incidence of OA and DM increase in the ageing population, there is an urgent need to increase efforts to understand the interaction of DM and OA and pain. Understanding the pathomechanisms leading to DM-induced OA and OA pain is important to move forward with the development of a personalized OA therapy depending on the OA phenotype.

References

1. **Safiri S**, **Kolahi A-A**, **Smith E**, **et al**. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the global burden of disease study 2017. *Ann Rheum Dis*. 2020;79(6):819–828.
2. **Seco-Calvo J**, **Sánchez-Herráez S**, **Casis L**, **et al**. Synovial fluid peptidase activity as a biomarker for knee osteoarthritis clinical progression. *Bone Joint Res*. 2020;9(11):789–797.
3. **Jayadev C**, **Hulley P**, **Swales C**, **Snelling S**, **Collins G**, **Taylor P**. Synovial fluid fingerprinting in end-stage knee osteoarthritis: a novel biomarker concept. *Bone Joint Res*. 2020;9(9):623–632.
4. **Akhbari P**, **Karamchandani U**, **Jaggard MKJ**, **et al**. Can joint fluid metabolic profiling (or "metabonomics") reveal biomarkers for osteoarthritis and inflammatory joint disease? *Bone Joint Res*. 2020;9(3):108–119.
5. **Qi X**, **Yu F**, **Wen Y**, **et al**. Integration of transcriptome-wide association study and messenger RNA expression profile to identify genes associated with osteoarthritis. *Bone Joint Res*. 2020;9(3):130–138.
6. **Brzeszczyńska J**, **Brzeszczyński F**, **Hamilton DF**, **McGregor R**, **Simpson AHRW**. Role of microRNA in muscle regeneration and diseases related to muscle dysfunction in atrophy, cachexia, osteoporosis, and osteoarthritis. *Bone Joint Res*. 2020;9(11):798–807.
7. **Shao L-T**, **Gou Y**, **Fang J-K**, **et al**. Parathyroid hormone (1-34) ameliorates cartilage degeneration and subchondral bone deterioration in collagenase-induced osteoarthritis model in mice. *Bone Joint Res*. 2020;9(10):675–688.
8. **Wang J**, **Zhou L**, **Zhang Y**, **Huang L**, **Shi Q**. Mesenchymal stem cells - a promising strategy for treating knee osteoarthritis. *Bone Joint Res*. 2020;9(10):719–728.
9. **Sözen T**, **Başaran Nursel Çalık**, **Tınazlı M**, **Özışık L**, **Calik Basaran N**, **Ozisik L**, **Başaran N**. Musculoskeletal problems in diabetes mellitus. *Eur J Rheumatol*. 2018;5(4):258–265.
10. **Courties A**, **Sellam J**. Osteoarthritis and type 2 diabetes mellitus: what are the links? *Diabetes Res Clin Pract*. 2016;122:198–206.
11. **Williams MF**, **London DA**, **Husni EM**, **Navaneethan S**, **Kashyap SR**. Type 2 diabetes and osteoarthritis: a systematic review and meta-analysis. *J Diabetes Complications*. 2016;30(5):944–950.
12. **Berenbaum F**. Diabetes-Induced osteoarthritis: from a new paradigm to a new phenotype. *Ann Rheum Dis*. 2011;70(8):1354–1356.
13. **Rosa SC**, **Gonçalves J**, **Judas F**, **Mobasheri A**, **Lopes C**, **Mendes AF**. Impaired glucose transporter-1 degradation and increased glucose transport and oxidative stress in response to high glucose in chondrocytes from osteoarthritic versus normal human cartilage. *Arthritis Res Ther*. 2009;11(3):R80.
14. **Ashrafizadeh H**, **Ashrafizadeh M**, **Oroojan AA**. Type 2 diabetes mellitus and osteoarthritis: the role of glucose transporters. *Clin Rev Bone Miner Metab*. 2020;18(1-3):1–17.
15. **Veronese N**, **Cooper C**, **Reginster J-Y**, **et al**. Type 2 diabetes mellitus and osteoarthritis. *Semin Arthritis Rheum*. 2019;49(1):9–19.
16. **Zhang W**, **Randell EW**, **Sun G**, **et al**. Hyperglycemia-related advanced glycation end-products is associated with the altered phosphatidylcholine metabolism in osteoarthritis patients with diabetes. *PLoS One*. 2017;12(9):e0184105.
17. **Chen YJ**, **Sheu ML**, **Tsai KS**, **Yang RS**, **Liu SH**. Advanced glycation end products induce peroxisome proliferator-activated receptor γ down-regulation-related inflammatory signals in human chondrocytes via Toll-like receptor-4 and receptor for advanced glycation end products. *PLoS One*. 2013;8(6):e66611.
18. **Laiguillon M-C**, **Courties A**, **Houard X**, **et al**. Characterization of diabetic osteoarthritic cartilage and role of high glucose environment on chondrocyte activation: toward pathophysiological delineation of diabetes mellitus-related osteoarthritis. *Osteoarthritis and Cartilage*. 2015;23(9):1513–1522.

19. **Luo S**, **Shi Q**, **Chen J**, **Wang H**, **Wu W**, **Zha Z**. Expression and significance of MMPs in synovial fluid, serum and PBMC culture supernatant stimulated by LPS in osteoarthritis patients with or without diabetes. *Exp Clin Endocrinol Diabetes*. 2019;127(04):195–202.
20. **Onur T**, **Wu R**, **Metz L**, **Dang A**. Characterisation of osteoarthritis in a small animal model of type 2 diabetes mellitus. *Bone Joint Res*. 2014;3(6):203–211.
21. **Ribeiro M**, **Figueroa L**, **Nogueira-Recalde PB**. Diabetes-accelerated experimental osteoarthritis is prevented by autophagy activation. *Osteoarthritis Cartilage*. 2016;24(12):2116–2125.
22. **Magnusson K**, **Hagen KB**, **Østerås N**, **Nordsletten L**, **Natvig B**, **Haugen IK**. Diabetes is associated with increased hand pain in erosive hand osteoarthritis: data from a population-based study. *Arthritis Care Res*. 2015;67(2):187–195.
23. **Schett G**, **Kleyer A**, **Perricone C**, **et al**. Diabetes is an independent predictor for severe osteoarthritis: results from a longitudinal cohort study. *Diabetes Care*. 2013;36(2):403–409.
24. **Eitner A**, **Pester J**, **Vogel F**, **et al**. Pain sensation in human osteoarthritic knee joints is strongly enhanced by diabetes mellitus. *Pain*. 2017;158(9):1743–1753.
25. **Eitner A**, **Hofmann GO**, **Schaible H-G**. Mechanisms of osteoarthritic pain. Studies in humans and experimental models. *Front Mol Neurosci*. 2017;10:349.
26. **Weiss E**. Knee osteoarthritis, body mass index and pain: data from the osteoarthritis initiative. *Rheumatology*. 2014;53(11):2095–2099.
27. **Miller RJ**, **Malfait A-M**, **Miller RE**. The innate immune response as a mediator of osteoarthritis pain. *Osteoarthritis Cartilage*. 2020;28(5):562–571.
28. **Bierhaus A**, **Fleming T**, **Stoyanov S**, **et al**. Methylglyoxal modification of Nav1.8 facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy. *Nat Med*. 2012;18(6):926–933.
29. **Brenn D**, **Richter F**, **Schaible H-G**. Sensitization of unmyelinated sensory fibers of the joint nerve to mechanical stimuli by interleukin-6 in the rat: an inflammatory mechanism of joint pain. *Arthritis Rheum*. 2007;56(1):351–359.10.1002/art.22282
30. **Eitner A**, **Culvenor AG**, **Wirth W**, **Schaible HG**, **Eckstein F**. Impact of diabetes mellitus on knee osteoarthritis pain and physical and mental status: Data from the osteoarthritis initiative. *Arthritis Care Res (Hoboken)*. 2021;73(4):540–548.

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