Diz Osteoartritinde COMP ve MMP-3 Düzeylerinin Radyografik ve Klinik Bulgularla İlişkisi

The Relationship of COMP and MMP-3 Levels with Radiographic and Clinical Findings in Knee Osteoarthritis

Araştırma
Research

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Özet

Amaç: Osteoartrit, çoğunlukla dizleri etkileyen en yaygın eklem hastalığıdır. Bu çalışmanın amacı diz osteoartriti olan hastalarda hastalığın radyolojik evreleri ve hastanın günlük yaşam aktivite düzeyleri ile serum kıkırdak oligomerik matriks proteini (COMP) ve matriks metaloproteinaz-3 (MMP-3) düzeyleri arasındaki ilişkiyi araştırmaktır.

Materyal ve Metod: Seksen beş hasta Kellgren-Lawrence ölçeğine göre üç gruba ayrıldı. 1. grup Evre I, 2. grup Evre II/III ve 3. grup Evre IV hastalar dahil edildi. Hastaların günlük yaşam aktivitelerinde ağrı şiddetini ve fonksiyonel durumlarını değerlendirmek için Görsel Analog Skala (VAS), Western Ontario ve McMaster Üniversiteleri Osteoartrit İndeksi (WOMAC), Lequesne indeksi ve Diz Yaralanması ve Osteoartrit Sonuç Skoru Kısa Formu (KOOS-PS) kullanıldı.

Bulgular: Her üç hasta grubunda da serum COMP ve MMP-3 düzeyleri benzer bulundu. Serum COMP düzeyleri ile VAS (p=0.682), Lequesne (p=0.941) skorları arasında zayıf korelasyon saptandı. Serum MMP-3 düzeyleri ile VAS (p= 0.911), Lequesne (p=0.636) ve KOOS-PS (p=0.965) arasında da zayıf bir korelasyon olduğu belirlendi.

Sonuç: Diz osteoartrit gruplarının farklı radyolojik evreleri ile günlük yaşam aktivitelerinde ağrı şiddeti ve fonksiyonel durum olan klinik parametreler ile serum COMP ve MMP-3 düzeyleri arasında anlamlı farklılık saptanmadı.

Anahtar Sözcükler: Diz, Osteoartrit, Radyografi, COMP, MMP-3, Fonksiyon, Ağrı

Abstract

Purpose: Osteoarthritis is the most common joint disease affecting the knee joints mostly. The aim of this study was to investigate the relationship between radiological stages of the disease and daily life activity levels of the patient and serum cartilage oligomeric matrix protein (COMP) and matrix metalloproteinase-3 (MMP-3) levels in patients with knee osteoarthritis.

Material and Methods: Eighty-five patients were divided into three groups according to Kellgren-Lawrence scale. In the 1st group Stage I, in the 2nd group Stage II/III and in the 3rd group Stage IV patients were included. Visual Analog Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lequesne algofunctional knee index, and Knee Injury and Osteoarthritis Outcome Score Short Form (KOOS-PS) were used to evaluate the severity of pain and functional status in daily life activities of patients.

Results: In all three patient groups serum COMP and MMP-3 levels were found to be similar. A weak correlation was found between serum COMP levels and VAS (p=0.682), Lequesne (p=0.941) scores. There was also a weak correlation between serum MMP-3 levels and VAS (p=0.911), Lequesne (p=0.636) and KOOS-PS (p=0.965).

Conclusion: No significant differences were found in serum COMP and MMP-3 levels between different radiological stages of knee osteoarthritis groups and the clinical parameters as severity of pain and functional status in daily life activities. Further studies with larger sample groups are needed on this issue.

Key Words: Knee, Osteoartritis, Radiography, COMP, MMP-3, Function, Pain

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Introduction

Among all joint diseases, osteoarthritis (OA) is the most common one, often affecting the knee joints. OA is defined as a disease that affects not only the cartilage, but also the synovia, ligaments, tendons, muscles, subchondral bone and the adipose tissue as well (1).

Multiple factors are known to play role in OA pathogenesis. Low-grade chronic inflammation has also been added to these factors in recent years (2). Mainly involving the cartilage, OA is a dynamic process that develops in response to mechanical and inflammatory effects (1,2). The increasing prevalence of OA in the last decade has amplified the importance of finding more effective preventive and therapeutic strategies based on reliable diagnostic and prognostic markers. Biochemical markers in OA are molecules that arise in the physiological cycle related to the bone and cartilage matrix, and they can be detected in body fluids. The most important purpose of marker measurement in OA is to identify cartilage damage in the early period when it has not yet been detected radiologically (3,4). In addition to early diagnosis, monitoring of disease activity, determination of disease severity, prediction of prognosis, and evaluation of response to treatment are other purposes of marker measurement (3,4). The high levels of matrix metalloproteinases (MMPs) in tissue play a key role in the destruction of aggrecan and type II collagen, which are the main components of cartilage (3). Li et al. showed that serum MMP-3 levels in patients with middle- and advanced-stage knee OA were significantly higher than in patients with early stage knee OA and healthy controls and suggested that serum MMP-3 measurement is a biomarker that can be used to diagnose knee OA and differentiate patients with advanced knee OA (5).

Cartilage oligomeric matrix protein (COMP) is a tissue-specific matrix protein that belongs to the thrombospondin family and is synthesized by chondrocytes. Serum COMP values have been found to be significantly higher in OA patients compared with controls and also in patients with advanced knee OA, the mean serum COMP value was found to be higher than in patients in the early stage (6).

This study's main and secondary objectives are to investigate the relationship between serum COMP and MMP-3 levels and radiological disease stage, daily life activities and functional levels in patients diagnosed with knee OA. And to determine whether serum levels of 2 biomarkers can discriminate radiographic damage (K-L grades).

Materials and Methods

Eighty-five patients who were diagnosed with knee OA according to the American College of Rheumatology (ACR) criteria were included in the study.

The study protocol was approved by the ethical committee of Hacettepe University (4.9.2018, GO 18/665-08).

Sample size calculation was performed a priori the study. Gpower Version 3.1.9.4 was used for this calculation. To detect a large effect size between three study groups (f=0.35) at a 0.05 type I error rate and %80 power at least eighty four subjects are needed.

Patients were enrolled in the study according to their applications with a sequential approach and all participants were informed about the study procedure, and the informed consent of each participant was obtained.

Each patient's age, gender, weight, height, educational background, occupation, additional diseases, and medications were recorded. Detailed physical examinations were performed by the same physician for each patient. The exclusion criteria were as follows: Previous trauma/orthopedic surgery, intraarticular injections (glucocorticoid, hyaluronic acid, platelet-rich plasma-PRP) within the last 6 months, systemic glucocorticoids in the last 3 months, analgesics/non-steroidal anti-inflammatory drugs (NSAIDs) in the last 24 hours, nutritional supplements containing collagen and/or glucosamine/chondroitin in the last 3 months, physical exercise before blood draw, cognitive impairment, severe vision, hearing and speech disorders, depression, orthopedic problems, neurological problems/diseases associated with neuropathic pain, inflammatory arthritis, uncontrolled metabolic problems,

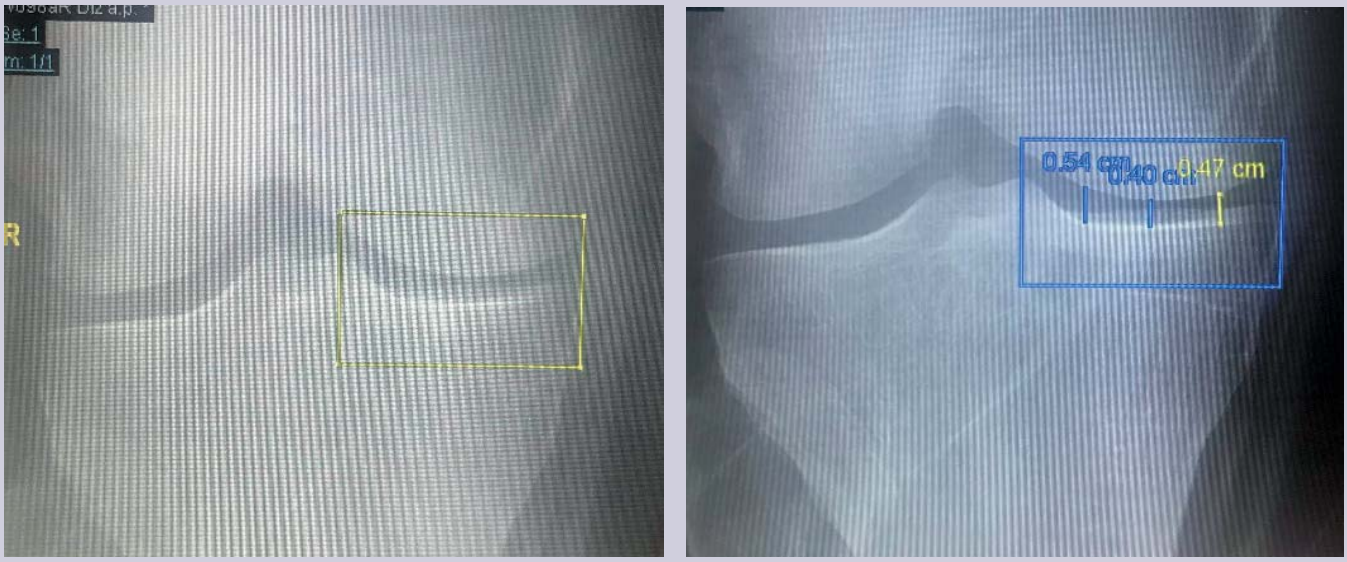


Figure 1: Digital measurement of Medial joint space width (MJSW)

immunosuppressive drugs, cardiovascular problems, active infection and inflammation, pregnancy, malign diseases.

Patient groups: The patients were divided into three groups according to the Kellgren–Lawrence (K-L) radiological staging system. K-L stage I patients were included in group 1, K-L stage II and III patients were included in group 2, and K-L stage IV patients were included in group 3.

Serum COMP and MMP-3 measurements: All the patients rested 1 hour before blood acquisitions. Blood samples were taken from patients for serum COMP and MMP-3 measurements. Approximately 4 cc of blood was taken from the patients for the study. Within 3 hours, the tubes were centrifuged (4000 rpm for 7 minutes), and serum was separated from blood cells. Separated sera were taken into Eppendorf tubes and stored at −40 °C until they were studied. The preserved sera were studied for each patient within 1.5 months. Serum COMP (COMP®, YLbiont, Shanghai, China) and MMP-3 (MMP-3®, YLbiont, Shanghai, China) levels were measured using sandwich enzyme immunoassay enzyme-linked immunosorbent assay (ELISA) kits. All biochemical measurements were made in accordance with the manufacturer's instructions. ELISA samples performed in dublicate.

Radiographic assessments: Knee radiographs are taken with the knees in a partial flexion position, which is much more reliable for assessing the condition of the tibiofemoral compartment (7). In this study, semiflexion radiographs of the patients were taken postero-anteriorly, with the knees in slight flexion and external rotation, bearing the patients' body weight. The film distance was positioned at a 10° angle at a distance of 1 m. The knee radiographs were re-evaluated according to the Kellgren–Lewrence radiological staging system, and the radiological disease stages were recorded (8). The medial joint space width (MJSW) was measured digitally with a computer as shown in the Figure 1. For the radiographic assessment to be more objective and measurable the narrowest part of the joint space was measured and a comparison of the millimetric data was made. First, the medial part of the joint was divided into three equal parts on the screen. Then, the lowest width was found for the right and left knee in each patient. The average of the values found for the right and left knees was considered the medial joint space width for each patient.

Pain and function evaluation: The severity of pain in patients and functional status in daily life activities were evaluated with the Visual Analog Scale (VAS) (9), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (10), the Lequesne index (11), and the Knee Injury and Osteoarthritis Outcome Score Short Form (KOOS-PS) (12).

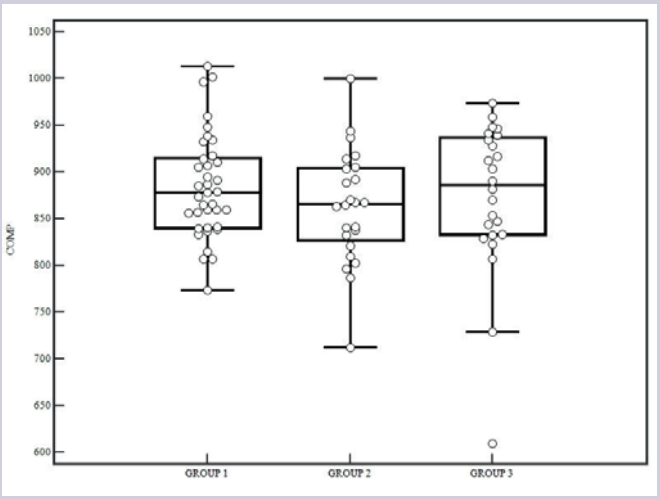
Statistical analysis: The Statistical Package for Social Sciences for Windows (SPSS) 21.0

program was used for the statistical analysis of the findings obtained in the study. Normality and homogeneity of variances were checked for parametric test assumptions. The difference between the groups in terms of numerical variables was evaluated by one-way analysis of variance if parametric test assumptions were met. Pairwise comparisons were done using Tukey's honestly significant difference (HSD) test. If the parametric test assumptions were not met, the data were evaluated with the Kruskal–Wallis test. The difference between the three groups in terms of categorical variables was examined using the Chi-square test. The relationship between numerical variables was determined using the Spearman correlation coefficient. A range of correlation coefficient from 0.10 to 0.29 was considered as poor, 0.30–0.59 as fair, 0.60–0.79 as moderate and 0.80–1 as very strong (Ref: Chan YH. Biostatistics 104: correlational analysis. Singap Med J. 2003;44(12):614–619.).
The following values were considered when interpreting the correlation coefficients: 0 indicated no linear relationship; +1/−1 indicated a perfect linear positive/negative relationship; a value between 0 and 0.3 (or between 0 and −0.3) indicated a weak linear positive (negative) relationship through a shaky linear rule; values ranging from 0.3 to 0.7 (or −0.3 to −0.7) indicated a moderate positive (negative) linear relationship; and values between 0.7 and 1.0 (or −0.7 and −1.0) indicated a strong positive (negative) linear relationship.
The co-efficient of variation for the COMP and MMP3 measurements are: 7,44% for COMP 40,18% for MMP3.

Table 1. Demographic characteristics of patient groups

	Group 1 (n=30)		**Group 2 (n=26)**		**Group 3 (n=29)**				**p.**
Age*									
	57.17=9.37		64.73=9.48		68.17=10.27				**<0.001**
Sex**							**Total**		**p**
Female	26	86.7%	24	92.3%	25	86.2%	75	88.2%	0.725
Male	4	13.3%	2	7.7%	4	13.8%	10	11.8%	
Employment**							**Total**		
Employed	10	33.3%	3	11.5%	9	31.0%	22	25.9%	
Unemployed Retired	20	66.7%	23	88.5%	20	69.0%	63	74.1%	
Education**							**Total**		**p**
Illiterate	3	10.0%	10	38.5%	7	24.1%	20	23.5%	0.032
Primary school	16	53.3%	13	50.0%	16	55.2%	45	52.9%	
Secondary school	4	13.3%	0	0,0%	3	10.3%	7	8.2%	
High school	3	10.0%	3	11.5%	1	3.4%	7	8.2%	
University	4	13.3%	0	0.0%	2	6.9%	6	7.1%	
Comorbidities**							**Total**		**p**
Yes	23	76.7%	23	88.5%	27	93.1%	73	85.9%	0.178
No	7	23.3%	3	11.5%	2	6.9%	12	14.1%	
Medication**							**Total**		**p**
Yes	15	50.0%	15	57.7%	22	75.9%	52	61.2%	0.114
No	15	50.0%	11	42.3%	7	24.1%	33	38.8%	
BMI									
	30.05#5.7		32.18#5.1		31.01+5.1				0.328

*ANOVA test
** Chi-square test



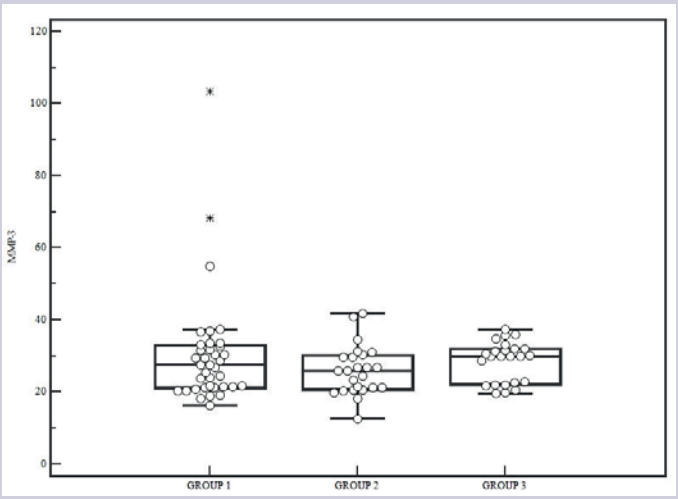


Figure 2a & 2b: Differences in serum COMP and MMP-3 levels between the patient groups

Results

The study included 30 patients in group 1, 26 patients in group 2, and 29 patients in group 3. The characterization of the study sample are included in the Table 1 below. There was a significant difference between the groups in terms of mean age (mean ± standard deviation [SD]: group 1 = 57.17 ± 9.37, group 2 = 64.73 ± 9.48, group 3 = 68.17 ± 10.27 years; $p < .001$). Group 1 was younger than the other groups. There was no significant difference in gender between the groups ($p = .725$). Moreover, there was no significant difference between the three groups in terms of body mass index (BMI; mean ± SD: group 1 = 30 ± 5.7, group 2 = 32.2 ± 5, group 3 = 31 ± 5.1; $p = .328$).

The mean serum COMP values were 886.44 ± 56.07 (min: 806.8–max: 1,013.5) ng/ml in group 1, 868.09 ± 57.86 (min: 712.2–max: 1,000.2) ng/ml in group 2 and 870.00 ± 78.95 (min: 609.7–max: 974.0) ng/ml in group 3 ($p = .727$). The mean serum MMP-3 values were 31.37 ± 17.19 (min: 16.3–max: 103.5) ng/ml in group 1, 25.41 ± 6.89 (min: 12.7–max: 40.9) ng/ml in group 2, and 28.88 ±5.72 (min: 19.8–max: 41.8) ng/ml in group 3 ($p = .082$). There were no significant differences in serum COMP and MMP-3 levels between the patient groups (Figure 2a, Figure 2b).

The mean MJSW values were 0.42 ±0.05 (min: 0.34–max: 0.55) cm in group 1, 0.32 ±0.09 (min: 0.16–max: 0.50) cm in group 2, and 0.03 ±0.06 (min: 0.00–max: 0.28) cm in group 3 ($p < .001$). The mean MJSW measurements of all three groups were found to be significantly different from each other.

The mean VAS values of the patients were 4.04 ±2.11 (min: 0.5–max: 8.1) in group 1, 5.88 ±1.79 (min: 1.5–max: 8.5) in group 2, and 7.63 ±1.26 (min: 5–max: 9.5) in group 3 ($p < .001$). The mean WOMAC values of the patients were found to be 26.14 ± 10.89 (min: 7.29–max: 58.33) in group 1, 41.18 ± 15.52 (min: 21.87–max: 81.25) in group 2, and 63.96 ±13.42 (min: 20.80–max: 90.62) in group 3 ($p < .001$). The mean Lequesne algo functional knee index values of the patients were found to be 6.07 ± 2.81 (min: 1.0–max: 12.0) in group 1, 9.27 ±3.41 (min: 4.0–max: 16.0) in group 2, and 13.76 ±2.89 (min: 8.0–max: 20.0) in group 3 ($p < .001$). The mean KOOS-PS values of the patients were 31.88 ± 9.65 (min: 14.82–max: 54.38) in group 1, 43.49 ±11.12 (min: 24.89–max: 71.84) in group 2, and 59.08 ±13.21 (min: 38.60–max: 91.76) in group 3 ($p < .001$).

The mean VAS, WOMAC, KOOS-PS, and Lequesne algofunctional knee index values of all three groups were found to be significantly different from each other. When these biomarkers and functional test scores were compared, there was weak correlation between COMP levels and VAS, Lequesne scores, weak negative correlation between COMP levels and WOMAC, KOOS-PS scores. There was weak correlation between serum MMP-3 levels and VAS, Lequesne and KOOS-PS scores, weak negative correlation between MMP-3 levels and WOMAC scores (Table 2).

Table 2. Correlation analysis

		WOMAC	Lequesne	KOOS-PS	MJSW	COMP	MMP-3
VAS	rho	0.726	0.738	0.730	-0.610	0.045	0.012
	p	<0.001	<0.001	<0.001	<0.001	0.682	0.911
WOMAC	rho	1.000	0.872	0.910	-0.707	-0.051	-0.013
	p	-	<0.001	<0.001	<0.001	0.643	0.906
Lasequesne	rho		1.000	0.870	-0.708	0.008	0.052
	p		-	<0.001	<0.001	0.941	0.636
KOOS-PS	rho			1.000	-0.681	-0.035	0.005
	p			-	<0.001	0.748	0.965
MJSW	rho				1.000	-0.070	-0.085
	p				-	0.526	0.441
COMP	rho					1.000	0.375
	p					-	<0.001
MMP-3	rho						1.000
	p						-

Spearman correlation
p: a number describing how likely it is that your data would have occurred by random chance.
rho: is a non-parametric test used to measure the strength of association between two variables.

Discussion

In this study, we investigated the relationship between serum COMP and MMP-3 levels with disease stage and daily living activities in patients with knee OA. In our study, two biochemical markers were evaluated together, and the radiographic measurements of the patients were evaluated with knee radiographs taken in a semi-flexion position. Serum COMP measurement can potentially be used in the diagnosis of OA and in predicting disease progression (4). Georgiev et al. evaluated serum COMP levels in 56 patients with primary knee OA and 31 healthy controls in their study. The serum COMP level was found to be significantly higher in the patient group compared with the control group. At the same time, the COMP level was found to be higher in K-L stage II/III patients than K-L stage I patients (6). In our study, we did not have a control group, so a comparison could not be made between healthy control and patient groups. The patients included in the study were grouped as stage I, stage II/III, and stage IV, and serum COMP levels were similar between the groups. In a study conducted by Das Gupta et al., COMP levels were measured in K-L stage II, III, and IV knee OA patients and healthy controls. As a result of this study, there was no statistically significant difference in COMP levels between the OA group and the healthy control group. In addition, there was no significant difference between different K-L stages and COMP levels in the OA group (13). These results seem compatible with ours.

In a study conducted by Sharif et al., 115 patients with knee OA were included. Serum COMP levels (at the beginning and every 6 months) and radiographic cartilage loss (at 0, 24, 36, and 60 months) were measured at the end of the study, the COMP level was found to be associated with progressive joint damage (14).

Vilım et al evaluated patients with symptomatic primary knee OA (KL stage I–III), and serum COMP levels were measured at the start of the study and 3 years after the study. And it was found that the COMP measurement could be a potential indicator of disease progression (15). However, some studies have shown that serum COMP measurement was not effective in predicting OA prognosis. For instance, Kraus et al. reported that serum COMP measurement is not useful as an indicator of worsening knee OA (16).

Serum COMP and MMP-3 levels were investigated in knee and hip OA in a recently published systematic review. It was found that COMP performance was moderately effective in distinguishing knee/hip OA patients from healthy individuals, but there was no statistically significant difference for MMP-3. However, the study also emphasized the need for further studies with a larger sample group (17).

COMP levels are associated with BMI and vary according to ethnicity and gender (18). In our study, there was no difference between the groups in terms of BMI and gender distribution. An another study investigated the relationship between serum COMP levels and renal and cardiovascular function test levels in patients with advanced OA. In this study, a significant positive correlation was shown between the COMP value and renal (cystatin C, creatinine, and estimated glomerular filtration rate (eGFR) and heart (N-terminal pro-B-type natriuretic peptide) markers. It is suggested that additional adjustment with eGFR may be required because renal failure may cause accumulation of COMP in serum (19). In our study, we did not have any patients with kidney failure in the groups and we did not evaluate cystatin and heart markers.

In advanced stages of OA, the levels of serum COMP decrease, probably due to its depletion in highly degenerated tissue. In some studies, it has been emphasized that the effects of comorbid diseases and advanced stage OA on COMP levels should be evaluated in more detail. In our study, we also had a patient group with isolated K-L stage-IV knee OA. The significant results in previous studies were mostly seen in the comparisons between K-L stage I, K-L stage II and III. It would be appropriate to consider this factor in evaluating the results of our study (17).

One study has shown that a 30-minute walking exercise can cause high serum COMP levels in both patients with knee OA and healthy age-matched individuals (20). In our study, the exercise status of the patients was asked about before the blood draw, and blood was drawn after 1 hour of rest. In addition, patients who had been involved in a recent physical therapy program were not included in the study.

Li et al. investigated serum MMP-3 levels in early stage knee OA patients, intermediate- to advanced-stage knee OA patients, and healthy controls. Serum MMP-3 levels were found to be significantly higher in patients with intermediate to advanced knee OA compared with patients with early stage knee OA and the control group. It was suggested that serum MMP-3 is a biomarker that can be used to diagnose OA and differentiate patients with advanced knee OA. In our study, because we did not have a control group, MMP-3 measurement could not be compared in healthy individuals and OA patients (5).

Some studies have revealed results that contradict the effectiveness of serum MMP-3 measurement in distinguishing patients with knee OA from healthy individuals. In a study performed by Georgiev et al. with a knee OA group and a healthy control group, it was found that serum MMP-3 levels were significantly higher in the knee OA group compared with the control group. However, there was no statistically significant difference in serum MMP-3 levels between the healthy control group and the group with K-L stage I. In addition, there was no significant difference in serum MMP-3 levels between the group with K-L stage II/III and the group with K-L stage I. In the same study, it was found that the serum levels of MMP-3 in the group with generalized OA were significantly higher than those in the localized OA group. In our study, similar to this research, no significant difference was found between serum MMP-3 levels in different K-L stages (6). Later Georgiev et al performed a study to evaluate serum MMP-3 levels as a prognostic marker for the progression of cartilage damage in patients with knee osteoarthritis and found that, significantly higher values of baseline MMP-3 levels were observed in patients with a registered progression of cartilage injury in the medial tibiofemoral compartment of the knee compared with patients with no progression (21).

Studies have shown that generalized OA is more common in patients with knee OA compared with hip OA. This might be considered one of the reasons for the prominent diagnostic performance of COMP in knee OA (22). A weak correlation was found between serum COMP

levels and VAS, Lequesne scores in our study and there was also a weak correlation between serum MMP-3 levels and VAS, Lequesne and KOOS-PS. Matejova et al stated that, their results indicated significant linear correlation of MMP-13 and COMP concentration with age, but not with OA severity (23).

The limitations of our study can be stated as the absence of a healthy control group, the small sample size, and the demographic characteristics of the patients. The strengths of our study are that the patients were assessed via radiographic staging and measurements of medial joint space width were evaluated using current radiographic techniques, and two different biochemical markers were studied together.

Conclusion

In conclusion, in our study, no statistically significant difference was found between the groups in serum MMP-3 and serum COMP levels in any of the three patient groups. When these biomarkers and functional test scores were compared, there was weak correlation between COMP levels and VAS, Lequesne scores, weak negative correlation between COMP levels and WOMAC, KOOS-PS scores. There was weak correlation between serum MMP-3 levels and VAS, Lequesne and KOOS-PS scores, weak negative correlation between MMP-3 levels and WOMAC scores. In addition, when medial joint space width (MJSW) were compared with other scores, a strong negative correlation was observed with WOMAC, Lequesne while a moderate negative correlation was found with VAS, KOOS-PS. There was weak negative correlation between medial joint space width and serum COMP, MMP-3 levels.
Although the use of these biomarkers to identify OA patients at an early stage seems effective, it should be kept in mind that they are more complex than expected and may not always be effective in individual studies.

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Conflicts of Interest

The authors do not have any conflicts of interest related directly or indirectly to this article.

Ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study. Participants' data were kept private and confidential.

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