Type 2 Diabetes Mellitus As a Risk Predictor for Knee Osteoarthritis: A Case Control Series Study among Iraqi People at Mosul City

Type 2 Diabetes Mellitus As a Risk Predictor for Knee Osteoarthritis (A Case Control Series Study among Iraqi People at Mosul City)
*Dr. Ali Salah Fadhil, MBChB-CABM, Lecturer in Internal Medicine
Department of medicine, Nineveh College of Medicine, University of Mosul

**Dr. Fakhir Yousif Hussain, MBChB-FIBMS
Assist. Prof. in Internal Medicine, Department of Medicine, College of Medicine, University of Mosul

***Dr. Sulieman Ahmad Salow, MBChB, Nineveh health directorate

Abstract

**Objective:** The aim of this study was to evaluate type 2 diabetes mellitus as a risk predictor of Knee Osteoarthritis (OA). **Design:** A case control series study. **Setting:** The present study had the approval from regional research committee of Nineveh Health Directorate, and the scientific research committee of Collage of Medicine, University of Mosul, Mosul, Iraq. The current study was performed during the period between Nov.1st, 2011 and Jun.1st, 2012 at Al-waffaa health center for diabetes researches and management, and at the rheumatology outpatient clinic at Ibn Sina teaching hospital. **Patients and methods:** The study was conducted on 65 patients; known cases of type 2 diabetes mellitus, whose ages range between 40 - 50 years old were randomly enrolled in the study. Another group consists of 65 patients non diabetics, matched for age with the patients group, and was kept as control group. Both studied groups were subjected to measurement of fasting blood sugar (FBS) and HbA1c was done for patients group to evaluate glycemic control. X-ray examination of both knees were obtained for both groups and taken in standing position (stress position), the findings were recorded according to the severity of osteoarthritis found on examination. **Results:** The data obtained from the study revealed that there is a significant difference, regarding knee joint space narrowing grading: grade 1 JSN (Joint Space Narrowing) was higher in diabetic group than non diabetic one, while grade 2 and grade 3 JSN were noted to occur only in diabetic group. Diabetic group patients have high numbers of osteophytes in grades 1, 2, 3 and 4. Diabetic patients have high numbers of subchondral sclerosis than non-diabetic ones. **Conclusion:** There was a positive correlation between diabetes mellitus type 2 and osteoarthritis of the knee joint, in other ward Type 2 diabetes predicts the development of severe OA of the knee independent of age and other known risks for OA. Our findings strengthen the concept of a strong metabolic component in the pathogenesis of OA.

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**Introduction**

Diabetes mellitus (DM) affects connective tissues in many ways and causes different alterations in periarticular and skeletal system (Arkkila and Gautier, 2003).

Several musculoskeletal disorders have been described in diabetic patients those can be divided into three categories:

A. disorders which represent intrinsic complications of diabetes, such as limited joint mobility or diabetic cheiroarthropathy, stiff hand syndrome, and diabetic muscular infarction.

B. disorders with an increased incidence among diabetics, such as Dupuytrens disease, shoulder capsulitis, neuropathic arthropathy, osteopenia (in type 1 DM), flexor tenosynovitis, septic arthritis, acute proximal neuropathy, proximal motor neuropathy, pyomyositis and the diffuse idiopathic skeletal hyperostosis (DISH) syndrome.

C. The disorders those possibly associated with diabetes have been proposed but not proven yet, such as osteoarthritis and the carpal tunnel syndrome (Arkkila and Gautier, 2003).

Arthritis is among the leading causes of disability, and osteoarthritis (OA) is the most common type of arthritis (Kremers H& Gabriel S, 2005).

Osteoarthritis is the most common cause of musculoskeletal disability and it is one of the most common joint disorders in the elderly (Flatharta et al., 2006).

It is now understood that OA is a disorder of the whole joint organ and not just the cartilage. At the macroscopic level, the key characteristics of an OA joint are swelling, fibrillation, erosion and eventual loss of articular cartilage, together with the remodeling of underlying bone resulting in subchondral sclerosis, bone cysts, an increase in metaphyseal bone and the development of osteophytes (Felson et al., 2000).

The end point of OA is eburation, in which the focal loss of cartilage at the articulating surface of a bone reaches the stage where the underlying bone exposed and subjected to increasingly localized overloading soft- tissue structures in and around the joint are also affected (Dawson et al., 2004) these structures include synovium, which undergo modest inflammatory infiltrates; ligaments, which are often lax; and bridging muscle, which become week (Brandit, 2010).

Knee OA, the most frequent form of lower extremity OA, was the primary diagnosis for 430,000 hospital discharges and 14 billion dollars of hospital charges in the 2004 US (Dillon et al., 2006), and 12.1% (annualized prevalence) of Americans age 60 years had symptomatic radiographic knee OA in the 1991–1994 (Jordan et al., 2007).

One statistic that has been used extensively to describe person-level risk is lifetime risk, which is the probability of developing a condition over the course of a lifetime. Lifetime risk has been reported for various chronic conditions and risk factors, including coronary heart disease, hypertension, diabetes, and breast cancer (Lloyd-Jones et al., 2004).

This measure conveys the risk of these conditions in terms that are understandable to both clinical and lay audiences. The knee is the most frequently involved joints site associated with disability in OA (Andriacchi et al., 2000).

Risk factors such as age, sex, trauma, overuse, genetic, and obesity can each make contributions to the
process of injury in different compartments of the joint; such risk factors can serve as initiators that promote abnormal biochemical processes involving the cartilage, bone, and synovium (Abramson and Attur, 2009).

Disability in knee OA is influenced by many factors including pain, increasing age, decreasing educational status, obesity, female gender, comorbidity, and quadriceps muscle weakness; the role of psychosocial factors, notably depression and anxiety, is less clear (Creamer et al., 2000).

### Patients, Materials and Methods

The present study had approval from regional research committee of Mosul health administration, and the scientific research committee of Collage of Medicine, University of Mosul, Mosul, Iraq. The study was performed during the period between Nov.1st, 2011 and Jun.1st, 2012 at Al-waffaa health center diabetic research and management, and in the rheumatology outpatient department at Ibn Sina teaching hospital.

**Study design:** Controlled case series collection

**Subjects**

**Diabetic patients**

Sixty five female and male patients, known to have type 2 diabetes mellitus (according to American diabetes association criteria) registered in Al-waffaa center, whose ages range between 40 - 50 years were randomly enrolled in the study.

**Inclusion criteria**

Diabetic patients whose ages range between 40 - 50 years old.

**Exclusion criteria**

1. History of trauma.
2. Inflammation: Local and Systemic inflammatory condition.
3. History of previous local injection.

5. Gout and pseudo gout crystals.
6. Mal alignment.
7. Neoplastic conditions.
8. History of operation for meniscectomy.
9. Endocrine disorders (acromegaly, thyroid diseases, cushing syndrome).
10. Age >50 years.

**Control group**

Sixty five females and males, non diabetics, matched for age with the patients group, were enrolled as control group.

**Data collection**

The data were collected directly from the studied patients by the investigator himself during interview after obtaining consent.

**Methods**

After an overnight fasting both of the patients and control groups, were subjected to the following biochemical and radiological assessment:

**Biochemical profile measurements**

Fasting blood sugar (FBS) was done for control group to exclude diabetes, while in patients group FBS and HbA1c were done to evaluate glycemic control. The World Health Organization definition of diabetes is for a single raised glucose reading with symptoms, otherwise raised values on two occasions, of either (Valdez, 2009).
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- fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or
- with a glucose tolerance test, two hours after the oral dose a plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

A glycated hemoglobin (HbA1c) of greater than 6.5% is another method of diagnosing diabetes as is a random blood sugar of greater than 11.1 mmol/l (200 mg/dL) in association with typical symptoms (Knowler et al., 2002).

The biochemical profiles were performed at the laboratory of Ibn Sina Teaching Hospital. Standard kits were used to measure biochemical profiles suggested in this study; tests performed and interpreted following instructions outlined in each kit.

Clinical and Radiological examination

Both groups were subjected to X-ray examination of both knees in standing position, and the findings were recorded according to the severity of osteoarthritis found in the examination.

Statistical Analysis

Standard statistical methods used to determine the mean and standard deviation. Paired t-test and two sample t-test were used to compare the results of various parameters among the studied groups. Linear regression analysis (Person Correlation Coefficients) (r) was performed for finding the degree of association between different parameters.

Some values expressed as Mean ± SD and P value of <0.05 was considered to be statistically significant.

Results

Table (1) shows the ages, FBS and HbA1c of all studied groups. There was no statistically significant difference between the age groups. FBS of the control subjects is within normal range, while those of diabetic patients is high when compared with the control group (P= 0.001).
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Table (1): The Ages, FBS of the studied groups, and HbA1c of diabetic patients. Data expressed as Mean±SD.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (N=65)</th>
<th>Diabetics (N=65)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>44.5±3.42</td>
<td>45.4±3.13</td>
<td>0.214</td>
</tr>
<tr>
<td>FBS (mmol/l)</td>
<td>5.61±0.77</td>
<td>10.0±4.18</td>
<td>0.001</td>
</tr>
<tr>
<td>HbA1c</td>
<td>---</td>
<td>8.3±1.70</td>
<td>---</td>
</tr>
</tbody>
</table>

Table (2) shows the results of the grading of right knee joint space narrowing (JSN) in both groups. Grade 1 JSN was higher in diabetic group, while grade 2 and grade 3 JSN was only observed in diabetic group.

Table (2): The X-Ray finding of the right knee joint of both studied groups. Data expressed as number and percentage.

<table>
<thead>
<tr>
<th>Grade of JSN</th>
<th>Control (N=65)</th>
<th>Diabetic (N=65)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Grade 0</td>
<td>38</td>
<td>58.5</td>
<td>10</td>
</tr>
<tr>
<td>Grade 1</td>
<td>27</td>
<td>42.5</td>
<td>39</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>0.0</td>
<td>13</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
</tr>
</tbody>
</table>

Table (3) shows the results of the grading of left knee joint narrowing space in both groups. There is a significant differences, grade 1 JSN was higher in diabetic group, while grade 2 and grade 3 JNS were only in diabetic group.
Table (3): The X-Ray finding (JSN) of the left knee joint of both studied groups. Data expressed as number and percentage.

<table>
<thead>
<tr>
<th>Grade of JSN</th>
<th>Control (N=65)</th>
<th>Diabetic (N=65)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Grade 0</td>
<td>39</td>
<td>60.0</td>
<td>7</td>
</tr>
<tr>
<td>Grade 1</td>
<td>26</td>
<td>40.0</td>
<td>42</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>0.0</td>
<td>13</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
</tr>
</tbody>
</table>

Table (4) shows the presence of the osteophyte of right knee joint in both groups. Diabetic group patients have high numbers of osteophytes in grades 1, 2, 3 and 4.

Table (4): The X-Ray finding (osteophytes) of the right knee joint Of both studied groups. Data expressed as number and percentage

<table>
<thead>
<tr>
<th>Grade of osteophytes</th>
<th>Control (N=65)</th>
<th>Diabetic (N=65)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Grade 0</td>
<td>54</td>
<td>83.1</td>
<td>40</td>
</tr>
<tr>
<td>Grade 1</td>
<td>11</td>
<td>16.9</td>
<td>16</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>0.0</td>
<td>5</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
</tbody>
</table>

Table (5) shows the presence of the osteophyte of left knee joint in both groups. Diabetic group patients have high numbers of osteophytes in grades 1, 2, 3 and 4.
Table (5): The X-Ray finding (osteoophytes) of the left knee joint of both studied groups. Data expressed as number and percentage.

<table>
<thead>
<tr>
<th>Grade of osteophytes</th>
<th>Control (N=65)</th>
<th>Diabetic (N=65)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Grade 0</td>
<td>57</td>
<td>87.7</td>
<td>38</td>
</tr>
<tr>
<td>Grade 1</td>
<td>8</td>
<td>12.3</td>
<td>19</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>0.0</td>
<td>4</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
</tbody>
</table>

Table (6) shows the correlation between FBS and joint narrowing space of left side (JSNL) in the studied groups, there are a statistically significant positive correlation \( p = 0.001, \) and \( 0.003 \) respectively.
Table (6): The correlation between FBS and JSN in the studied groups. Data expressed as Mean±SD.

<table>
<thead>
<tr>
<th>The side</th>
<th>FBS (in millimeter)</th>
<th>JSN (in millimeter)</th>
<th>r</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left knee</td>
<td>7.86±3.71</td>
<td>0.79±0.71</td>
<td>0.252</td>
<td>0.001</td>
</tr>
<tr>
<td>Right knee</td>
<td>7.86±3.71</td>
<td>0.77±0.71</td>
<td>0.259</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Discussion

Several studies have reported an association of early OA and diabetes. Both large and small joint OA have been reported to be increased in type 2 diabetes. However, OA of the weight-bearing joints in type 2 diabetic patients may be related to their obesity and not to the diabetes itself. It is not yet known whether diabetes is a risk factor for OA independent of obesity (Kim et al., 2001).

The current study involved 130 individuals divided into two groups of 65 individuals. The study was designed to investigate the prevalence of knee osteoarthritis in patients with type 2 diabetes mellitus in comparison with non diabetic patients. Sixty five patients type 2 diabetics, regularly followed up at the Al-Waffa Center for Diabetes management and research in Mosul, were enrolled in the study. The mean age of the patients was 45.4±3.13 years and the mean duration of the diabetes disease was 10.1 years.

Sixty five apparently healthy, non diabetic subjects their mean age 44.5±3.42 years were enrolled as control group.

The groups were matched concerning the number and their ages as confirmed statistically by the absence of significant differences between the studied groups. This matching of individual groups number, and age may exclude any effect of these parameters on the results of the study.

The diabetic patients in our study were uncontrolled chronic patients, and the FBS reported among such patients were high as compared with the controls 10.0±4.18; 5.61±0.77 mmol/l respectively (Table 1).

Higher levels of FBS in patients with diabetes are thought that they have poor glycemic control, and will lead to cellular damage and are ultimately responsible for the complications of diabetes (Guerci et al., 2001), including nephropathy, retinopathy, neuropathy and macro and microvascular damage (Salman, 2004).

The data obtained in the present study which demonstrated high uncontrolled level of FBS was in agreement with the data reported in the majority of the previous studies (Cagliero, 2003).

Higher level of glucose was observed among IDDM and NIDDM patients (13.4, 11.1 mmol/l, respectively) compared to control group (4.8 mmol/l)( Cagliero, 2003), measured FBS in 2 types of diabetic patients, newly diagnosed type 2 patients and patients on oral hypoglycemic agents. Both types of diabetic patients showed higher FBS (198 mg/dl for newly diagnosed and 185 mg/dl for the oral hypoglycemic
group) compared to control group (90 mg/dl).

High FBS, was also reported by (Mark et al., 2008) who demonstrated FBS of 205.47 mg/dl for the diabetic patients and 96.95 mg/dl for controls. In other study which evaluated glycemic state of the diabetic patients by measuring FBS and HbA1C. Both parameters were identified higher than those identified in the control group (Orozco et al., 2008).

The elevated FBS in the diabetic patients demonstrated in the present study may add some light on the fact that the majority of prolonged duration of diabetic with uncontrolled FBS may contribute to the appearance of diabetic complications. The existence of a significant positive correlation between FBS and osteoarthritis (JSN and osteophyte) in both knee joints of diabetic group is an indicator of the probable effect of diabetes in the occurrence of osteoarthritis.

Diabetes is widely known to induce metabolic derangement leading to oxidant-antioxidant imbalance (Davis et al., 2009). The increase in oxidative stress may probably be related to the abnormal metabolic milieu such as hyperglycemia, dyslipidemia, and elevated free fatty acids, which commonly occur in patients who have diabetes and less than perfect glycemic control (Gorman & Krook 2011).

Hyper-glycemia may lead to an increased generation of free radicals via multiple mechanisms such as glucose auto oxidation, non-enzymatic glycation, the polyol pathway and reduced antioxidant defense system (Davis et al., 2009).

The pathophysiology of these disorders in diabetic patients is not obvious. It could be associated with connective tissue disorders, such as the formation of abnormally glycosylated end products or the impaired degradation of byproducts, it could be indirectly related to the vasculopathy and neuropathy commonly complicating the primary disease, or finally, it could be attributed to a combination of factors (Douloumpakas et al., 2012).

A study done by (Andrianakos et al., 2006), the prevalence of osteoarthritis in type 2 diabetic patients was found to be significantly higher than the estimated prevalence in the general population. In a large study on osteoarthritis including 1026 patients, the mean fasting glucose concentration was higher in subjects with osteoarthritis (OA) than in subjects without OA (Cimmino and Cutolo, 1990).

Diabetes was observed to be accompanied by an increased production of free radicals and/or impaired antioxidant defense capabilities, indicating a central contribution for reactive oxygen species in the onset, progression and pathological consequences of disease (Anabela and Carlos, 2006).

The results of our study may be explained by motor and sensory dysfunction of muscle may be important factors in the pathogenesis of articular damage.

It is well accepted fact that patients with OA have muscle weaknesses and a vibratory sense loss in the regional OA joint. Interestingly, this neurological dysfunction is present locally and throughout the body, suggesting a generalised alteration of the peripheral nervous system. Two main neurological syndromes have been described in diabetes.

The first is the Charcot neuroarthropathy, a rare but devastating complication leading to joint deformity and eventually amputation or secondary OA. The second is a symmetric, mainly sensory polyneuropathy often accompanied by autonomic neuropathy. This latter diabetic neuropathy could be one of the suggested alterations of the peripheral nervous system seen in patients with OA leading to muscle
weaknesses and joint laxity (Berenbaum, 2011).

This speculates that such peripheral nerve impairment induced by diabetes could be an added risk factor for OA in patients with diabetes.

**Conclusion:** Knee joint space narrowing grade 1 was higher in diabetic group than non diabetics, while grade 2 and grade 3 JSN were noted to occur only in diabetic patients also diabetic patients have high numbers of osteophytes in grades 1, 2, 3 and 4, these findings strengthen the concept of a strong metabolic component in the pathogenesis of OA hence, we can consider Type 2 DM as a predictor for the development of severe OA of the knee independent of age and other known risks for OA.

**Recommendations:** Regular attendance at diabetes outpatient clinics to identify advice and educate those patients regarding their DM state control.

1- Diabetics should have their joints and specifically knee joints examined routinely for OA.

**References**

study HIIPPOKRATIA ; 11, 4: 216-218


الخلاصة

إن الهدف من هذه الدراسة هو معرفة انتشار التهاب مفصل الركبة السوفاني لدى المرضى المصابين بداء السكر من النمط الثاني وبالتالي تحري صلاحية كون داء السكر من النمط الثاني كعامل خطورة استقصائي لالتهاب الركبة السوفاني.

أجرت هذه الدراسة على عينة عشوائية تتكون من 65 مريض مصابين بداء السكر من النمط الثاني والذين تتراوح أعمارهم بين 40-50 سنة.

المجموعة الثانية وهي العينة الضابطة تتكون من 65 شخص غير مصابين بداء السكر من نفس الفئة العمرية.

تم إرسال جميع الأشخاص والمصابين في الدراسة من المجموعة الأولى لا جراء فحص نسبة السكر في الدم قبل تناولهم الإفطار (فحص HbA1c) وفحص (FBS) للمجموعة الأولى فقط. وكذلك تم إرسالهم لا جراء الفحوص الشعاعية لمفصل الركبتين في كلا المجموعتين وتم تسجيل النتائج حسب وجود المؤشرات الدالة على وجود سوفان الركبة.

استخلصت الدراسة وجود علاقة إيجابية بين داء السكر من النمط الثاني والتهاب مفصل الركبة السوفاني مما يؤيد وجود علاقة إيجابية جدلية قوية وراء التغيرات المتقدمة لالتهاب مفصل الركبة السوفاني ومن هذا يمكن اقراح داء السكر من النمط الثاني كعامل خطورة يمكن من خلاله توقع احتمالية حصول التهاب مفصل الركبة السوفاني بعد عزل كل من عامل تقدم العمر وعوامل الخطر الأخرى التي استثنتها الدراسة لتصويب النتائج.