Knee Osteoarthritis in Type 2 Diabetes Mellitus: Does Insulin Therapy Retard Osteophyte Formation?

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Key Words

Osteoarthritis · Diabetes mellitus · Insulin · Kuwait

Abstract

Objective: The aim of this study was to investigate whether or not radiographic changes observed in knee osteoarthritis (OA) in type 2 diabetes mellitus (T2DM) patients on insulin therapy differed from those not on insulin. **Material and Methods:** A cross-sectional study was performed in 311 subjects: 211 T2DM patients and 100 without diabetes (controls) in Mubarak Hospital, Kuwait. Patients were categorized into 3 groups: T2DM patients not on insulin (G1, n = 99), T2DM patients on insulin (G2, n = 112) and a nondiabetic control group (G3, n = 100). Plain X-ray of both knees was used to assess the changes of knee OA and graded using the Kellegren-Lawrence scale (0–4) and the Osteoarthritis Research Society International Atlas grading scale (0–3). A total of 622 knee X-rays were evaluated. SPSS version 21.0 was used for data analysis. **Results:** A highly significant association ($p < 0.0001$) was observed for joint space narrowing (JSN) as well as for osteophyte formation between the three groups. Comparing G2 and G3, a highly significant association ($p < 0.0001$) was retained for JSN [201 (89.7%) vs. 199 (99.5%)] and for osteophyte formation [26 (11.7%) vs. 72 (36.0%)]. Comparing G1 and G2, significantly less osteo-

phyte formation was noted in G2 patients compared to G1 patients [26 (11.7%) vs. 39 (19.7%), $p = 0.02$]. Multivariate logistic regression analysis showed that the G2 group had less chance of osteophyte formation than either the G1 group or G3 control group (OR = 0.294, $p = 0.008$ and OR = 0.098, $p < 0.001$, respectively). **Conclusion:** Our findings show that T2DM patients with OA knees on insulin therapy have less radiographic osteophytes compared to T2DM patients not on insulin.

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Introduction

Osteoarthritis (OA) is one of the most common disabling diseases and has become a growing health care problem because of its increasing prevalence worldwide [1, 2]. The main phenotypes described are age-related, posttraumatic, hormonal, genetic and metabolic OA. A higher prevalence of OA has been reported among patients with metabolic syndrome, and diabetes mellitus (DM) was reported as an independent predictor for OA [1–5]. Hyperglycemia and OA interact at both local and systemic levels. Local effects of oxidative stress and advanced glycation end products lead to matrix stiffness, subchondral bone destruction and chondrocyte dysfunc-

tion [6]. As a result of hyperglycemia, low-grade systemic inflammation contributes to a toxic internal environment that exacerbates OA [1, 6]. The other suggested reason attributed to the correlation between DM and OA is diabetic peripheral neuropathy leading to muscle weakness and joint laxity in OA [1]. The lack of agreement between X-ray evidence of OA and a patient's report of pain at the site has also been attributed to diabetic neuropathy [7]. Still, because of the inconsistencies and limitations of observational studies, a conclusive association between DM and OA has not been determined [1, 8]. The incidence of an aging population, metabolic syndrome and OA is exponentially increasing worldwide [1–4], and this trend is also seen in the Kuwaiti population [9, 10]. Hence, research in this field for new treatments of OA has become mandatory.

Concepts of insulin therapy for OA have been proposed in the past decades [11]. The anabolic effect of insulin on connective tissue and its role as a potent growth factor for connective tissue has been described [11–13]. Early studies performed on whole animals, organs or tissues indicated that insulin is required for the optimal production of sulfated mucopolysaccharides and collagen, two major components of connective tissue [14–17]. In experiments conducted on articular cartilage explants harvested from patients undergoing knee joint replacement, Cai et al. [11] reported that insulin inhibited nitric oxide production and stimulated matrix synthesis by counteracting the deleterious effect of interleukin 1 (IL-1), high levels of which are usually found in arthritic joints. Another observation relating to insulin therapy was made by Nieves-Plaza et al. [8], who reported that patients with DM who did not use insulin for their condition had a 4.44-fold increased risk of hand or knee OA.

Radiographic features of bone and cartilage seen in OA are the result of degenerative changes as evidenced by articular cartilage thinning and joint space narrowing (JSN), and proliferative changes evidenced by concomitant repair activity with new cartilage and bone growth resulting in osteophytosis and subchondral sclerosis. Limited studies [8, 12] have been conducted on the effect of insulin on radiographic features and osteophyte formation in OA in diabetic patients. Horn et al. [12] reported that osteophyte formation, as well as other radiographic indicators of joint repair, are less marked in type 2 DM (T2DM) patients with OA compared to nondiabetic patients with OA. Hence, the aim of our study was to evaluate whether or not the radiographic changes of knee OA differed between T2DM patients on insulin and those not on insulin therapy.

Subjects and Methods

Study Population

A cross-sectional study was performed on a total of 311 subjects consisting of 211 T2DM patients and 100 nondiabetic control subjects during a period of 12 months, from September 2012 to August 2013. Consecutive T2DM patients with knee pain were enrolled from the diabetic clinics of Mubarak Al-Kabeer Hospital, Kuwait. T2DM was defined as a fasting plasma glucose level ≥ 7.0 mmol/l on at least two occasions, or Hb A1C $\geq 6.5\%$ [18].

Among the 211 T2DM patients (86 males, 125 females; aged 38–86 years), 20 were only on an exercise regime and not on any medication for diabetes, and 79 were on oral hypoglycemic agents alone. These 99 patients were grouped as the noninsulin group (G1). Thirty-six patients were on insulin alone and 76 were on both insulin and oral hypoglycemic agents. These 112 patients were included in the category of diabetic patients on insulin (G2). The duration of insulin therapy was ≥ 5 years, with a total insulin daily requirement ranging from 40 to 80 IU, given subcutaneously in 1–3 divided doses. Nondiabetic subjects referred for knee pain to Physical Medicine and Rehabilitation clinics served as controls (G3). Exclusion criteria were patients with inflammatory rheumatic diseases, malignancy, hyperparathyroidism, renal disease or liver disease. All the patients were studied according to the protocol approved by the Ethics Committees of the Faculty of Medicine, Kuwait University, and the Ministry of Health in accordance with the provisions for human research established in the Declaration of Helsinki.

Written informed consent was obtained from each participant. Details of knee pain, clinical examinations of the knees, height, weight, BMI (calculated using the standard formula: weight divided by height in meters squared), diabetic history with regard to the duration of diabetes and diabetic treatment in subjects with T2DM were collected and recorded on Performa. Biochemical parameters were measured as part of their routine diabetic workup.

Study Methodology

Knee function was assessed using the Lequesne index for knee OA [19], which is a ten-question survey given to patients suffering from the condition. It is composed of five questions relating to pain or discomfort, one question dealing with maximum distance walked and four questions about activities of daily living. The total questionnaire is scored on a scale from 0 to 24. A Lequesne index up to 10 is considered to be good and >10 is viewed as poor, with higher scores indicating that there is greater functional impairment.

A standard X-ray weight-bearing, anterior-posterior image of both knees was taken for all patients. OA of the knee was ascertained using the American College of Rheumatology classification criteria [20, 21]. Both the Kellgren-Lawrence (K-L) the Osteoarthritis Research Society International (OARSI) classification systems were used to assess the radiographic images. The K-L grades (range 0–4) are as follows: 0 – normal; 1 – doubtful narrowing of joint space and possible osteophyte lipping; 2 – definite osteophytes and possible narrowing of joint space; 3 – definite narrowing of joint space and some sclerosis and possible deformity of bone ends; 4 – significant osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends [22]. The OARSI classification grades (range 0–3) are as follows: 0 – normal; 1 – mild narrowing (1–33% narrowed); 2 – moderate narrowing (34–66%); 3 – severe narrowing (67–100%). The OARSI grades were given for medial and lateral tibiofemoral compartments. [23].

Statistical Analysis

Results were analyzed using the Statistical Package for Social Sciences version 21.0 (SPSS Inc., Chicago, Ill., USA). Descriptive statistics were used to describe the variables. Categorical variables were compared by χ^2 test and mean values of continuous variables were compared by ANOVA. Binary logistic regression analysis was used to ascertain the association of osteophyte formation with insulin therapy with and without adjustment for the confounding effects of gender, BMI and age. Values of $p < 0.05$ were considered to be statistically significant.

Results

A total of 622 knee X-rays were evaluated. Two investigators (K.J. and D.S.) assessed and scored all the radiographs, blinded to the clinical details of subjects. The inter-reader agreement was 90% for cases of JSN and 81% for osteophytes cases. Differences were resolved by the readers reaching a consensus interpretation of radiographs.

The demographic characteristics of the participants in the cohort are shown in table 1. Among the cohorts the differences between gender and BMI were statistically significant ($p < 0.001$ and < 0.039 , respectively). The evaluation of functional or pain scores (Lequesne index score) among cohorts did not show any statistically significant differences ($p = 0.106$).

Blood sugar was controlled with a target of HbA1C between 7 and 8% in our diabetic subjects. The mean HbA1C % value for the nondiabetic control group (G3) was 5.5 ± 2.0 , and there was no statistical difference in values of HbA1C between the noninsulin (G1) and insulin (G2) T2DM patients (7.6 ± 2.0 vs. 7.9 ± 2.1 , respectively, $p = 0.124$).

The mean $\pm$ SD K-L score was similar in the three groups: 2.22 ± 0.7 (G1), 2.27 ± 0.8 (G2) and 2.37 ± 0.8 (G3; $p > 0.161$). However, a significant difference ($p = 0.016$) was observed in the grading of K-L scores among cohorts, with a higher grading (i.e. grade 4) observed in the non-diabetic control group [G3: 16 (8.0%)] than in the diabetic patients [G1: 8 (4.0%) and G2: 8 (3.6%)].

OARSI grading showed highly significant differences ($p > 0.0001$) between G1, G2 and G3, respectively, for JSN [175 (88.4%) vs. 201 (89.7%) vs. 199 (99.5%)] and osteophyte formation [39 (19.7%) vs. 26 (11.7%) vs. 72 (36.0%)]. Comparing the insulin group and control subjects (G2 vs. G3), the highly significant difference ($p < 0.0001$) for both JSN [201 (89.7%) vs. 199 (99.5%)] and for osteophyte formation [26 (11.7%) vs. 72 (36.0%)] was maintained, whereas comparing the insulin and noninsulin T2DM

Table 1. Demographic characteristics of the T2DM patients and controls

	G1: non-insulin (n = 99)	G2: insulin (n = 112)	G3: controls (n = 100)	p
Mean age $\pm$ SD, years	57.8 $\pm$ 8.9	60.3 $\pm$ 9.5	57.1 $\pm$ 9.4	0.059
Range	39–80	38–79	27–80	
<50 years	22 (23.2)	15 (13.6)	20 (20.0)	0.189
>50 years	72 (76.6)	95 (86.4)	80 (80.0)	
Gender				
Male	46 (46.5)	40 (35.7)	12 (12.0)	<0.001
Female	53 (53.5)	72 (64.3)	88 (88.0)	
Duration of diabetes				
<10 years	35 (38.5)	17 (15.7)	–	<0.001
>10 years	56 (61.5)	91 (84.3)	–	
BMI				
<30	34 (47.9)	31 (35.6)	45 (54.9)	0.039
>30	37 (52.1)	56 (64.4)	37 (45.1)	
Functional score (Lequesne index score)				
Good (≤ 10)	44 (55.7)	36 (40.4)	42 (42.9)	0.106
Poor (> 10)	35 (44.3)	53 (59.6)	56 (57.1)	

Values are n (%) unless otherwise indicated.

Fig. 1. The percentage of study subjects with JSN and osteophytes.

patients (G1 vs. G2) revealed no association [175 (88.4%) vs. 201 (89.7%), $p = 0.386$] for JSN, although significantly less osteophytes were observed in G2 [26 (11.7%)] compared to G1 patients [39 (19.7%), $p = 0.022$; table 2]. The percentage of G1, G2 and G3 subjects with JSN and osteophytes are shown in figure 1.

Table 2. Association between radiographic K-L score, and OARSI score for JSN and osteophyte formation between the noninsulin, insulin and control groups

	Total (n = 622)	G1: noninsulin (n = 198)	G2: insulin (n = 224)	G3: controls (n = 200)	p
<i>Radiographic K-L score</i>					
Mean score $\pm$ SD (range)		2.22 $\pm$ 0.7 (0–4)	2.27 $\pm$ 0.8 (0–4)	2.37 $\pm$ 0.8 (1–4)	0.161
Grade 0	12 (1.9)	4 (2.0)	8 (3.6)	0	0.016
Grade 1	72 (11.6)	23 (11.6)	20 (8.9)	29 (14.5)	
Grade 2	296 (47.6)	105 (53.0)	107 (47.8)	84 (42.0)	
Grade 3	210 (33.8)	58 (29.3)	81 (36.2)	71 (35.5)	
Grade 4	32 (5.1)	8 (4.0)	8 (3.6)	16 (8.0)	
<i>JSN</i>					
Absent	47 (7.6)	23 (11.6)	23 (10.3)	1 (0.5)	<0.0001
Present	572 (92.4)	175 (88.4)	201 (89.7)	199 (99.5)	
<i>Osteophyte formation</i>					
Absent	485 (78.0)	159 (80.3)	198 (88.4)	128 (64.0)	<0.0001
Present	137 (22.0)	39 (19.7)	26 (11.7)	72 (36.0)	
Grade 0	483 (77.5)	158 (79.8)	198 (88.4)	127 (63.5)	<0.0001
Grade 1	114 (18.3)	28 (14.1)	15 (6.7)	71 (35.5)	
Grade 2	20 (3.2)	10 (5.1)	8 (3.6)	2 (1.0)	
Grade 3	5 (0.8)	2 (1.0)	3 (1.3)	0	

Values are n (%) unless otherwise indicated. Association for JSN between G2 and G3: $p < 0.0001$, and between G1 and G2: $p > 0.05$. Association for osteophyte formation between G2 and G3: $p < 0.001$, and between G1 and G2: $p = 0.022$.

Binary logistic regression analysis for osteophyte formation between the cohorts generated odds ratio (OR), 95% confidence interval (CI) and p values for the predictive role of various variables, as shown in table 3. Unadjusted analysis for osteophyte formation between G2 and G3 showed a significant association (OR = 0.233, 95% CI = 0.142–0.385, $p < 0.001$), which persisted after adjusting for gender, BMI and age (OR = 0.098, 95% CI = 0.042–0.230, $p < 0.001$). Similarly, between G1 and G2 there was also a significant association for unadjusted analysis (OR = 0.535, 95% CI = 0.312–0.917, $p < 0.023$) which remained after adjustment for gender, BMI and age (OR = 0.294, 95% CI = 0.119–0.722, $p < 0.008$).

Discussion

In this study the degree of osteophyte formation as well as cartilage loss was greater in control subjects and in T2DM patients not receiving insulin than T2DM patients on insulin therapy. The lack of a difference in the K-L scores relative to other parameters that revealed a differ-

Table 3. Binary logistic regression analysis for osteophyte formation

Variable	OR	95% CI	p value
<i>T2DM patients on insulin and controls (G2 and G3)</i>			
Crude OR for each variable (unadjusted)			
G2	0.233	0.142–0.385	<0.001
G3 (reference)	1.000		
Multivariate analysis (adjusted for all variables)			
G2	0.098	0.042–0.230	<0.001
G3 (reference)	1.000		
<i>T2DM patients not on insulin and on insulin (G1 and G2)</i>			
Crude OR for each variable (unadjusted)			
G2	0.535	0.312–0.917	0.023
G1 (reference)	1.000		
Multivariate analysis (adjusted for all variables)			
G2	0.294	0.119–0.722	0.008
G1 (reference)	1.000		

The dependent variable was osteophytes ($\pm$) and the independent variable was patient group.

ence between the patient groups could be explained as follows. Whilst both K-L and OARSI are semiquantitative radiographic tools that provide an assessment of the extent of knee OA, the K-L scoring system is used to assess the OA status of the entire tibiofemoral joint, whereas the OARSI scoring system describes the extent of OA in the medial and lateral compartments separately. Therefore, they are not designed to be interchangeable.

Our findings are consistent with those of Cai et al. [11] who reported a beneficial effect of insulin in the treatment of OA. OA is characterized by loss of cartilage matrix molecules, proteoglycans (PG) and collagens. Articular cartilage from diabetic mice had lower basal levels of PG synthesis than nondiabetic controls. Cai et al. [11] demonstrated that local insulin treatment increased PG synthesis and thus increased matrix synthesis as well as decreasing matrix breakdown. Matrix breakdown is one of the earliest and most destructive features of arthritis. Osteophyte formation and cartilage loss, the most typical pathologic findings in OA patients, is secondary to matrix loss and breakdown. Thus, inhibition of this process and stimulation of new matrix molecules would be expected to promote tissue and joint repair.

Another mechanism whereby insulin decreases matrix breakdown is through the inhibition of aggrecanase activity. In addition, insulin inhibits nitric oxide production and antagonizes IL-1, which each have detrimental effects on chondrocytes and other cell types within the joint. Furthermore, insulin is a poor mitogen of osteoblasts and fibroblasts, which are necessary for the formation of bony nodules or osteophytes. Cai et al. [11] also showed that the response of cartilage to insulin did not diminish with age or disease; thus, insulin has potential as a treatment for OA at different stages of joint destruction.

It is not clear how systemic or exogenous insulin administration may differ in its impact on the skeleton compared with local delivery, which would have a much lesser impact on glycemic response and metabolism [13]. Spanheimer [24] reported that systemic administration of insulin can at least partially reverse the defects in connective tissue metabolism. While insulin may have direct effects on connective tissue, reversal of defects in connective tissue metabolism by the systemic administration of insulin could be due to circulating factor(s) induced by insulin and not due to the direct effect of insulin on connective tissue.

Our findings were consistent with those of Horn et al. [12] who observed that osteophytes were less marked in T2DM patients than in nondiabetic patients with OA. A

possible explanation for these observations and the effect of insulin therapy on osteophytes formation could be related to the fact that diabetic microvascular disease attenuates osteogenesis and diminished proteoglycan synthesis leading to inhibition of insulin-dependent mesenchymal cell proliferation, which may attribute to reduced osteophyte formation in diabetic patients. Another postulation for osteophyte formation is changes in the stress distribution in periarticular and subchondral bone. Diminished physical activity in DM patients was attributed to the fewer osteophytes observed in DM patients in the study [12].

In our study, only 45% of the nondiabetic controls were obese as compared to 52.1% of the noninsulin and 64.4% of the insulin-treated T2DM patients ($p = 0.039$). Alterations in connective tissue metabolism in the OA joint due to DM may have been compounded by the metabolic effects of obesity. However, after adjustment for BMI (as well as age and gender), our T2DM patients on insulin treatment remained less predictive for the presence of radiographic osteophytes.

Obesity in itself is a risk factor for OA independent of DM and is associated with insulin resistance and hyperinsulinemia [25, 26]. In animal experiments, Griffin et al. [27] demonstrated that diet-induced obesity increases the risk of symptomatic features of OA through changes in musculoskeletal function and pain-related behaviors. Furthermore, the independent association of systemic adipokine levels with knee OA severity supports a role for adipose-associated inflammation in the molecular pathogenesis of obesity-induced OA. Issa and Griffin [28] reviewed the pathobiology of obesity and OA and highlighted the role of proinflammatory metabolic factors in increasing the risk of OA. Adipose tissue, in particular infrapatellar fat, is a local source of inflammatory mediators that are increased with obesity and have been shown to increase cartilage degradation in cell and tissue culture models. Furthermore, Altuntaş et al. [29] investigated the association between articular damage in diabetes at gene expression and protein levels, and concluded that insulin reduces the amount of ADAMTS12 (A disintegrin and metalloproteinase with thrombospondin motifs 12), an enzyme in humans that is encoded by the ADAMTS12 gene. This enzyme causes a delayed recovery of cartilage tissue and its reduction by insulin can contribute to the recovery of cartilage tissue. These experiments were conducted on OUMS-27 cell lines from chondrosarcoma cells which have chondrocytic properties.

Our study design was cross-sectional and assessed only anteroposterior knee films, which are routinely used

in population surveys. However, radiographic assessment by two experienced musculoskeletal physicians with an inter-reader agreement of 90% for JSN and 81% for osteophytes was good enough to achieve the aims of the study.

Conclusion

In this study of OA of the knee, T2DM patients on insulin therapy had less radiographic osteophytes than both T2DM patients who were not on insulin and healthy control subjects. As the impact of insulin treatment on the

biomechanical properties of the intact skeleton remains unclear, further longitudinal studies are needed to address issues such as the mode and dose of administration to maximize insulin effectiveness for OA management, methods to increase the stability of locally administered insulin, and also to delineate the mechanisms underlying these observations.

Disclosure Statement

The authors have no conflicts of interest to declare in relation to this work.

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