Impact of Metabolic Factors on the Incidence and Intensity of Knee Osteoarthritis in a Sample of Iraqi Patients

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Abstract

Background: Osteoarthritis (OA) is a leading cause of physical disability, morbidity and lessened quality of life, mainly in elderly people. It characterized by inflammation, breakdown, and consequent loss of cartilage of the joints. OA usually associated with obvious risk factors, like obesity, age, inflammation and joint injury, in addition to quality of diet and some metabolic factors. Purpose: To evaluate the role of obesity and different metabolic factors on the incidence and severity of symptoms in patients with knee osteoarthritis. Methods: Fourth patients with painful knee OA were randomly selected at the outpatient clinic of Baghdad teaching hospital. All patients diagnosed with OA in one or both knee joints. The patients were allocated into two groups: Group A: Include 20 non-obese patients diagnosed with knee OA. Group B: Include 20 overweight and obese patients diagnosed with knee OA. A validated, self-administered questionnaire method known as Western Ontario Mac Master Osteoarthritis Index (WOMAC) which includes evaluation of pain, stiffness and physical function, were done. FBG, TC, LDL, TG, HDL cholesterol, in addition to serum leptin, IL-1β and TNF-α were measured for both groups to be statistically evaluated. Results: The results showed a significant differences (P<0.05) between group A and group B regarding to BMI, serum leptin, TG, LDL, IL-18 and TNF-α (less values in group A), in addition to WOMAC score and serum HDL (more values in group A). However, no significant differences (P<0.05) seen for FBG and TC between both groups. Conclusion: This study clearly demonstrated that increasing body weight with the presence of other metabolic factor can strongly enforce and accelerate many process involved in the pathogenesis of OA, including inflammatory response, cartilage degradation and bone remodeling.

Keywords: Osteoarthritis, Obesity, Metabolic syndrome, inflammation, WOMAC.

Introduction

Osteoarthritis (OA) is a debilitating condition characterized by inflammation, breakdown, and consequent loss of cartilage of the joints (1).

OA is a leading cause of physical disability, morbidity, excess health care utilization and lessened quality of life, mainly in elderly people (2).

Osteoarthritis characterized by modulation of joint structural, that defined as focal destruction of articular cartilage, remodeling of subchondral bone and, in advance case, generation of osteophytes at the joint edges, as well as an illness determined by symptoms, like weakness, pain, sleep disturbance and mood alterations (3).

Severity of hip and knee OA have been reported to be linked with excess all-cause mortality (4,5). OA usually associated with obvious risk factors, like obesity, age, inflammation and joint injury. The participation of diet and some metabolic factors is still under investigation (6).

Obesity is considered as potent predictors of OA development (7). Increasing weight can modify joint loading and lead to damages the joint, this abnormal joint loads can precipitate changes in the structure, composition, and mechanical properties of particular cartilage (8).

In the United States, population-based study suggest prevalence rates ranging from 1% in
people aged 25-34 with severe radiographic disease to about 30% in people with age 75 and above (9). Metabolic syndrome (Met S) is a bunch of cardio-metabolic disorders that outcome from the growing prevalence of obesity. Central obesity, insulin resistance, hypertension and dyslipidemia are the major components of Met S (10).

Previous studies revealed a strong link between central obesity with the elevated risk for type-2 diabetes mellitus (T2DM) and cardiovascular diseases (CVDs) and (11, 12). Another study have been reported the association of rheumatoid arthritis (RA) and osteoarthritis (OA) with a high prevalence of CVDs (13). For example, mortality increased 50% in patients with RA with co-existence of CVDs (14, 15). Moreover, the alteration of pro-inflammatory adipokines secretion patterns that associated with pathologic dysfunction of fat mass, could be the link between rheumatic diseases and CVDs (16,17). Adipose tissues considered as metabolic endocrine organ have the ability to stimulate the secretion of adipocytokines; like adiponectin, leptin and resistin. Adipocytokines play a pivotal role in cartilage homeostasis and affect osteoarthritis either by direct joint degradation or by controlling the inflammatory processes locally at joint (8).

Diabetes mellitus (DM) and hyperglycemia seemed to be contributed in pathogenesis of OA in some epidemiological studies (18, 19).

Moreover, the link between the two diseases may be boosted by the mischievous role of high glucose through the accumulation of advanced glycation end products (AGEs), promotion of systemic inflammation and increasing oxidative stress (20, 21). Study by (Hamada et al 2016) revealed that there is a link between production of synovial tumor necrosis factor alpha (TNF-α) and insulin resistance to the pathology of OA (22).

In obese diabetic patients, the development of synovial insulin resistance can attenuate the activity of insulin to suppress the production of inflammatory and catabolic mediators that promote OA (23). No precise mechanism can elucidate the influence of lipid profile on the incidence of OA. However, there is evidence that high levels of high density lipoprotein (HDL) in the synovial fluid have a protective effect (24). Other study found that elevated levels of total cholesterol (TC) and triglyceride (TG) are associated with asymptomatic bone marrow lesions in middle-aged women (25). Epidemiological data reported a positive correlation between systemic levels of cytokines, leptin, and resistin with types and grade of OA, while adiponectin association is controversial (1). In previous studies, adiponectin, leptin and resistin levels have been disclosed in the plasma and synovial fluid of osteoarthritic patients (26, 27), and leptin expression has been directly correlated with the grade of cartilage degeneration (28).

The pro-inflammatory cytokines are contributed to the initiation and progression of OA process. The most predominant are IL-1β, IL-1α and TNF-α. IL-1β is strongly associated with cartilage destruction. However, TNF-α appears to drive the inflammatory process. Furthermore, they can provoke chondrocytes and synovial cells to produce more cytokines such as IL-6, IL-8, as well as, stimulate production of PGE2 and proteases (29).

**Patients and Methods**

This study was carried out over a period from Feb 2017 to Sep 2017. Fourty patients with painful knee OA were randomly selected at the outpatient clinic of Baghdad teaching hospital. All patients diagnosed with symptomatic and radiologic evidence of OA in one or both knee joints.

The Patients were allocated into Two Groups

Group A: Include 20 non-obese patients diagnosed with knee OA.

Group B: Include 20 overweight and obese patients diagnosed with knee OA.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m²). In this study, BMI ranged from 18.6 to 34.3 kg/m². BMI < 25 kg/m² indicate normal weight. BMI ≥ 25 kg/m² indicate overweight, and BMI ≥ 30 kg/m² indicate obesity.

Blood specimens were taken from fasting patients to measure fasting blood glucose (FBG), TC, LDL, TG, HDL cholesterol, in addition to serum leptin, IL-1β and TNF-α.

Clinical symptoms were assessed for all patients by direct interview through a questionnaire method known as Western Ontario MacMaster Osteoarthritis Index (WOMAC) which includes evaluation of pain, stiffness and physical function. A total of 24 items are asked thus making a possible
maximum score of 96. Final score is expressed in percentage and calculated by dividing individual’s score by total score and multiplying that by 100 \((30)\). The plasma levels of all parameters were measured using specific kits for ELISA. Statistical analysis was accomplished using independent sample t-tests, as well as Pearson correlation is suitable to evaluate any associations. Data was analyzed using SPSS Windows-based software version 16 and P-values <0.05 were considered to be statistically significant.

**Results & Discussion**

Obesity and metabolic disorders may contribute to the incidence and progression of OA. Obesity may inspire many systemic effects related to OA, including roles for troubled glucose and disturbed lipid metabolism\(^{(30)}\). In obese patients with OA, the activity of inflammatory mediators originated from adipose tissue (adipokines, free fatty acids, and reactive oxygen species), as well as mechanical overload on the joints provide evidence to the increased incidence and prevalence of OA, which led to the appearance of a new OA phenotype-metabolic syndrome (MetS)-associated OA \(^{(31)}\). Table (1) shows the demographic data of the studied sample of patients with a majority of female patients, age ranged from 41 to 74 years old. The average age of 62.12 ± 4.8 in non-obese patients and 53.42 ± 5.7 in overweight and obese patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-Obese Patients</th>
<th>Overweight &amp; Obese Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>62.12 ± 4.8</td>
<td>53.42 ± 5.7</td>
</tr>
<tr>
<td>Female No. (%)</td>
<td>11 (55%)</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>Male No. (%)</td>
<td>9 (45%)</td>
<td>7 (35%)</td>
</tr>
</tbody>
</table>

*Age values are presented as mean ± SD*

In the present study, a highly significant difference was found regarding to BMI value between the two groups. Many studies revealed the influence of reducing body weight to alleviate symptoms of knee OA, as a part of management. \(^{(32-34)}\). Study by Bliddal, H et al, demonstrated that weight reduction through intensive low calorie diet was linked to a significant decrease in joint pain, according to the Western Ontario Mac Master Osteoarthritis Index (WOMAC) \(^{(35)}\). Table (2), Figure (1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-Obese Patients</th>
<th>Overweight &amp; Obese Patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m(^2))</td>
<td>21.94±1.89</td>
<td>28.21±1.54</td>
<td>0.000</td>
</tr>
<tr>
<td>S. Leptin (ng/ml)</td>
<td>8.82±1.71</td>
<td>10.66±1.94</td>
<td>0.003</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>119.35±25.81</td>
<td>127.15±25.96</td>
<td>0.347</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>195.6±49.83</td>
<td>228.7±61.59</td>
<td>0.069</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>224.45±50.74</td>
<td>262.2±59.35</td>
<td>0.037</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>36.2±6.21</td>
<td>31.8±4.98</td>
<td>0.018</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>116.06±37.29</td>
<td>150.99±56.09</td>
<td>0.026</td>
</tr>
<tr>
<td>IL-16 (pg/ml)</td>
<td>327±52.68</td>
<td>372.75±58.63</td>
<td>0.013</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>59.3±5.01</td>
<td>63.15±3.77</td>
<td>0.009</td>
</tr>
<tr>
<td>WOMAC score</td>
<td>70.8±8.82</td>
<td>62.05±9.145</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Values are presented as mean ± SD*

Although there are no significant differences between groups in regards to FBS and TC level, the lower levels in non-obese group can reflect the role of these elevated values in OA.

However, the participants in this study demonstrated significant differences concerning to LDL, HDL, TG and serum leptin between two groups. Table (2), Figure (1) & (2). Recent epidemiological study supported the concept that DM is an independent risk factor for OA; the direct effects of hyperglycemia have been reported to cause cell damage and promote inflammation by many mechanisms in different tissue related to diabetic complications \(^{(36)}\). High glucose level also demonstrates the induction of IGF-1 resistance which may compromise collagen synthesis \(^{(37)}\). As indirect effects, high glucose may stimulate the formation and accumulation of (AGEs) in OA cartilage which play a pro-inflammatory and pro-catabolic role, mediated by activation.
of their specific receptor (RAGE), on chondrocytes and synovial cells (30).

Figure 1: BMI and serum levels of Leptin & FBS in non-obese & overweight/obese newly diagnosed OA patients

Figure 2: Serum levels of TC, TG, and HDL & LDL in non-obese & overweight/obese newly diagnosed OA patients

The role of the low-density lipoprotein (LDL) cholesterol in the pathology of OA is apparent (38). Two studies by Gierman et al. (2012 and 2014) showed that rich-fat diet can increased cartilage damage regardless to body weight, and this effect could be frustrated by using lipid lowering agent; atorvastatin, suggesting a cholesterol-mediated mechanism for cartilage damage (39, 40). Another study by de Munter et al. (2016) showed that elevated cholesterol levels aggravate ectopic bone formation and synovial inflammation in OA (41).

Furthermore, previous data has indicated a potential role for HDL dysfunction in the pathogenesis of OA; depend on evidence that functional HDL was greatly decreased in OA patients. There is no precise mechanism elucidate how could lipid metabolism drive to OA. However, there is evidence that the higher levels of HDL detected in the synovial fluid have a protective effect (42). Furthermore, a study by Garcia-Gil et al (2017) reported that the development of OA may associate with the toxic effect of cholesterol at the joint itself (43). According to cross-sectional analyses, a positive relationship was reported between triglyceride level and clinical symptoms of knee OA (44). The high serum level of triglyceride is a sign of metabolic disorders that derived from central obesity, which could enhance the effect of disturbed lipid on cartilage metabolism. This can up-regulate proliferation of adipocytes, which could competitively inhibit proliferation and differentiation of musculoskeletal cells (45).

Moreover, each 1-unit elevation in triglyceride level was associated with 9% and 5% increases in the risk of clinical knee OA prevalence and onset, respectively (44). Other studies have shown paradoxical results on the relationships between TC, TG, LDL levels and OA incidence. Dahaghin et al (2007) showed no association between OA and TC/HDL ratio (46). While Frey et al (2017) detected an association between incident OA and hyperlipidemia, but at younger ages only
Leptin is a hormone derived from adipose tissue, acts through a specific receptor to regulate food intake, energy expenditure and body weight. In most cases of obesity, high circulating levels of leptin, in which the resistance process to the hormone, could be partly responsible of disturbances on body weight regulation. High levels of leptin present in serum and synovial fluid of obese individuals.

Additionally, the intensity of leptin effect in chondrocytes and its levels in synovial fluid strongly correlate with cartilage destruction score and pain in hip and knee OA, respectively. Leptin, by its catabolic effect, can stimulate the human synovial fibroblasts to increase expression of the cytokines IL-6 and IL-8 and their catabolic effect. Therefore, leptin might be involved in initiation and aggravation of synovial inflammation.

In fact, on closer inspection, the mechanisms linking OA to obesity seem to be multifactorial, biomechanical link was purely considered. Several studies demonstrated that the mechanical stress may lead to the release of the series of pro-inflammatory mediators from different joint tissues, these may include IL-6, IL-8, interleukin (IL)-1beta, cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), receptor activator of nuclear factor-kappa B ligand, matrix metalloproteinase (MMP)-2, MMP-3, MMP-9, MMP-13, and fibroblast growth factor-2. In the present study, IL-1β and TNF-α was measured and significantly higher levels obtained in overweight & obese patients in regards to non-obese patients. TNF-α is a cytokine implicated in systemic inflammation and usually results in acute phase reaction.

In obese individuals, by it is direct effects on the insulin signaling pathway, TNF-α may encourage insulin resistance, and thus contributes in the pathogenesis of type 2 DM and obesity. In OA patients, elevated levels of TNF-α are detected in synovial fluid, synovial membrane, cartilage, and subchondral bone.

TNF-α suppress synthesis collagen type II, proteoglycans and cartilage link protein (HAPLN1), which are the major components of extracellular matrix (ECM), which normally responsible for stabilization and maintaining cartilage tensile strength and elasticity. Furthermore, TNF-α possess an aggravating effect on inflammation by stimulating the synthesis and release of some proinflammatory cytokines and chemokines: IL-6, IL-8. Study by Stannus et al. (2010) showed that the degree of knee cartilage loss is positively correlated with increasing circulatory level of TNF-α, suggesting that systemic low-grade inflammation in fact plays a role in OA pathogenesis. Table (2), Figure (3).

IL-1β, a proinflammatory cytokine, is suggested to be involved in the development of obesity and insulin resistance. IL-1β partially mediates the effect of macrophages on insulin signaling and proinflammatory response in human adipocytes. Moreover, many experimental data demonstrated that IL-1β may act as regulator in the translation of obesity-associated inflammation toward insulin resistance. IL-1β, as an inflammatory and catabolic cytokine, participates in the pathophysiology of OA via different ways. Recent studies have reported that increasing pro-inflammation...
Factors such as TNF-α, IL-1β, and IL-6, have been found in OA cartilage, which are considered important factors in the development of OA. Chondrocytes, obtained from OA patients, excessively produce nitric oxide (NO), PG, TNF-α, IL-1β, IL-6, and IL-8 which have an important role in the pathophysiology of OA. Additionally, evidence has approved that IL-1β can enhance catabolic metabolism of chondrocytes by up-regulating metalloproteinases (MMPs). Moreover, TNF-α and IL-1β have been detected to cause mitochondrial dysfunction and enhance apoptosis in chondrocytes. To assess pain, stiffness, and physical function of the participants during this study, Western Ontario MacMaster Osteoarthritis Index (WOMAC), a health assessment questionnaire in rheumatology, was measured. According to the results, the severity of pain, stiffness, and physical dysfunction was significantly higher in overweight and obese patients compared to that of normal weight patients. Table (2), Figure (4).

In general, the presence of MetS components in addition to obesity is an increased risk of OA as compared to the presence of obesity only. Obesity-related metabolic factors, particularly hyperglycemia and formation of AGEs have been associated with excess collagen stiffness, changes in the mechanical properties of the extracellular matrix, and decline in proteoglycan synthesis, thereby possibly give rise to cartilage degradation. Alteration of adipokines levels and over expression of proinflammatory agents and degradative enzymes, driving to inhibit the synthesis of cartilage matrix and stimulate subchondral bone remodeling. In the current study, effects of disturbed lipid metabolism, high levels of glucose, leptin and proinflammatory cytokines, in addition to the significant positive correlation between BMI and both TNF-α levels and WOMAC score that shown in Figure (5) and Figure (6) respectively, altogether can strengthening the concept deals with the of obesity in the development & progression of OA.
Conclusion

The results reported in this study clearly indicated that increasing body weight with the presence of other metabolic factor can strongly enforce and hasten many process involved in the pathogenesis of OA, including inflammatory response, cartilage degradation and bone remodeling. That is why weight loss is recommended for patients with symptomatic OA by all major rheumatology management guidelines.

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