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The Relationship of Inflammatory Indicators and Metabolic Syndrome with Gonarthrotic Cartilage Degeneration: A Novel Glance

Gonartrotik Kıkırdak Dejenerasyonunun Metabolik Sendrom ve İnflamatuar İndikatörler İle İlişkisi: Yeni Bir Bakış

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ABSTRACT

Objective: The combination of a number of metabolic abnormalities such as high body mass index (BMI), central obesity, low high-density lipoprotein (HDL), high triglycerides, high blood pressure, and hyperglycemia is defined as metabolic syndrome (MetS). This study aimed to clarify the effect of metabolic syndrome components on joint degeneration and investigate the relationship between systemic inflammatory response and end-stage osteoarthritis clinical course.

Material and Methods: Fifty-seven patients, who underwent total knee arthroplasty due to primary knee osteoarthritis, were classified according to metabolic syndrome diagnosis criteria. Their medial and lateral tibial plateau specimens were graded histopathologically according to Osteoarthritis Research Society International scoring system (OARSI).

Results: 33 patients were performed right total arthroplasty (57.9%), 24 were performed left (42.1%). The mean age was 68.46 ± 6.88 (range 57 to 85). The mean BMI value was 30.31 ± 5.26 (range 20.2 to 48). According to the International Diabetes Foundation (IDF) 2005 metabolic syndrome (MetS) diagnostic criteria; 31.5% (n = 18) of the patients did not have MetS, while 68.4% (n = 39) had. There was no statistically significant relationship between tibial plateau OARSI scores and metabolic syndrome (p> 0.05). Besides, these OARSI scores and the operation side, hypertension, and BMI had no statistically significant relationship (p> 0.05).

Conclusions: Metabolic syndrome components may play a role in initiating the osteoarthritic process via adipokines, but we could not identify certain effects of pro-inflammatory mediator components on tibial plateau cartilage degeneration with histopathological scores till end-stage arthritic progress.

Keywords: Knee, Osteoarthritis, Metabolic Syndrome, Cartilage Degeneration, Inflammatory Mediators

ÖZ

Amaç: Yüksek vücut kitle indeksi (BMI), merkezi obezite, yüksek yoğunluklu lipoprotein (HDL) seviyesi düşüklüğü, yüksek trigliserid, yüksek tansiyon ve hiperglisemi gibi bir dizi metabolik anormalliğin kombinasyonu metabolik sendrom (MetS) olarak tanımlanır. Bu çalışma metabolik sendrom bileşenlerinin eklem dejenerasyonuna etkisini ve sistemik iltihabi cevapla son evre osteoartritin klinik gidişatı arasındaki ilişkiyi araştırmayı amaçlamaktadır.

Material ve Metod: Primer diz osteoartriti sebebiyle total diz artroplastisi uygulanan elliyedi hasta, metabolik sendrom tanı kriterlerine göre sınıflandırıldı ve Uluslarasarası Osteoartrit Araştırma Grubu (Osteoarthritis Research Society International - OARSI) skorlama sistemine göre medial ve lateral tibial plato örnekleri histopatolojik olarak evrelendi.

Bulgular: 33 hastaya sağ (% 57.9), 24 hastaya sol (% 42.1) total diz artroplastisi uygulandı. Ortalama yaş 68.46 ± 6.88 idi (57-85). Ortalama BMI değeri 30.31 ± 5.26 idi (20.2 - 48). Uluslarası Diabet Kuruluşu'nun (International Diabetes Foundation - IDF) 2005 metabolik sendrom tanı kriterlerine göre; % 31.5 (n = 18) hastada metabolik sendrom yokken, % 68.4 (n = 39) hastada vardı. Tibial plato OARSI skorlarıyla metabolik sendrom tanı kriterleri arasında istatistiksel anlamlı bir ilişki bulunamadı (p> 0.05). Ayrıca OARSI skorlarıyla opere taraf, hipertansiyon ve BMI arasında da istatistiksel anlamlı bir ilişki yoktu (p> 0.05).

Sonuç: Metabolik sendrom bileşenleri adipokinler yoluyla osteoartrit gelişimini başlatıcı etkiye sahip olabilse de, tibia plato kıkırdağı dejenerasyonu ile proinflamatuar mediatörler arasında artritik sürecin son evresine kadar devam eden bir ilişki tespit edemedik.

Anahtar kelimeler: Diz, Osteoartrit, Metabolik Sendrom, Kıkırdak Dejenerasyonu, İnflamatuar Mediatör

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INTRODUCTION

Osteoarthritis (OA) is a disease of diarthrodial (synovial) joints characterized by clinical pain and functional limitation, osteophytes and narrowing in the joint space, and histopathological changes in cartilage and bone density. In the pathogenesis of OA, increases in pro-inflammatory cytokines, especially IL-1, TNF, and IL-6 in the synovial fluid and synovial membrane, have been shown to play essential roles. Inflammatory cytokines play essential roles in activating neutrophils, lymphocytes, and platelets, which can also affect themselves [1]. Levels of acute-phase protein, and other findings, such as anemia, thrombocytosis, and leukocytosis, may vary in response to inflammation. In knee OA, different intraarticular injections have been shown to reduce lipid peroxidation in synovial fluid [2]. The World Health Organization (WHO) defined weight classifications based on the Body Mass Index (BMI = kg / m2) over 20 years old: below 18.5: underweight, 18.5–24.9: normal weight, 25.0–29.9: pre-obesity, 30.0–34.9: obesity class I, 35.0–39.9: obesity class II, above 40: obesity class III.

The combination of several metabolic abnormalities such as low high-density lipoprotein (HDL) levels, central obesity, high triglyceride levels, high blood pressure, and hyperglycemia is defined as metabolic syndrome (MetS) [3]. The International Diabetes Foundation (IDF) declared MetS diagnostic criteria in 2005 [4]. According to these criteria, BMI> 30kg / m² and central obesity (waist circumference; male ≥ 94 cm, female ≥ 80 cm), and patients with any two of the following four factors were considered as MetS: 1) Triglycerides ≥ 150 mg / dL. 2) Low HDL (in men <40 mg / dL in women <50 mg / dL) or specific treatment for lipid abnormality. 3) Hypertension (systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mm Hg or previously diagnosed and treated high blood pressure). 4) High fasting plasma glucose (FPG) ≥ 100 mg / dL or previously diagnosed type 2 diabetes. So multiple risk factors that predispose to OA, can easily be found collectively in MetS [5].

The coincidence of OA and obesity, especially in weight-bearing knee joints, is well-known [6] and may predict increased chronic mechanical stress as a risk factor. However, in cartilage explant experiments, the application of excessive mechanical stress led to the release of pro-inflammatory cytokines and mediators that promoted disruption, causing joint inflammation and cartilage matrix destruction [7]. There has been increasing evidence that synovium's inflammatory and destructive response plays a significant role in OA [8]. However, it is still unclear to what extent the inflammation and immune response effectively initiate the joint's destructive process [9].

We hypothesized that the MetS criteria might not be effective in degeneration until the end-stage of osteoarthritis development. This study aimed to histopathologically investigate the effect of MetS components on joint degeneration and the relationship between systemic inflammatory response and end-stage OA clinical course.

MATERIAL AND METHODS

This study was initiated after obtaining approval from the local Ethics Committee (decision number: 2018/164). Fifty-seven patients diagnosed with primary gonarthrosis and underwent total knee arthroplasty between 2018 and 2019 were included in the study after obtaining informed consent forms and meeting inclusion criteria. Patients' height, weight, waist circumference, blood pressure measurements, and biochemical data were retrospectively obtained from the hospital archive. Biochemical analyses, white blood cell count (WBC), platelet count (PC), lymphocyte count (LC), and C-reactive protein (CRP) had been measured from each patient's intravenous blood sample by standard laboratory methods.

Tibial proximal cut samples during the arthroplasty procedure were sent to the medical pathology laboratory in 10% formaldehyde. After macroscopic examination, medial and lateral tibial plateaus were cut horizontally, and they were decalcified with 20% formic acid. Samples were sliced to 3 µm thick sections with a microtome after routine follow-up. The sections taken were stained with Hematoxylin and Eosin (H&E) and examined microscopically. The cartilage degeneration observed in tibia samples was scored using the Osteoarthritis Research Society International (OARSI) scoring like Pritzker, K.P. et al. described [10]. Scoring is based on microscopic examination

and consists of 6 grades accordingly (Figure 1 a-f).

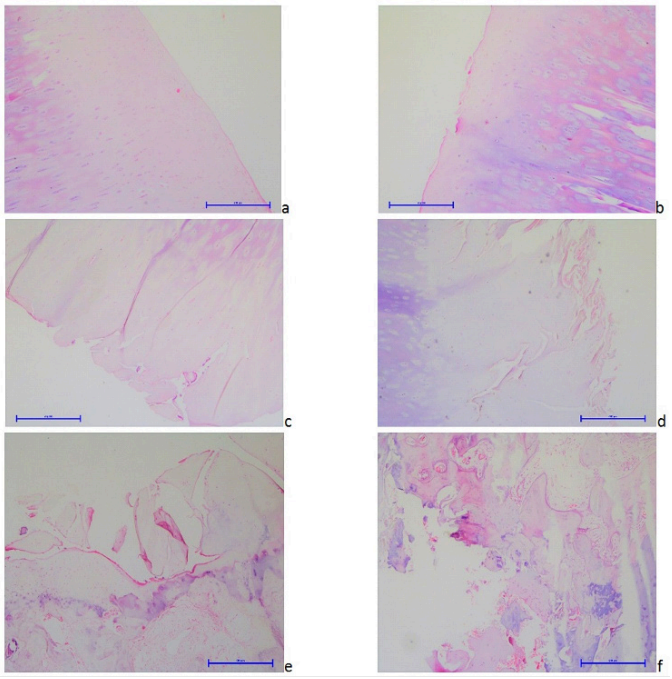

Figure 1: Figure shows microscopic examination of medial tibial plateau degeneration and consists of 6 grades accordingly Osteoarthritis Research Society International (OARSI) scoring. a. Slight superficial irregularity and fibrillation- Grade 1, b. Focal fibrillation progressing from superficial to medium zone - Grade 2, c. Vertical fissures progressing to middle shingles- Grade 3, d. Cartilage matrix loss, erosion- Grade 4, e. Microfractures extending to the bone - Grade5, f. Micro forties, repair tissue- Grade 6. Hematoxylin and Eosin (H&E) staining

Based on WHO categorization, Body Mass Index (BMI) was calculated for each patient. All patients included in the study were evaluated according to the IDF 2005 MetS diagnostic criteria and divided into two groups: MetS (-) and MetS (+) which were compared in this present study.

Patients who presented active infection, malignancy, chronic gastrointestinal diseases, patients using any drugs with potential effects on the gastrointestinal or coagulation system, patients with secondary gonarthrosis were excluded from the study. That was because of the altered response of inflammatory cytokines and difficulty in diagnosing MetS.

Statistical Analysis: NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Rate, Minimum, Maximum) and the distribution of the data were evaluated with the Shapiro-Wilk Test. ANOVA test was used for group comparisons of three or more quantitative data with normal distribution, and the Kruskal-Wallis test was used for comparison of three or more groups with no normal distribution. The Student-T test was used to compare two groups with a normal distribution of quantitative data, and the Mann-Whitney U test was used to compare two groups without normal distribution. Chi-square was used to determine the relationship between qualitative data. Significance was evaluated at $p < 0.05$ levels.

RESULTS

Right total arthroplasty was performed in 57.9% (n = 33), and left total arthroplasty was performed in 42.1% (n = 24) of the 57 patients included in the study. The age value ranged from 57 to 85, with an average of 68.46 ± 6.88. Other data of the patients were given in Table 1.

Table 1. Demographic and inflammatory data of patients.

	Mean±SD	Min-Max (Median)
Age	68,46±6,88	57-85 (67)
Body Mass Index	30,31±5,26	20,2-48 (29,6)
Waist Circumferance	96,65±15,33	70-142 (96)
Fasting Plasma Glucose	121,26±46,35	86-388 (108)
HDL	53,07±12,45	30-87 (50)
LDL	128,19±36,47	52-206 (128)
Total Collesterol	211,88±37,49	129-289 (214)
Neutrophyle/ Lymphocyte	2,62±2,11	1,2-15,16 (2)
Platelet/Lymphocyte	140,72±59,68	55-350 (126)
C-reactive Protein	5,88±4,1	3-22 (4)

BMI value ranged from 20.2 to 48, with an average of 30.31 ± 5.26. While 10.5% (n = 6) of the patients were pre-obese, 40.4% (n = 23) were obesity class 1, 42.1% (n = 24) obesity class 2 and 7% (n = 4) obesity class 3. 36.8% (n = 21) of the patients were hypertensive, 63.2% (n = 36) were not. According to the IDF 2005 MetS diagnostic criteria; 31.5% (n = 18) of the patients did not have MetS, while 68.4% (n = 39) had.

Although most of the patients had MetS, there was no statistically significant relationship between tibial plateau cartilage degeneration scores and the presence of MetS ($p > 0.05$). Thus, there was no statistically significant difference in end-stage knee OA whether or not having MetS. When the

relationship between cartilage degeneration scores and other parameters (surgery side, hypertension, and BMI scores) was evaluated, no statistically significant correlation was found (p> 0.05).

Degeneration was higher in the medial tibia plateau (p <0.05). That is because varus gonarthrosis can be seen more frequently than valgus gonarthrosis among the population. No statistically significant relationship was found when medial tibial plateau degeneration was compared with other parameters (p> 0.05) (Table 2).

Table 2. Comparison of medial tibial plateau degeneration and other parameters

Parameter	OARSI score	n	Mean±SD	Min-Max (Median)	p
LDL	≤ 3	18	134,17±39,14	62-206 (135)	[a]0,406
	> 3	39	125,44±35,36	52-191 (128)	
Total Collesterol	≤ 3	18	217,83±41,02	146-289 (218,5)	[a]0,420
	> 3	39	209,13±35,98	129-278 (212)	
Waist Circumferance	≤ 3	18	94,61±18,45	70-142 (89)	[b]0,253
	> 3	39	97,59±13,83	71-136 (97)	
Fasting Plasma Glucose	≤ 3	18	123,61±67,12	94-388 (107,5)	[b]0,503
	> 3	39	120,18±33,86	86-234 (109)	
HDL	≤ 3	18	56,11±13,93	39-87 (54)	[b]0,319
	> 3	39	51,67±11,62	30-81 (50)	
Neutrphyle/ Lymphocyte	≤ 3	18	2,89±3,24	1,2-15,16 (1,91)	[b]0,424
	> 3	39	2,49±1,35	1,2-8,75 (2,17)	
Platelet/ Lymphocyte	≤ 3	18	154,78±72,83	71-350 (131,5)	[b]0,405
	> 3	39	134,23±52,34	55-295 (125)	
CRP	≤ 3	18	6,58±5,64	3-22 (4)	[a]0,892
		39	5,56±3,2	3-15 (4)	

[a]Student T Testi [b]MannWhitney U Testi

DISCUSSION

In this study, degeneration in synovial cartilage was evaluated histopathologically in end-stage knee OA patients who underwent total knee arthroplasty; and the relationship between MetS and systemic inflammatory response parameters was investigated. There have been studies about comparing incidence or symptom severity between MetS and OA, but we compared both tibial plateau specimens histopathologically with MetS. Our findings showed that there was no significant relationship between the cartilage degeneration seen in OA patients and MetS components and systemic inflammatory markers. However, the statistically significant difference between medial and lateral tibial plateau cartilage degeneration (independent of BMI) reminded the deviation of the mechanical axis medially in varus knees in terms of altering load balance.

OA is characterized by pathological inflammation associated with localized cartilage loss and remodeling of the bone adjacent to the cartilage. OA involves a slow and effective repair process. However, in some people, this situation cannot be compensated and results in symptomatic OA as a result of recurrent traumas or inadequate repair mechanisms, so this may explain why the disease comes with a wide range of clinical conditions in different patients, even in the same patient in different joints.

The frequency of hand OA in obese and pre-obese individuals has been shown to be a 2-fold increase in risk independent of excessive mechanical stress [11]. If it cannot be fully explained by excessive mechanical stress, then the relationship between obesity and hand OA reveals a systemic link between the two conditions mediated by adipokines [12]. Therefore, increased adiposity may help the progression of low-grade systemic inflammation, which also induces an increase in osteoarthritic inflammation.

The adipose tissue in obese individuals is known to secrete adipokines (leptin, adiponectin) and pro-inflammatory cytokines (TNFα, IL-6, or IL-1), which interact with each other and are also associated with OA [13]. These adipokines are involved in immune and inflammatory response processes as well as the regulation of glucose and adipocyte metabolism [14]. So they can play roles in both weight-bearing and non-weight-

bearing joints. These cytokines can also be released from certain cells, such as chondrocytes and synoviocytes. Leptin and visfatin have been well described in the osteoarthritic joint [15]. The production of these adipokines has been shown to be similar to chondrocyte activation accompanied by mechanical stress and pro-inflammatory cytokines in vitro [16].

The exact definition of MetS is variable because more than one criterion has been developed [17]. Nevertheless, OA may be associated with MetS or its components [18]. The prevalence of MetS in OA is higher than in those without OA (59 % vs. 23 %). MetS in OA is associated with worse pain and functional scores and advanced radiographic changes [19]. Furthermore, histological and immunohistochemical investigations revealed that the fat stored in the joints of patients with MetS and OA, and the fat on an experimental OA model had different secretion activity of the pro-inflammatory adipokines through adipocytes in the synovial membrane, infrapatellar fat pad, and abdominal fat. In the vast NHANES III cohort study conducted in the general population of America, the prevalence of MetS observed in patients with OA was increased even when adjusted according to age and BMI [20], and a similar Japanese study supported this thought [21]. So we believe having MetS components baseline may affect initiating the arthritic process through several immune and inflammatory ways. But the question is: does this relationship last till the end stages of OA?

Konstari et al. stated that the number of MetS components or any individual component did not predict an increased risk of knee OA. They only found that elevated plasma fasting glucose was associated with a reduced risk of incident knee OA in their 32-year follow-up study [22]. Our histopathological results also showed that MetS might not affect OA progress in the long term.

Only overweighting may not be a risk factor for cartilage degeneration. Disruption of joint homeostasis and OA progress is clearly and crucially associated with adipokines. However, the interaction between the adipokine network, especially the interplay between inflammatory paths and mechanical and metabolic processes in the cartilage and bone disorders, still remains unclear. Evidently, further investigations are needed to elucidate the intimate mechanisms regulating peripheral and central adipokines activity, which may also be advantageous for future treatment of OA [23]. Nevertheless, this present study showed that end-stage OA needs more explanation of several reason interactions.

Among the major limitations of our study, the vast majority of patients were female patients with varus gonarthrosis. Moreover, of course, statistical data may become more reliable with larger series of cases. However, this study reminded us that initiation of OA has different paths to lead end-stage of the disease.

Conclusion: Nevertheless, overweighting is as important as the mechanical loading axis in the onset of weight-bearing joint OA. MetS and its components have certain effects via adipokines at the beginning of the arthritic process. However, we could not show this effect in the long-term until the end-stage histopathologically.

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