Associations between the radiographic phenotypes and the presence of metabolic syndrome in patients with knee osteoarthritis

Abstract

Background/Aim: We aimed to investigate the associations between the radiographic phenotypes and the presence of metabolic syndrome (MetS) in patients with knee osteoarthritis (OA).

Materials and Methods: We evaluated women age 40 and over who presented to our outpatient clinics with knee pain and fulfilled the clinical and radiographic criteria for the classification of idiopathic OA of the knee. Patients were categorized into two groups concerning dominant radiographic phenotype. We included consecutive 50 patients in each group. All patients were evaluated in terms of MetS according to the revised diagnostic criteria of the International National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), as well as the World Health Organization (WHO).

Results: Overall MetS prevalence was found to be 79% according to the NCEP ATP III-MetS criteria and 65% according to the WHO-MetS criteria. Prevalence of MetS was higher in the joint space narrowing (JSN)-Dominant group compared to the osteophyte (O)-Dominant knee OA group, but the difference did not reach statistical significance. However, in subgroup analysis (54 patients), in which we excluded patients with a past medical history of type 2 diabetes mellitus (DM), the prevalence of NCEP ATP III-MetS was statistically significantly higher in the JSN-Dominant group compared to the O-Dominant group [22 (75.9%) vs 12 (48%) respectively, $p = 0.03$]. Logistic regression analysis in the subgroup demonstrated that the presence of NCEP

ATP III-MetS was an independent risk factor for JSN-Dominant knee OA phenotype [OR and 95% CI = 3.48 (1.09 - 11.13)].

Conclusion: The prevalence of MetS is quite high in patients with knee OA and is particularly pronounced in patients with JSN-Dominant radiographic phenotype. Moreover, our results suggest that MetS is an independent risk factor for JSN-Dominant knee OA in patients with no past medical history of DM.

Key words: Osteoarthritis, knee, metabolic syndrome

1. Introduction

Osteoarthritis (OA) is a chronic articular disease involving both cartilage degeneration and bony changes. It is thought that the pathogenesis of the disease consists of variable degrees of mechanical factors and inflammatory mechanisms, which might be triggered by metabolic factors and tissue destruction end products. Several factors associated with disease pathogenesis and progression have been investigated which includes obesity. It is believed that obesity affects disease occurrence and progression with two distinct mechanisms. One of them is articular degeneration arising from mechanical overload and the other is systemic and local inflammation related to obesity [1,2]

Metabolic syndrome (MetS) is a clinical picture that includes at least 3 of these conditions: central obesity, dyslipidemia, hypertension, diabetes mellitus (DM), or hyperglycemia [3,4]. The intersection of MetS and OA is the production of inflammatory cytokines related to obesity and originating from adipose tissue. Several inflammatory pathways which are involved in the pathogenesis of MetS are also responsible for the pathogenesis of OA. Many studies have examined the prevalence of MetS in the population with knee OA or have attempted to examine the relationship

between MetS and knee OA [5,6]. However, none of these studies investigated the effect of MetS on the radiographic phenotype of OA. We have previously studied radiographic phenotypes of obese patients with knee OA and demonstrated that the association between obesity and osteophyte formation was stronger than that of joint space narrowing (JSN) [7]. The present study aimed to investigate the associations between the radiographic phenotypes and MetS in patients with knee OA.

2. Materials and methods

In our study, female patients 40 years and older who presented with knee pain to the rheumatology and/or orthopedics outpatient clinics in Health Sciences University, Samsun Research and Training Center and fulfilled the 1986 ACR "clinical and radiographic OA" classification criteria of knee OA were included [8]. The knee radiographs were evaluated by a single rheumatology specialist experienced in grading [7]. Osteophyte formation and JSN of each radiography were graded according to the revised atlas of the Osteoarthritis Research Society International (OARSI) [9]. A painful knee was included for radiographic evaluation. When both knees were painful, the knee with more advanced radiographic findings was included. Detailed grading of the knee radiographs concerning osteophytes (grade 0–3) and JSN (grade 0–3) according to the revised OARSI atlas were done [9]. In this grading system, osteophytes are evaluated at 4 sites (medial femoral condyle, medial tibial plateau, lateral femoral condyle, lateral tibial plateau) and JSN is evaluated at 2 sites (medial and lateral). The highest grade at any site was used for classification of the radiographic phenotype and each subject was assigned to one of the following 2 groups: Osteophyte (O) -Dominant (if the maximum

osteophyte score is greater than the maximum JSN score), JSN-Dominant (if the maximum JSN score is greater than the maximum osteophyte score).

Based on the prevalence of MetS in the population aged 40 and over in our country (54.5%) [10], the number of patients required to be included in both groups at 80% power, 95% confident interval, and $p < 0.05$ statistical significance was calculated as 50.

The weight and height of all the patients were measured and body mass index (BMI) was calculated [weight (kg) / height (m2)]. In patients with no history of hypertension blood pressure was measured. Waist circumference and hip circumference were measured and waist/hip circumference ratio was calculated per patient. Venous blood samples were obtained for fasting blood glucose, high-density lipoprotein (HDL), triglyceride (TG) levels following 12 hours of fasting. Albumin/ creatinine ratio was measured and calculated in spot urine samples. 75 gr oral glucose tolerance test was performed for patients who had fasting blood glucose levels between 100 - 110 mg/dl. The patients were classified into 3 groups according to the 2-hour glucose results obtained in the 75 g glucose tolerance test according to the World Health Organization (WHO) criteria [11]: Type 2 DM (glucose level 200 mg /dl and above), impaired glucose tolerance (glucose level between 140-199 mg /dl) and impaired fasting glucose (glucose level below 140 mg /dl). Fasting insulin and hemoglobin A1c (HbA1c) levels were obtained from all patients, except those with a past medical history of Type 2 DM. Homeostasis Model of Assessment (HOMA) index was used for the diagnosis of insulin resistance [(fasting glucose × fasting insulin) / 405]. HOMA index greater than 2.7 was accepted as insulin resistance [12]. All patients were evaluated in terms of MetS using both National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) revised by National Heart, Lung, Blood Institute/American Heart Association and

WHO criteria [3,4]. According to the NCEP ATP III for the diagnosis of MetS, there should be three or more of the following five criteria: 1) Abdominal obesity, given as waist circumference (> 102 cm in men, > 88 cm in women), 2) TG ≥ 150 mg/dL, 3) HDL cholesterol (< 40 mg/dL in men, < 50 mg/dL in women), 4) Blood pressure ≥130 / ≥ 85 mmHg, 5. Fasting glucose ≥ 110 mg/dL (3). According to WHO for the diagnosis of MetS, there should be three or more of the following six criteria at least being about glucose metabolism disorder (impaired fasting glucose, impaired glucose tolerance or DM and/or insulin resistance): 1) Impaired glucose tolerance, impaired fasting glucose or DM, 2) Insulin resistance, 3) Antihypertensive medication and/or high blood pressure (≥140 / ≥90 mmHg), 4) Plasma triglycerides ≥150 mg/dL 5) HDL cholesterol (<35 mg/dL in men or <39 mg/dL in women), 5) BMI >30 kg/m2 and/or waist: hip ratio >0.9 in men, >0.85 in women, 6) Urinary albumin excretion rate ≥20 μg/min or albumin: creatinine ratio ≥30 mg/g (4)

The following patients were excluded from the study;

1. Patients who refused to be a volunteer for the study
2. Patients with secondary knee OA
3. Disabled patients who cannot remain in the standing position
4. Patients who have had an intraarticular injection into the knee joint
5. Patients with prior history of knee trauma
6. Patients with prior history of knee surgery
7. Patients with type 1 DM
8. Patients receiving any lipid-lowering therapy

9. Patients under glucocorticoid therapy patients with C reactive protein levels above the upper limit of the normal range

2.1.Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as number (%). The student's t-test was used for the comparisons of the continuous variables. The Chi-square test was used for the comparison of categorical variables. Logistic regression analysis was used for assessing independent risk factors. The enter method was used in the logistic regression analysis, and the presence of MetS, BMI, and age was included in the analysis as independent risk factors. The reproducibility of the radiographic evaluations was assessed using the weighted kappa (κ) statistics. A p-value less than 0.05 was accepted as significant.

3. Results

3.1.Reproducibility of the radiographic evaluations

The radiographs from 50 randomly selected subjects were re-graded by the same observer one month after the first evaluation for intra-observer variability. The reproducibility of both osteophyte and JSN assessments was excellent. Intra-observer reproducibility was better for osteophyte assessments compared to JSN assessments ($\kappa = 0.92$ for osteophyte scores and $\kappa = 0.82$ for JSN scores).

3.2.Main group analysis

We categorized patients into two groups concerning the radiographic phenotype: O-Dominant vs JSN-Dominant and included 50 patients in each group. A total of 100 patients were studied. The mean ± SD age of the study population was 62 ± 6. Overall,

MetS prevalence was 79% according to NCEP ATP III-MetS criteria and 65% according to WHO-MetS criteria.

Age, height, weight, BMI, waist circumference, hip circumference, waist/hip circumference ratio, fasting blood glucose levels, HDL levels, and TG levels all were found to be similar between JNS-Dominant and O-Dominant groups (Table 1). Prevalence of NCEP ATP III-MetS was higher in the JNS-Dominant group when compared to the O-Dominant group, but this difference was not statistically significant [42 (84%) vs 37 (74%) respectively and $p = 0.22$]. Similarly, the prevalence of WHO-MetS was higher in the JNS-Dominant group when compared to the O-Dominant group, but this difference was also not statistically significant [34 (68%) vs 31 (62%) respectively and $p = 0.53$).

3.3.Subgroup Analysis

A subgroup was created to exclude patients who were previously diagnosed with type 2 DM and were already on treatment. Patients who were newly diagnosed with type 2 DM per results of the above-described study parameters were not excluded since they had not received any treatment yet.

The subgroup consisted of 54 patients. Mean age was 62 ± 7 years and the overall prevalence of NCEP ATP III-MetS was 63% (34 of 54 patients), while the prevalence of WHO-MetS was 42.5% (23 of 54 patients).

Age, height, weight, BMI, waist circumference, hip circumference, waist/hip circumference ratio, fasting blood glucose levels, HDL levels, TG levels, HbA1c level HOMA index, and frequency of insulin resistance all were found to be similar between JSN-Dominant and O-Dominant subgroups (Table 2). The prevalence of NCEP

ATP III-MetS was statistically higher in the JSN-Domaiant subgroup compared to the O-Dominant subgroup [22 (75.9%) vs 12 (48%) respectively, p = 0.03]. The prevalence of WHO-MetS was also statistically higher in the JSN-Dominant subgroup compared to the O-Dominant subgroup [16 (55%) vs 6 (24%) respectively, p = 0.02].

Logistic regression analysis for the subgroup showed that the presence of NCEP ATP III-MetS was an independent risk factor for JSN-Dominant knee OA phenotype [OR and 95% CI = 3.41 (1.07 - 10.83) and p = 0.04]. When BMI was taken into account in risk factor analysis, it was found that significance was not lost [OR and 95% CI = 3.48 (1.09 - 11.13) and p = 0.04] (Table 3). Similarly, the presence of WHO-MetS was found to be a significant risk factor for JSN-Dominant knee OA phenotype [OR and 95% CI = 3.97 (1.22 - 12.96) and p = 0.02]. Likewise, it was found that the result did not change when BMI was taken into account in the risk factor analysis [OR and 95% CI = 4.07 (1.24 - 13.44) and p = 0.02] **(Table 3).**

4. Discussion

In the present study, the prevalence of MetS in the patients with knee OA was 79% in the main group using NCEP ATP III-MetS criteria and 65% using WHO-MetS criteria. The prevalence rates of MetS for the subgroup with no past medical history of Type 2 DM, were 63% and 42.5%, respectively. According to the TEKHARF study data conducted in our country, the prevalence of MetS in the general population was reported to be 54.5% in women aged 40 and over [10]. Therefore, our results suggest that, in patients with knee OA, regardless of the criteria used, the prevalence of MetS is higher than the general population.

Metabolic syndrome and knee OA are two important public health problems with similar risk factors, similar pathogenetic mechanisms, and high prevalence. Many studies have been conducted on the relationship between knee OA and MetS to date. These studies contain conflicting results. In a recently published meta-analysis, Xie et al. found that the presence of MetS is an independent risk factor for radiographic knee OA [13]. However, some large-scale studies, including the Framingham OA study and the Chingford cohort, reported that there is a significant relationship between MetS and knee OA, but this relationship disappears when body weight or BMI factors are taken into account [6,14-18]. In the present study, we hypothesized that the development of osteophyte and JSN could be due to different pathogenetic mechanisms, and hence, we categorized patients with knee OA concerning the radiographic phenotypes, JSN-Dominant vs O-Dominant. Although MetS tended to be more frequent in the JSN-Dominant phenotype, the difference did not reach statistical significance. However, in the subgroup analyses, in which we excluded those with a past medical history of type 2 DM, we demonstrated that the prevalences of NCEP ATP III-MetS and WHO-MetS were statistically higher in the JSN-Dominant group compared to the O-Dominant group. Moreover, in this subgroup, we determined that the presence of MetS is an independent risk factor for the development of JSN-Dominant knee OA phenotype and we found that this effect is independent of BMI. As is known, obesity is an important risk factor for the development of knee OA. In many publications on the pathogenesis of knee OA, obesity is an independent risk factor, especially for osteophyte development [7, 19, 20]. In another study we conducted using the same methodology, involving 734 female patients aged 40 and over, we found that the presence of obesity increased the risk of O-Dominant knee OA phenotype 7.17 times [7]. In the

pathogenesis of knee OA, JSN occurs primarily as a result of cartilage loss. In another study supporting these findings, Pan et al. followed 435 patients for 10.7 years and found that the cartilage volume loss observed in the medial tibial plateau was significantly higher in individuals with MetS than in individuals without MetS on magnetic resonance imaging [21]. Therefore, all of these findings suggest that MetS, but not obesity per se, is a significant risk factor for the development of knee OA with JSN dominant phenotype. In addition, we could hypothesize that the Kellgren and Lawrence (K-L) radiographic staging system used in the previous studies might have led to conclusions suggesting that the relationship between MetS and knee OA was mostly related to obesity since the presence of a definite osteophyte is required for radiographic OA in this system [22]. Hence, this staging system might have led to the exclusion of those with JSN-Dominant phenotype from these studies. Therefore, in the present study, in addition to the ACR clinical and radiographic classification criteria for knee OA, we graded the osteophytes and degree of JSN using the revised OARSI atlas [9]. Moreover, unlike most previous studies we used two different sets of criteria for MetS analyses, strengthening the reliability of the results of the present study.

There are limitations of our study. We think that the major limitation is the inclusion of patients with a past medical history of type 2 DM since they were on medical therapy which might have modified their MetS status. It is also possible that inflammatory pathways that may be playing roles in the development of knee OA might have been also affected by these medications. This might have failed to detect any difference when diabetics under treatment were included in analyses.

In conclusion, our results suggest that the development of osteophyte and JSN, which are two important components of the radiography in knee OA, might have different

pathogenetic mechanisms. Our results also suggest that MetS is an independent risk factor for the development of JSN-dominant phenotype, rather than the O-Dominant phenotype, in knee OA patients with no past medical history of DM and this is not

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Table 1. Demographical, anthropometrical, and biochemical parameters of the study population.

Mean ± SD	**JSN-dominant (n:50)**	**O-dominant (n:50)**	**P**
Age (years)	61 ± 7	63 ± 5	0.17
Height (m)	160 ± 4	159 ± 5	0.62
Weight (kg)	88 ± 12	89 ± 12	0.79
BMI (kg/m²)	35 ± 5	35 ± 5	0.97
Waist circumference (cm)	116 ± 10	115 ± 11	0.61
Hip circumference	126 ± 12	126 ± 12	0.92

(cm)			
Waist / hip ratio	0.93 ± 0.1	0.92 ± 0.1	0.54
Fasting glucose (mg/dL)	126 ± 54	120 ± 44	0.55
HDL (mg/dL)	50 ± 13	51 ± 11	0.81
TG (mg/dL)	167 ± 105	161 ± 96	0.77

BMI: Body Mass Index, **HDL:** High-Density Lipoprotein, **TG:** Triglyceride

Table 2. Demographical, anthropometrical, and biochemical parameters in the subgroup with no past medical history of type 2 DM.

	JSN-Dominant (n:29)	**O-Dominant** (n:25)	**P**
Age (years)	62 ± 8	62 ± 5	0.64
Height (m)	160 ± 4	159 ± 4	0.56

Weight (kg)	86 ± 12	86 ± 13	0.95
BMI (kg/m²)	34 ± 5	34 ± 5	0.81
Waist circumference (cm)	113 ± 11	112 ± 10	0.66
Hip circumference (cm)	126 ± 11	126 ± 11	0.69
Waist/ hip ratio	0,90 ± 0,08	0,89 ± 0,1	0.36
Fasting glucose (mg/dL)	96 ± 12	96 ± 9	0.86
HbA1c	4,9 ± 0.3	5 ± 0,3	0.53
HDL (mg/dL)	53 ± 15	52 ± 10	0.77
TG (mg/dL)	139 ± 61	128 ± 51	0.48
HOMA	3,3 ± 1,9	2,7 ± 1,4	0.20
Insulin resistance [n (%)]	15 (52%)	7 (28%)	0.08

Unless otherwise stated, data are presented as mean ± SD. **BMI:** Body Mass Index, **HbA1c:** Hemoglobin A1c, **HDL:** High-Density Lipoprotein, **TG:** Triglyceride, **HOMA:** Homeostasis Model of Assessment, DM: Diabetes mellitus

Table 3. Results of logistic regression analysis for the JSN-Dominant knee OA phenotype in subgroup patients

	NCEP ATP III			WHO		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age	0.98	0.89 - 1.07	0.60	0.98	0.89 - 1.07	0.65
BMI	1.01	0.89 - 1.14	0.90	1.02	0.90 - 1.16	0.71
MetS	3.48	1.09 - 11.13	0.04	4.07	1.24 - 13.44	0.02

NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III**,** **WHO:** World Health Organization**, BMI:** Body Mass Index, **MetS:** Metabolic Syndrome