Association of Metabolic Syndrome and Its Components with Knee Osteoarthritis

Shahpoor Maddah and Jamileh Mahdizadeh

School of Medicine, Semnan University of Medical Sciences, Semnan, Iran

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Abstract- The association of obesity and other metabolic conditions with osteoarthritis is under debate; however, a strong link between metabolic disturbances is suggested to contribute to increased incidences and progression of osteoarthritis. We examined the association of metabolic syndrome and its components with the incidence of knee osteoarthritis in Iranian population. A community-based study was conducted on a total of 625 Iranian volunteers with the complaint of knee pain. Weight-bearing and anteroposterior plain radiographs of both knees were taken on the day of admission. Metabolic syndrome was diagnosed using the modified Adult Treatment Panel III of the National Cholesterol Education Program criteria. Prevalence rates of metabolic syndrome were 22.5% in males and 11.6% in females (P=0.002). The prevalence rate of knee osteoarthritis was 20.0% in males and 43.8% of females (P<0.001). In both genders, osteoarthritis group had higher serum levels of triglyceride and systolic blood pressure in comparison with non-osteoarthritis group. Women with osteoarthritis had higher Body Mass Index (BMI), however, this association was not observed in men. In females, the presence of osteoarthritis was significantly associated with the presence of metabolic syndrome, with the risk of metabolic syndrome in the osteoarthritis group at 2.187 fold the risk in the non-osteoarthritis group. But, the presence of osteoarthritis was not associated with metabolic syndrome in males. Metabolic syndrome mainly through high BMI is associated with knee osteoarthritis in the Iranian women, but neither metabolic syndrome nor any related components are associated with knee osteoarthritis in men.

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Keywords: Metabolic syndrome; Knee osteoarthritis; Body mass index; Blood pressure; Lipid

Introduction

Osteoarthritis is one of the most frequent clinical conditions leading to significant chronic and restrictive disability, especially in elderly population. The overall prevalence of this disease is notably higher in both developed countries due to obesity and metabolic disturbances as well as in developing countries because of inappropriate nutritional habits and improper physical activity. According to recent reports, the prevalence of osteoarthritis in Iran as a developing country is estimated 12.3 to 19.3 percents in the different rural and urban areas (1). Various risk factors have been identified for predisposing individuals especially the elderly to osteoarthritis including female sex, obesity, previous knee injury, and event underlying inflammatory disorders. Among these, obesity seems to be the most important factor (2-4). The pathophysiological association of obesity and other metabolic conditions with osteoarthritis is under debate; however, a strong link between genetic, metabolic, and endocrinologic factors is suggested to contribute to increased incidences and progression of osteoarthritis (5-7). Besides, recent striking finding has shown a linear association between the presence of the degree of atherosclerosis and osteoarthritis (8). Moreover, the relationship between risks factors for atherosclerosis such as obesity, diabetes mellitus, lipid disturbances, and hypertension and development of osteoarthritis can strengthen hypothesis related to the association between osteoarthritis and a cluster of these metabolic risk factors as metabolic syndrome (9,10). It seems that excessive inflammatory cytokine production and atherogenic events damaging vascular bed mediated by obesity, insulin resistance, lipid metabolism disturbances, and hypertension induce abnormal changes in the microvasculature of subchondral bone and thus may explain association between metabolic syndrome and development of

Corresponding Author: Sh. Maddah
School of Medicine, Semnan University of Medical Sciences, Semnan, Iran
Tel: +98 912 1316370, Fax: +98 23 33462041, E-mail address: shahpoor201@gmail.com

osteoarthritis (11-15). However, despite the high prevalence of both osteoarthritis and metabolic syndrome in our population, there is no information on the association between these two prevalent clinical conditions in our country. The present study aimed to examine the association of metabolic syndrome and its components with the incidence of knee osteoarthritis in a sample of Iranian population.

Materials and Methods

A community-based study was conducted on a total of 625 Iranian volunteers older than 18 years (125 male and 500 female) with the complaint of knee pain referred to an educational referral hospital from 2012 to 2013. Participants with a previous history of major trauma, rheumatoid arthritis, or a non-skin cancerous lesion were excluded from this study. For diagnostic assessment of knee osteoarthritis, weight-bearing and anteroposterior plain radiographs of both knees were taken on the day of admission. Scores were given to each knee radiograph according to the Kellgren–Lawrence (K–L) grade of 0, 1, 2, 3 or 4 (16). The presence of radiographic knee osteoarthritis was defined as a K–L grade of 2, 3 and 4. Hence, participants were classified into two groups of the non-knee osteoarthritis group or knee osteoarthritis group. Baseline clinical characteristics were collected by interviewing and the review of clinically recorded files on the day of admission. The following data were included for analysis: general characteristics including age and sex, current smoking history (patients regularly smoke a tobacco product/products one or more times per day or have smoked in the 30 days prior to admission) (17), hypercholesterolemia (total cholesterol ≥5.0 mmol/l, HDL-cholesterol ≤1.0 mmol/l in men, or ≤1.1 mmol/l in women, triglycerides≥2.0 mmol/l) (18), family history of CAD (first degree relatives before the age of 55 in men and 65 years for women) (19), hypertension (systolic blood pressure≥140 mmHg and/or diastolic≥90 mmHg and/or on antihypertensive treatment) (20), and diabetes mellitus (symptoms of diabetes plus plasma glucose concentration≥11.1 mmol/l or fasting plasma glucose ≥7.0mmol/l or 2-hp≥11.1 mmol/l) (21). Weight was measured on a calibrated balance-beam scale, and height was measured in an upright position using a stadiometer. Body mass index (BMI) was calculated as weight divided by height squared (kg/m2). Blood pressure was measured twice in the left arm by an examining physician using a mercury column sphygmomanometer (Korotkoff phases me and V) after the subject had been at rest in the seated position for five minutes. Blood samples were collected from participants on the morning after an overnight fasting, and analyzed at a national central laboratory and a fasting plasma lipid profile (including total cholesterol, low-density lipoprotein [LDL] cholesterol, HDL cholesterol, and triglyceride levels), and blood glucose were also measured. Metabolic syndrome was diagnosed using the modified Adult Treatment Panel III of the National Cholesterol Education Program criteria: three of five among BMI greater than 30 kg/m2, elevated triglycerides (≥150 mg/dL or drug treatment), reduced HDL (≤40 mg/dL in men, ≤50 mg/dL in women or drug treatment), elevated arterial blood pressure (≥130 mm Hg systolic, ≥85 mm Hg diastolic or drug treatment), and elevated fasting glucose (≥100 mg/dL or drug treatment) (22).

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Continuous variables were compared using t test or and/or non-parametric Mann-Whitney U test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the groups. Categorical variables were, on the other hand, compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5 were observed. Correlation between quantitative variables was assessed using the Pearson's correlation coefficient test. For the statistical analysis, the statistical software SPSS version 19.0 for windows (SPSS Inc., Chicago, IL) and the statistical package SAS version 9.1 for windows (SAS Institute Inc., Cary, NC, USA) were used. *P* values of 0.05 or less were considered statistically significant.

Results

With regard to the prevalence rates of metabolic syndrome, these were 22.5% (28 out of 125) in males and 11.6% (48 out of 500) in females (P=0.002). It was significantly higher in males than in females (P<0.001) (Table 1). The prevalence rate of knee osteoarthritis was 20.0% in males and 43.8% in females, and this was significantly higher in females (P<0.001) (Table 1).

Table 1. The prevalence rate of radiographic knee osteoarthritis in study participants

	Male (N = 125)	Female (N = 500)	*P*-value
Age	55.46 ± 11.6	54.44 ± 12.1	0.396
K–L grading			
Grade 0	42 (33.6)	60 (12.0)	< 0.001
Grade 1	58 (46.4)	221 (44.2)	0.658
Grade 2	18 (14.4)	148 (29.6)	< 0.001
Grade 3	6 (4.8)	54 (10.8)	0.042
Grade 4	1 (0.8)	17 (3.4)	0.120
Prevalence rate of OA	25 (20.0)	219 (43.8)	< 0.001

As for the differences in baseline characteristics between the groups with and without osteoarthritis, in both males and females, the osteoarthritis group was significantly older than the other group (P<0.001). Regarding different components of metabolic syndrome, in both sexes, osteoarthritis group had higher serum levels of triglyceride and also systolic blood pressure in comparison with non-osteoarthritis group. However, no differences were observed between the two groups in terms of BMI and diastolic blood pressure in males, but not in females so that those with osteoarthritis had higher BMI (table 2).

Table 2. Comparison of metabolic syndrome and its main components between those with and without osteoarthritis

	Male			Female		
	Without OA (n = 100)	With OA (n = 25)	*P*-value	Without OA (n = 281)	With OA (n = 219)	*P*-value
Age (years)	48.52 ± 10.66	62.40 ± 12.56	< 0.001	47.75 ±9.85	61.12 ± 8.22	< 0.001
BMI (kg/m2)	23.25 ± 3.11	23.50 ± 3.90	0.506	22.78 ± 4.25	25.14 ± 4.58	0.002
Triglyceride (mg/dl)	80.9 ± 10.46	134.4 ± 11.71	< 0.001	86.81 ± 9.98	126.12 ± 14.60	< 0.001
HDL cholesterol (mg/dl)	53.47 ± 12.74	56.22 ± 10.28	0.011	59.56 ± 14.45	62.91 ± 12.78	0.011
Systolic blood pressure (mmHg)	125.45 ± 11.4	136.62 ± 9.98	< 0.001	119.40 ± 7.78	132.10 ± 10.10	< 0.001
Diastolic blood pressure (mmHg)	74.14 ± 8.85	75.58 ± 8.71	0.100	78.15 ± 7.79	79.18 ± 5.59	0.091
Hyperlipidemia (%)	11 (11.0)	5 (20.0)	0.228	25 (8.9)	55 (25.1)	< 0.001
Hypertension (%)	25 (25.0)	8 (32.0)	0.478	62 (22.1)	112 (51.1)	< 0.001
Diabetes mellitus (%)	7 (7.0)	2 (8.0)	0.863	3 (1.1)	9 (4.1)	0.030
Smoking habit (%)	31 (31.0)	8 (32.0)	0.923	4 (1.4)	2 (0.9)	0.608
Metabolic syndrome (%)	21 (21.0)	6 (24.0)	0.744	14 (5.0)	40 (18.3)	< 0.001

In males group, no significant differences were found between osteoarthritis and non-osteoarthritis subgroups regarding prevalence rate of hyperlipidemia, hypertension, smoking, and diabetes mellitus. However, in females group, hyperlipidemia, hypertension, and diabetes mellitus were all more prevalent in osteoarthritis group than in non-osteoarthritis group. In regard to the association between metabolic syndrome and knee osteoarthritis, there was no difference in the prevalence rate of metabolic syndrome between the osteoarthritis and non-osteoarthritis groups in males (P=0.744); however, that of metabolic syndrome in the osteoarthritis group was significantly higher than in the non-osteoarthritis group in females (P<0.001) (Table 2). In risk factors for metabolic syndrome, age was significantly associated with the presence of metabolic syndrome in males (OR=1.378, P=0.014). However, the presence of osteoarthritis was not associated with metabolic syndrome in males. Besides, in females, the presence of osteoarthritis was significantly associated with the presence of metabolic syndrome, with the risk of metabolic syndrome in the osteoarthritis group at 2.187 fold the risk in the non-osteoarthritis group (Table 3).

Table 3. Odds ratio of metabolic syndrome according to radiographic knee osteoarthritis, age, and smoking habit

Item	*P*-value	Odds Ratio	95% Confidence Interval	
Male				
Osteoarthritis	0.221	0.599	0.278	1.036
Age	0.014	1.378	1.112	3.579
Smoking habit	0.869	0.319	0.147	1.779
Female				
Osteoarthritis	0.027	2.187	1.420	4.478
Age	0.046	1.114	1.099	1.587
Smoking habit	0.575	0.745	0.574	1.015

Discussion

The current study aimed to examine the association of osteoarthritis with metabolic syndrome and its definitive components. In other words, we also examined whether the presence of osteoarthritis could effectively predict increased risk of metabolic syndrome adjusted for potential confounders including sex, advanced age, and current smoking. In the first step, a strong association was revealed between metabolic syndrome and knee osteoarthritis, but this significant association was specified only to females, not to the male group. In this regard, women with osteoarthritis had a higher rate of BMI than female non-osteoarthritis group. On the other hand, among five definitive components of metabolic syndrome, high BMI mediates the association between metabolic syndrome and knee osteoarthritis in women. Meanwhile, no parameter of metabolic syndrome was significantly associated with knee osteoarthritis in male participants. Regarding increased risk of osteoarthritis mediated by obesity, some identified mechanisms for this causal effect include the direct mechanical effect of obesity on knee osteoarthritis, pro-inflammatory conditions destructing cartilages of the knee, and also increased the risk of embolism in arthroplasty or other orthopedic surgeries following weight gain (23-26).

In the current study, the association between metabolic syndrome and osteoarthritis was demonstrated even after adjusting age and smoking. Similarly, Engström *et al*., (27) showed that metabolic syndrome was associated with an increased incidence of knee osteoarthritis when adjusted for age, sex and social factors in a Western population-based study. Comparable to these results, they reported that this was largely explained by increased BMI. Gandhi *et al*., also (28) reported that metabolic syndrome is a risk factor for osteoarthritis in Asians; however, they could not show this association after adjusting for confounding factors. A probable reason for this can be related to ignoring the severity of osteoarthritis and its relation with the presence of metabolic syndrome so that in some studies, participants with knee osteoarthritis had mild osteoarthritis while some other studies considered patients who had undergone total knee arthroplasty or high tibial osteotomy that might have more severe knee osteoarthritis.

In the present study, osteoarthritis was only associated with obesity but not with other components of metabolic syndrome. There is a general consensus that knee osteoarthritis is strongly associated with obesity that the subjects with BMI >30 kg/m2 show a 4.2 − 6.8 times higher incidence of knee osteoarthritis than control ones (29,30). The prevalence of knee osteoarthritis has been known to be significantly higher in female patients in Asian populations (31-33). Sex differences have been noted for osteoarthritis and its association with metabolic syndrome at epidemiological, radiographic, circulating biomarker, hormonal, and cellular levels. Firstly, clear variability was revealed with regard to lower knee cartilage volume in women than in men assessed by magnetic resonance imaging (MRI). Also, the observed sex difference in this association may be attributed to differences in sex hormones, as lower levels of estradiol and its catabolic metabolite, urinary 2-hydroxyestrone (34-36). These reasons may explain significant association between osteoarthritis and metabolic syndrome mainly with obesity only in women not in men.

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