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Relationship between Type 2 Diabetes Mellitus and Osteoarthritis

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Abstract— *Type 2 diabetes mellitus (T2DM), Overweight (obesity), and osteoarthritis (OA) are chronic disorders that commonly coexist. While the mechanical effects of increased body weight on joints may explain lower limb OA; in this review we wanted to see the relation between T2DM and OA and how T2DM plays a role in OA pathogenesis. The impact of T2DM on the progression of OA is a topic of investigation. T2DM causes OA through two key pathways: oxidative stress and low-grade chronic inflammation, both of which are caused by persistent hyperglycemia and insulin resistance. T2DM is a risk factor for the advancement of OA and has a detrimental influence on the results of arthroplasty. Some of the most commonly prescribed anti-OA medications, such as paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroid injections have been linked to safety concerns, while other anti-OA medications, such as glucosamine and intra-articular hyaluronic acid, may be safe in OA patients with T2DM. In this review we conducted a thorough assessment to see the relationship between T2DM and OA.*

Keywords—*Type 2 Diabetes Mellitus, Osteoarthritis (OA), Bone Remodeling, Fracture Healing, Bone Marrow Dysfunction.*

I. INTRODUCTION

Type 2 diabetes mellitus (T2DM) and osteoarthritis (OA) are two frequent illnesses whose incidence is expected to rise [1, 2]. Because of their high incidence and common risk factors, OA and T2DM usually coexist. The link between OA and obesity is well-established [3], and obesity is common in patients with T2DM [4, 5]. Aging has long been recognized as a risk factor for T2DM and OA. T2DM is expected to affect 4.6 million persons in the United States aged between 18 – 44 years, 14.3 million people aged between 45–64 years, and 12.0 million people aged ≥ 65 years [6]. Similarly, radiographically characterised knee OA affects 14 percent of those over 25 years and 37 percent of those over 60 years [7].

T2DM is a common, complicated illness with a hereditary component and environmental risk factors, including bad lifestyle behaviors that contribute to overweight and obesity. The disease's prevalence rises sharply with age, with T2DM afflicting more than 10 % of the population over the age of 65 years. The condition is caused by a deficiency in insulin production by pancreatic beta-cells, as well as cellular insulin resistance, which is seen mostly in skeletal muscles and the liver, but sometimes in other tissues [8, 9]. Prolonged hyperglycemia, both fasting and postprandial, causes AGEs, oxidative stress, and low-grade inflammation, as well as damage to the arteries, mostly in the heart, kidneys, eyes, and nerves, but also in other tissues [10].

Nearly half of T2DM patients (47.3 %) had some kind of arthritis [11]. OA is a condition that affects the joints of the hand, hip, and knee. Aside from the numerous localizations, OA has been classified into phenotypes such as age-related, metabolic syndrome (MetS)-related (closely associated to abdominal obesity), genetic-related, and post-traumatic OA [12, 13]. The mechanical impact of overweight/obesity on joints may readily explain lower limb OA in MetS-associated OA [14]. Other MetS components, such as dysglycemia (which is similar to prediabetes), elevated blood pressure, and atherogenic dyslipidemia, may all have a role in OA pathogenesis, either together or separately [15–17]. It is important to note that, according to the unified criteria, more than three-quarters of T2DM patients have MetS [18]. Hypertension, dyslipidemia, and the number of MetS factors present have been found to be substantially linked with the severity of symptomatic knee OA; however, no connection between the severity of radiographic knee OA and MetS factors has been reported in the same research [19].

We want to examine if T2DM is associated to OA outside of weight gain and if T2DM has a role in OA pathogenesis in this review. The impact of T2DM on the progression of OA is also a topic of investigation. There are a variety of pharmacologic therapy options available that can help control the symptoms of OA. However, evidence is emerging that some of the most often given anti-OA medicines, including as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), are dangerous [20–23]. In addition, we looked at the

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data to see if the presence of T2DM raises any extra safety concerns for the treatment of OA.

II. Incidence and progression of OA in people with T2DM

Although a causal relationship between T2DM and OA has been shown, a link between the two has yet to be established. Louati et al. discovered a substantial link between OA and T2DM in a meta-analysis of 49 studies with over 1 million individuals (N = 1,192,518) [14]. The odds ratio (OR) of T2DM in the OA population vs. non-OA population was 1.41 (95 percent CI 1.21, 1.65), and T2DM was found to be 14 percent of patients with OA. The total prevalence of OA in T2DM patients compared to non-T2DM patients (OR) was 1.46 (95 percent CI 1.08, 1.96). The prevalence of OA among patients with T2DM was 30% in this cohort (mean age 61 years) (38 percent hand OA, 12 percent hip OA, and 17 percent knee OA) [14]. The prevalence of OA in patients with T2DM was likewise high in another meta-analysis that included only trials adjusting for weight or body mass index (BMI), with an OR of 1.25 vs. non-T2DM population (95 percent CI 1.05, 1.46) [24].

The evidence for a link between T2DM and the location of OA is mixed; several studies including a meta-analysis [3, 14] identified a link between T2DM and hand OA. In patients with T2DM aged 55-62 years had a two-fold greater risk of hand OA than non-diabetics, which was linked to pain in erosive hand OA [25, 26]. Although the number of OA and/or diabetes patients may have been overestimated due to diagnostic ambiguities, a recent case-control research employing a UK population-based database of adults aged 30-90 years revealed no significant connection between T2DM and hand OA [27]. Further research on the link between diabetes and erosive hand OA is needed.

T2DM has been reported to be a risk factor for disease progression in males with established knee OA, based on yearly measurement of joint space narrowing (JSN), but no correlations between MetS or other metabolic variables and radiographic advancement have been found [28]. T2DM is a risk factor for arthroplasty that is independent of other factors. T2DM doubles the risk of severe OA requiring arthroplasty after adjusting for age, BMI, and other possible variables (HR = 2.1; 95 percent CI 1.1,3.8; p=0.023). T2DM has been linked to more severe OA symptoms and structural abnormalities in joints [29].

In contrast, no link was established between DM (almost 20 times more T2DM than type 1 diabetes in this cohort) and total joint replacement (TJR) of the hip or knee among OA patients with or without DM in a population-based case-control research (N = 94,609) [24]. T2DM may have a detrimental influence on arthroplasty results, including a higher risk of post-surgical mortality, worse functional outcomes, a higher rate of infection, and a higher requirement for revision arthroplasty [10]. Some arthroplasty results may be related to metabolic effects on joint tissues, such as poor bone repair, while others may represent general T2DM concerns associated with major surgical operations, all of which can add a significant amount of money to clinical treatment [10].

III. Importance of anti-diabetic medications

An analysis of longitudinal data from the Osteoarthritis Initiative study found that medication-treated diabetes has no effect on knee OA incidence (OR = 0.53; 95 percent CI 0.23, 1.5), but does reduce knee OA progression, as measured by JSN or knee replacement therapy (OR = 0.66; 95 percent CI 0.44–0.98) [30].

Metformin is the first anti-diabetic medicine that is indicated for the treatment of T2DM. There was no connection between prescription metformin medication at baseline and OA result throughout follow-up in a UK cohort trial established within the Consultations in Primary Care Archive of 3,217 individuals with T2DM (adjusted HR = 1.02; 95 percent CI: 0.91, 1.15) [31]. Patients with OA and T2DM who received combination NSAIDs and metformin medication had lower joint replacement surgery rates than those who did not (adjusted HR = 0.742; 95 percent CI 0.601, 0.915; p = 0.005) in a case-control study conducted in Taiwan [32]. It has been claimed that this impact is due to a decrease in pro-inflammatory factors linked with metformin combination treatment. Metformin, as well as other thiazolidinediones, are anti-diabetic drugs that have been found to have anti-inflammatory properties [33]. Despite encouraging results from animal in vivo research, a major population-based case-control study in the UK utilising the Clinical Practice Research Data-link found no evidence for thiazolidinediones having a disease-modifying osteoarthritic impact [34]. Finally, no clinical evidence on novel antidiabetic medicines such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists or sodium-glucose cotransporter type 2 (SGLT2) inhibitors is available yet.

IV. Pathophysiology of OA and its association with diabetes mellitus

OA is a complicated illness that affects the articular cartilage, subchondral bone, and synovium in all joints. Low-grade inflammation is linked to OA both locally and systemically [35]. The extracellular matrix of articular cartilage contains chondrocytes, which are responsible for the extracellular matrix's formation. One of cartilage's functions is to absorb mechanical stresses between two mobile bone surfaces; in OA, this stress is followed by an increase in chondrocyte production of pro-inflammatory mediators such as cytokines (interleukin-1β [IL-1β]), tumour necrosis factor alpha (TNF-α), radical oxygen species, AGEs, and prostaglandins. The synthesis of proteolytic enzymes (matrix metalloproteinases [MMPs] and aggrecanases) that breakdown the cartilage matrix increases as a result of the local inflammation.

T2DM causes OA in two ways:

1) Chronic hyperglycemia, which causes oxidative stress, overproduction of pro-inflammatory cytokines, and AGEs in joint tissues; and

2) Insulin resistance, which may play a role locally but also indirectly through the systemic low-grade inflammatory state [35].

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Leptin, a prominent adipokine produced mostly by adipose tissue, has been shown to accelerate chondrocyte death as well as enhance chondrocyte cytokine and MMP production [36]. Elevated free fatty acids (FFAs) are also related with insulin resistance and obesity, which may affect OA development [37].

- *Role of insulin*

The function of insulin in OA is still debated, especially because high insulin levels are linked to insulin resistance in T2DM, making it difficult to discern between insulin's effects and those linked to insulin resistance [38, 39]. Human chondrocytes have functioning insulin receptors that respond to normal insulin levels. Normal chondrocytes have more insulin receptors than OA chondrocytes, and certain responses are reduced while others are completely active [40]. Excess insulin, as observed in T2DM patients, has been linked to cartilage degeneration.

Insulin inhibits autophagy by decreasing LC3 II expression and boosting Akt and rpS6 phosphorylation in immortalised human chondrocytes and primary human chondrocyte cultures. In T2DM and OA, autophagy is a critical homeostatic process in articular cartilage that is disrupted. After insulin therapy, there was a loss of proteoglycans and an increase in MMP-13 and IL-1β expression. Furthermore, as compared to healthy persons and non-diabetic OA patients, chondrocytes from diabetes patients with OA had lower LC3 and higher p-rpS6 expression [41].

Insulin resistance and T2DM are frequently caused by visceral obesity, which is a major source of pro-inflammatory cytokines, resulting in low-grade chronic metabolic inflammation and joint structural damage [42]. Insulin resistance can affect joint tissue not only because of local insulin resistance in diabetic synovial membranes [43], but also because of systemic low-grade inflammation [35]. In obese OA patients with T2DM, the synovium has been reported to develop insulin resistance [44]. Insulin is a key negative regulator of synovial inflammation and catabolism, and insulin resistance in obese people reduces insulin's capacity to inhibit the generation of inflammatory and catabolic mediators that contribute to OA [43]. Although the systemic function of MetS in OA pathogenesis is now widely established, new research pathways are being followed to further understand the insulin resistance or MetS-associated OA phenotype [45].

- *Diabetes mellitus and its impact on cartilage*

Cartilage is a non-vascularized, non-innervated tissue that obtains nutrition through the joint cavity through its link with subchondral bone and synovial fluid. Chondrocytes are glycolytic cells that express glucose transporters (GLUT) (particularly GLUT-1, GLUT-3, and GLUT-9) and can sense glucose levels in the medium and adjust GLUT expression in normal settings [46]. OA causes chondrocytes to lose their ability to adjust to local glucose levels, resulting in increased glucose absorption and possible glucose toxicity [47]. Locally high glucose concentration reduces chondrogenic differentiation of mesenchymal, muscular, and adipose-derived stem cells, potentially reducing cartilage repair that is already compromised in OA [35].

Severely high glucose levels have a negative impact on chondrocyte metabolism. Human OA chondrocytes respond to high glucose levels by becoming more inflammatory and degradative. Under high glucose concentrations, AGEs are known to accumulate in cells and tissues, and they also build with age in OA cartilage, altering its mechanical qualities such as stiffness and resistance. The presence of AGEs has been linked to cartilage degeneration [48], albeit this link has not been shown universally [49]. RAGE (receptor of AGE) and toll-like receptors can also cause a pro-inflammatory and pro-catabolic phenotype in chondrocytes. Peroxisome proliferator-activated receptor gamma (PPAR-γ), which promotes oxidative stress (mitochondrial reactive oxygen species and nitric oxide) and cytokine production by chondrocytes, is inhibited by activation of these receptors [50]. In chondrocytes, a high glucose rate enhances MMP expression and oxidative stress, as well as the influence of IL-1β on cytokine release.

- *Diabetes mellitus and its impact on synovium*

The synovium's reaction to hyperglycemia is less well known. Oxidative stress promotes pro-angiogenic factor production in synovial fibroblasts when glucose levels are high [51]. Pro-inflammatory cells are known to be induced by synovial angiogenesis on a local level. In vivo models of diabetes cause higher synovial inflammation [52], which is consistent with clinical observations of more synovitis in diabetic individuals with knee OA than non-diabetic people [29]. When compared to the synovium of OA patients without diabetes, the synovium of T2DM patients had significantly more macrophages and had much higher TNF-α levels. In addition, insulin-dependent phosphorylation of insulin receptors and the serine/threonine kinase Akt (a key player in the intracellular cascade of insulin action) was inhibited in cultures of OA fibroblast-like synoviocytes from T2DM patients, indicating that insulin resistance exists in the synovium of T2DM patients with OA [44].

- *Diabetes mellitus and its impact on subchondral bone*

Diabetes has been linked to a reduction in bone remodelling, and high fasting glucose levels have been linked to bone marrow lesions in the knee joint, which have been linked to OA structural damage [53]. Lower bone mineral density and increased porosity, regardless of weight, indicate subchondral bone loss in diabetic advanced knee OA [54]. Diabetic patients' subchondral bone accumulates more AGE than non-diabetic patients' subchondral bone, which may affect the mechanical resistance of subchondral bone and have pro-inflammatory effects [55].

- *Role of Diabetes mellitus in microvascular changes*

Diabetes is well known for causing microvascular changes that increase the risk of osteoarticular conditions such as inflammatory periarthritis of the shoulder [56], Dupuytren's contracture [57], shoulder hand syndrome of the upper extremities and Charcot joints [58], which frequently affect the lower extremities (e.g. ankle, disappearing bones of the foot) [58].

A similar mechanism (the existence of microvascular alterations) appears to be involved in the link between diabetes and OA. Multiple artery inlets and venous exits can be seen in subchondral bone. The nutritive artery, periosteal arteries, metaphyseal arteries, and epiphyseal arteries are all present in the case of long bones (such as the hip) [59]. Long bones' subchondral regions, in particular, are extensively vascularized, implying significant nutritional needs [60]. Diabetes can cause relevant microvascular alterations; therefore it's possible that diabetes can raise the risk of OA via this pathway as well.

III. Role of Physical Exercise in the Prevention and Management of T2DM

Physical exercise and body weight management are becoming more widely acknowledged as significant techniques for the prevention and treatment of noncommunicable illnesses [61]. While physical exercise is acknowledged as a key component of OA therapy [62], the presence of lower limb OA (hip or knee) might limit the ability to engage in physical activity. For those with T2DM, both adequate diet and physical activity can be part of a healthy lifestyle and may help prevent T2DM. Lifestyle management, which encompasses diabetes self-management, education and support, medical nutrition, and physical exercise, is recognized by the American Diabetes Association (ADA) as a critical component of diabetes treatment [63]. Most adults with T2DM should engage in 150 minutes or more of moderate-to-vigorous intensity aerobic activity per week, along with 2-3 sessions of resistance exercise per week, and flexibility and balance training 2-3 times per week for older adults with T2DM, according to the American Diabetes Association.

Concerns about the absence of physical activity in the general population have prompted a call to action in the United States [64] to make physical activity evaluation and prescription a medical standard of treatment in everyday practice. While there is no strong evidence that diet or physical activity alone can reduce or delay the onset of T2DM in people with impaired glucose tolerance ('pre-diabetic' people) [65, 66].

Physical activity-based intervention programmers have been shown to reduce the probability of acquiring T2DM in high-risk adults by half [67–69], and the decrease in incidence can last for up to ten years after the first intervention [70]. Weight reduction, higher insulin sensitivity, enhanced endothelium function, and improved autonomic nervous system function are all biologically plausible processes by which physical exercise may be connected to a decreased risk of T2DM [71]. Exercise improves systemic glucose homeostasis and does not reduce insulin secretion in people with T2DM [72]. Physical activity and exercise have been shown to improve blood pressure, lipid profiles, and body composition, all of which are important variables in diabetes and cardiovascular disease [73]. Long-term follow-up of a lifestyle intervention in patients with impaired glucose intolerance revealed a substantial decrease in both cardiovascular and all-cause mortality [74].

IV. Safety and Efficacy of Anti-Osteoarthritis Medicines in Diabetic Patients

- *Paracetamol*

Despite the fact that paracetamol has no effect on pain, physical function, or stiffness, it is commonly utilised as a first-line rescue analgesic in OA [62, 75, 76]. Furthermore, growing evidence of paracetamol-related gastrointestinal, cardiovascular, hepatic, and renal side effects raises concerns about its long-term usage, particularly at the higher end of typical analgesic dosages [20].

With widespread, unrestricted paracetamol usage, reports of non-overdose paracetamol-associated acute liver failure requiring transplantation and staggered paracetamol overdoses resulting in paracetamol-induced hepatotoxicity are a reason of concern [77, 78]. Abnormal liver function tests are roughly four times more probable in those who use paracetamol [79]. In roughly 50-70 percent of people with T2DM, non-alcoholic fatty liver disease (NAFLD) and the more severe variant, steatohepatitis (NASH), occur commonly [80, 81]. They impact those who have high levels of aminotransferases as well as those who have normal amounts [82]. Obesity and T2DM are frequently linked to NAFLD, and both can enhance the risk and severity of hepatotoxicity from a variety of medicines, including paracetamol [83, 84]. Although there is minimal evidence [85], potentiation of injury cannot be ruled out since paracetamol hepatotoxicity and liver abnormalities in NAFLD/NASH-associated liver alterations share certain similar pathways.

Furthermore, evidence show that paracetamol toxicity is exacerbated in diabetic animal models [87], whereas metformin may protect against paracetamol hepatotoxicity [88, 89]. In the absence of more clinical evidence, high-dose paracetamol should be used with care in patients with T2DM and advanced NAFLD/NASH who have OA-related pain.

While it is currently thought that paracetamol can be given to patients with liver disease, studies to better understand changes in paracetamol metabolism, efficacy, and toxicity will be invaluable [90]. As the prevalence of lifestyle-related liver diseases like NAFLD rises, studies to better understand changes in paracetamol metabolism, efficacy, and toxicity will be invaluable. According to a short research, patients with T2DM had a harder time eliminating paracetamol than healthy controls [91].

- *Non-steroidal anti-inflammatory drugs (NSAIDs)*

1. *NSAIDs and renal risk* - Acute kidney injury (AKI), chronic renal disease, and cardiovascular disease have all been associated to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) [21]. T2DM causes renal failure, and T2DM and hypertension are the leading causes of end-stage renal disease, accounting for more than half of all cases [92]. In high-risk groups, NSAID usage is linked to an increased risk of hospitalization; for example, for every 10,000 patients treated with NSAIDs for 30 days, there were 20 more hospitalizations in the diabetic population compared to those who were not treated with NSAIDs [93, 94].

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When compared to non-NSAID users in the general population, NSAID users had a 3-fold higher chance of acquiring AKI for the first time [95]. NSAID users are more likely to have hypertension (83 percent), arthritis (71 percent), heart failure (44 percent), CKD (36 percent), and diabetes (35 percent) [21]. Although antihypertensive medications provide cardiovascular advantages, caution should be used when they are combined with NSAIDs. Furthermore, AKI induced by NSAIDs and angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), or diuretics is a commonly documented adverse medication event, with roughly one-quarter of cases resulting in significant AKI [96]. The use of some cardiovascular medicines has been linked to a five-fold increase in the risk of AKI. Diuretics pose the highest risk, and the risk increases when NSAIDs and diuretics are used together, as well as NSAIDs and calcium channel blockers [95]. Users of loop diuretics or aldosterone antagonists, those who are over 75 years old, and those with renal impairment have the highest risk of AKI [97, 98].

NSAID consumption is frequent among AKI survivors, with around 68 percent of survivors using NSAIDs both before and after the AKI incident. NSAID usage is substantially related with a history of arthritis and paracetamol use, but not with prevalent CKD or diabetes [21].

Anti-diabetic drugs are commonly used with diuretics and renin-angiotensin system blockers (ACEI, ARB) [99]. Dapagliflozin, canagliflozin, empagliflozin, and ipragliflozin are SGLT2 inhibitors that promote glucosuria, osmotic diuresis, and natriuresis in people with T2DM [100]. Even though certain severe side effects have been documented, SGLT2 inhibitors are typically well tolerated [101]. Because of an increased risk of orthostatic hypotension and dehydration, which can lead to renal impairment, caution is especially advised in the elderly population, especially those who are using loop diuretics. Despite the positive renal safety results published in clinical cardiovascular outcome studies, sporadic data showed that AKI might be a danger [102]. As previously discussed, a severe reduction in kidney function can occur at any time, and is frequently linked to an acute illness or certain co-administered drugs, such as NSAIDs [102]. As a result, the safety of SGLT2 inhibitors in conjunction with NSAIDs needs additional research. NSAIDs should be avoided in individuals using SGLT2 inhibitors, according to current recommendations [22].

2. *NSAIDs and cardiovascular risk* - Cardiovascular disease is a significant burden among T2DM patients; approximately one-third to half of all individuals with T2DM has coronary heart disease, which is the major cause of early mortality in T2DM patients. T2DM is an independent risk factor for all forms of coronary heart disease, notably heart failure, angina pectoris, re-infarction disability, and sudden cardiac death, with rates at least double those of non-diabetic individuals [103].

   There is a risk of gastrointestinal and cardiovascular (CV) damage with all non-selective NSAIDs and COX-2 inhibitors [23, 104, 105]. As a result, drug selection within the available NSAIDs class has been influenced by the safety profile, which takes into account various risk factors as well as the patient's coexisting illnesses and medical conditions [62]. While it was previously thought that the NSAID's selectivity for the COX-2 enzyme governed the CV toxicity profile, recent findings suggest that CV risk may be drug specific; rofecoxib is the only NSAID associated with an increased risk of CV events compared to all other NSAIDs [106], though etoricoxib may have a greater risk than celecoxib, and celecoxib poses a similar risk to naproxen and a lower risk of major CV [107, 108]. Treatment with rofecoxib, but not celecoxib or naproxen, caused a substantial rise in 24-hour systolic blood pressure in individuals with T2DM, hypertension, and OA at similarly effective dosages for OA therapy [109].

   The cardiovascular risk of diclofenac beginning was compared with the other standard NSAIDs, paracetamol in a recent study employing Danish population-based health registries. Within 30 days of start, the incidence of significant adverse cardiovascular events among diclofenac users rose by 50% compared to non-initiators, 20% compared to paracetamol or ibuprofen initiators, and 30% compared to naproxen initiators. Although persons with a low or moderate baseline risk (i.e., diabetes mellitus) had the highest relative risk of major adverse cardiovascular events, those with a high baseline risk (i.e., prior myocardial infarction or heart failure) had the highest absolute risk [110]. In a study of diabetic patients treated in primary care in Saudi Arabia, inappropriate NSAID administration was identified in 66% of patients with a high cardiovascular risk, contradicting current clinical guidelines and regulatory agency advice [111].

3. *Topical NSAIDs* - Topical NSAIDs are effective for OA of the hands and knees, with significantly less systemic distribution than oral NSAIDs [112, 113]. Long-term topical diclofenac sodium 1 percent treatment is safe in the subpopulation of patients with an elevated risk of NSAID-related adverse events, such as the elderly and those with comorbidities of T2DM, hypertension, and cardiovascular disease, according to observational studies and post-hoc analysis of pooled data from placebo-controlled trials [114, 115].
4. *SYSADOAs* - Gradual Acting Symptomatic Drugs in Osteoarthritis (SYSADOAs) are a group of drugs that have been shown in long-term studies to have a moderate symptomatic impact with a slow start of action and, in some cases, a joint structure-modifying effect [116–121]. They primarily consist of glucosamine (both prescription crystalline glucosamine sulphate [pCGS] and over-the-counter glucosamine sulphate or hydrochloride), chondroitin sulphate, diacerein, and avocado soybean unsaponifiables, all of which have varying levels of effectiveness [122–125]. Clinical studies and systematic reviews show that the SYSADOAs glucosamine and chondroitin sulphate have a very high safety profile [126–129], with some adverse effects with diacerein and avocado soybean unsaponifiables [130, 131]. Clinical investigations

and meta-analyses have found no evidence of chondroitin sulphate, diacerein, or avocado soybean unsaponifiables causing T2DM or interfering with glucose metabolism. However, based on exact molecular ideas, worries have been raised throughout time about glucosamine's putative interaction with glucose metabolism.

Insulin resistance is defined by lower rates of insulin-mediated glucose absorption, such as into skeletal muscle or adipocytes, which is a primary contributor to the pathophysiology of T2DM. Insulin resistance is generated or worsened by hyperglycemia, and in vitro studies demonstrate that glucose-induced insulin resistance is associated with a decrease in the recruitment of intracellular glucose transporters to the cell surface. Glucosamine is a byproduct of glucose metabolism that has been demonstrated to substitute for glucose and promote glucose transport desensitization in vitro [132]. In fact, in vitro studies have shown that high glucosamine levels can boost the activity of the hexosamine pathway, a metabolic mechanism that acts as a nutrient sensor and regulates insulin sensitivity and glucose absorption [133]. In vitro (in rats), the effects of glucosamine on insulin resistance via the hexosamine pathway have been seen, mostly at extremely high doses [134]. This route for supposed glucosamine toxicity received a lot of attention since it was mistakenly assumed that it was also the mechanism of action for the therapeutic benefit in OA (stimulation of proteoglycans synthesis).

However, repeated studies of parenteral glucosamine administration to humans at similar high concentrations failed to produce similar results, indicating species differences in sensitivity or possible mechanistic differences, such as the hexosamine pathway's less operational relevance in the regulation of insulin sensitivity in humans [135, 136]. In normoglycemic participants and most subjects with hyperglycemia, insulin sensitivity impairment, pre-diabetes, or diabetes, clinical studies at oral recommended dosages for OA therapy demonstrated no impact with glucose metabolism [137, 138]. Additional analyses of the GUIDE research indicated that 6 months of pCGS (1500 mg/day) has no effect on plasma glucose levels in the general population or hyperglycemic patients [139, 140]. Systematic evaluations of the effects of glucosamine on glucose metabolism in humans reveal that normal, diabetic, and pre-diabetic individuals tolerate glucosamine at standard oral dosages in humans or OA patients in clinical trials well [141, 142]. However, in several of the latter subjects, a small number of clinical trials have found non-significant interference tendencies. In the PROOF study, overweight women who received pCGS therapy for 2.5 years and up to 6.5 years had a non-significant rise in glycated haemoglobin levels [143, 144]. As a result, based on the summary of Product Characteristics for pCGS, it is fair to urge care when starting glucosamine medication in diabetic patients, with no particular advice for other patients [145].

5. *IA corticosteroids* - Because of their anti-inflammatory effects, intra-articular (IA) corticosteroid injections may be utilised for local symptomatic management of joint arthritis. Locally administered corticosteroids have been proven to be absorbed into the systemic circulation [146]. Parentally-administered steroids are known to affect glucose metabolism and can cause abnormal blood glucose levels in patients with diabetes, which may be a concern when administering IA corticosteroid injections.

   Because of their anti-inflammatory effects, intra-articular (IA) corticosteroid injections may be utilised for local symptomatic management of joint arthritis. Locally administered corticosteroids, on the other hand, have been proven to be absorbed into the systemic circulation [146]. Parentally-administered steroids are known to affect glucose metabolism and can cause abnormal blood glucose levels in patients with diabetes, which may be a concern when administering IA corticosteroid injections. Following IA corticosteroid injections, all trials indicated an increase in blood glucose levels, which was classified as significant in four studies and reached a peak of 500 mg/dL. Peak glucose levels might occur anywhere from several hours after injection to 10-15 days afterwards. As a result, diabetic patients should monitor their blood glucose levels for 24-48 hours after IA corticosteroid injections for a possible risk of hyperglycemia, and antihyperglycemic therapy should be modified accordingly. Insulin-treated T2DM patients frequently require temporary insulin dosage up-titration following IA corticosteroid injections. Patients with diabetes who use insulin should be urged to check their blood glucose levels twice day after obtaining an intra-articular corticosteroid injection to see if they require short-acting insulin.

6. *Hyaluronic acid* - Intra-articular hyaluronic acid (IAHA) is a local therapy aimed at avoiding the systemic adverse effects commonly seen after intra-articular corticosteroid injection (which is especially challenging in people with T2DM) or oral analgesics and NSAIDs [148]. The outcomes obtained with IAHA have been found to be comparable to those obtained with continuous oral NSAID therapy in the short and medium term, i.e. giving moderate symptomatic alleviation of knee OA pain, function, and stiffness [149]. From 8 to 26 weeks after therapy, IAHA was superior to IA corticosteroids in terms of knee pain [150]. For OA, IAHA is a safe alternative to oral NSAIDs and opioids; a systematic review and meta-analysis of the safety of 18 HA products including over 13,000 patients reported a very low frequency of adverse events, the most prevalent of which were transitory local responses that resolved quickly [151].

   IAHA injections have shown clinical improvement in knee OA patients and appear to offer a favorable benefit-risk balance among pharmaceutical treatments [152, 153]. The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO) recommends using IAHA in patients with knee OA who remain symptomatic despite continuous or intermittent treatment with conventional pharmacologic treatment modalities, such as paracetamol, SYSADOAs, and NSAIDs, as well as in patients who have co-morbidities that prevent the use of NSAIDs or IA corticosteroids, such

as diabetic patients [148, 154, 155]. Even in patients who had multiple HA cycles over several years and had diabetes as a prevalent comorbidity (16 percent of patients), no interaction of IAHA treatment in OA with glucose metabolism or relationship with hyperglycemia has been found in the existing literature to date [156]. HA appears to be safe in diabetic individuals, and a meta-analysis found that it aids in the treatment of diabetic foot by speeding up wound healing [157], implying a possible function for HA in the treatment of OA in diabetics.

- *Bariatric surgery* - Obesity has long been recognized as a risk factor for T2DM [5] and OA [158, 159]. Obesity hastens the onset of OA in the knee and hip by causing biomechanical and systemic inflammatory alterations in the joints [159]. Bariatric/metabolic surgery has shown to be the most effective operation for improving glucose control, with many patients reporting long-term diabetic remission. The success can be attributed to various endocrine and metabolic benefits in addition to the impressive and long-term weight loss [160]. In addition to correcting hyperglycemia, bariatric surgery improves the various components of MetS, hypertension, atherogenic dyslipidemia, and insulin resistance, all of which contribute to improved CV outcomes [161]. In addition, some studies [162–164] found a decrease in low-grade inflammation and inflammatory markers.

The improvement of several rheumatic illnesses and a reduction in medication use (steroids and NSAIDs) are linked to a reduction in the inflammatory pathway following weight loss attained by bariatric surgery [165]. In (morbidly) obese and obese adult patients with T2DM, bariatric surgery with subsequent significant weight reduction is likely to improve knee pain, joint function, and stiffness. However, based on the present data, further high-quality research are required [159, 166]. Over the course of three years, a large percentage of participants with severe obesity who underwent bariatric surgery improved in pain, physical function, and walk time compared to baseline, but the percentage of participants who improved in pain and joint function decreased between year 1 and year 3 [167].

According to a comprehensive study and meta-analysis, bariatric surgery prior to total hip or total knee arthroplasty did not significantly lower complication rates or enhance clinical result for most peri-operative outcomes [168]. Patients who had total hip or knee arthroplasty following bariatric surgery had a shorter operational time and stayed in the hospital for a shorter period of time [169]. The best time for orthopedic and bariatric surgery is yet unknown. The use of bariatric surgery for risk reduction prior to total joint arthroplasty has financial and ethical issues [170]. Fundamental clinical concerns about the best therapy of obesity with T2DM and lower extremity OA remain unanswered, and future partnerships across disciplines providing care to patients with both should be the focus of future collaborations [159].

V. Conclusion

While T2DM and OA are known to regularly occur together (associated with obesity/overweight and frequently in the setting of MetS), whether there is a causative association between the two conditions remains a research concern. An analysis of research with over 1 million participants reveals a strong link between T2DM and OA, with individuals with T2DM having an increased risk of OA even when body weight is reduced. Studies that correlate T2DM to hand OA raise the question of whether DM has an influence on the pathophysiology of OA beyond what can be explained, such as the mechanical impact of overweight/obesity (which frequently accompanies T2DM) on lower limb OA. Further research on the link between pain in erosive hand OA and diabetes (in type 2 but also type 1, which might be linked to low-grade inflammation due to MetS) is needed. T2DM is thought to play a role in OA pathogenesis via two major pathways: oxidative stress caused by chronic hyperglycemia, which leads to an overproduction of pro-inflammatory cytokines and AGEs in joint tissue, and insulin resistance, which can affect both local and systemic low-grade chronic inflammation. Dysglycemia, including T2DM, is only one aspect of MetS; it has to be shown if other aspects of MetS, such as elevated blood pressure and atherogenic dyslipidemia, have an influence on OA pathogenesis, either collectively or separately.

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