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Original Research Article

Association Between Osteoarthritis and Type 2 Diabetes Mellitus

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Abstract

Osteoarthritis and type 2 diabetes mellitus are two common chronic illnesses that significantly strain healthcare systems around the globe. Given the possible synergistic effects of type 2 diabetes mellitus and osteoarthritis on metabolism and joint health, their comorbidity is a significant problem, particularly in people who are overweight or obese. The aim of our study was to assess and examine the literature regarding the prevalence, association, symptoms, physical function, and shared risk factors of T2DM and OA. Osteoarthritis and type 2 diabetes mellitus are both characterised by chronic low-grade systemic inflammation, which is crucial to their development. We conducted a critical review of the literature to explore the association between T2DM and OA, whether any association is site-specific for OA, and whether the presence of T2DM impacts on OA outcomes. Furthermore, we found that common risk variables, such as metabolic syndromes and demography, may influence the relationship between DM and OA; however, more study is needed on this topic as well. Extensive future study is required to properly determine the effect of chronic medication usage, as there is conflicting information regarding whether medication use contributes positively or negatively to the connection between DM and OA.

Keywords: Osteoarthritis, Type 2 diabetes mellitus, Association, Demography.
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Introduction

Osteoarthritis (OA) and type 2diabetes mellitus (T2DM) are two wide spread chronic conditions that execute a considerable problem on healthcare systems world-wide. One of the most prevalent chronic conditions affecting the joints is osteoarthritis. About 26 million people in the United States are thought to have OA, which affects roughly 16% of the world's population (Cui et al., 2020). The average annual cost per patient for OA exceeds USD 2000 [12, 19, 31, BMUS, 2018]. Approximately 34% of persons over 65 have OA, and the frequency is known to rise with age [17]. Osteophyte production, synovial inflammation, and cartilage degradation are the hallmarks of osteoarthritis (OA), which most commonly affects the knee, hip, hands, and spine. The most prevalent symptom that has to be treated is pain. N umerous factors, including age, sex, obesity, and other comorbidities like diabetes mellitus, might affect how severe pain is.

The number of joints affected and their placements can be used to categorise steoarthritis: three or more joints are affected by generalised OA (GOA) [17], whereas fewer than three joints are affected by localised OA [21]. In terms of discomfort, functional impairment, and a lower quality of life, those with GOA may exhibit severe symptoms or worse outcomes. Prior research has demonstrated that individuals with multiple joint OA and total knee replacement experience increased pain and decreased physical function [24]. Compared to localised OA, GOA has a bigger impact on joint replacement results, quality of life, and functionality. GOA patients may experience significant difficulties in their everyday activities, which could have an adverse effect on their basic independence and self-care [11]. Further research is needed regarding GOA in terms of prevalence, sites, and related risk factors.

The number of people with type 2 diabetes mellitus (T2DM) is increasing worldwide; according to the International Diabetes Federation, 463 million people had the condition in 2019 and 700.2 million would by 2045 [26]. From 1.5% in 1971 to 13.7% in 2016, the prevalence of type 2 diabetes mellitus (T2DM) among South Korean adults has quickly increased over the past few decades [2]. In Korea, diabetes mellitus cost the country USD 18,293 million in 2019 [23]. Furthermore, when the number of complications from diabetes mellitus grew from one to three or more, the per capita cost rose by almost four times, from USD 3991 to USD

11,965 [23]. Cardiovascular disease, cerebrovascular disease, peripheral vascular disease, and all-cause mortality are among the comorbidities that patients with type 2 diabetes are more likely to have. In order to lessen this disease burden, preventive measures for type 2 diabetes have been highlighted [9]. The two primary features of type 2 diabetes are insulin resistance in the target tissue and a related insufficient synthesis of insulin by pancreatic β-cells [13].

Review of Literature

The study was conducted by Paul and Gnanamoorthy, (2023), the literature involved 251 individuals with a history of type 2 diabetes. The study excluded patients having a history of contractures from any source, rheumatoid arthritis and scleroderma diagnoses, and other risk factors such heart or kidney illness. Every participant underwent a comprehensive clinical history that included a past medical history, a physical examination, a prayer test, a tabletop sign, and passive finger extension. Following a diagnosis of diabetic cheiroarthropathy, patients were evaluated for the existence of microvascular problems using clinical examination, fundus examination, monofilament test, and microalbuminuria screening.

Another study was estimated that the prevalence of OA was 52% in people with T2DM and 27% in people without T2DM (Centers for Disease Control and Prevention, 2008). A significant frequency of T2DM in OA populations and vice versa has been documented in numerous research [14, 22, 25]. Kim et al. (2016), found that the prevalence of knee OA was 42.4% in individuals with type 2 diabetes mellitus (T2DM) and 35.4% in those without T2DM in large population research (n=9541) (Nieves-Plaza et al., 2013). According to a different small study (n = 202), the prevalence of OA was 49% among T2DM patients and 26.5% among non-T2DM patients [25]. However, according to a larger population-based study (n = 7714), the prevalence of hyperglycemia was 13% in those without OA and 30% in those with OA [25].

Kwon et al, (2023), used information from a sizable, prospective, community-based cohort study to assess the relationship between OBS and the incidence of type 2 diabetes. Data from 7369 Korean Genome and Epidemiology Study (KoGES) participants between the ages of 40 and 69 were examined. For T2DM incidence of sex-specific OBS tertile groupings, univariable and multivariable Cox proportional hazard regression models were used to determine the hazard ratio (HR) and 95% CI. During the average follow-up period of 13.6 years, T2DM was diagnosed in 880 women and 908 men. In comparison to the reference lowest tertile group, the middle and highest tertile groups' fully-adjusted HR (95% CI) for incident T2DM were 0.86 (0.77–1.02) and 0.83 (0.70–0.99) for males and 0.94 (0.80–1.11) and 0.78 (0.65–0.94) for women. People who have a high OBS are less likely to develop type 2 diabetes. This suggests that changing one's lifestyle to include more antioxidant-rich foods could help avoid type 2 diabetes.

There is increasing evidence that links OA to T2DM. In order to better understand this relationship, it is crucial to study and assess relevant literature and compile the results. Therefore, our review's objective was to assess and examine the literature regarding the prevalence, association, symptoms, physical function, and common risk factors of T2DM and OA.

Methods

A web search using PubMed, Scopus, Web of Science, and Google Scholar was used to find all of the reviewed publications. "Osteoarthritis" and "diabetes" were among the keywords. Only full-length human studies papers published in English were used in this review article.

Association between Osteoarthritis and T2DM: OA and T2DM have been linked to potential processes, according to earlier findings (King and Rosenthal, 2015; Veronese, 2019). Low-grade inflammation, both systemic and local, is linked to the possible pathogenesis of OA (Courties and Sellam, 2016). The articular cartilage of the joints is made up of extracellular matrix, which contains chondrocytes. The formation of extracellular matrix is carried out by these cells [5, 6, 7]. The primary role of cartilage is to absorb shock and tension between two bone surfaces. These processes are aberrant in OA, and chondrocytes produce pro-inflammatory mediators like prostaglandins, cytokines, tumour necrosis factors, reactive oxygen species, and advanced glycation end products (AGE).

Proteolytic enzymes known as matrix metalloproteinases (MMPs) and aggrecanases are elevated in response to all of these inflammatory stimuli. The cartilage matrix is destroyed as a result of these enzymes. There are two possible ways that T2DM in OA state could contribute to joint injury. The first mechanism is through persistent hyperglycemia, which raises oxidative stress and causes joints to produce more pro-inflammatory cytokines and AGEs. The second route involves insulin resistance, which may cause low-grade inflammation that has detrimental effects both locally and systemically. Leptin secretion from adipose tissue may cause chondrocyte injury and death by increasing the production of cytokines and MMPs [5,6,7].

The relationship between OA and T2DM has been the subject of numerous investigations. A substantial correlation was discovered by two meta-analyses [20, 30]. In one, Louati et al., (2015) did a major meta-analysis of 49 studies (including cross-sectional, case-control, and cohort studies) and found that the prevalence of OA was 29.5% among 5788 patients with DM and 14.4% among 645,089 patients with OA. This meta-analysis also showed that, in comparison to the non-DM group, the risk of OA was significantly linked with DM, as evidenced by an odds ratio (OR) with a 95% confidence interval (95% CI) of 1.46, 95% CI [1.08 to 1.96]. Our most recent research looked at the relationship between T2DM and pain in T2DM patients after adjusting for potential confounders including medication. After adjusting for pain and metabolic syndrome drugs, this investigation found a significant correlation between T2DM and pain in OA patients (n = 819) [66]. After controlling for covariates such as age, sex, OA locations, BMI, depression, hypertension, dyslipidaemia, and medication use (pain medications such as opioids, non-opioids, and benzodiazepines; anti-diabetic; antihypertensive; antilipemic; and anti-depressants) within 90 days of the index date, this study found that DM was significantly associated with increased pain severity in individuals with OA.

This study included limitations, such as a retrospective design and the use of diagnostic codes, which could have affected the findings because misclassification bias is frequent in clinical settings. It is advised to use a second confirmation code to increase accuracy. Furthermore, OA was found to be substantially related with a higher risk of DM than the non-OA population (OR = 1.41, 95% CI [1.21 to 1.65]). The primary outcome of several of the studies in this review paper was joint replacement, and there was no control for other risk factors such age, sex, obesity, and different definitions of OA and DM. With fewer included trials (n = 10), the other meta-analysis by Williams et al, (2016) produced findings that were comparable. Studies that looked at the relationship between OA and DM in a smaller group (n = 16,742 patients) even after adjusting for BMI were included in this meta-analysis. The existence or progression of OA with DM as an independent factor was the primary result.

A strong correlation between OA and the existence of DM was discovered in this meta-analysis by Williams (OR = 1.21, 95% CI [1.02 to 1.41]), and this correlation persisted even after adjusting for BMI. It was limited, nevertheless, as several included studies' primary outcomes were joint replacement and self-reported diabetes mellitus. OA is a complicated illness that affects the synovium, subchondral bone, and articular cartilage in every joint. Low-grade inflammation is linked to OA both locally and systemically. Its development is controlled by the chondrocytes that comprise the extracellular matrix of articular cartilage. In OA, chondrocytes produce more pro-inflammatory mediators, such as prostaglandins, AGEs, radical oxygen species, tumour necrosis factor alpha (TNF-α), and cytokines like interleukin-1β [IL-1β], after cartilage absorbs mechanical stresses between two moving bone surfaces. Matrix metalloproteinases [MMPs] and aggrecanases, two proteolytic enzymes that break down the cartilage matrix, are produced in greater quantities as a result of the local inflammation.

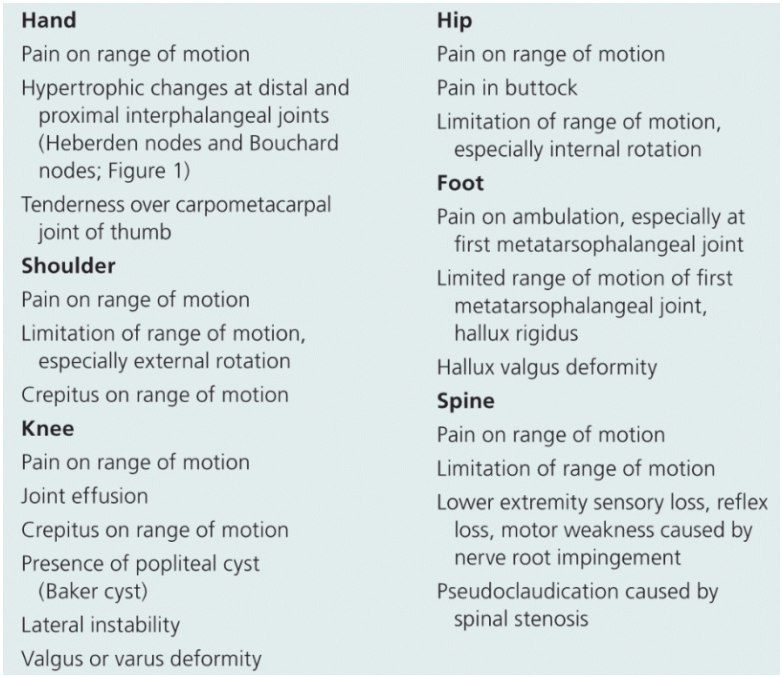

Figure 1: Signs and Symptoms of Osteoarthritis [27]

Physiology and Risk Factors of T2DM: A complex interaction of metabolic, genetic, and environmental factors is one of the reasons that contribute to the occurrence of type 2 diabetes. Even though the genetic basis of an individual's predisposition to type 2 diabetes is strong due to non-modifiable risk factors (ethnicity and family history/genetic predisposition), epidemiological studies show that many cases of the disease can be prevented by improving the main modifiable risk factors (obesity, low physical activity, and an unhealthy diet) (Guariguata et al., 2014; American Diabetes Association, 2013).

T2DM Outcomes / Complications Cardiovascular Risk: As described in the previous sections, T2DM is a multisystem disease with a strong correlation with CVD development (Gast et al., 2012). T2DM leads to a two- to four-fold increase in the mortality rate of adults from heart disease and stroke and is associated with both micro- and macro-vascular complications, the latter consisting of accelerated atherosclerosis leading to severe peripheral vascular disease, premature coronary artery disease (CAD) and increased risk of cerebrovascular diseases (Haffner, et al., 1998; Beckman et al., 2002; Nesto, 2004) 20. These factors lead to T2DM being considered a significant risk factor for CVD (NCEP, 2002), likely through the involvement of several molecular mechanisms and pathological pathways. These include the role of IR in atherosclerosis, vascular function, oxidative stress, hypertension, macrophage accumulation and inflammation (Davidson and Parkin, 2009; Bornfeldt et al., 2011; Reaven et al., 20012; Laakso and Kuusisto, 2014). These include IR's involvement in inflammation, oxidative stress, atherosclerosis, vascular function, macrophage accumulation, and hypertension (Davidson and Parkin, 2009; Bornfeldt et al., 2011; Reaven et al., 20012; Laakso and Kuusisto, 2014).

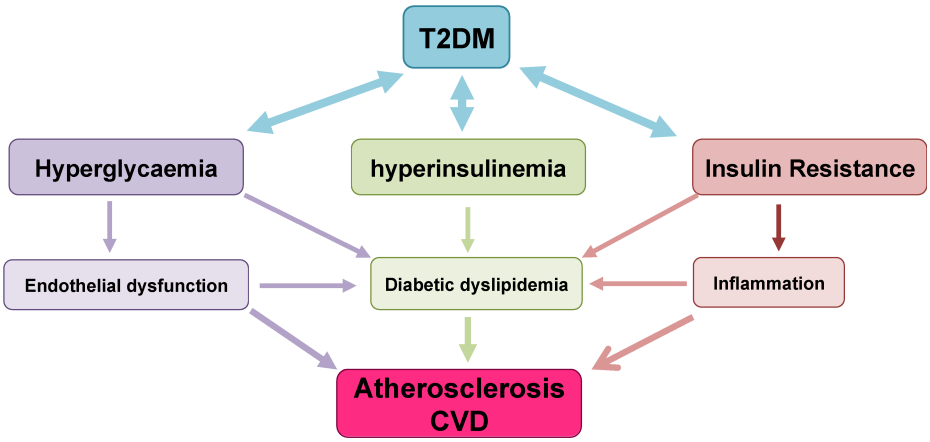

Figure 2: Factors implicated in cardiovascular risk outcomes from T2DM and the interactions between them [13]

The pathophysiology of OA and its connection to diabetes: All joint tissues—articular cartilage, subchondral bone, and synovium—are impacted by the complicated illness known as osteoarthritis (OA). Low-grade inflammation is linked to both local and systemic OA [5]. The extracellular matrix that makes up articular cartilage is made up of chondrocytes, which are in charge of its formation. TNF-a, cytokines (interleukin-1b [IL-1b]), radical oxygen species, AGEs, prostaglandins, and other pro-inflammatory mediators are among the pro-inflammatory mediators that are produced by chondrocytes in OA in response to mechanical stresses between two mobile bone surfaces. Matrix metalloproteinases [MMPs] and aggrecanases, two proteolytic enzymes that break down the cartilage matrix, are produced in greater quantities as a result of this local inflammation. Chronic hyperglycemia, which causes oxidative stress, an excess of pro-inflammatory cytokines, and AGEs in joint tissues, and insulin resistance, which may contribute locally as well as through the systemic low-grade inflammatory state, are the two main ways that type 2 diabetes has a pathogenic effect on OA.[5]

A prominent adipokine released mostly by adipose tissue, leptin can stimulate chondrocyte synthesis of MMP and cytokines while simultaneously encouraging death [6]. Elevated free fatty acids (FFAs) are also linked to obesity and insulin resistance, which may influence the course of OA [29].

Conclusion

The reviewed literature indicates that OA and T2DM coexist and are linked to occurrence and evolution, which strengthens the clinical evidence supporting the association. However, after

adjusting for risk factors like age, sex, and BMI, some research has indicated a negligible correlation.

Although there is little data to draw firm conclusions, we discovered that DM may exacerbate knee OA discomfort. Therefore, more research is required to determine whether DM makes OA pain worse.

Furthermore, we found that common risk variables, such as metabolic syndromes and demography, may influence the relationship between DM and OA; however, more study is needed on this topic as well. Extensive future study is required to properly determine the effect of chronic medication usage, as there is conflicting information regarding whether medication use contributes positively or negatively to the connection between DM and OA.

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