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KNEE OSTEOARTHRITIS AND DIABETES: UNRAVELLING THE LINK BETWEEN HYPERGLYCAEMIA AND JOINT HEALTH

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ABSTRACT:
Background: Degenerative joint disorders like osteoarthritis typically affect weight-bearing joints like the spine, hips, and knees. For people who experience it, pain and a decrease in joint flexibility can severely impair their quality of life, make it difficult to accomplish daily tasks, and limit their mobility. Hyperglycaemia, a defining feature of diabetes, can accelerate cartilage degradation, induce inflammation, and lead to joint degeneration. Additionally, the natural ability of cartilage to renew itself may be hampered in diabetics due to poor circulation and nerve damage, which would be harmful to joint health. Therefore, it is essential to look at the relationship between the symptoms of osteoarthritis in the knee and the hyperglycaemic state in diabetics. This study aims to determine whether knee osteoarthritis progression and the hyperglycaemic condition in diabetics are related.
Methods: For this systematic review, academic publications were retrieved from reputable search engines, including Google Scholar, IEEE Xplore, Springer, and Elsevier. The literature search used relevant keywords to find solutions to the study questions. The publications were thoroughly assessed utilising the PRISMA systematic review strategy.
Results: According to the review, hyperglycaemia and the progression of osteoarthritis in the knee are clearly related, with high glucose levels causing inflammation and cartilage deterioration. Compared to non-diabetics, diabetic individuals displayed more discomfort and functional impairments.
Conclusion: In osteoarthritis, poor glycaemic management can accelerate the degradation of the knee joint. Physiotherapy and diabetes control together may enhance joint health and general function.

KEYWORDS: osteoarthritis, diabetes, AGEs, cartilage, progression

INTRODUCTION

Osteoarthritis (OA) is a multifactorial retrogressive disease characterised by morphological and biochemical alterations to the joint capsule and synovial membrane, bone hypertrophy, and articular cartilage loss at the margins [1]. One of the most frequent reasons for disability in adulthood is OA. Due to several variables related to chronic osteoarthritis, activity limitation is one of the primary consequences [2-4]. These factors can also cause other related health issues [5,6]. The chance of developing OA rises dramatically every ten years beyond the age of forty-five, with the medial compartment of the knee being the most typical location of OA manifestation [7-9].
Approximately 470 million individuals globally suffer from diabetes mellitus (DM), a common non-communicable condition [10]. Chronic hyperglycaemia, which occurs throughout fasting and after meals, is a defining feature of DM. It is linked to advanced glycated end products (AGEs), oxidative stress, and low-grade inflammation, which harm the kidneys, heart, eyes, nerves, and other tissues [11,12]. Diabetic patients are thought to have faster OA progression and more challenging OA management [13]. OA and DM frequently coexist because of similar risk factors like ageing and obesity [14-16].
Research exploring the association between knee osteoarthritis (KOA) and diabetes is crucial because of its rising incidence and related risk factors, such as obesity, inflammation, and a sedentary lifestyle. Investigating the link between OA and diabetes can help improve preventive efforts, guide therapeutic management, and fill gaps in an underexplored area of healthcare.

Research questions

The PICO framework serves as the foundation for the research questions.

- What is the overall incidence of knee OA in diabetics?
- Does the course of knee OA get impacted by hyperglycaemia?
- How hyperglycaemia affect the knee joint health?

METHODOLOGY

Inclusion and exclusion criteria:

A few specified criteria were applied to the initial pick, which included the language used in the paper, the year of publication, and the subject's significance to the desired field.

- Research articles that were written entirely in English are included in this study.
- The review contains studies that evaluated diabetes or hyperglycaemia with osteoarthritis in the knee.
- To ensure relevance and current evidence, only papers published within the last 15 years were examined in the review.
- The review omitted studies that did not provide sufficient detail or methodological quality to evaluate the relationship of diabetes and hyperglycaemia with knee OA
- Articles from reputable publishers, such as Elsevier, Springer, Wiley, BMC, and others, were included in this study.
- After reading the abstracts of those research, the publications that describe the domain that the paper is presenting are included.

Search strategy

A comprehensive literature examination was done using databases like PubMed, Embase, the Cochrane Library, and Web of Science to investigate the connection between knee osteoarthritis and hyperglycaemia or diabetes. "Knee osteoarthritis," "diabetes", "hyperglycaemia" and "disease progression" were among the search phrases used. Only English-language papers up to 2024 were included in the search. To guarantee a thorough capture of pertinent research, the search phrases were combined and refined using Boolean operators (AND, OR). A PRISMA model, which depicts the information flow across the multiple review processes, has served as the foundation for the selection process for an article. It displays the quantity of retrieved articles along with the information that is left out. The PRISMA framework is shown in Figure 1.

Resources

This research first looked via credible academic search engines like Google Scholar, IEEE Xplore, Springer, and Elsevier to obtain material for the study. Our primary focus during the search was on academic publications that covered the particular topic and were released between 2009 and 2024.

Selection of databases

The paper was located and selected from a number of trustworthy sources, including Web of Science (WOS), Scopus, and Science Citation Index Expanded (SCIE), based on titles relevant to our inquiry. These databases were chosen because of their reputation for academic dependability as well as their broad coverage of journal articles in a variety of academic fields.

Selection of the paper

Following an in-depth analysis of journals associated with our primary keywords, 110 papers were selected for this methodical assessment. These publications were chosen for our study according to predefined criteria that indicated their eligibility. A graphical representation of the search results for this review is shown in Figure 1.

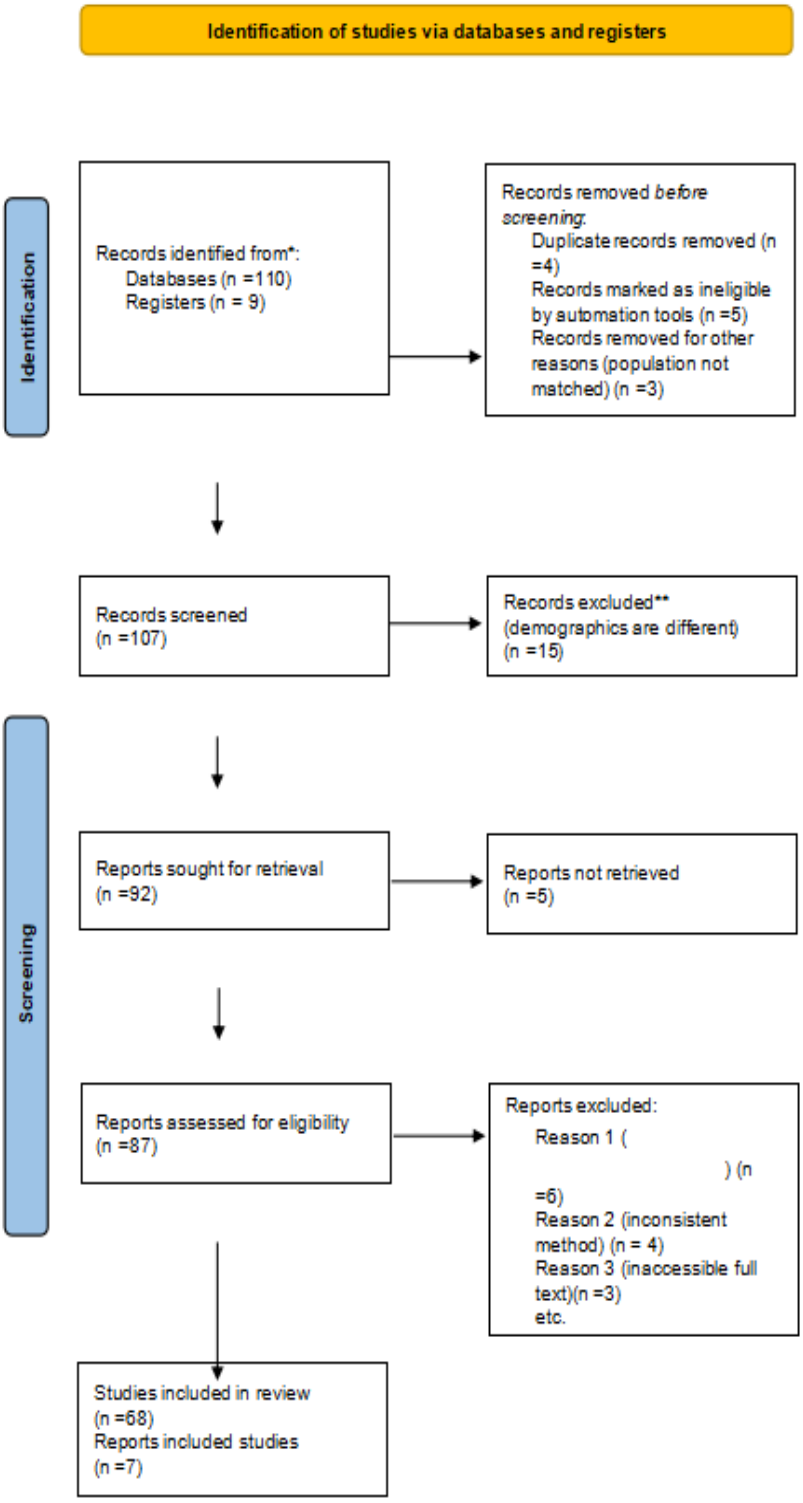

Figure 1: PRISMA framework

LITERATURE REVIEW

A literature analysis on the association between KOA and diabetes is useful because it synthesises available research, finds knowledge gaps, and shows patterns of similar risk variables. Researchers can better understand how diabetes affects OA progression, guide clinical decision-making, and create focused therapies by analysing available information. Furthermore, a thorough literature evaluation can lay the groundwork for future studies and influence healthcare practices to improve outcomes for individuals with both illnesses.

Association of knee osteoarthritis incident with diabetes:

In a study involving 495,327 participants in cross-sectional analyses (2006–2010) and 16,875 participants in longitudinal analyses (2014–2016), Carvalho-e-silva et al. came to the conclusion that those with type 2 diabetes are more likely to experience discomfort in their knee, hip, shoulder, or neck [17].

Schett et al. implemented population-based cohort research that followed 927 men and women between the ages of 40 and 80 over 20 years using age and a sex-stratified random sample. The investigation concluded that Type 2 diabetes, regardless of age or BMI, predicts the development of severe OA [18].
Ahmed et al. (2017) stated that hyperglycaemia may encourage cartilage deterioration and joint inflammation [19]. Therefore, In the following table (Table 1), we will try to ascertain the usual incidence of osteoarthritis in people with diabetes.

Table 1: Incidence of knee OA in diabetic persons

Author	Aim of the study	Study design	Outcome measures	Sample size	Findings	limitations
Pathak et al [20]	to ascertain the risk factors and incidence of OA* in the hands and knees in people with diabetes	Cross-sectional	X-ray, modified Kuppuswamy SES scale,	258	People with diabetes have a greater chance of developing OA*.	Due to the cross-sectional design, no causal link was discovered. Second, the study is hospital-based with a small sample size.
AlKuwaity et al [21]	to ascertain the incidence and contributing variables of OA* in the knee in the elderly	Cross-sectional	predesigned questionnaire	238	Knee OA* is linked to diabetes, hypertension, female sex, and age.	Sample size is small
Afifi et al [22]	to determine the primary knee OA* incidence in a group of Egyptian individuals suffering from MetS** and to investigate the connection between knee OA's * radiographic, functional, and clinical manifestations and the metabolic syndrome and its elements.	Cross-sectional	WOMAC***, Kellgren Lawrence radiographic rating scale, BMI (Body Mass Index)	60	Knee OA*, which is associated with significant pain, an elevated impaired functioning score, and more extensive radiographic abnormalities, is often identified in patients with MetS**. The most prevalent elements of MetS** for patients having knee OA* are abdominal obesity, hypertension, and diabetes.	Treatment approaches are not discussed
Liu et al [23]	for determining the frequency of knee OA* and the factors that contribute to it	Cross-sectional	interviewer-administered questionnaire, X-ray	3428	There is a correlation between diabetes, metabolic syndrome, and knee OA*.	The only diagnosis method applied was symptomatic. The survey's information came from a single, limited area's epidemiology
Zheng et al [24]	to evaluate the connection between glycaemic management and the risk of symptomatic knee OA*	cohort	glycosylated haemoglobin (HbA1c) level, fasting blood glucose level	10730	An increased risk of developing incident knee OA* has been closely correlated with elevated HbA1c and fasting blood glucose levels.	Late complications were not studied

Note:
*Osteoarthritis,

**metabolic syndrome,
***Western Ontario and Mc-Master University Osteoarthritis Index

The association between knee OA symptoms and progression and hyperglycaemia:
Chen et al. investigated the relationship between cartilage degradation and alterations in the microstructure, strength, and subchondral bone remodelling in the knees of T2D patients. They concluded that aberrant subchondral bone remodelling and mechanical and microstructural deficiencies are the hallmarks of type 2 diabetes knees and are linked to worsened cartilage deterioration [25]. Nielen et al. demonstrate in a cross-sectional study involving 3491 participants that patients with type 2 diabetes are more likely to get knee OA and pain [26].
Yoshimura and colleagues researched to elucidate the connection between the onset of knee KOA and the metabolic syndrome (MetS) elements of dyslipidaemia, hypertension, obesity, and decreased glucose tolerance. After much consideration, they concluded that MetS and OA are strongly related [27].
Several research endeavours have been conducted to ascertain the correlation between hyperglycaemia and the characteristics and advancement of knee osteoarthritis manifestations. Table 2 below provides an overview of some of the articles.

Table 2: Hyperglycaemia and knee OA symptoms and progression

Author	Aim of the study	Study design	Outcome measures	Sample size	Findings	limitations
Alenazi et al [28]	To investigate if T2M* and the degree of pain in individuals with localized OA** are related.	Retrospective study	Numerical pain rating scale, HbA1c value	819	T2D* was associated with higher pain intensity in those with localized OA**, and inadequate glucose control was associated with higher pain levels in those with both T2D* and localized OA**.	inadequate knowledge of radiography or OA** grading. The patient's diabetes treatment regimen is not taken into account either.
Foreman et al [29]	to examine changes in knee joint radiography over eight years in individuals with and without diabetes mellitus.	Longitudinal	x-ray	295	People with diabetes have a significantly higher incidence of degenerative joint disease, which also worsens, occurs more frequently, and advances more quickly in them.	The level of hyperglycaemia is not considered
Rogers-soeder et al [30]	To investigate correlations between incident radiographic knee OA** and diabetes and indicators of aberrant glucose metabolism.	cohort	x-ray, fasting glucose level	987	The probability of incidence of radiographic knee OA** was not correlated with diabetes mellitus or increased levels of markers of impaired glucose utilization after adjusting for BMI.	Only fasting glucose level is taken into consideration. Data on diabetes type is not available. Only tibiofemoral OA** is studied
Alenazi et al [31]	to look at the connection between diabetes and the pattern of knee pain as well as the link between the two.	Cross-sectional	Numerical rating scale	1390	Distribution of knee discomfort on both sides, as well as increased pain severity, were linked to diabetes	The cross-sectional design of the study makes it impossible to determine a

					mellitus.	causal relationship between diabetes and knee discomfort. There was no availability of glucose control.
Eitner et al [32]	to determine if those with OA** and diabetes have worse knee pain and overall health	Cross-sectional	KOOS***, numeric rating Scale,	2481	When compared to OA** participants without diabetes, those with diabetes reported more physical and psychological problems as well as severe knee pain.	Owing to the study's design, the correlation between diabetes and OA** results
Kalamegam et al [33]	To better understand the connection between diabetes and functional impairment caused by OA**.	Cross-sectional	WOMAC▲	290	Diabetes aggravates OA** patients' functional impairment, especially impairing their total disability and physical function.	self-reported data, cross-sectional methodology, and absence of longitudinal follow-up.
Eymard et al [34]	to ascertain how knee osteoarthritis evolves radiographically and how diabetes and other components of the metabolic syndrome influence this	Post hoc analysis	WOMAC▲, VAS▲▲, X-ray	559	For patients with established knee OA**, only T2DM* predicted reduced joint space.	The study was based only on medical history, silent or unrecognised metabolic diseases were ignored
Ganeb et al [35]	to evaluate the severity and trends of knee pain in individuals with OA** and diabetes mellitus.	Cross-sectional	WOMAC▲, KOOS***, VAS▲▲	100	Diabetes duration showed a statistically significant positive correlation with VAS▲▲, KOOS***, and WOMAC▲.	The sex difference was not taken into consideration

Note:
*Type 2 diabetes mellitus
**osteoarthritis,
***Knee Injury and Osteoarthritis Outcome Score,
▲Western Ontario and Mc-Master University Osteoarthritis Index
▲▲visual analogue scale

Hyperglycaemia and its effect on the knee joint:

Ibrahim Njoto investigated in 2021 the effect of hyperglycaemia on the emergence of microscopic morphological damage in OA cartilage employing rat models. The length of hyperglycaemia increased the amount of cartilage deterioration in the OA group when compared to the DM group. A number of sclerotic conditions, a more severe reduction in the columnar configuration of chondrocytes, a fissure in the cartilage that reached the middle layer, a change in matrix integrity, and a deeper abrasiveness of the superficial articular layer were found to be caused by an increase in the duration of hyperglycaemia [36].

Using autopsies of people without a history of joint disease, Ribero et al. examined the effects of increased insulin and glucose, characteristics of type 2 diabetes, on cartilage homeostasis by extracting normal human articular cartilage from the tibial plateaus and femoral condyles. An examination of the cultured cell line through histological analysis suggests that diminished autophagy could be one of the processes underlying the rapid degeneration of cartilage in diabetics [37].

Patients with type 2 diabetes have OA cartilage that responds more strongly to inflammatory stress. Deficits in nuclear factor-erythroid 2-related factor (Nrf-2) antioxidant system could account for the increased inflammatory response of OA cartilage in T2DM patients [38].

Thus, a better understanding of how metabolic disorders can affect joint health requires an examination of the link between diabetes, hyperglycaemia, and the knee joint. The function of joints and general movement may be significantly impacted by diabetes and high blood sugar levels. Researchers might improve patient outcomes and lessen the burden of joint-related difficulties by exploring this relationship as it may provide light on potential risk factors for joint-related problems in diabetic patients and help create early intervention techniques. Better management and preventative techniques for the treatment of diabetes patients may also benefit from this knowledge. Table 3 summarizes a few studies looking at the correlation between diabetes and knee OA.

Table 3: Consequences of hyperglycaemia and diabetes on the knee joint

Author	Aim of the study	Study design	Outcome measures	Sample size	Findings	limitations
Neuman et al [39]	to use magnetic resonance-based T2 relaxation time measurements to look into the long-term impact of diabetes on cartilage degradation over 24 months.	Cross-sectional	Magnetic resonance-based T2 relaxation time, Kellgren–Lawrence score	392	Diabetes seems to be associated with a higher probability of early osteoarthritis and faster articular cartilage degradation in the knee.	It is unclear what kind of diabetes there is, how long it has been there, or how old the patient was when diagnosed.
Dubey et al [40]	to assess the correlation between both types of diabetes and knee osteoarthritis in all age groups and genders.	experimental	phenome-wide association study, histopathologic and Western blot studies	37,353 T1DM*, 1,218, 254 T2DM** (dry test),	Results show a substantial correlation between diabetes mellitus and knee osteoarthritis. Deteriorated articular cartilage and proteoglycans are indicated by the presence of AGE***, MMP-1▲, and decreased levels of cartilage-specific proteins (Col II ▲▲, SOX9▲▲▲, AGN†)	Clinical parameters and mechanistic insight were not examined.
M.M. McNulty [41]	to ascertain whether and how hyperglycaemia influences cellular phenotype to encourage faster osteoarthritis progression.	experimental	Histological analysis	11 mice model	When cultivated in vitro under hyperglycaemic circumstances, chondrocytes outperformed normal glucose controls in terms of cellular alkaline phosphatase activity.	The mice with hyperglycaemia weighed a little bit more than the controls.
Hamada et al [42]	to assess how insulin and TNF†† function in	Experimental	Immunohistochemistry, Immunofluorescence,	Human tissue from	The advanced progression of osteoarthritis observed in	The effects of diabetes mellitus duration

	triggering osteoarthritis alterations		Immunoprecipitation and western blot analysis	17 subjects	T2DM** appears to be mediated by TNF††. Insulin has an anti-inflammatory and protective function in the synovium; however, diabetes with insulin resistance may reduce this function and increase osteoarthritis.	was not studied
Tsai et al [43]	to research the molecular signalling pathways that cause human synovial fibroblast cells to produce VEGF††† when exposed to elevated glucose levels.	experimental	Western blotting	Not specified	According to the findings, human synovial fibroblasts express more VEGF††† when exposed to hyperglycaemia	No research was done on the effects of diabetes mellitus duration.
Wen et al [45]	to evaluate the subchondral bone loss in individuals with osteoarthritis who also have type 2 diabetes and hypertension as comorbidities.	Cross-sectional	CT scan, histological analysis	43	These findings suggest a biological relationship between the loss of bone at the subchondral plate of the bone in knee osteoarthritis and the coexisting diseases of hypertension and type 2 diabetes.	Small sample size, due to the study design causative effects of comorbidities were not addressed, the clinical record and non-routine examination were the sources of the clinical and laboratory data.
Davies-Tuck et al [46]	to investigate, in adults without knee complaints or diabetes, the connection between serum glucose concentration and knee anatomy.	longitudinal cohort	Fasting serum glucose, MRI	179	Adverse structural alterations at the knee were linked to higher fasting blood glucose concentration in women, but not in males.	There existed a delay between the measurement of fasting glucose and the initial assessment of knee anatomy.

Note:
*type 1 diabetes mellitus
**type 2 diabetes mellitus
***advanced glycation end products
▲matrix-metalloprotienase-1

▲▲Type II Collagen
▲▲▲SRY-BOX transcription factor 9
†aggrecan
††tumour necrosis factor
†††vascular endothelial growth factor

DISCUSSION

Changes in joint mechanics and anatomy, along with increasing articular cartilage loss and degeneration, are the hallmarks of KOA, the most common inflammatory lesion in orthopaedics. Afterwards, the meniscus, periarticular ligaments, subchondral bone changes, and synovium are affected [46-48]. Research indicates that those with diabetes have a significantly higher risk of developing osteoarthritis in their knees when compared to the rest of the population [49,50]. Both metabolic and biomechanical variables are thought to have a role in the co-occurrence of diabetes and knee OA [51-53]. Many studies indicate that the systemic effects of obesity, hyperglycaemia, and low-grade chronic inflammation, which together cause degenerative changes in the knee joint, increase the prevalence of OA in people with diabetes [54-57]. This increased incidence emphasises how crucial it is to treat diabetes as a major risk factor when controlling and treating knee OA. Nielen et al. used a population-based case-control study involving 94609 participants to assess the risk of hip or knee replacement in adults with diabetes mellitus. The current study's findings corroborate the notion that women's OA is associated with hyperglycaemia and other elements of the metabolic syndrome [58].

There has been a lot of discussion about the connection between knee OA symptoms and advancement and hyperglycaemia. Advanced glycation end products (AGEs) and elevated oxidative stress are linked to chronic hyperglycaemia, and both conditions can worsen inflammatory pathways [59-62]. For those with diabetes, this results in increased joint discomfort, and stiffness, and accelerates cartilage degradation [63,64]. Individuals with uncontrolled blood sugar levels are more likely than those without diabetes to have more severe knee OA symptoms, and the problem advances more quickly [65-67].

Furthermore, because hyperglycaemia alters the biochemistry of the subchondral bone and cartilage, it makes it more difficult for these tissues to heal and function normally, endangering the skeletal strength of the knee joint [68]. The buildup of AGEs in cartilage impairs the collagen matrix, which lowers the tissue's capacity to tolerate mechanical stress—a crucial function for joint health [69, 70]. Moreover, inflammation brought on by hyperglycaemia damages synovial tissue, increasing joint effusion and cartilage deterioration [71,72]. Also, the long-term hyperglycaemia-associated subchondral bone sclerosis accelerates joint degradation and increases the diminution of the joint aperture seen in advanced OA [73]. Comparing the levels of cartilage oligomeric matrix protein (COMP) in synovial fluid (SF) and glycaemic control measures in T2DM patients with primary KOA against those without, Vartti et al. investigated the connection between KOA and T2DM. Their results showed a robust correlation between the two disorders; also, T2D may affect SF COMP levels in individuals who had or did not have primary KOA [74].

In summary, there are several ways in which diabetes—specifically, hyperglycaemia—and osteoarthritis of the knee interact. The emergence of and symptoms of osteoarthritis OA are significantly influenced by hyperglycaemia; nevertheless, because of its direct impact on the architecture of the knee joint, complete therapy approaches that target both metabolic regulation and joint preservation are necessary. Reducing the burden of knee OA in diabetes patients requires early identification of at-risk individuals and a multidisciplinary approach integrating joint-specific medicines and glycaemic management.

There are some limitations to the study. For the review, more high-quality literature was required. Although OA knee cases were our primary focus, other joints also require investigation. Investigating any local or general osteoarthritis difficulties that can exacerbate the disease is also necessary. Although this evaluation revealed that hyperglycemia influences the course of osteoarthritis, more research utilizing biomarker analysis and radiography should be conducted.

CONCLUSION

The correlation between knee osteoarthritis OA and hyperglycaemia is intricate and multidimensional. Being a defining feature of diabetes, hyperglycaemia adds to oxidative stress, aberrant cartilage metabolism, and systemic inflammation, all of which may hasten the development of knee OA. Increased susceptibility to joint injury, articular cartilage deterioration, and disruption of tissue homeostasis are among the reasons why elevated glucose levels might negatively affect joint function. On the other hand, knee OA's discomfort and limited mobility can have a detrimental effect on one's level of physical activity, which exacerbates hyperglycaemia and perpetuates a vicious loop between the two disorders.

REFERENCES

1. Madry, H., Luyten, F. P., & Facchini, A. (2012). Biological aspects of early osteoarthritis. Knee Surg Sports Traumatol Arthrosc, 20, 407-422.
2. McDonough, C. M., & Jette, A. M. (2010). The contribution of osteoarthritis to functional limitations and disability. Clin Geriatr Med.26(3), 387-399.
3. Machado, G. P., Gignac, M. A., & Badley, E. M. (2008). Participation restrictions among older adults with osteoarthritis: a mediated model of physical symptoms, activity limitations, and depression. Arthritis Care Res 59(1), 129-135.
4. van Dijk GM, Veenhof C, Schellevis F, Hulsmans H, Bakker JP, Arwert H, Dekker JH, Lankhorst GJ, Dekker J. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. BMC Musculoskelet Disord. 2008 Dec;9:1-0.

5. Vogiatzis, I., Zakynthinos, G., & Andrianopoulos, V. (2012). Mechanisms of physical activity limitation in chronic lung diseases. Pulm med. 2012(1), 634761
6. Jones, N. L., & Killian, K. J. (2000). Exercise limitation in health and disease. N Engl J Med. 343(9), 632-641.
7. Vincent, K. R., Conrad, B. P., Fregly, B. J., & Vincent, H. K. (2012). The pathophysiology of osteoarthritis: a mechanical perspective on the knee joint. PM R, 4(5), S3-S9.
8. Wise, B. L., Niu, J., Yang, M., Lane, N. E., Harvey, W., Felson, D. T., ... & Multicenter Osteoarthritis (MOST) Group. (2012). Patterns of compartment involvement in tibiofemoral osteoarthritis in men and women and in whites and African Americans. Arthritis Rheum. 64(6), 847-852.
9. Lawrence, R. C., Felson, D. T., Helmick, C. G., Arnold, L. M., Choi, H., Deyo, R. A., ... & National Arthritis Data Workgroup. (2008). Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. Arthritis Rheum. 58(1), 26-35.
10. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, Song X, Ren Y, Shan PF. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep. 2020 Sep 8;10(1):1-1.
11. Verzijl N, Bank RA, TeKoppele JM, DeGroot J. AGEing and osteoarthritis: a different perspective. Curr Rheumatol Rev. 2003 Sep 1;15(5):616-22.
12. King KB, Rosenthal AK. The adverse effects of diabetes on osteoarthritis: update on clinical evidence and molecular mechanisms. Osteoarthritis cartilage. 2015 Jun 1;23(6):841-50.
13. Courties A, Sellam J. Osteoarthritis and type 2 diabetes mellitus: what are the links?. Diabetes Res Clin Pract. 2016 Dec 1;122:198-206.
14. Alenazi AM, Alhowimel AS, Alshehri MM, Alqahtani BA, Alhwoaimel NA, Segal NA, Kluding PM. Osteoarthritis and diabetes: Where are we and where should we go?. Diagn. 2023 Apr 10;13(8):1386.
15. Harman D. The biologic clock: the mitochondria?. J Am Geriatr Soc. 1972 Apr;20(4):145-7.
16. Trounce I, Byrne E, Marzuki S. Decline in skeletal muscle mitochondrial respiratory chain function: possible factor in ageing. Lancet. 1989 Mar 25;333(8639):637-9.
17. Carvalho-e-Silva AP, Ferreira ML, Ferreira PH, Harmer AR. Does type 2 diabetes increase the risk of musculoskeletal pain? Cross-sectional and longitudinal analyses of UK biobank data. Semin Arthritis Rheum. 2020 Aug 1 (Vol. 50, No. 4, pp. 728-734). WB Saunders.
18. Schett G, Kleyer A, Perricone C, Sahinbegovic E, Iagnocco A, Zwerina J, Lorenzini R, Aschenbrenner F, Berenbaum F, D'Agostino MA, Willeit J. Diabetes is an independent predictor for severe osteoarthritis: results from a longitudinal cohort study. Diabetes care. 2013 Feb 1;36(2):403-9.
19. Ahmed HS, Tahir NT. Association between diabetes mellitus and knee osteoarthritis. Iraq Med. J. 2017 Oct 2;1(3).
20. Pathak BG, Rahini S, Manapurath RM. The proportion of hand and knee osteoarthritis and its associated risk factors among an urban diabetic population. "Int J Acad Med. 2022 Apr 1;8(2):102-8.
21. AlKuwaity KW, Mohammad TN, Hussain MA, Alkhanani AJ, Ali AM. Prevalence and determinant factors of osteoarthritis of the knee joint among elderly in Arar, KSA. Egypt J Hosp Med. 2018 Jul 1;72(9):5173-7.
22. Afifi AE, Shaat RM, Gharbia OM, Boghdadi YE, Eshmawy MM, El-Emam OA. Osteoarthritis of knee joint in metabolic syndrome. Clin Rheumatol. 2018 Oct;37:2855-61.
23. Liu Y, Zhang H, Liang N, Fan W, Li J, Huang Z, Yin Z, Wu Z, Hu J. Prevalence and associated factors of knee osteoarthritis in a rural Chinese adult population: an epidemiological survey. BMC Public Health. 2015 Dec;16:1-8.
24. Zheng J, Huang X, Huang J, Meng B, Li F, Liu H, Chen L, Zhou R, Zou M, Wu X. Association of diabetes mellitus status and hyperglycaemia with symptomatic knee osteoarthritis. Arthritis Care Res. 2023 Mar;75(3):509-18.
25. Chen Y, Huang YC, Yan CH, Chiu KY, Wei Q, Zhao J, Guo XE, Leung F, Lu WW. Abnormal subchondral bone remodeling and its association with articular cartilage degradation in knees of type 2 diabetes patients. Bone Res. 2017 Nov 7;5(1):1-2.
26. Nielen JT, Emans PJ, van den Bemt B, Dagnelie PC, Schram MT, Stehouwer CD, Schaper NC, Denissen KF, de Vries F, Boonen A. Association of type 2 diabetes mellitus with self-reported knee pain and clinical knee osteoarthritis: the Maastricht study. Diabetes & metabolism. 2018 Jun 1;44(3):296-9.
27. Yoshimura N, Muraki S, Oka H, Tanaka S, Kawaguchi H, Nakamura K, Akune T. Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. Osteoarthritis cartilage. 2012 Nov 1;20(11):1217-26.
28. Alenazi AM, Obaidat SM, Alshehri MM, Alothman S, Gray C, Rucker J, Waitman LR, Kluding PM. Type 2 diabetes affects joint pain severity in people with localized osteoarthritis: a retrospective study. Pain Med. 2020 May 1;21(5):1025-31.
29. Foreman SC, Neumann J, Joseph GB, Nevitt MC, Liu F, Lynch JA, McCulloch CE, Link TM. Subjects with diabetes mellitus have higher prevalence, incidence and progression of knee osteoarthritis assessed over 8 years: data from the osteoarthritis initiative. Osteoarthritis Cartilage. 2018 Apr 1;26:S223.
30. Rogers-Soeder TS, Lane NE, Walimbe M, Schwartz AV, Tolstykh I, Felson DT, Lewis CE, Segal NA, Nevitt MC, Multicenter Osteoarthritis (MOST) Study Group. Association of diabetes mellitus and biomarkers of abnormal glucose metabolism with incident radiographic knee osteoarthritis. Arthritis care res. 2020 Jan;72(1):98-106.
31. Alenazi AM, Alshehri MM, Alothman S, Alqahtani BA, Rucker J, Sharma N, Segal NA, Bindawas SM, Kluding PM. The association of diabetes with knee pain severity and distribution in people with knee osteoarthritis using data from the osteoarthritis initiative. Sci rep. 2020 Mar 4;10(1):3985.

32. Eitner A, Culvenor AG, Wirth W, Schaible HG, Eckstein F. Impact of diabetes mellitus on knee osteoarthritis pain and physical and mental status: data from the osteoarthritis initiative. Arthritis care research. 2021 Apr;73(4):540-8.
33. Kalamegam, S., Shah, P. B., & Damodaran, A. (2024). Diabetes and Functional Impairment in Osteoarthritis: Investigating Correlations, Associations, and Progression. Cureus, 16(7).
34. Eymard F, Parsons C, Edwards MH, Petit-Dop F, Reginster JY, Bruyère O, Richette P, Cooper C, Chevalier X. Diabetes is a risk factor for knee osteoarthritis progression. Osteoarthritis cartilage. 2015 Jun 1;23(6):851-9.
35. Ganeb SS, Egila SA, Hasan WA, Freeh EE. The Association of Diabetes with Knee Pain Severity and Patterns in People with Knee Osteoarthritis. Egypt J Hosp Med. 2023 Jul 1;92(1).
36. Njoto I. Hyperglycaemia duration impact on anatomical damage level of osteoarthritic articular cartilage in rat models with diabetes mellitus type 1. Russ Open Med J. 2021;10(3):304.
37. Ribeiro M, de Figueroa PL, Blanco FJ, Mendes AF, Caramés B. Insulin decreases autophagy and leads to cartilage degradation. Osteoarthritis Cartilage. 2016 Apr 1;24(4):731-9.
38. Vaamonde-Garcia C, Courties A, Pigenet A, Laiguillon MC, Sautet A, Houard X, Kerdine-Römer S, Meijide R, Berenbaum F, Sellam J. The nuclear factor-erythroid 2-related factor/heme oxygenase-1 axis is critical for the inflammatory features of type 2 diabetes–associated osteoarthritis. J Biol Chem. 2017 Sep 1;292(35):14505-15.
39. Neumann J, Hofmann FC, Heilmeier U, Ashmeik W, Tang K, Gersing AS, Schwaiger BJ, Nevitt MC, Joseph GB, Lane NE, McCulloch CE. Type 2 diabetes patients have accelerated cartilage matrix degeneration compared to diabetes free controls: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2018 Jun 1;26(6):751-61.
40. Dubey NK, Ningrum DN, Dubey R, Deng YH, Li YC, Wang PD, Wang JR, Syed-Abdul S, Deng WP. Correlation between diabetes mellitus and knee osteoarthritis: a dry-to-wet lab approach. Int J Mol Sci. 2018 Oct 3;19(10):3021.
41. McNulty MM, Schroeder WG, Bucknell AL, Rosenthal AK, King KB. Hyperglycaemia increases incidence of osteophyte formation in a mouse model of osteoarthritis. Osteoarthritis Cartilage. 2015 Apr 1;23:A268-9.
42. Hamada D, Maynard R, Schott E, Drinkwater CJ, Ketz JP, Kates SL, Jonason JH, Hilton MJ, Zuscik MJ, Mooney RA. Insulin suppresses TNF-dependent early osteoarthritic changes associated with obesity and type 2 diabetes. Arthritis Rheum (Hoboken). 2016 Jun;68(6):1392.
43. Tsai CH, Chiang YC, Chen HT, Huang PH, Hsu HC, Tang CH. High glucose induces vascular endothelial growth factor production in human synovial fibroblasts through reactive oxygen species generation. Biochim Biophys Acta. 2013 Mar 1;1830(3):2649-58.
44. Wen CY, Chen Y, Tang HL, Yan CH, Lu WW, Chiu KY. Bone loss at subchondral plate in knee osteoarthritis patients with hypertension and type 2 diabetes mellitus. Osteoarthritis Cartilage. 2013 Nov 1;21(11):1716-23.
45. Davies-Tuck ML, Wang Y, Wluka AE, Berry PA, Giles GG, English DR, Cicuttini FM. Increased fasting serum glucose concentration is associated with adverse knee structural changes in adults with no knee symptoms and diabetes. Maturitas. 2012 Aug 1;72(4):373-8.
46. Du X, Liu ZY, Tao XX, Mei YL, Zhou DQ, Cheng K, Gao SL, Shi HY, Song C, Zhang XM. Research progress on the pathogenesis of knee osteoarthritis. Orthop Surg. 2023 Sep;15(9):2213-24.
47. Doherty M. Risk factors for progression of knee osteoarthritis. Lancet. 2001 Sep 8;358(9284):775-6.
48. Sharma L. Osteoarthritis of the knee. N Engl J Med. 2021 Jan 7;384(1):51-9.
49. Cheng YJ, Imperatore G, Caspersen CJ, Gregg EW, Albright AL, Helmick CG. Prevalence of diagnosed arthritis and arthritis-attributable activity limitation among adults with and without diagnosed diabetes: United States, 2008–2010. Diabetes care. 2012 Aug 1;35(8):1686-91.
50. Louati K, Vidal C, Berenbaum F, Sellam J. Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. RMD open. 2015 Jun 1;1(1):e000077.
51. Badley EM, Zahid S, Wilfong JM, Perruccio AV. Relationship between body mass index and osteoarthritis for single and multisite osteoarthritis of the hand, hip, or knee: findings from a canadian longitudinal study on aging. Arthritis Care Res. 2022 Nov;74(11):1879-87.
52. Kuusalo L, Felson DT, Wang N, Lewis CE, Torner J, Nevitt MC, Neogi T, Multicenter Osteoarthritis Study Group. Metabolic osteoarthritis–relation of diabetes and cardiovascular disease with knee osteoarthritis. Osteoarthritis Cartilage. 2021 Feb 1;29(2):230-4.
53. Visser AW, De Mutsert R, Le Cessie S, Den Heijer M, Rosendaal FR, Kloppenburg M. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. Ann Rheum Dis. 2015 Oct 1;74(10):1842-7.
54. Courties A, Gualillo O, Berenbaum F, Sellam J. Metabolic stress-induced joint inflammation and osteoarthritis. Osteoarthritis Cartilage. 2015 Nov 1;23(11):1955-65.
55. Tanwar P, Naagar M, Maity MK. Relationship between Type 2 Diabetes Mellitus and Osteoarthritis. Int Res J Pharm Med Sci. 2023;6(2):59-70.
56. Halabitska I, Babinets L, Oksenych V, Kamyshnyi O. Diabetes and Osteoarthritis: Exploring the Interactions and Therapeutic Implications of Insulin, Metformin, and GLP-1-Based Interventions. Biomedicines. 2024 Jul 23;12(8):1630.
57. Kulkarni P, Martson A, Vidya R, Chitnavis S, Harsulkar A. Pathophysiological landscape of osteoarthritis. Adv Clin Chem. 2021 Jan 1;100:37-90.
58. Nielen JT, Emans PJ, Dagnelie PC, Boonen A, Lalmohamed A, de Boer A, van den Bemt BJ, de Vries F. Severity of diabetes mellitus and total hip or knee replacement: a population-based case–control study. Medicine. 2016 May 1;95(20):e3739.
59. Nowotny K, Jung T, Höhn A, Weber D, Grune T. Advanced glycation end products and oxidative stress in type 2 diabetes mellitus. Biomolecules. 2015 Mar 16;5(1):194-222.

60. Li Q, Wen Y, Wang L, Chen B, Chen J, Wang H, Chen L. Hyperglycaemia-induced accumulation of advanced glycosylation end products in fibroblast-like synoviocytes promotes knee osteoarthritis. Exp Mol Med. 2021 Nov;53(11):1735-47.
61. Saudek DM, Kay J. Advanced glycation endproducts and osteoarthritis. Curr Rheumatol Rep. 2003 Jan;5(1):33-40.
62. Concetta Aiello F, Maria Trovato F, Anna Szychlinska M, Imbesi R, Castrogiovanni P, Loreto C, Musumeci G. Molecular links between diabetes and osteoarthritis: the role of physical activity. Curr Diabetes Rev. 2017 Feb 1;13(1):50-8.
63. Dubey NK, Wei HJ, Yu SH, Williams DF, Wang JR, Deng YH, Tsai FC, Wang PD, Deng WP. Adipose-derived stem cells attenuates diabetic osteoarthritis via inhibition of glycation-mediated inflammatory cascade. Aging Dis. 2019 Jun;10(3):483.
64. Wang HJ, Giambini H, Chen JW, Wang QS, Hou HG, Luo SM, Chen JY, Zhuang TF, Chen YF, Wu TT, Zha ZG. Diabetes mellitus accelerates the progression of osteoarthritis in streptozotocin-induced diabetic mice by deteriorating bone microarchitecture, bone mineral composition, and bone strength of subchondral bone. Ann Transl Med. 2021 May;9(9).
65. Larkin ME, Barnie A, Braffett BH, Cleary PA, Diminick L, Harth J, Gatcomb P, Golden E, Lipps J, Lorenzi G, Mahony C. Musculoskeletal complications in type 1 diabetes. Diabetes care. 2014 Jul 1;37(7):1863-9.
66. Franke S, Rüster C, Pester J, Hofmann G, Oelzner P, Wolf G. Advanced glycation end products affect growth and function of osteoblasts. Clin Exp Rheumato. 2011 Aug;29(4):650.
67. Laiguillon MC, Courties A, Houard X, Auclair M, Sautet A, Capeau J, Fève B, Berenbaum F, Sellam J. Characterization of diabetic osteoarthritic cartilage and role of high glucose environment on chondrocyte activation: toward pathophysiological delineation of diabetes mellitus-related osteoarthritis. Osteoarthritis Cartilage. 2015 Sep 1;23(9):1513-22.
68. Chen YJ, Chan DC, Lan KC, Wang CC, Chen CM, Chao SC, Tsai KS, Yang RS, Liu SH. PPARγ is involved in the hyperglycaemia-induced inflammatory responses and collagen degradation in human chondrocytes and diabetic mouse cartilages. J Orthop Res. 2015 Mar;33(3):373-81.
69. Weiss RE, Gorn AH, Nimni ME. Abnormalities in the biosynthesis of cartilage and bone proteoglycans in experimental diabetes. Diabetes. 1981 Aug 1;30(8):670-7.
70. Kayal RA, Tsatsas D, Bauer MA, Allen B, Al-Sebaei MO, Kakar S, Leone CW, Morgan EF, Gerstenfeld LC, Einhorn TA, Graves DT. Diminished bone formation during diabetic fracture healing is related to the premature resorption of cartilage associated with increased osteoclast activity. J Bone Miner Res. 2007 Apr 1;22(4):560-8.
71. Gui T, Lin YK, Huan SW, Li YH, Wang BH, Yang J, Gu RH, Liu Q, Li ZY, Li SM, Chen YF. Elevated expression of ICAM-1 in synovium is associated with early inflammatory response for cartilage degeneration in type 2 diabetes mellitus. J Cell Biochem. 2019 Aug;120(8):13177-86.
72. Njoto I, Soekanto A, Ernawati E, Abdurrachman A, Kalim H, Handono K, Soeatmadji DW, Fatchiyah F. Chondrocyte intracellular matrix strain fields of articular cartilage surface in hyperglycaemia model of rat: cellular morphological study. Med Arch. 2018 Nov;72(5):348.
73. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, Kington RS, Lane NE, Nevitt MC, Zhang Y, Sowers M. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med. 2000 Oct 17;133(8):635-46.
74. Arellano Perez Vertti RD, Aguilar Muniz LS, Moran Martinez J, Gonzalez Galarza FF, Arguello Astorga R. Cartilage oligomeric matrix protein levels in type 2 diabetes associated with primary knee osteoarthritis patients. Genet Test Mol Biomarkers. 2019 Jan 1;23(1):16-22.