The Association between Knee Osteoarthritis Progression and Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Abstract

Background: Diabetes mellitus (DM) and osteoarthritis (OA) are commonly increased in prevalence and commonly occur together, both of them are leading causes of disability. The relationship between Diabetes mellitus (DM) and osteoarthritis (OA) is not known, consequently, the purpose of this study to identify if there is an association between them.

Aim of Study: To investigate the association between diabetes mellitus and knee osteoarthritis and the effect of diabetic type or diabetic duration on the progression of knee osteoarthritis through a systematic review.

Material and Methods: Systematic searches were done on the following electronic databases MEDLINE / PubMed, Cochrane Library, Web search, SAGE, Google scholar, Scopus, since the inception of these databases from February 2022-February 2023.

Results: Fifty studies were included in the current review, 32 studies of them were included to identify the association between diabetes and knee OA, Ten studies were used to calculate the risk of knee osteoarthritis in diabetic patients, among 4148 patients, the overall OR was 1.24 (CI 1.14 to 1.35). Seven studies were used for the risk of DM in an OA versus non-OA subjects, among 2468 patients, the overall OR was 2.26 (1.28 to 4.01). The mean OA prevalence among diabetic patients was 34.29%, while DM prevalence among OA patients was 23.45%.

Conclusion: Diabetes mellitus is strongly associated with knee OA, and each of them is a major cause of others as seen by higher OA prevalence in diabetic patients and vice versa.

Key Words: Knee osteoarthritis — Diabetes mellitus — Systematic review.

Introduction

IN the US and around the world, the prevalence of diseases including diabetes mellitus (DM) and osteoarthritis (OA) is expected to rise [1,2]. A growing body of research demonstrated that DM may negatively impact articular tissues and worsen OA, as well as the consequent rise in the coexistence of these two disorders.

The most common chronic joint condition and a major contributor to pain and disability worldwide is knee osteoarthritis [3]. It is a degenerative articular condition characterized by discomfort, mild to severe synovial inflammation, changed subchondral and peri-cartilaginous bone, and degraded articular cartilage. Damage to the cartilage is the last common endpoint in OA [4].

In healthy, asymptomatic, undamaged knees, the prevalence of magnetic resonance imaging (MRI) characteristics indicative of OA ranged from 4% to 14% in young adults to 19% to 43% in older adults aged 40 years [5]. In addition to age, additional factors that affect prevalence rates include levels of physical activity and the type of MRI sequences used [6].

A metabolic disorder called diabetes mellitus is brought on by a breakdown in the body’s system for processing glucose [4]. Although type 1 and type 2 diabetes inclinations vary, data on the incidence and prevalence of diabetes in children and adolescents have increased over the past few decades [7].

Type 1 diabetes (T1DM), which accounts for more than 90% of all instances of diabetes in children, is extremely prevalent in different nations, within countries, and among different ethnic populations [8]. Over 387 million adults worldwide currently have type 2 diabetes (T2D), and by the year 2035, that number is expected to rise to 592 million [9].

The investigation of the relationship between the metabolic syndrome (MetS) and its related elements as potential risk factors for the onset and progression of OA has drawn greater attention in recent years. Studies have shown that inflammatory mediators released from adipose tissue may harm the
metabolism of joints as well as other organs, despite the fact that the precise mechanism connecting both disorders is not yet fully understood [10-12].

Additionally, numerous efforts have been made to show a connection between persistent hyperglycemia and harm to the articular cartilage.

In fact, chondrocytes exposed to high levels of extracellular glucose may produce and deposit more advanced glycation end products (AGEs) and reactive oxygen species (ROS), which can cause inflammation and extracellular matrix damage [13-15]. Through the activation of IL-1β and IL-12 among other cytokines, the disruption in glucose metabolism might affect the metabolism of chondrocytes and influence the development and progression of OA [16].

Material and Methods

This systematic review was reported in accordance with PRISMA principles & registered on PROSPERO (CRD42018081494) [17].

Information sources and search strategy:

Systematic searches were conducted on the following electronic databases EMBASE, MEDLINE / PubMed, Cochrane Library Web search, Scopus, SAGE, and Google Scholar including publications since the inception of these databases until February 2023.

Medical Subject Headings (MeSH) and free-text phrases were combined in the search technique, related to (association OR correlation OR link OR relation OR relationship) between (knee arthritis OR osteoarthritis OR arthrosis OR degenerative joint disease OR knee degenerative joint disease) and (diabetes mellitus, hyperglycemia, metabolic syndrome) OR the effect of diabetes on osteoarthritis (progression OR advance OR advancement).

Because this systematic review is regarded as an update of a previously published study and is being conducted in light of the publication as a significant new research with some modifications to the research questions as well as the inclusion and exclusion criteria, we searched the databases starting at their inception. We looked for pertinent publications in the reference lists of the included articles.

Eligibility criteria:

This review was considering all studies that involve all ages, BMI male and female with or without primary knee osteoarthritis and diabetes mellitus (type 1 OR type 2). The patient had at least a grade 2 composite OA score, equivalent to grade 2 on Kellgren and Lawrence (KL) grade in at least one knee, and the patient with diabetes diagnosed by taking a blood sample or self-reported DM.

Studies were excluded if:

- Knee OA brought on by injuries and other problems.
- Systemic and connective tissue illnesses.
- Metabolic bone disease.
- Previous knee arthroscopy or surgery.
- Acute or persistent infection.
- Smoking, pregnancy, and cancer.
- Medicines used as corticosteroids.
- Scientific articles written in languages other than English.
- Poster presentations, editorials, letters, and conference proceedings.

Study selection:

Mendeley Desktop (version 1.17.11) was used to import all titles and abstracts, and it was from there that we eliminated duplicates and articles that didn’t fit the inclusion criteria. Two reviewers (HA and KA) separately decided which papers met the preceding eligibility requirements as relevant. Both reviewers’ lists were reviewed, and the full text of any papers they both identified was obtained. Consensus was used to resolve judgment differences. As a final arbiter, SF, a third reviewer, was used. Fig. (1) displays a flowchart of the study selection process. When necessary, we also got in contact with the main authors to ask for further information or data clarification.

Data extraction:

The required data was separately extracted by two reviewers (HA and KA). They compared their results to ensure that all pertinent data had been successfully extracted. The following items were extracted: Author and year of publication, title, type of study, research site, participant characteristics (diabetic group characteristics, OA and non-OA group characteristics) sample size, sex, age, weight, height, and body mass index), outcome (diagnosis of OA, knee OA severity), Exposure (diagnosis of diabetes, type of diabetes, associated metabolic disorder), outcome measure, result, authors conclusion.

Quality assessment:

Using the Newcastle-Ottawa Scale (NOS), a risk-of-bias evaluation measure for observational studies that is endorsed by the Cochrane Collaboration, two researchers (KA, HA) independently evaluated the quality of selected publications. The NOS is a tool commonly used in medicine as it is a validated instrument and with a long history of reliability. To avoid major disagreement between authors, 3 articles as pilot studies were assessed by 2 researchers (KA & HA) before starting the actual assessment. Discussion ensued until agreement was reached in order to resolve evaluation disagreements.
Eight components make up the NOS, which are divided into three categories: Comparison, outcome (cohort studies), and exposure (case-control studies), depending on the type of investigation. A number of response alternatives are offered for each issue. The highest quality studies are given a maximum of one star for each item, with the exception of the item linked to comparability, which allows the assignment of two stars. This star system is used to enable a semi-quantitative assessment of study quality. There are 0 to 9 stars in the NOS. Regardless of study quality, all studies were included in this review. Cohen’s Kappa was used to determine how well the two reviewers agreed.

**Statistical methods:**

The prevalence of diabetes among OA patients and vice versa was calculated. 95% confidence intervals (CIs) and OR were taken into account as the effect sizes for all studies in this meta-analysis. The Cochran Q test and I^2 statistics were used to determine the degree of heterogeneity among the studies, with an I^2 between 50% and 90% potentially indicating significant heterogeneity [20].

We constructed random effects models using the inversed variance approach to pool the estimates from several studies due to the inter-study variability, and we then summarized the findings using forest plots. The link between diabetes and OA was expressed using odds ratios as the effect estimate. p-values less than 0.05 were used to show statistical significance.

By excluding one study at a time, sensitivity analyses were carried out, and a pooled estimate for the studies that remained were then computed. We intended to assess whether a single study significantly influenced the outcomes. RevMan, version 5.2, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, was used for the majority of analyses.

**Results**

Total of 933 references were presented in the search results of the chosen databases. A total of 831 references were checked for relevancy after duplicates were eliminated. After abstract assessment, 853 of these were eliminated because they didn’t match the requirements for inclusion. More thorough analysis was done on the remaining 80 references’ complete texts. Finally, 50 papers in total met the criteria for inclusion in our evaluation (Fig. 1). The two reviewers that examined the references agreed on 81% of the questions. 23 papers were used in the descriptive analysis, while 17 of the 50 studies contributed data for the meta-analysis.

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### Identification of studies via databases and registers

<table>
<thead>
<tr>
<th>Identified records from*: Databases (n = 933)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pubmed 700</td>
</tr>
<tr>
<td>- Google Scholar 81</td>
</tr>
<tr>
<td>- Scopus 70 Web of science 50</td>
</tr>
<tr>
<td>- Cochrane 12</td>
</tr>
<tr>
<td>- SAGE 19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Before the screening, records were deleted:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Removed duplicate records (n=831)</td>
</tr>
<tr>
<td>- Records that automated tools have flagged as ineligible (n = )</td>
</tr>
<tr>
<td>- Records removed for other reasons (n = )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Records after the title &amp; abstract screened (n=80)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Records excluded** (n=853)</th>
</tr>
</thead>
</table>

| Requests for retrieval of reports (n=5) |

| Evaluation of reports for eligibility (n=61) |

| Studies that were included (n=50) |

| No reports could be found (n=1) |

<table>
<thead>
<tr>
<th>Reports excluded: We excluded the articles with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Secondary knee OA from trauma or another illness.</td>
</tr>
<tr>
<td>- Previous knee surgery or arthroscopy for connective tissue disease or a systemic condition.</td>
</tr>
<tr>
<td>- Metabolic bone disease.</td>
</tr>
<tr>
<td>- Acute or chronic infection.</td>
</tr>
<tr>
<td>- Pregnancy, malignancy, smoking.</td>
</tr>
<tr>
<td>- Drug as corticosteroids studies published in a language other than English.</td>
</tr>
<tr>
<td>- Conference proceedings, editorial, letters, poster presentation.</td>
</tr>
</tbody>
</table>

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Fig. (1): Flow diagram.
**Characteristics of included studies:**

Eighteen studies of the 50 studies were cohort studies [21-38]. While eight case control studies [39-45], and twenty-four cross sectional studies [41-64]. Study characteristics showed in Table (1).

**Quality assessment result:**

Study quality was assessed using the Newcastle-Ottawa scoring system. The majority of studies presented good quality. Thirty four studies took good quality [3,21-28,30-41,44,48,51,52,53,56,58,60-63,65,68].

Fourteen studies have fair quality, not using an appropriate selection for sample [25,42,46,47,49,50,54,55,57,59,64,66], outcome measure [25,46,48,64], and inappropriate comparability [46,54,55,57,67]. Two studies have poor quality [43,45].

Results from using the Newcastle Ottawa scale are shown in Table (1) seventeen cohort studies were graded of good quality and one study fair quality, while there were five case-control studies graded of good quality, one fair, and two poor-quality assessments. There were twelve cross-sectional studies graded as good quality and twelve studies graded as fair quality.

**Prevalence of OA among patients with DM:**

The prevalence was calculated by using the 13 studies of patients with DM, sex of them cohort studies [25,27,29,30,35]. Five of them were cross-sectional studies [46,47,50,53,57]. Two of them are case-control studies [41,69]. For 4403 patients with DM, the mean OA prevalence was 34.29%.

**Prevalence of DM among patients with OA:**

The prevalence was calculated by using the 18 studies of patients with OA, three of them cohort studies, we used the baseline data [22,32,36]. Ten of them as cross-sectional studies [48,52,54,58,60-64,66]. Five of them are case-control studies [3,40,42,43,45]. For 12361 patients with OA, the DM prevalence was 23.45%.

**Associations between OA and DM:**

Fifty studies were included in the current review, forty-four of them were used to determine the association between OA and DM, and six studies did not have baseline data for the association.

Forty four articles investigated the association between knee OA and DM; 27 studies of them concluded that there was a significant relationship or at least reported an OR >1 in the text.

Murata et al. [56]; Arellano-Perez et al. [3] & Dubey et al. [46] reported the association between DM and OA by measuring certain substances in the synovial fluid they found elevated expression of TLR4 and MMP13, higher concentrations of cartilage oligomeric matrix protein in synovial fluid (SF COMP) in the synovium of osteoarthritis patients with high hemoglobin Alc (HbA1c) concentrations, Matrix metalloproteinase-1, aggrecan (AGN), type II collagen (Col II), SOX9, and increased carboxymethyl lysine (advanced glycation end product) are all signs of damaged articular cartilage and proteoglycans. Meniscal degeneration was linked to higher fasting glucose and HbA1c levels, according to [44].

According to osteophytes-defined radiographic knee OA prevalence, cardiometabolic dysfunction persists within subgroups distinguished by obesity status and gender [51]. In each BMI category, phenotypes of body size with metabolic abnormalities were more closely associated with knee osteoarthritis than their metabolically healthy counterparts [54].

Sex studies used MRI and showed an increased change in cartilage characteristics articular cartilage T2 values were greater and more heterogeneous, indicating increased articular cartilage degradation and meniscus alteration related to diabetes [25,26,30,32,34,50] in addition to study by Altinel et al. [40] showed quadriceps buckling was more prevalent in diabetic patients.

Handa et al. [50] and Zaharia et al. [64] used radiological assessment and measuring isometric knee extension strength (KES), ROM, and WOMAC questionnaire, they found that OA is one of the related musculoskeletal diseases that is associated with type 2 DM with lower ROM and lower balance skill, in addition, a study by Fatemi et al. [48] reported high prevalence of musculoskeletal manifestations associated with DM, Knee osteoarthritis is one of this manifestation. Abourazzak et al. [41] conclude that knee OA is one of the articular and articular manifestations in diabetic patients. MetS and its components are largely related to worse pain trajectories through central obesity, according to Pan et al. [57] and Xie et al. [60], implying that MetS may cause the development and maintenance of poorer pain trajectories.

Afifi et al. [69] determine the elevated prevalence of Knee OA among diabetic patients, with worse pain, a higher functional impairment score, and more advanced radiographic abnormalities, in addition, a study by Puenpatom& Victor. [57] found that people with OA had greater prevalences of all cardiovascular risk factors than people without OA overall. Diabetes patients were more likely to have knee OA than non-diabetic controls [55].

Yasuda et al. [61] and Lee et al. [53] found that when the number of metabolic syndrome (MetS) components increased, the severity of knee osteoarthritis generally increased. Four studies showed that DM was associated with higher pain severity that increased with more MetS components, unilateral and bilateral distribution. Regional knee pain, which was linked to moderate to severe walking-related knee pain but not localized or diffuse knee pain, and slower walking speed [47,48,52,63].
<table>
<thead>
<tr>
<th>Authors and year of publication</th>
<th>Type of study</th>
<th>Research site</th>
<th>N</th>
<th>Age (range or average)</th>
<th>Diagnosis of OA</th>
<th>Diagnosis of diabetes</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engstrom et al., (2009)</td>
<td>Cohort</td>
<td>Sweden</td>
<td>5082</td>
<td>46-68</td>
<td>- First knee arthroplasty or high tibial osteotomy in combination</td>
<td>Fasting plasma glucose ≥5.6 mmol/L</td>
<td>Good</td>
</tr>
<tr>
<td>Yoshimura et al., (2012)</td>
<td>Cohort</td>
<td>Mountainous and coastal areas</td>
<td>1690</td>
<td>63.9 (11.8)</td>
<td>Radiographic</td>
<td>Serum HbAlc level 5.5%</td>
<td>Good</td>
</tr>
<tr>
<td>Eymard et al., (2015)</td>
<td>Cohort</td>
<td>18 countries</td>
<td>559</td>
<td>62.2-63.4</td>
<td>Symptomatic and radiographic</td>
<td>Medical history reported by patients</td>
<td>Good</td>
</tr>
<tr>
<td>Pan et al., (2020)</td>
<td>Cohort</td>
<td>Australia</td>
<td>1,099</td>
<td>50-80 years</td>
<td>Symptomatic and radiographic</td>
<td>Fasting plasma glucose &gt; 5.6 mmol/L</td>
<td>Good</td>
</tr>
<tr>
<td>Onkarappa et al., (2020)</td>
<td>Cohort</td>
<td>India</td>
<td>41</td>
<td>- The average age of Mets-OA patients is 54.3 Non-Mets OA age is 57</td>
<td>Symptomatic and radiographic</td>
<td>Fasting blood sugar &gt; 100 mg/dl</td>
<td>Good</td>
</tr>
<tr>
<td>Stürmer et al., (2001)</td>
<td>Cross-sectional</td>
<td>Germany</td>
<td>809</td>
<td>63±71</td>
<td>Radiographic</td>
<td>By a history or use of antihyperglycemics.</td>
<td>Fair</td>
</tr>
<tr>
<td>Konstari et al., (2021)</td>
<td>Cohort</td>
<td>Finland</td>
<td>6,274</td>
<td>30-98</td>
<td>Symptomatic</td>
<td>Elevated plasma fasting glucose (5.6 mmol/L)</td>
<td>Good</td>
</tr>
<tr>
<td>Ashmei et al., (2021)</td>
<td>Cross-sectional</td>
<td>USA</td>
<td>20</td>
<td>40-70</td>
<td>Radiographic, MRI</td>
<td>Fasting glucose (FG), hemoglobin A1c (HbA1c)</td>
<td>Fair</td>
</tr>
<tr>
<td>Lee et al., (2019)</td>
<td>Cross-sectional</td>
<td>Korea</td>
<td>8,491</td>
<td>50-79</td>
<td>Radiographic</td>
<td>Fasting glucose ≥100 mg/dl or undergoing treatment for diabetes; Blood glucose fasting (≥100mg/DL)</td>
<td>Good</td>
</tr>
<tr>
<td>Franco et al., (2020)</td>
<td>Cross-sectional</td>
<td>Portuguese</td>
<td>416</td>
<td>73±5.6</td>
<td>Radiographic</td>
<td>HbAlc level ≥5.5%</td>
<td>Good</td>
</tr>
<tr>
<td>Yoshimura et al., (2011)</td>
<td>Case-control</td>
<td>Japan</td>
<td>1690</td>
<td>65.2 (12.0)</td>
<td>Radiographic</td>
<td>HbAlc level ≥5.5%</td>
<td>Good</td>
</tr>
<tr>
<td>Han et al., (2013)</td>
<td>Case-control</td>
<td>Korean</td>
<td>2234</td>
<td>40-90 years</td>
<td>Symptomatic</td>
<td>Fasting glucose ≥100 mg/dl</td>
<td>Good</td>
</tr>
<tr>
<td>Golightly et al., (2021)</td>
<td>Cohort</td>
<td>USA</td>
<td>4093</td>
<td>61±10.5</td>
<td>Radiographic, symptomatic</td>
<td>By history</td>
<td>Good</td>
</tr>
<tr>
<td>Afifi et al., (2018)</td>
<td>Case-control</td>
<td>Egypt</td>
<td>60</td>
<td>MetS group age 52.8±8.0</td>
<td>Radiographic, symptomatic</td>
<td>Fasting glucose ≥100 mg/dl or patient using anti-diabetic drugs</td>
<td>Good</td>
</tr>
<tr>
<td>Altinel et al., (2007)</td>
<td>Case-control</td>
<td>Turkey</td>
<td>61</td>
<td>Control group age 49.8±8.1</td>
<td>Radiographic, symptomatic</td>
<td>Oral antidiabetics, and glycated hemoglobin A (HbA1c) levels</td>
<td>Poor</td>
</tr>
<tr>
<td>Funck et al., (2019)</td>
<td>Cohort</td>
<td>Europe</td>
<td>384,838</td>
<td>56.8±8.0</td>
<td>Symptomatic</td>
<td>Self-reported diabetes + a hospital diagnosis of type 2 diabetes</td>
<td>Good</td>
</tr>
<tr>
<td>Ether et al., (2021)</td>
<td>Cross-sectional</td>
<td>United state</td>
<td>2481</td>
<td>45-79 years</td>
<td>Radiographic, symptomatic</td>
<td>Self-reported diagnosis of prior DM</td>
<td>Good</td>
</tr>
<tr>
<td>Zheng et al., (2022)</td>
<td>Cohort</td>
<td>China</td>
<td>17,619</td>
<td>58 years on average</td>
<td>Symptomatic</td>
<td>HbA1c 6.5% (48 mmamol), self-reported medical diagnosis, or acknowledged use of medications that lower blood sugar</td>
<td>Good</td>
</tr>
<tr>
<td>Li et al., (2016)</td>
<td>Case-control</td>
<td>China</td>
<td>70</td>
<td>50-75 years</td>
<td>Radiographic, symptomatic</td>
<td>A prior diagnosis of diabetes with treatment or a fasting plasma glucose (FPG) of less than 6.1 mmol/L</td>
<td>Good</td>
</tr>
<tr>
<td>Zaharia et al., (2021)</td>
<td>Case-control</td>
<td>Germany</td>
<td>66</td>
<td>58.7±10.9</td>
<td>Symptomatic, Radiographic</td>
<td>Fasting blood glucose and HbA1c greater than 6.5</td>
<td>Fair</td>
</tr>
<tr>
<td>Murata et al., (2019)</td>
<td>Cross-sectional</td>
<td>Tokyo, Japan</td>
<td>342</td>
<td>73.9±0.7</td>
<td>Radiographic</td>
<td>HbA1c ≥6.5 and HbA1c &lt;6.5</td>
<td>Good</td>
</tr>
<tr>
<td>Abourazzak et al., (2014)</td>
<td>A cross-sectional</td>
<td>Morocco</td>
<td>116</td>
<td>61±10 years (35-92 years)</td>
<td>Symptomatic</td>
<td>HbA1c levels were &gt;8.0%</td>
<td>Fair</td>
</tr>
</tbody>
</table>
Diagnosis of diabetes

Overall quality

- **FPG ±126 mg/dL and HbAlc $6.5%**: Good
- **Random blood glucose, for the diabetic group**: Fair
  - 219.1± 116.9 non diabetic group 95.6±13.3
- **Fasting blood glucose (FBG)** reached an average of 470 mg/dL in diabetic KOA
- **HbAlc>5.8%**: Poor
- **Using medication or having a fasting blood sugar level of 100 mg/dL or higher.**
  - (1) diabetes that has been diagnosed by a doctor based on at least one hospital stay or at least two outpatient visits within a two-year period;
  - (2) diabetes was self-reported on the survey; or
  - (3) medication usage for diabetes one year prior to the enrollment date.
- **Fasting plasma glucose >5.6 mmol/1**: Good
- **Serum glucose 100 mg/dL**: Fair
- **Diabetes patients must have a fasting blood sugar (FBS) of 126 mg/dL or a 2-hour postprandial plasma blood sugar (GTT) of 200 mg/dL, while prediabetic subjects must have impaired FBS (100-125 mg/dL) or impaired GTTs (2-hour postprandial plasma blood sugar of 140-199 mg/dL).**
- **Self-report of diabetes.**
  - 1) Diabetic symptoms plus a blood glucose level of 200 mg/dL or 2) a fasting blood glucose level of 126 mg/dL or 3) a 2-hour plasma glucose level of 200 mg/dL during an oral glucose tolerance test

**Table (1): Studies characteristics and overall quality.**

<table>
<thead>
<tr>
<th>Authors and year of publication</th>
<th>Type of study</th>
<th>Research site</th>
<th>N</th>
<th>Age (range or average)</th>
<th>Diagnosis of OA</th>
<th>Diagnosis of diabetes</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arellano Perez Vertu et al., (2019)</td>
<td>Case-control</td>
<td>Northern Mexico</td>
<td>231</td>
<td>&gt;30</td>
<td>Radiographic</td>
<td>FPG ±126 mg/dL and HbAlc $6.5%</td>
<td>Good</td>
</tr>
<tr>
<td>Horn et al., (1992)</td>
<td>Case-control</td>
<td>Indiana</td>
<td>73</td>
<td>&gt;40</td>
<td>Radiographic</td>
<td>Random blood glucose, for the diabetic group</td>
<td>Fair</td>
</tr>
<tr>
<td>Dubey et al., (2018)</td>
<td>Cross-sectional</td>
<td>Taiwan</td>
<td>1,255,607</td>
<td>30-89</td>
<td>Proteins levels</td>
<td>Fasting blood glucose (FBG) reached an average of 470 mg/dL in diabetic KOA</td>
<td>Good</td>
</tr>
<tr>
<td>Inoue et al., (2011) Shin, D. (2014)</td>
<td>Case-control</td>
<td>Japan</td>
<td>795</td>
<td>&gt;20 years</td>
<td>Radiographic</td>
<td>HbAlc&gt;5.8%</td>
<td>Poor</td>
</tr>
<tr>
<td>Kendzerska et al., (2018)</td>
<td>Cohort</td>
<td>Ontario, Canada</td>
<td>16362</td>
<td>≥55 years</td>
<td>Symptomatic</td>
<td>(1) diabetes that has been diagnosed by a doctor based on at least one hospital stay or at least two outpatient visits within a two-year period; (2) diabetes was self-reported on the survey; or (3) medication usage for diabetes one year prior to the enrollment date.</td>
<td>Good</td>
</tr>
<tr>
<td>Pan et al., (2020)</td>
<td>Cohort</td>
<td>Southern Tasmania</td>
<td>435</td>
<td>50 years</td>
<td>MRI scans</td>
<td>Fasting plasma glucose &gt;5.6 mmol/1</td>
<td>Good</td>
</tr>
<tr>
<td>Lee et al., (2015)</td>
<td>A cross-sectional</td>
<td>Korea</td>
<td>1,549</td>
<td>50 years</td>
<td>Radiographic</td>
<td>Serum glucose 100 mg/dL.</td>
<td>Fair</td>
</tr>
<tr>
<td>Fatemi et al., (2015)</td>
<td>Cross-sectional</td>
<td>Iran</td>
<td>313</td>
<td>30-79</td>
<td>Symptomatic</td>
<td>Diabetes patients must have a fasting blood sugar (FBS) of 126 mg/dL or a 2-hour postprandial plasma blood sugar (GTT) of 200 mg/dL, while prediabetic subjects must have impaired FBS (100-125 mg/dL) or impaired GTTs (2-hour postprandial plasma blood sugar of 140-199 mg/dL).</td>
<td>Good</td>
</tr>
<tr>
<td>Neumann et al., (2019)</td>
<td>Cohort</td>
<td>USA</td>
<td>488</td>
<td>63.14±9.09</td>
<td>MRI scans</td>
<td>Self-administered questionnaire</td>
<td>Good</td>
</tr>
<tr>
<td>Karvonen-Gutierrez et al., (2012)</td>
<td>Cross-sectional</td>
<td>USA</td>
<td>1,066</td>
<td>≥60</td>
<td>Radiographic</td>
<td>Assessment-insulin resistance (HOMA-IR)</td>
<td>Good</td>
</tr>
<tr>
<td>Nieves-Plaza et al., (2013)</td>
<td>A cross-sectional</td>
<td>Hispanics from Puerto Rico</td>
<td>202</td>
<td>51.6 (13.1) years</td>
<td>Symptomatic</td>
<td>1) Diabetic symptoms plus a blood glucose level of 200 mg/dL or 2) a fasting blood glucose level of 126 mg/dL or 3) a 2-hour plasma glucose level of 200 mg/dL during an oral glucose tolerance test</td>
<td>Good</td>
</tr>
<tr>
<td>Jungmann et al., (2013)</td>
<td>Cohort</td>
<td>Modern Western society</td>
<td>403</td>
<td>45-60 (mean age 52.1±3.9)</td>
<td>MRI</td>
<td>Self-report of diabetes.</td>
<td>Good</td>
</tr>
<tr>
<td>Niu et al., (2017)</td>
<td>Cohort</td>
<td>United States</td>
<td>991</td>
<td>≥40</td>
<td>Radiographic</td>
<td>Fasting glucose level (110 mg/dL).</td>
<td>Good</td>
</tr>
<tr>
<td>Chanchek et al., (2018)</td>
<td>Cross-sectional</td>
<td>United States</td>
<td>416</td>
<td>63.0±8.9y (45 to 79 years)</td>
<td>MRI</td>
<td>Self-reported type 2 diabetes (DM) managed with either oral medicine or insulin</td>
<td>Fair</td>
</tr>
<tr>
<td>Neumann et al., (2018)</td>
<td>Cohort</td>
<td>USA</td>
<td>392</td>
<td>45-79 years</td>
<td>Radiographic</td>
<td>Self-administered questionnaire</td>
<td>Fair</td>
</tr>
<tr>
<td>Rogers-Soeder et al., (2020)</td>
<td>Cohort</td>
<td>United States</td>
<td>987</td>
<td>50-79 years</td>
<td>Radiographic</td>
<td>Self-reported diagnosis of DM, use of anti-diabetic medications in the past 30 days, or a fasting glucose of ≥126 mg/dL.</td>
<td>Good</td>
</tr>
<tr>
<td>Kuusalo et al., (2021)</td>
<td>Cohort</td>
<td>USA</td>
<td>4796</td>
<td>50-79 years</td>
<td>Radiographic</td>
<td>Self-reported DM Comorbidity Index</td>
<td>Good</td>
</tr>
<tr>
<td>Alenazi et al., (2020)</td>
<td>Cross-sectional</td>
<td>United States</td>
<td>1790</td>
<td>69 (8.7) years</td>
<td>Symptomatic</td>
<td>Self-reported DM Comorbidity Index</td>
<td>Good</td>
</tr>
</tbody>
</table>
# Table 1: Count.

<table>
<thead>
<tr>
<th>Authors and year of publication</th>
<th>Type of study</th>
<th>Research site</th>
<th>N</th>
<th>Age (range or average)</th>
<th>Diagnosis of OA</th>
<th>Diagnosis of diabetes</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidwai et al., (2016)</td>
<td>Cross-sectional</td>
<td>Karachi</td>
<td>413</td>
<td>&gt;40</td>
<td>Radiographic</td>
<td>Not mentioned</td>
<td>Fair</td>
</tr>
<tr>
<td>Puempatama &amp; Victor, (2009)</td>
<td>Cross-sectional</td>
<td>United States</td>
<td>7714</td>
<td>218 years</td>
<td>Radiographic</td>
<td>Fasting blood glucose concentration 110 mg/dL.</td>
<td>Good</td>
</tr>
<tr>
<td>Handa et al., (2023)</td>
<td>Cohort</td>
<td>Tehran</td>
<td>101</td>
<td>61.3 years</td>
<td>Radiographic</td>
<td>Hemoglobin A1C level</td>
<td>Fair</td>
</tr>
<tr>
<td>Xie et al., (2017)</td>
<td>A cross-sectional</td>
<td>China</td>
<td>5764</td>
<td>&gt;40</td>
<td>Radiographic</td>
<td>Blood sample FPG ≥ 100 mg/dL (5.6 mmol/L) or currently undergone drug</td>
<td>Good</td>
</tr>
<tr>
<td>Alenczi et al., (2020)</td>
<td>Cross-sectional</td>
<td>United States</td>
<td>148</td>
<td>45 to 79</td>
<td>Radiographic</td>
<td>Self-reported</td>
<td>Good</td>
</tr>
<tr>
<td>Tootsi et al., (2017)</td>
<td>Case-control</td>
<td>Tartu in Estonia</td>
<td>55</td>
<td>OA = 65±7 control =61±8</td>
<td>Radiographic</td>
<td>Blood samples</td>
<td>Good</td>
</tr>
<tr>
<td>Yasuda et al., (2018)</td>
<td>Cross-sectional</td>
<td>Japan</td>
<td>119</td>
<td>45-88 years</td>
<td>Radiographic</td>
<td>Random blood glucose level ≥ 200 mg/dL</td>
<td>Fair</td>
</tr>
<tr>
<td>Yerima &amp; Addis, (2017)</td>
<td>A cross-sectional</td>
<td>Nigeria</td>
<td>244</td>
<td>18-73 years</td>
<td>Radiographic</td>
<td>Fasting glucose &gt; 5.6 mmol/L</td>
<td>Good</td>
</tr>
<tr>
<td>Yoshimura et al., (2015)</td>
<td>Cohort</td>
<td>Mountainous and coastal regions</td>
<td>1,690</td>
<td>s.3980</td>
<td>Radiographic</td>
<td>Serum HbA1c level 5.5%</td>
<td>Good</td>
</tr>
</tbody>
</table>

## Fig. (3): Risk of diabetes mellitus in knee osteoarthritis.

## Fig. (2): Risk of knee osteoarthritis in diabetic patients.
Whereas 16 studies displayed no association between knee OA and DM [23-24,28,29,31,35,39X-44,54,57,64,67]. For the meta-analysis, we cannot combine data on the association between DM and knee osteoarthritis because of variations in data presented in studies and diagnostic criteria.

**The association between DM and progression of knee OA:**

Eighteen studies demonstrated an association between DM and progression of knee OA. The sample size, length of follow-up, diagnostic criteria, and definition of progression varied significantly between investigations.

The sample size ranged from 41 to 384,838 individuals. The duration of follow-up ranged from 6 months to 12 years. At baseline, OA was diagnosed using four separate criteria: Magnetic resonance imaging (MRI), self-reported confirmed by radiography and/or medical records, Kellgren/Lawrence (K/L) grade, and the American College of Rheumatology. Although the studies differed in their definition of progression, five studies characterized OA progression as joint space narrowing (JSN) alone [25,29,31,36,37]. Two studies classified OA progression as a first knee arthroplasty or high tibial osteotomy along with an OA diagnosis [21,23]. MRI [26,30,34], symptomatic [27,28,38] and 5 used a combination of JSN and asymptomatic [22,24,32,33,35]. For the meta-analysis, no ORs were available for the association between DM and the progression of the knee because of variations in diagnostic and progression criteria.

**Meta-analysis:**

**Risk of knee osteoarthritis in diabetic patients:**

Ten studies were used to calculate the risk of knee osteoarthritis in diabetic patients [25,27,29,30,35,48,50,53,57,69]. For the risk of OA in DM versus non-DM subjects, among 4148 patients, the overall OR was 1.24 (CI 1.14 to 1.35), with high heterogeneity ($I^2=80\%$) (Fig. 2).

**Risk of diabetes mellitus in knee osteoarthritis:**

Seven studies were utilized to investigate the risk of DM in OA people vs. non-OA subjects in 2468 patients. Because $I^2=93\%$, a random-effects model was utilized to calculate the overall OR, which was 2.26 (1.28 to 4.01) [34,40,43,54,60,62,63]. By eliminating the low-quality papers from our sensitivity analysis, we were able to strengthen the results, but the degree of heterogeneity remained same (Fig. 3).

**Discussion**

Diabetes millets have been related to OA for years, but their significance to OA remains unclear and conflicting in several studies. This study discovered a direct association between diabetes and structural knee OA deterioration, rather than just chronic joint discomfort. This finding not only supports additional research into the primary risk factor for OA, diabetes, from the tissue to the molecular level, but it also provides a new way of thinking about OA etiology and treatment strategies.

This systematic review and meta-analysis intended to define the association between knee Osteoarthritis and Diabetes Mellitus. This study outcome showed that there is a strong association between diabetes and knee OA in addition the prevalence of diabetes among OA patients and vice versa was calculated, and the results showed that the mean OA prevalence was 34.29% among 4403 diabetic patients, the DM prevalence was 23.45% among 12361 OA patient that means both disease is leading cause for others.

Our findings are consistent with recent systematic reviews [70,71], which found minimal evidence to suggest that poor glucose metabolism was a risk factor for OA, even though the current research shows a link between knee OA and diabetes mellitus. This contradicts the findings of two prior meta-analyses on the same subject [72,73].

When compared to the two prior meta-analyses, our new findings have several advantages. Our updated literature search found several new and bigger cohort studies that revealed a relationship between DM and knee OA [25,30], although two of them showed no association [29,35].

Ten studies were used to calculate the risk of knee osteoarthritis in diabetic patients, for the risk of OA in DM versus non-DM subjects, among 4148 patients, the overall OR was 1.24 (CI 1.14 to 1.35), with high heterogeneity ($I^2=80\%$).

The heterogeneity between studies was substantial, most likely due to changes in OA diagnosis criteria, DM definition, and study types and quality. To account for this heterogeneity, we conduct a sensitivity analysis to see if the relationship between OA and DM was maintained after eliminating papers with poor methodology, and we found that it did in all sensitivity analyses.

Seven studies were utilized to investigate the risk of DM in OA people vs non-OA subjects in 2468 patients. Because $I^2=93\%$, a random-effects model was utilised to calculate the overall OR, which was 2.26 (1.28 to 4.01). By eliminating the low-quality papers, we conducted sensitivity analyses to reinforce the results, but the heterogeneity remained unchanged.

There is a different mechanism that may explain this association; may hyperglycemia tends to shift the cartilage homeostasis towards degeneration by increasing in the serum levels of COMP in MetS-OA group compared to non-MetS OA group. However, serum PIIANP levels were comparable in both the groups. This indicates predominant effect
of MetS on increased rate of degeneration without any significant effect on reparative process [32], increased meniscal degeneration by higher WORMS meniscus sum [44], elevate the expression of Toll-like receptor 4 (TLR4) that was associated with catabolic response via regulation of matrix metalloproteases (MMPs) [56], destruction of joint cartilage by an increase in synovial fluid (SF) cartilage oligomeric matrix protein (COMP) concentrations in T2D subjects. It was observed that the non-KOA/T2D patients had a greater concentration of SF COMP levels. Given that exposure to high glucose environments may cause cartilage matrix breakdown, this may be a sign of early OA in diabetic people without symptoms on the knee joint or severity of OA [3]. Greater knee structural deterioration, stratified by the severity of the diabetes, and greater knee deterioration in diabetics with more severe diabetestes, as shown by the use of insulin and the existence of diabetic comorbidities. According to Neuman et al., the overproduction and accumulation of AGEs may be triggered by a hyperglycemic environment, which may alter the hyaline cartilage’s tensile properties. This may ultimately increase the cartilage’s stiffness and fragility, making it more susceptible to damage and degeneration [32].

A vicious cycle that maintains metabolic dysregulation and worsens joint symptoms is created by the fact that diabetes-related increased articular cartilage degeneration promotes cartilage degeneration and joint inflammation, enriching advanced glycation end products and impeding optimal joint cushioning faster deterioration of the cartilage matrix in the knee of diabetics, indicating a higher loss of collagen content with a disruption of the collagen network in the extracellular matrix with more water influx, in the deeper layers of the cartilage in the diabetics, findings which are different from non-diabetics and also different from the normal evolution of cartilage degenerative disease, which starts at the superficial layer of diabetic knees, possibly causing accelerated OA [1,25,50]. Obesity showed the closest association with knee osteoarthritis. Abdominal obesity might affect knee OA development by the combined metabolic effects of adipose tissue and mechanical stress of body weight [54].

Falsarella et al. [49] & Kidwai et al. [52] conclude that knee OA is associated with WC, addition Han et al. [39] agreed with this opinion and showed that WC was associated with knee OA in female.

The association between diabetes mellitus and knee OA is still debates; we need further research with high-quality studies with defined patient characteristics and with defined diabetic type and duration to decrease heterogeneity to reach a real association. The implication of our study is to control DM and OA and take precautions to avoid progression if one of them is developed and to stop this vicious cycle.

The strength of our study is that it is based on pre a planned study protocol that included a systematic search of EMBASE, MEDLINE / PubMed, Cochrane Library Web search, Scopus, and SAGE, to obtain pertinent studies, the majority of studies were cohort studies presented good quality. We performed sensitivity analyses and excluding the poor quality studies to strengthen the result.

The considerable degree of heterogeneity among the studies was the primary drawback of the current investigation. This might be accounted for by the population’s varied features as seen in the numerous research. The random effect models have been used as a result. Despite efforts to reduce this through sensitivity studies in multiple subgroups, there was still a significant amount of variability Second, we draw the conclusion that research using case-control and cross-sectional designs, as well as the vast majority of investigations, failed to specify the type of diabetes mellitus.

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NEETHAN S. and KASHYAP S.R.: Type 2 diabetes and
العلاقة بين تطور الالتهاب العظمي المفصلي للركبة وداء السكري
(دراسة منهجية وتحليل إحصائي)

إن الفرض من هذه الدراسة معرفة العلاقة بين تطور الالتهاب العظمي المفصلي للركبة وداء السكري. تم تحديد 50 دراسة خلال البحث الإلكتروني في 7 قواعد البيانات منذ البداية وحتى شهير فبراير 2023.

كانت 18 دراسة مهنية رسمية في حين أن ثمانية دراسات ب밀حكة و42 دراسة مستعراضة تم استخدام مقياس نيوكاسيل أونو، وهو مقياس لتقييم مخاطر الالتهاب. الدراسات القائمة على الملاحظة التي أقرتها مؤسسة كورونو، جمعت بحثي بتقييم جودة النشرات المختارة بشكل مستقل. أغلبية الدراسات كانت من نوعية جيدة 24 من نوعية جيدة 14 من نوعية معتدلة 2 من نوعية ضعيفة.

استخدام عشرة دراسات لمعالجة الإصابة بالالتهاب مفصل الركبة في مرضى السكري، من بين 480 مريضاً كان معدل الأرجحية الكلي 0.72 في حين تم استخدام سبع دراسات لتحقيق في مخاطر الإصابة بمرض السكري في الأشخاص المصابين بالالتهاب مفصل الركبة مقابل الأشخاص غير المصابين بالالتهاب مفصل الركبة في 2014 مريضاً، وكان معدل الأرجحية 0.72.

كان التأبين بين الدراسات كبيراً، على الأرجح بسبب التغيرات في معايير تشخيص التهاب مفصل الركبة. وتشخيص مرض السكري، وأنواع الدراسة وجودتها. لحساب عدم التجانس هذا، تم إجراء تحليل الاحصائي لمعرفة ما إذا كانت العلاقة بين التهاب مفصل الركبة ومرض السكري قد تم الحفاظ عليها بعد استبعاد الأوراق ذات القيمة السببية، ووجدنا أنها فعلاً في جميع تحليلات الاحصائية.

أظهرت ثمانية عشرة دراسة وجود علاقة بين مرض السكري وتطور التهاب الركبة. اختُفِ حجم العينة وطول التتابع ومعايير التشخيص وتعريف التقدم اختلافًا كبيرًا بين التحقيقات.

كان متوسط انتشار التهاب مفصل الركبة بين مرضى السكري 24٪ بينما كان معدل انتشار مرض السكري بين مرضى التهاب مفصل الركبة 24/2٪.