Clinical Reviews in Bone and Mineral Metabolism
https://doi.org/10.1007/s12018-020-09270-7

REVIEW PAPER

Type 2 Diabetes Mellitus and Osteoarthritis: the Role of Glucose Transporters

Hadis Ashrafizadeh[1] · Mohadeseh Ashrafizadeh[2] · Ali Akbar Oroojan[3]

Abstract

Type 2 diabetes mellitus (T2DM) and osteoarthritis (OA) are the most common chronic diseases worldwide. Previous studies indicate the involvement of glucose transporters (GLUTs) in the development of OA induced by diabetes—specifically, the increased glucose level inside the cell and its positive effect on cytokines' or AGE receptors' activity. Thus, a study was conducted to investigate whether T2DM increases the chance of developing OA and what role GLUTs play in causing this disease. To identify the research question in this scoping review, a preliminary search was carried out in the PubMed database, looking at studies of T2DM and OA and their association with GLUTs. Searches for articles in English were carried out in the PubMed database. The search components were first evaluated using a MeSH term system. The search terms were divided into three groups: T2DM, OA, and GLUT. After removing duplicates from the original search ($n = 3252$), 864 studies were retrieved for the screening stage. A total of 104 studies were included in the selection phase, and, in the end, 36 studies were eligible. According to the studies, four themes—T2DM and GLUTs, OA and GLUTs, T2DM and OA, and T2DM and OA and GLUTs—were found to classify the findings. In conclusion, GLUT-1 composition in the plasma membrane of articular cell and chondrocyte increases glucose uptake in hyperglycemic conditions. This event leads to increased levels of inflammatory cytokines—such as IL-1β, TGF-β1, and MMP—oxidative stress, and AGEs. Therefore, these alterations induce the deleterious effects of glucotoxicity at the joint surface, which ultimately leads to OA.

Keywords Type 2 diabetes mellitus · Osteoarthritis · GLUT · Inflammation

Introduction

Diabetes mellitus is a common chronic disease that is highly prevalent in the elderly in industrialized countries. Recent statistics show that diabetes affects 382 million adults worldwide. It is predicted that it will impact 10.4% of the adult population by 2040, up from 8.8% in 2015. Type 2 diabetes is a chronic, progressive disease characterized by high blood glucose levels. It accounts for approximately 90% of diagnosed diabetes cases and is highly associated with mobility restrictions, especially in the elderly [1, 2]. Osteoarthritis (OA), meanwhile, is a common degenerative age-related disease that produces a growing of disability worldwide. About 18% of women and 9.6% of men over the age of 60 have symptomatic OA, and a quarter of them are unable to do daily tasks. It is predicted that 130 million people will suffer from OA by 2050. The pathology of OA is multifactorial—involving submuscular bone remodeling, synovial inflammation, and the destruction of articular cartilage. In addition to age and sex, the main factors contributing to osteoarthritis are physical inactivity (especially in type 2 diabetes), obesity, and joint damage [3–5]. OA is characterized by joint destruction and inflammation and, depending on the number of joints involved, may be classified as local or generalized OA. Generalized OA affects three or more joints, while local OA affects fewer than three joints [6]. Among the mechanisms that cause osteoarthritis are cellular senescence, especially cartilage cells in the articular tissue, and age-related joint destruction. It has been shown that the overexpression of various

✉ Ali Akbar Oroojan
aliakbar_oroojan@yahoo.com

[1] Nursing and Midwifery School, Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[2] Department of Sport Pathology and Corrective Exercises, Faculty of Physical Education and Sport Sciences, Allameh Tabataba'i University, Tehran, Iran

[3] Department of Physiology, Faculty of Medicine, Student Research Committee, Dezful University of Medical Sciences, Dezful, Iran

Published online: 16 May 2020

cytokines is involved in the pathogenesis of OA. Cytokines, including tumor necrosis factor alpha (TNF-α), play an important role in the disruption of catabolism and anabolism in human chondrocytes. TNF-α can induce nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and prostaglandin E2 (PGE-2) synthase, thereby regulating the course of inflammatory responses [7]. Cartilage destruction that occurs in OA is caused by articular homeostasis disorder, which is activated by inflammatory mediators—such as cytokines, lipid mediators, and reactive oxygen species (ROS)—that are produced by synocytes. Adipokines act on the synovial membrane of the joint to release a number of activated macrophages. These, in turn, increase inflammatory cytokines such as interleukin-1β (IL-1β), TNF-α, and ROS. The synovium is composed of synovial macrophages and fibroblast-like synoviocytes (FLSs). FLSs mediate cartilage destruction in OA. FLS is activated by pro-inflammatory cytokines and cytokine-independent pathways, including IL-1β. Matrix metalloproteinase (MMP)-3 and MMP-13 are mainly secreted by FLSs; high levels of MMPs may be the major cause of OA. The nuclear factor-kappaB (NF-κB) pathway controls the mechanical, inflammatory, and oxidative stress pathways that can be a potential therapeutic target in OA [8, 9].

Osteoarthritis (OA) and type 2 diabetes mellitus (T2DM) are the most common chronic diseases worldwide, affecting 15 and 8.5% of the population, respectively [6]. Initial evidence for diabetes and osteoarthritis is from the 1960s. Bilateral radiography in diabetic patients showed osteoarthritis in the hip joints that was not present in non-diabetic patients. In addition, epidemiological studies suggest that diabetes plays an independent role in the pathogenesis and progression of osteoarthritis. Glucose plays a key role, as a major source of energy and an important precursor for chondrocytes and the synthesis of glycosaminoglycan and glycoprotein. An increase in blood sugar through diabetes results in advanced glycation end products (AGEs) that bind to their receptors, thereby stimulating pro-inflammatory and pro-oxidant reactions. Like diabetes, OA is also characterized by a decrease in the activity of endogenous antioxidant enzymes, which leads to oxidative stress and, subsequently, the progression of the disease process. Aside from the imbalance in antioxidant/pre-oxidant status in diabetes, T2DM is characterized by a decrease in the number of osteoblasts and a decrease in the process of bone formation [10, 11]. In type 2 diabetes patients, a significant decrease in the number of GLUTs present in the cell membrane occurs due to impaired distribution. The result of this event is an increase in the blood glucose level [12]. Blood glucose concentration is normalized by restoring the quantity of GLUT-1 and GLUT-4 proteins to normal levels in the plasma membrane without altering insulin levels. This indicates that blood glucose concentration directly regulates the quantity of GLUT-1 and indirectly regulates the quantity of GLUT4 at the cell surface [13]. Chondrocytes are glycolytic cells that can sense glucose concentration in the environment and regulate GLUT expression—such as GLUT-1, GLUT-3, and GLUT-9—under normal conditions. The capacity of chondrocytes to adapt to local glucose levels during OA is lost, leading to high glucose uptake and glucotoxicity. Therefore, chronically high levels of glucose in the environment lead to inflammatory effects on chondrocytes, disrupting their metabolism during OA [14]. Based on previous studies, and based on the involvement of glucose transporters in the development of OA induced by diabetes—specifically, the increased glucose level inside the cell and its positive effect on cytokines' or AGE receptors' activity—the present study was conducted to investigate whether T2DM increases the chance of developing OA and what role glucose transporters play in causing this skeletal disorder.

Methods

Type of Article

The present study is a scoping review according to Arksey and O'Malley's modified methodology [15, 16]. A scoping review is a knowledge-based research project that summarizes a relatively large set of inputs or studies and combines them with the aim of producing new mechanisms, methods, and results to guide future research. This review study can be as a primary research to systematic review and meta-analysis studies [16]. This scoping review consists of the 6 identifying research questions, identifying relevant studies, selecting studies during two stages including selection and screening, charting information or data, and gathering, summarizing, and declaration of results [16]. The PRISMA-ScR checklist designed by Tricco et al. for systematic scoping review research was used to write this study [17].

Research Questions and Relevant Studies

To identify the research question, a preliminary search was carried out in the PubMed database in studies of T2DM, OA, and their association with glucose transporters without any limiting agents. Searching for articles related to English until Jan. 1, 2020, has been done in the PubMed database. The search components were first evaluated using the MeSH term system. The search terms were divided into three groups of T2DM, OA, and glucose transporters and were used in

combination with each other. The search strategy for the PubMed database is as follows (Table 1):

Inclusion criteria included the type of publication (article, book, pepper conference), language (English), and type of study (primary and secondary studies) performed at any time in each country and examined the relationship between T2DM, OA, and the role of glucose transporter.

Study Selection

All studies in the search phase were transferred to EndNote (X7) software. At the screening stage, the title and abstract of the articles were reviewed by the researcher. A study that did not comply with the research objectives was excluded. During the selection phase, the full text of the paper was reviewed by two researchers (PRISMA flowchart).

Data Charting

The following data were included: First author's name, year of publication, type of publication, type of study design, sample size, research population, sampling method, main purpose of research, key results, gender, mean age, and in intervention studies (number of test groups and control, duration of follow-up, type of intervention) were extracted from all studies (Appendix, data extraction form).

Gathering, Summarizing, and Declaration of Results

Data analysis was performed based on data extraction form. In this study, the relationship between T2DM and OA, T2DM and glucose transporter, and OA and glucose transporter; the impact of T2DM and OA; and the role of glucose transporter in the development of OA and treatment of T2DM and OA with a focus on the role of glucose transporter have been reported. Then, the results were reported using different tables.

Ethical Code

Because this study is a secondary study and review, it is not necessary to obtain an ethical code.

Results

Study Properties

After removing duplicates from the original search ($n = 3252$), 864 studies were retrieved for the screening stage. A total of 105 studies were included in the selection phase, and at the end, 37 studies were eligible and qualified (Fig. 1). The specifications in the studies are listed, categorized, and summarized in Table 1. Ninety-two percent of the studies were articles. Seventy-two percent were primary and 28% were secondary. All of the studies were published in English. Eighty-four percent of the studies

Table 1 Search syntax of this study

Number	Search syntax	Results
1	(Osteoarthr*[tiab] OR Osteoarthrosis[tiab] OR (Arthriti*[tiab] AND Degenerative[tiab]) OR "Degenerative Arthritides"[tiab] OR "Degenerative Arthritis"[tiab] OR "Osteoarthrosis Deformans"[tiab])	72,930
2	(("Diabetes Mellitus"[tiab] AND Noninsulin-Dependent[tiab]) OR ("Diabetes Mellitus"[tiab] AND Ketosis-Resistant[tiab]) OR ("Diabetes Mellitus"[tiab] AND "Ketosis Resistant"[tiab]) OR "Ketosis-Resistant Diabetes Mellitus"[tiab] OR ("Diabetes Mellitus"[tiab] AND "Non Insulin Dependent"[tiab]) OR ("Diabetes Mellitus"[tiab] AND Non-Insulin-Dependent[tiab]) OR "Non-Insulin-Dependent Diabetes Mellitus"[tiab] OR ("Diabetes Mellitus"[tiab] AND Stable[tiab]) OR "Stable Diabetes Mellitus"[tiab] OR ("Diabetes Mellitus"[tiab] AND "Type II"[tiab]) OR NIDDM[tiab] OR ("Diabetes Mellitus"[tiab] AND "Noninsulin Dependent"[tiab]) OR ("Diabetes Mellitus"[tiab] AND Maturity-Onset[tiab]) OR ("Diabetes Mellitus"[tiab] AND "Maturity Onset"[tiab]) OR "Maturity-Onset Diabetes Mellitus"[tiab] OR "Maturity Onset Diabetes Mellitus"[tiab] OR MODY[tiab] OR ("Diabetes Mellitus"[tiab] AND Slow-Onset[tiab]) OR ("Diabetes Mellitus"[tiab] AND "Slow Onset"[tiab]) OR "Slow-Onset Diabetes Mellitus"[tiab] OR "Type 2 Diabetes Mellitus"[tiab] OR "Noninsulin-Dependent Diabetes Mellitus"[tiab] OR "Noninsulin Dependent Diabetes Mellitus"[tiab] OR "Maturity-Onset Diabetes"[tiab] OR (Diabetes[tiab] AND Maturity-Onset[tiab]) OR "Maturity Onset Diabetes"[tiab] OR "Type 2 Diabetes"[tiab] OR (Diabetes[tiab] AND "Type 2"[tiab]) OR ("Diabetes Mellitus"[tiab] AND Adult-Onset[tiab]) OR "Adult-Onset Diabetes Mellitus"[tiab] OR ("Diabetes Mellitus"[tiab] AND "Adult Onset"[tiab]))	147,163
3	("Glucose Transporter" OR "Glucose Transport Facilitators" OR "SLC2A Proteins" OR "Glucose Transport Protein" OR "GLUT Proteins")	17,941
4	Publication date: up to Jan. 1, 2020	-
5	1 AND 2	380
6	2 AND 3	2854
7	1 AND 3	17
8	1 AND 2 AND 3 AND 4	1

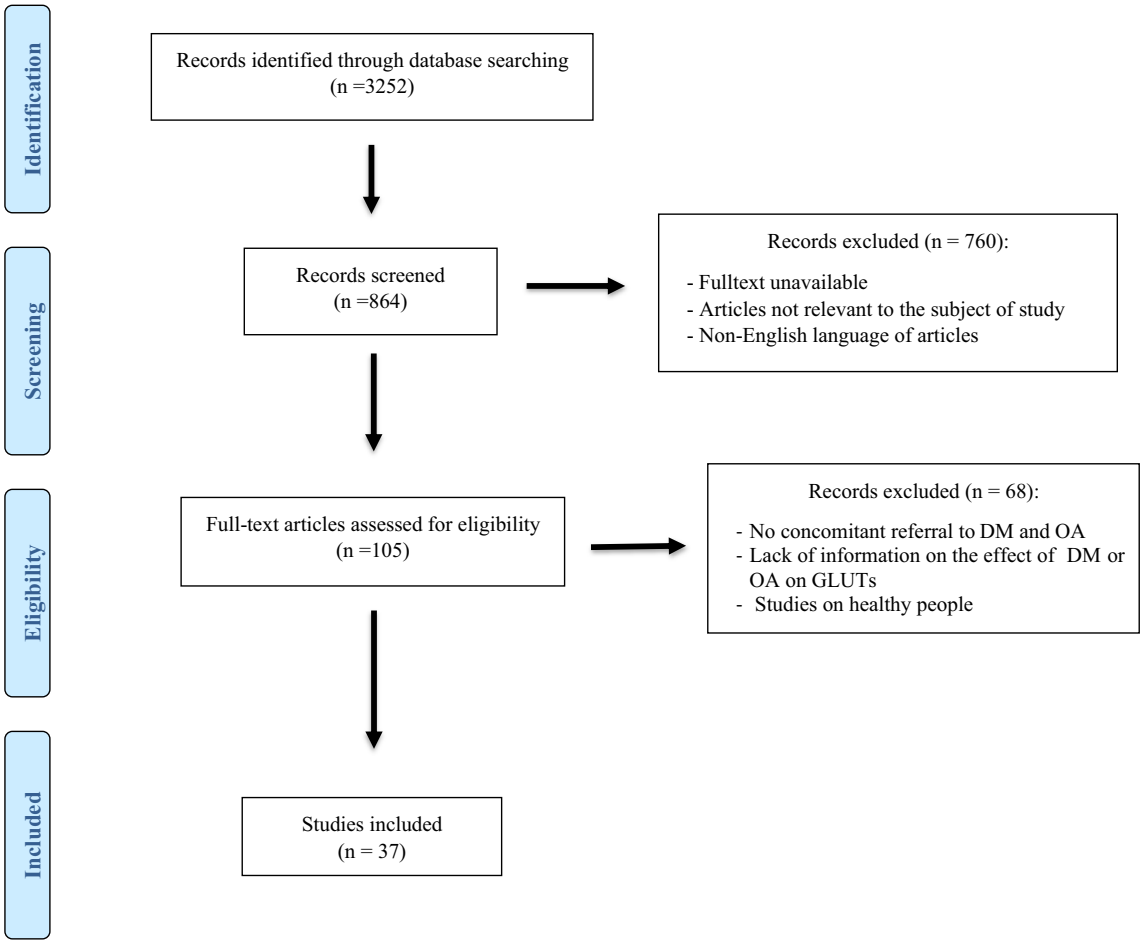

Fig. 1 PRISMA flow diagram

were conducted from 2011 to 2019 and 16% from 1992 to 2010. The study population of the articles was 58% human, 6% animal, and 4% cellular. Also, 32% of the studies had no explicit mentions to the research community because of the review articles. The statistical population included 10% of T2DM, 30% of patients with OA, and 60% of T2DM patients with OA. Also, the mean sample size in 27% of the studies was less than 50, 16% between 51 and 150, 3% between 151 and 250, and 16% more than 250. In 38% of studies, due to the review articles, there was no clear mention to sample size. The minimum sample size was 4 persons and the maximum sample size was 1,255,607. The age of participants in 16% of the studies was between 18 and 50 years old and 39% were over 50.

Methodological Properties

The methodological characteristics of the studies are listed, categorized, and summarized in Table 2. Sixty-nine percent of the studies were original papers. The research methodology was categorized into observational, interventional, and experimental studies. Thirteen percent of them were cross-sectional, 16% were case-control and cohort, and 40% were experimental. The type of sampling in 19% of studies was random and 47% of studies were non-random.

T2DM, OA, and GLUT Assessment

According to the studies, 4 themes were found to classify the findings. Five percent of in vivo studies were focused on T2DM and GLUTs, 16% on OA and GLUTs, 51% on T2DM and OA, and 8% on T2DM and OA and GLUTs. Three percent of in vitro studies were paying attention to animal cells and 17% to human cells. Each of these 4 topics is discussed in detail in the "Discussion" section.

Discussion

T2DM and OA

There are two types of OA. Primary osteoarthritis is the most common and is associated with aging and genetic inheritance factors; up to 60% of all OA cases are thought to result from genetic factors. This type of OA occurs in joints such as fingers,

Table 2 Characteristics of articles

Characteristics of articles				Number	Percent
Content type of studies		Article		34	92
		Conferences		1	3
		Book		2	5
Type of article		Original research	Cross-sectional study	5	13
			Case-control and cohort	6	16
			Experimental study	15	40
		Non-original research	Review	10	27
			Letter to the editor	1	4
Year of publication		1992–2010		6	16
		2011–2019		31	84
Population	Human	Female		16	32
		Male		13	26
	Animal	Female		0	0
		Male		3	6
	Cell			2	4
	Not mentioned (review and letter to the editor)			16	32
Statistical society		Diabetes		2	10
		Osteoarthritis		6	30
		Diabetes and osteoarthritis		12	60
Sample size (number of article)		≤ 50		10	27
		51–150		6	16
		151–250		1	3
		≥ 251		6	16
		Not mentioned (review and letter to the editor)		14	38
Average of age (number of article)	Human	18–50		7	16
		Over 50		17	39
	Animal	Under 3 months		3	7
		Over 3 months		1	3
	Not mentioned (cell and review and letter to the editor)			15	35
In vivo research		Diabetes and GLUTs		2	5
		Osteoarthritis and GLUTs		6	16
		Diabetes and osteoarthritis		19	51
		Diabetes and osteoarthritis and GLUTs		3	8
In vitro research		Animal cell research		1	3
		Human cell research		6	17
Type of sampling		Random sampling		7	19
		Non-random and census sampling		18	47
		Not mentioned		13	34

thumbs, the spine, hips, knees, and great (big) toes. Secondary osteoarthritis is related to specific disorders such as inflammatory arthritis, diabetes, and obesity [18]. Additionally, a variety of musculoskeletal disorders are associated with DM and can cause significant disabilities; these conditions include shoulder capsulitis, limited joint mobility, trigger finger, Dupuytren's contraction, carpal tunnel syndrome, OA, and other rare complications. People with T2DM also have an increased risk of arthritis complications. The pathophysiology leading to OA disorders in patients with DM is not well known. High levels of glucose caused by T2DM may affect cell function and damage extracellular matrix components of the connective tissue. High blood glucose levels can also cause inflammation and cartilage destruction through oxidative stress and accumulation of inflammatory mediators and AGEs [19–21]. Thus, it could be suggested that T2DM contributes to secondary types of OA by inducing inflammation and destruction in the joints [22]. Synovium in T2DM patients is associated with higher levels of TNF-α and macrophages than non-diabetic patients tend to have. This finding may explain the severity of OA in T2DM patients when compared with non-diabetic patients [23]. Articular cartilage is a tissue associated with low cell turnover, and we hypothesize that autophagy may be one of the pathways regulating the effects of hyperglycemia and hypertension on joint integrity. In fact, autophagy plays an important role in articular cartilage, regulating the removal of dysfunctional organs and macromolecules. Previous studies of autophagy dysfunction have been reported in relation to OA and T2DM [24]. Potential mechanisms of bone calcium buildup and bone remodeling in adults with T2DM have been suppressed by the accumulation of calcium in bones. When bone remodeling is reduced, the secondary mineralization stage becomes longer. AGEs found in the urine and serum of people with T2DM can bind to type 1 collagen nitrogen in the bone. The bonding of AGEs increases the number of carboxyl groups on the surface of collagen fibers, which act as nucleation sites for the formation of hydroxyapatite. Regardless of the mechanism of high mineral buildup in bone samples from adults with T2DM, imbalances in minerals and collagen can lead to a denser and

more fragile material in the bone that requires less energy to break [25, 26]. A very loose network of corrugated collagen fibers was observed, along with absolute loss of chondrocytes, in OA mice. Extensive vertical dislocation from the articular surface to the subchondral bone and fibrillation were also observed. In general, the control group showed no signs of structural damage, whereas extensive pathological changes were exhibited in the diabetic knee OA group [27]. It could therefore be suggested that T2DM induces OA by increasing the levels of TNF-α and AGEs inside the cells, which leads to a decrease in bone mineralization.

Impact of Diabetes on the Joint

Effects of Diabetes on the Cartilage Surface, Synovium, and Subchondral Bone

Such progress has occurred on the role of high glucose concentrations in articular tissues, especially chondrocytes. Chondrocytes are glycolytic cells that express GLUTs—especially GLUT-1, GLUT-3, and GLUT-9. These cells are able to sense glucose concentrations in the environment and regulate GLUT expression and its membrane composition. Under glucose-deprived conditions, normal chondrocytes increase GLUT-1 expression and membrane incorporation, while this event leads to decreases in hyperglycemia. This capacity of natural chondrocytes to control local glucose levels is impaired during OA, which may lead to increased glucose uptake inducing glucotoxicity [21]. Some diabetic models have shown that diabetes increases synovial inflammation, especially in T2DM models. These results are similar to the clinical observation of synovitis in knee OA among diabetic patients when compared with non-diabetics using ultrasound examination [21]. With diabetes, the risk of developing OA is doubled. In summary, elevated levels of MMP-1, MMP-7, MMP-8, MMP-9, MMP-10, and MMP-12 in synovial fluid may be among the reasons that diabetic patients suffer from OA [28]. In diabetic and hypertensive patients with advanced knee OA requiring arthroplasty, subchondral bone loss with low bone density and higher porosity increases. Finally, AGEs accumulate in the subchondral bone of diabetic patients more than non-diabetic patients, which may affect mechanical resistance under non-cerebral pressures and show inflammatory effects [21]. Therefore, diabetes can induce joint destruction by increasing glucotoxicity, MMPs, and AGEs in the cartilage surface, synovium, and subchondral bone levels. These effects can occur through GLUTs—especially GLUT-1.

Glucose Transporters

Glucose enters cells by facilitating release or secondary active transport in the intestine and kidneys with sodium. Glucose transporters (GLUTs) work to release glucose to the cell membranes. They are different from sodium-dependent glucose transporters, SGLT 1 and SGLT 2, responsible for the secondary active transport of glucose in the intestine and the renal tubes. Seven glucose carriers (GLUT 1–7) have been identified [29]. Glucose transporters are now divided into three subclasses. Class I contains the first glucose transporters (GLUT 1–4), which is distinct in terms of tissue distribution, kinetic properties, and hormonal regulation. GLUT-1 is found in most tissues but is particularly abundant in erythrocytes and endothelial and epithelial boundaries of blood, such as the blood-brain barrier, retina, and placenta. GLUT-2 is a low isoform that is expressed in Langerhans islands of the pancreas, liver, and intestinal tissues. GLUT-3 is primarily expressed in the brain, where it is exclusively localized in neurons. GLUT-3 non-neuronal expression sites include the placenta, sperm, and human platelets. GLUT-3, like GLUT-1, is a high-affinity transporter but differs from GLUT-1 in glucose transport. Its turnover is seven times greater than GLUT-1, making GLUT-3 one of the fastest glucose transporters. GLUT-4 is an "insulin-responsive" isoform that is expressed in the skeletal muscle, heart, white and brown adipose tissue, and tissues that respond to insulin or shrinkage with increased glucose levels. Class II comprises the fructose transporters such as GLUT-5 and three poorly characterized proteins (GLUT-7, GLUT-9, and GLUT-11). Class III GLUT/SLC2A members are characterized by a lack of a glycosylation site in extracellular loop 1 and the presence of such a site in loop 9. Although these carriers do not carry glucose, they are a polyol transporter and are included in class III [30]. GLUT-1, the major membrane protein, was the first carrier of pure membrane. This glucose transporter is encoded by the SLC2A1 gene, which contains 3–5% of the total membrane protein. Reduced glucose, mannose, galactose, glucosamine, and ascorbate can be transported with GLUT-1, although glucose is the major physiological substrate for GLUT-1. GLUT-1 activation is mainly caused by cell stressors such as azide, osmotic stress, methylene blue, and glucose deprivation [31].

Glucose Transporter and the Bone Joint

Several members of the glucose-facilitating carrier family, including GLUT/SLC2A transporters, have been identified in human articular chondrocytes. Among them, GLUT-1 is of particular importance because its level can be regulated by both anabolic and catabolic stimuli, whereas other glucose transducers, such as GLUT-3, are not affected by those stimuli. In addition, several cell types have been shown to alter GLUT-1 content by altering blood glucose concentration and glucose transport rate [32].

The Role of T2DM on GLUTs and Development of OA

By altering GLUT/SLC2A expression and high blood glucose levels, diabetes-induced OA results in altered type 2 collagen

synthesis by chondrocytes, which ultimately leads to the destruction of these cells [33]. The facilitation of glucose transport is the first rate-limiting step of glucose metabolism in chondrocytes, and therefore, its regulation is an important determinant of chondrocyte homeostasis. At the protein level, many members of the GLUT family have been identified in human chondrocytes—including GLUT-1, GLUT-3, GLUT-6, GLUT-8, GLUT-9, and GLUT-10. GLUT-4, however, has not been identified. Among these, GLUT-1 appears to be particularly important since it is regulated by anabolic and catabolic stimuli as well as by extracellular glucose concentrations [34–36]. It has been observed that the expression of messenger RNA (mRNA) for GLUT-1, the major glucose carrier, increases when hexokinase 2 (HK2) mRNA is present in OA patients [37]. OA cartilage cells exposed to high glucose are unable to regulate GLUT-1, which results in increased glucose uptake. Chondrocytes under high glucose conditions—in particular, those stimulating IL-1β—lead to the increased synthesis of GLUT-1 and GLUT-9 in articular cartilage cells. Additionally, compared with cartilage from non-diabetic patients, OA cartilage from diabetic patients responds more strongly to a pro-inflammatory stress. This phenotype is responsible for the activation of persistent inflammatory cells—including increased GLUT expression, glucose uptake, and oxidative stress—as well as the polyol pathway [38]. Stimulation with 30 ng/ml of IL-1β increased GLUT-1 mRNA expression similarly in normal and OA chondrocytes compared to untreated cells. This suggests that OA chondrocytes regulate glucose transport and GLUT-1 levels in response to IL-1β. Also, the total GLUT-1 protein count was significantly decreased in normal chondrocytes incubated with 30 mM glucose for 18 or 48 h, but this protein did not change in cultured OA cells under similar conditions (30 mM glucose). ROS production is involved in the pathophysiology of OA. Their prolonged production when OA chondrocytes are exposed to excessive amounts of glucose is likely to damage those cells and aggravate catabolic processes that can lead to the progression of OA in diabetic patients. Lysosome degradation may be another mechanism involved in inhibiting high glucose–induced GLUT-1 regulation in normal chondrocytes. These observations agree with studies of other cells in which high glucose, or diabetic conditions led to the return of GLUT-1 to the intracellular compartment and its subsequent degradation by lysosomes. Other studies have shown that normal human chondrocytes regulate extracellular glucose concentrations by modulating GLUT-1 synthesis and degradation through the lysosome pathway. This negative regulation could be an important pathogenic mechanism by which conditions involving elevated blood glucose, such as DM and other conditions with impaired glucose metabolism, facilitate degenerative changes in chondrocytes and OA progression [32]. Another study found that TGF-β1, which is known to maintain chondrocyte homeostasis, stimulates glycolysis by regulating important glycolytic factors, including GLUT-1 and hexokinase 2, while simultaneously reducing oxidative phosphorylation in the cartilage of human osteoarthritis cells (HACs). It was revealed that distinct metabolic programs are induced by TGF-β1 in HACs, which could reveal a new mechanism involved in the pathogenesis of OA by regulating cellular metabolism [39]. Pyruvate kinase M2 (PKM2) is upregulated to a greater extent in OA chondrocytes than in healthy control chondrocytes. Furthermore, in OA chondrocytes, ATP expression was lower than in healthy control chondrocytes. Loss-of-function experiments showed that PKM2, mediated by lentivirus transmission, can significantly suppress glucose utilization, lactate secretion, and GLUT-1 transport in glycolysis [40]. Thus, GLUT-1 has an important effect on the induction of OA during diabetes, and this transporter can increase the chance of OA occurrence via the upregulation of PKM2, ROS, and TGF-β in chondrocytes (Fig. 2).

Treatment of T2DM and Its Effect on GLUT in OA Patients

In the study of the effect of glibenclamide on GLUT-1 and GLUT-3 basal protein levels, it was concluded that GLUT-1 protein levels in grade 2, 3, and 4 osteoarthritic membrane cells treated with 10 nM glibenclamide significantly increased. Also, a significant decrease in GLUT-3 protein level occurred in chondrocytes of grade 1, 2, and 3 osteoarthritic membrane cell groups treated with glibenclamide 10 nM. The inability of OA chondrocytes to downregulate GLUT-1 and GLUT-3 protein levels in response to glibenclamide mimics their inability to regulate high extracellular glucose concentrations. However, the changes induced by glibenclamide in the total amount of GLUT-1 and GLUT-3 were not associated with a decrease in chondrocyte transport capacity at any degree of OA. This suggests that even though K channel activation (ATP) regulates access to GLUT-1 and GLUT-3, other mechanisms are involved in regulating glucose transport capacity in human chondrocytes. High glucose–induced inhibition of GLUT-1 has been shown to degrade in lysosomes. Thus, K channel activation (ATP) may be regulated by GLUT-1 and possibly GLUT-3 proteins, or increasing intracellular reserves lysosomal degradation [35]. Therefore, it could be suggested that glibenclamide improved OA in T2DM conditions via downregulating GLUT-1 and GLUT-3 proteins and decreasing chondrocyte glucose transport capacity, which can cause glucotoxicity and increase levels of inflammatory variables.

Conclusion

In conclusion, GLUTs are clearly involved in the progression of OA. GLUT-1 composition in the plasma membrane of

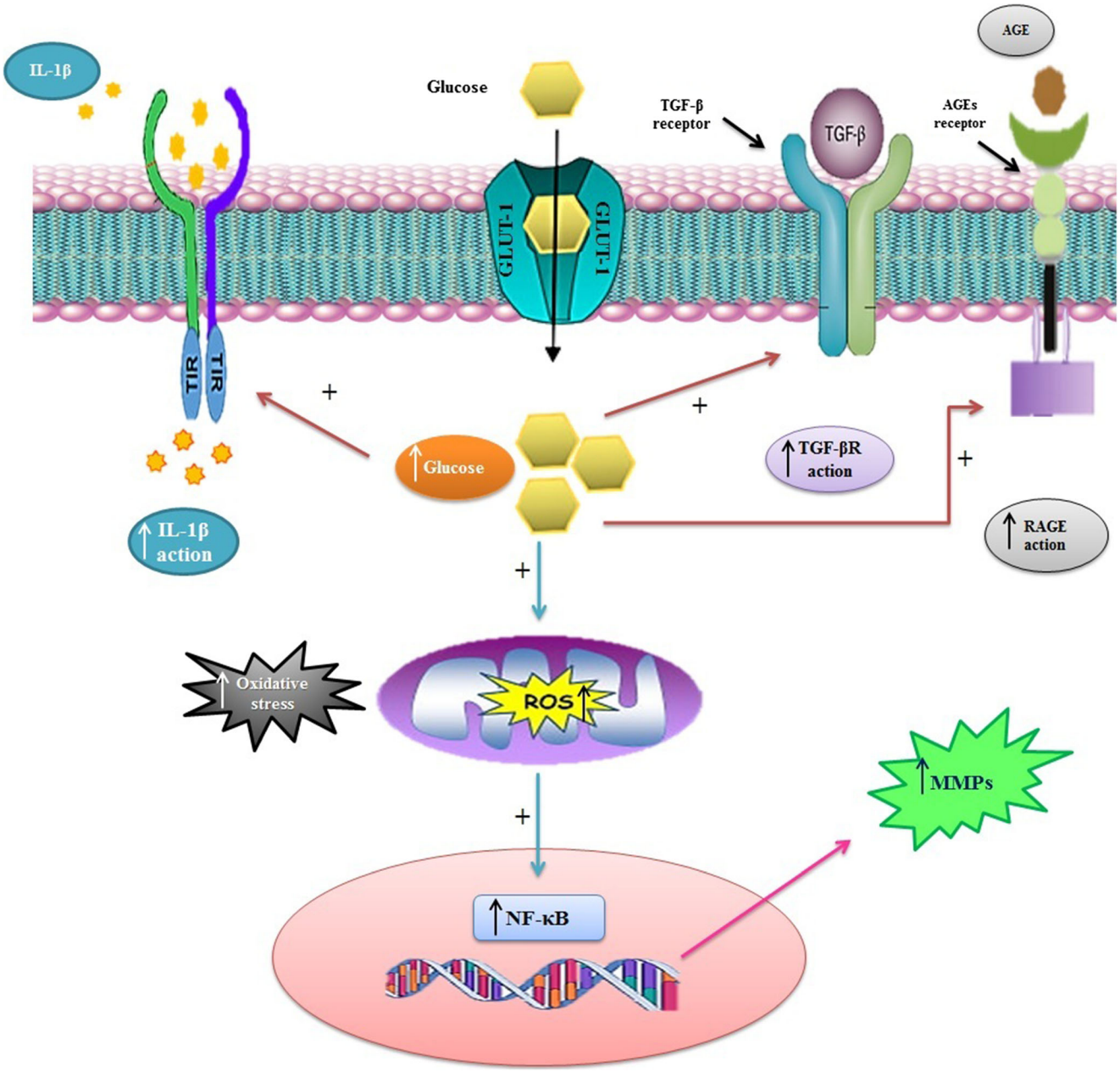

Fig. 2 The role of T2DM and GLUTs in the development of OA

articular cell and chondrocyte in hyperglycemic conditions increases glucose uptake in these cells. This event may lead to increased levels of inflammatory cytokines such as IL-1β, TGF-β1, and MMP, as well as oxidative stress and AGEs in joints or articular cartilage cells (via their receptors). These alterations induce both the deleterious effects of glucotoxicity at the joint surface and OA; however, future studies are required to clarify the precise mechanism and mediators involved in this disease.

Acknowledgments We would like to thank the vice-chancellor of research affairs of Dezful University of Medical Sciences, Dezful, Iran, for its assistance in the production of this scoping review research.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Appendix

Table 3 The characteristics of eligible and remained studies

Number	Author	Publication year	Sample size	Study population	Aims	Methodology	Key finding	Language	Sex	Age	Type of sampling	Type of study
1	Adeyemi WJ	2019	49	Animal	Investigate the effects of single or combined administration of salmon calcitonin and omega-3 fatty acids on selected biomarkers in induced diabetic osteoarthritic male Wistar rats.	Experimental	The combined administration of salmon calcitonin and omega-3 fatty proffer better therapeutic effects than the single therapy. Therefore, they could be used in the management of diabetic-osteoarthritic condition.	English	Male	10–12 weeks old	Random	Original article
2	Alenazi AM	2019	3855	Human	Examine the prevalence of T2DM in people with GOA compared with LOA and to investigate the association between demographic risk factors and chronic diseases with GOA compared with LOA.	Retrospective analysis	This study found a higher prevalence of T2DM in people with GOA when compared with LOA. People with chronic diseases including T2DM, hypertension, and dyslipidemia had significantly and independently increased odds of GOA when compared with those without chronic diseases.	English	Female	66.43 ± 11.02 years old	Non-random	Original article
3	Arellano Perez Vertti RD	2019	231	Human	1. To evaluate the association between type 2 diabetes mellitus (T2D) and primary knee osteoarthritis (KOA) 2. To compare synovial fluid (SF) cartilage oligomeric matrix protein (COMP) concentrations and glycemic control parameters in patients with T2D, with and without primary KOA.	Case-control	1. A strong association between T2D and primary KOA. 2. The presence of T2D may have an influence in SF COMP levels 3. The glycemic control parameters and duration of diabetes may be useful as an indirect indicator of SF COMP levels.	English	Male and female	42–87 years old for the KOA group and 30–76 years old for the non-KOA group	Non-random	Original article
4	Balkhi B	2019	5457	Human	To measure the adherence rates of oral antidiabetic drugs (OADs) in patients with type 2 diabetes mellitus (T2DM) and assess the relationship of glycemic control and adherence to OADs	Cross-sectional	This study supports the growing concern of non-adherence to OADs among patients with T2DM in Saudi Arabia.	English	Male and female	18 years and older	Non-random	Original article
5	Barrett KE	2019	-	-	Review of medical physiology	-	-	English	-	-	-	Book
6	Bi J	2019	60	Cell culture	Based on the anti-inflammatory properties of the dipeptidyl peptidase-4 (DPP-4) inhibitor and its expression in chondrocytes, the possible effect of the DPP-4 inhibitor vildagliptin in chondrocytes was tested.	Experimental	The DPP-4 inhibitor vildagliptin exerts a protective effect against TNF-α-induced chondrocytes senescence and This DPP-4 inhibitors could have potential therapeutic application in the treatment of OA.	English	-	-	Random	Original article
7	Bianchi L	2016	-	Human	Analyzes the role of different biological mechanisms explaining the association between diabetes and mobility disability, focusing on decline in muscle strength and muscle quality	Review	This review demonstrated the biological pathways responsible for skeletal muscle dysfunction in type 2 diabetes and analyzes the role of decline in muscle strength and quality on the association between diabetes and mobility disability.	English	Male and female	-	-	Review article
8	Chen Y	2017	141	Human	Assessment of subchondral bone remodeling that led to deteriorated microstructure and strength in T2D patients.	Case-control	T2D patients have abnormal subchondral bone remodeling and microstructural impairments which were associated with the exacerbated cartilage	English	Male and female	66 ± 5 years old	Non-random	Original article

Table 3 (continued)

Number	Author	Publication year	Sample size	Study population	Aims	Methodology	Key finding	Language	Sex	Age	Type of sampling	Type of study
							degradation in knees. Hence, this study suggested that abnormal subchondral bone remodeling may be an underlying mechanism by which T2D aggravates knee OA.					
9	Courties A	2016	r	Human	Development of the available evidence of an association between OA and diabetes.	Review	1. Epidemiological association between OA and type 2 diabetes is robust, beyond their common association with age or obesity. 2. Type 2 diabetes is now considered as an additional risk factor of OA.	English	Male and female	-	-	Review article
10	Courties A	2017	-	Human	Interest in the metabolic syndrome (MetS)–associated osteoarthritis phenotype is increasing. Here, this study summarizes recently published significant findings.	Review	1. Obesity-associated inflammation can affect osteoarthritis progression in mouse models, independent of mechanical stress due to excess weight. 2. MetS has a cumulative and negative effect on hand osteoarthritis occurrence, independent of weight. 3. Fat intake could affect knee osteoarthritis progression independent of weight because of the possible beneficial role of n-3 PUFAs and deleterious role of cholesterol. 4. Risk of cardiovascular diseases is increased with osteoarthritis mainly because of physical inactivity but possibly also low-grade inflammation. 5. Controlling metabolic comorbidities may have a beneficial effect on osteoarthritis, especially in obese patients.	English	Male and female	-	-	Review article
11	DeFronzo RA	2004	-	-	Assessment of T2DM pathogenesis	-	-	English	-	-	-	Book
12	Dubey N	2018	1,255,607	Human and animal	It was conducted dry-to-wet lab research approaches to assess the correlation of T1DM and T2DM with KOA among all age and genders of Taiwanese population.	Case-control and experimental	1. Higher strength of association between DM and KOA was confirmed in non-obese diabetic mice. 2. It was revealed that DM is strongly associated with KOA, and obesity may not be a confounding factor.	English	Male and female	Human (female: 80–89; male: 50–59 years old) and mice (male: 7 week old)	Human	
	(non-random) and mice (random)	Original article										
13	Duclos M	2016	-	Human		Review		English		-	-	

Table 3 (continued)

Number	Author	Publication year	Sample size	Study population	Aims	Methodology	Key finding	Language	Sex	Age	Type of sampling	Type of study
					1. To explore the links between obesity, T2D and OA, with a focus on the effect of ectopic (intra-abdominal) localization of the fat mass. 2. To define the functional consequences of OA in this population, which often has other comorbidities, and how to treat and prevent it.		Prevention of obesity-related OA must be the focus in high-risk subjects, such as those who are obese with metabolic syndrome > "metabolically healthy" obese, have T2D, and normal weight subjects with abdominal obesity (defined as waist circumference > 102 cm for men and 88 cm for women).		Male and female			Review article
14	Funck-Brentano T	2019	384,838	Human	To identify causal risk factors for knee, hip, and hand OA.	Cross-sectional	BMI exerts a major causal effect on risk of OA at the weight-bearing joints such as knee and hip but not at the hand.	English	Male and female	37–76 years old	Non-random	Original article
15	Garcia-Carbonell R	2016	-	Human and animal	To evaluate whether changes in glucose metabolism in RA fibroblast-like synoviocytes (FLS) could play a role in inflammation and joint damage.	Experimental	Targeting metabolic pathways is a novel approach to understanding the mechanisms of disease. Inhibition of glycolysis may directly modulate synoviocyte-mediated inflammatory functions and could be an effective treatment strategy for arthritis.	English	-	Human (-) and mice (8–12 weeks old)	Non-random	Original article
16	Hajiaghaalipour F	2015	-	-	This study focused on the structure and function of the flavonoids and highlighted the anti-diabetic effects of the flavonoids in the management of T2DM.	Review	This review highlights the recent findings on beneficial effects of flavonoids in the management of diabetes with particular emphasis on the investigations that explore the role of these compounds in modulating glucose transporter proteins at cellular and molecular level.	English	-	-	-	Review article
17	Juybari KB	2019	18	Cell culture	To investigate whether atorvastatin (ATO) can restore the high glucose (HG) induced impaired chondrogenic gene expressions via inhibiting NF-jB expression in C28I2 chondrocyte cell line.	Experimental	1. ATO could significantly decrease HG-induced inflammation in the cultured C28I2 chondrocytes through the activation of canonical NF-jB signaling pathway. 2. The beneficial effects of ATO may be owing to its anti-inflammatory properties. 3. Treatment with ATO may provide an effective approach to prevent HG-induced cartilage destruction in clinical setting.	English	-	-	Random	Original article
18	Klip A	1992	-	-	To integrate the recent developments in the regulation of glucose transporter subcellular distribution in skeletal muscle with the regulation of glucose uptake into this tissue in vivo.	Review	Muscular contraction can translocate glucose transporters from the inner to the PM in a manner that is quantitatively similar to the effect of insulin in the resting muscle.	English	-	-	-	Review article
19	Laiguillon M-C	2015	20	Human and animal	To examine the relationship between OA and T2DM	Experimental	OA cartilages from DM patients showed increased	English	Human	(female) and mice (-)	Human (65 years	Random

Table 3 (continued)

Number	Author	Publication year	Sample size	Study population	Aims	Methodology	Key finding	Language	Sex	Age	Type of sampling	Type of study
							responsiveness to IL-1β-induced inflammation. Accordingly, high glucose enhanced IL-1β-induced inflammation in cultured chondrocytes via oxidative stress and the polyol pathway.				old) and mice (5- to 6-day-old)	
Original article												
20	Luo S	2019	55	Human	To ascertain the expression difference of MMPs and function in mononuclear cells after stimulating by lipopolysaccharide (LPS) in OA patients with or without diabetes.	Case-control or experimental	1. High levels of MMP-1, MMP-7, MMP-8, MMP-9, MMP-10, and MMP-12 in the synovial fluid might be one of important reasons that diabetes patients are more frequently suffered from OA. 2. Inflammation-induced malfunction of mononuclear cells would stimulate MMP-8 and MMP-9 secretions to various extents.	English	Male and female	From 37.6 ± 9.8 to 70.4 ± 8.3 years old	Non-random	Original article
21	Majjad A	2018	376	Human	Assessing the prevalence and associated factors of musculoskeletal (MS) disorders in Moroccan diabetic patients.	Cross-sectional	MS disorders are frequent in this population and associated with various factors. HbA1c level does not appear to be associated with development of MS disorders.	English	Male and female	45–62 years old	Non-random	Original article
22	McNulty AL	2005	7	Human	To evaluate the dehydroascorbate (DHA) transport mechanisms in human chondrocytes.	Experimental	Chondrocytes transport DHA via the GLUTs and that this transport mechanism is modestly selective for L-DHA.	English	-	-	Non-random	Original article
23	Mobasheri A	2002	-	-	The importance and role of nutritional factors such as glucose and glucose-derived sugars in the development, maintenance, repair, and remodeling of cartilage.	Review	Present a novel hypothesis regarding the role of glucose transport and metabolism in cartilage physiology and pathophysiology and speculate that supplementation with sugar-derived vitamins and nutraceuticals may benefit patients with degenerative joint disorders.	English	-	-	-	Review article
24	Neumann J	2018	141	Human	To assess the associations between serum/urine biomarkers for osteoarthritis (OA) and magnetic resonance (MR) imaging measures of cartilage composition and joint structure.	Cross-sectional	This study revealed correlations between serum bio-markers of OA (serum hyaluronan (sHA), serum cartilage oligomeric matrix protein (sCOMP), serum matrix metalloproteinase-3 (sMMP3), and Urine Carboxy-Terminal Telepeptides of type II Collagen (uCtX-II)) with MRI parameters (T2)) measures of cartilage extra-cellular matrix degeneration.	English	Female	45–79 years old	Non-random	Original article

Table 3 (continued)

Number	Author	Publication year	Sample size	Study population	Aims	Methodology	Key finding	Language	Sex	Age	Type of sampling	Type of study
25	Pritchard J	2013	35	Human	To determine whether trabecular bone mineralization differed in adults with type 2 diabetes compared to adults without type 2 diabetes.	Case-control	The combination of elevated mean calcium concentration in bone and lower mineralization heterogeneity in adults with T2DM may have deleterious effects on the biomechanical properties of bone.	English	Male and female	≥65 years old	Non-random	Original article
26	Ribeiro M	2016	10	Human	To investigate the effects of high glucose and insulin, characteristics of T2D, on cartilage homeostasis.	Experimental	It was demonstrated that decreased autophagy might be a mechanism by which diabetes influences cartilage degradation. Pharmacological activation of autophagy may be an effective therapeutic approach to prevent T2D-induced cartilage damage.	English	-	Healthy patients (54 ± 1.41 years old), non-diabetic OA patients (78.75 ± 11.52 years old), diabetic OA patients (70.75 ± 10.17 years old)	Non-random	Original article
27	Rosa S	2011	53	Human	To determine whether human chondrocytes express the insulin receptor (InsR) and compared its abundance and function in normal and osteoarthritis (OA) human chondrocytes.	Experimental	1. Human chondrocytes express functional InsR that respond to physiologic insulin concentrations. 2. The InsR seems to be more abundant in normal than in OA chondrocytes.	English	Male and female	Multi-organ donors (18–53 years old) and patients undergoing total knee replacement (58–82 years old)	Non-random	Original article
28	Rosa SC	2009	33	Human	To compare the ability of normal and OA chondrocytes to regulate their glucose transport capacity in conditions of insufficient or excessive extracellular glucose and to identify the mechanisms involved and eventual deleterious consequences, namely the production of reactive oxygen species (ROS).	Experimental	1. Normal human chondrocytes adjust to variations in the extracellular glucose concentration by modulating GLUT-1 synthesis and degradation which involves the lysosome pathway. 2. Impaired GLUT-1 downregulation may constitute an important pathogenic mechanism by which conditions characterized by hyperglycemia, like DM, can promote degenerative changes in chondrocytes that can facilitate the progression of OA.	English	-	Multi-organ donors (28–35 years old) and patients undergoing total knee replacement surgery (52–77 years old)	Non-random	Original article
29	Rufino AT	2013	30	Human	1. Elucidating the subunit composition of K (ATP) channels expressed in human chondrocytes. 2. Determining whether K(ATP) channels play a role in regulating the abundance of two major glucose transporters in chondrocytes, GLUT-1 and GLUT-3, and the glucose transport capacity of human chondrocytes exposed to hyperglycemia-like conditions.	Experimental	K (ATP) channels are potential components of a broad glucose sensing apparatus that modulates glucose transporters and allows human chondrocytes to adjust to varying extracellular glucose concentrations. This function of K (ATP) channels seems to be impaired in OA chondrocytes.	English	-	Multi-organ donors (24–70 years old) and patients undergoing total knee replacement surgery (60–76 years old)	Non-random	Original article
30	Schett G	2013	927	Human	To evaluate if type 2 diabetes is an independent risk predictor for severe osteoarthritis (OA).	Cohort	Type 2 diabetes predicts the development of severe OA independent of age and BMI.	English	Male and	40–80 years old	Non-random	Original article

Table 3 (continued)

Number	Author	Publication year	Sample size	Study population	Aims	Methodology	Key finding	Language	Sex	Age	Type of sampling	Type of study
							Also a strong metabolic component was occurred in the pathogenesis of OA.		fe-male			
31	Skou ST	2018	-	Human	An evidence-based approach is greatly needed to address the future burden and associated costs of not only symptoms and impairments in OA, but also physical inactivity.	Letter to the editor	Recommendations for the implementation of exercise therapy are hard to dispute in light of strong supporting evidence, reduced potential harms compared with other common OA treatments such as analgesia and surgery, and its beneficial effects on overall health.	English	-	-	-	Letter to the editor
32	Thomas S	2018	-	-	Since diet may potentially affect OA, this study reviewed the literature on the relationship between nutrition and OA risk or progression, aiming to provide guidance for clinicians.	Review	1. A strong association between OA and raised serum cholesterol together with clinical effects in statin users suggests a potential benefit of reduction of cholesterol by dietary means. 2. Patients should ensure that they meet the recommended intakes for micronutrients such as vitamin K, which has a role in bone/cartilage mineralization. 3. Evidence for a role of vitamin D supplementation in OA is unconvincing.	English	-	-	-	Review article
33	Veronese N	2019	-	-	The consequence of T2DM on OA outcomes is a question of research interest.	Review	The selection of therapy to treat OA symptoms in patients with T2DM may require careful consideration of the evidence based to avoid untoward safety issues.	English	-	-	-	Conference
34	Wang C	2018	4	Human	This study investigates the effect of TGF-β or bone morphogenetic protein (BMP) signaling on energy metabolism in human articular chondrocytes (hACs).	Experimental	It was revealed distinct metabolic programs induced by TGF-β1and BMP2 in hACs, suggesting that the regulation of cellular metabolism may represent a new mechanism underlying the pathogenesis of OA.	English	-	-	Random	Original article
35	Wittenauer R	2013	-	Human	The issues presented by the lack of both reliable diagnostics and medicines that can reverse the progression of osteoarthritis must be addressed through further research in order to effectively reduce the large health and economic burden of osteoarthritis.	Review	Osteoarthritis is a chronic progressive disease that is one of the leading causes of disability among elderly populations throughout the world. It causes pain, disability and impaired movement, which places a large burden (both in terms of health and economics) on individuals, communities, and health systems. While there are several	English	-	-	-	Review article

Table 3 (continued)

Number	Author	Publication year	Sample size	Study population	Aims	Methodology	Key finding	Language	Sex	Age	Type of sampling	Type of study
							therapies available for symptomatic treatment that mitigate pain, there are no medicines that can reverse or halt the progression of the disease. This pharmaceutical gap must be addressed in order to reduce the burden of OA.					
35	Yang X	2018	12	Human	It was investigate the function of pyruvate kinase M2 (PKM2) on OA chondrocyte glycolysis and the collagen matrix generation in vitro.	Experimental	PKM2 modulates the glycolysis and extracellular matrix generation, providing the vital role of PKM2 on OA pathogenesis and a novel therapeutic target for OA.	English	-	Total knee arthroplasty patients (> 60 years old) and trauma amputation patients (< 35 years old)	Non-random	Original article
36	Yang Y	2018	70	Animal	To evaluate the potential protective effects of oral carnosine (CAR) supplements to ameliorate type 2 diabetes mellitus (T2DM)-induced osteoarthritis (OA) in rats and its mechanism.	Experimental	It was indicated that oral CAR had chondroprotective effects on T2DM-induced OA through the reactive oxygen species (ROS)/NF-κB pathway.	English	Male	-	Random	Original article

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