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Molecular mechanisms linking diabetes mellitus type 2 and osteoarthritis: Role of hyperglycemia and hyperinsulinemia

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Recent epidemiologic and experimental data reinforced the concept that diabetes mellitus (DM) especially type 2 (DM 2) is an independent risk factor for osteoarthritis (OA), the most prevalent and highly debilitating musculoskeletal disorder. Besides a systemic inflammatory response that can affect joint tissues and contribute to OA pathogenesis, whether and how hyperglycemia, the hallmark of DM 2, directly affects joint tissues and cells remains to be unraveled. Direct and indirect effects of hyperglycemia on chondrocytes and other joint tissue cells have been identified and shown to induce inflammatory and catabolic responses that can lead to the characteristic joint destruction of OA. Our studies showed that human chondrocytes sense the extracellular glucose concentration and adjust their glucose transport capacity, avoiding oxidative stress. This ability is lost in aged OA chondrocytes, leading to inflammatory, anti-anabolic and catabolic responses in human OA chondrocytes. Available anti-diabetic therapies, however, don't seem to prevent OA, suggesting that other factors besides hyperglycemia contribute to joint tissue damage or that the glycemic control achieved is insufficient. Thus, we investigated the role of hyperinsulinemia in chondrocyte homeostasis. Our results show that high insulin concentrations activate inflammatory signaling pathways and catabolic responses and impair autophagy leading to osteoarthritis both *in vitro* and *in vivo*. Elucidating how high glucose and high insulin concentrations both alone and in combination, modulate joint tissue homeostasis will identify the molecular mechanisms by which DM 2 contributes to OA development and progression and disclose novel targets for development of innovative therapeutic strategies. Furthermore, understanding how antidiabetic drugs affect joint tissue cells and whether they can counteract the deleterious effects of high glucose and/or high insulin also needs to be investigated so that DM 2 patient therapy can be improved to minimize OA development and progression.

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