International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2017; **20:** 1942–1949

ORIGINAL ARTICLE

Adiponectin: is it a biomarker for assessing the disease severity in knee osteoarthritis patients?

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Abstract

Aim: The results of previous studies regarding the role of adiponectin in the pathogenesis of osteoarthritis (OA) are controversial. The aim of this study is to investigate the relation of plasma adiponectin levels with clinical and radiological disease severity in knee OA patients.

Method: Sixty patients with knee OA and 25 healthy controls were included in the study. Patients were divided into two subgroups: lean (Group 1, $n = 30$) and obese (Group 2, $n = 30$). Healthy controls were accepted as Group 3 ($n = 25$). Pain intensity was measured with a visual analogue scale (VAS), functional disability with Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Quality of Life (QoL) with Short Form-36 (SF-36). Also all patients were radiologically evaluated and graded according to Kellgren–Lawrence (KL) scale. Plasma concentrations of adiponectin levels were measured by enzyme-linked immune-sorbent assay (ELISA).

Results: Serum adiponectin levels were higher in OA patient subgroups than those in the control group but the difference did not reach a significant level after adjustments for age, gender and body mass index ($P = 0.078$). There was a positive correlation between adiponectin concentration and KL grading scores. Additionally, there was a positive correlation between adiponectin levels and clinical variables (VAS and WOMAC total scores) in patient subgroups ($r = 0.326$ $P = 0.012$, $r = 0.583$ $P < 0.001$, respectively). SF-36 scores were inversely associated with adiponectin levels.

Conclusion: Plasma adiponectin concentrations were associated with both clinical and radiological disease severity in knee OA patients. Thus, adiponectin hormone might be a potential clinically useful biomarker while assessing disease severity in the future.

Key words: disease aetiology, osteoarthritis, pathogenesis.

INTRODUCTION

Osteoarthritis (OA) is a chronic joint disease with pain and deformity followed by chronic disability.[1,2] The knee is one of the most commonly involved joint and has a prevalence of symptomatic OA as high as 20.9% over 40 years of age according to a study conducted in a region of Turkey.[3] Obesity is a well-known risk factor that has been a subject of many studies.[4,5] Recent studies have shown that obesity is not just a mechanical factor for OA but also has many complex metabolic pathways in disease pathology.[6,7]

Adipose tissue is considered as an endocrine organ besides its lipid storage function.[8,9] More than 50 adipokines were identified which have roles in lipid

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metabolism, the fibrinolytic system, the complement system and steroid metabolism. Adiponectin hormone, which is the most abundantly secreted adipose tissue protein, is a 244 amino acid, 30 kDa peptide product of the *apM1* gene. In 1995, Scherer first described adiponectin as a similarly structured hormone to complement factor C1q.[10,11] Since then, adiponectin has been intensely studied in many metabolic conditions such as insulin sensitivity, cardiovascular system diseases (atherosclerosis, myocardial infarction) inflammatory and anti-inflammatory pathways. Although adiponectin hormone is claimed to have inflammatory and anti-inflammatory functions, its role in OA disease still remains a question. There are several studies researching the role of adiponectin in the pathophysiology of OA. However, the results of the studies seem to be contradictory. Although some studies suggest its protective effects on joints,[12–15] others assert the catabolic effects of the hormone in disease pathophysiology.[16–22]

In this study, we aimed to measure the levels of adiponectin hormone that is considered to play a role in OA pathophysiology in OA patients; and to determine the relationship between plasma adiponectin levels and disease severity. According to our literature research, this is the first study that investigates the correlation of adiponectin levels with all clinical, laboratory and radiological aspects of OA.

MATERIALS AND METHODS

Patients and samples

Sixty patients who met the clinical and radiological criteria of knee OA according to American College of Rheumatology (ACR) and 25 healthy control volunteers were included in the study. Because of the reason that adiponectin levels were reported to be associated with cardiometabolic and inflammatory disorders,[23–25] exclusion criteria were set as coronary heart disease, chronic kidney failure, types 1 and 2 diabetes mellitus, hypertension, pregnancy and inflammatory rheumatic diseases.

Patients were visited once. Patients' ages, gender, disease duration, height and weight, body mass index (BMI), employment status, occupational status, job characteristics and trauma history were recorded. BMI were calculated as body weight divided by the square of height in meters (kg/m^2). After detailed history was obtained, patients underwent physical examination. Besides general physical examination, knee range of motion, presence of crepitus, tenderness and swelling of the joints were assessed. Routine blood tests (complete blood count, fasting blood glucose level, liver and kidney function tests) and electrocardiography were performed to exclude chronic cardiac and metabolic diseases.

Blood samples were taken after 12 h fasting between 06:00–08:00 h from the forearm vein. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and rheumatoid factor (RF) levels were immediately measured. Specimens which were separated from the same blood samples for determining levels of adiponectin hormone were also immediately centrifuged and collected in a −20°C cooling refrigerator for bulk measurement. After collection of all samples, serum adiponectin levels were studied with enzyme-linked immune-sorbent assay (Human Adiponectin ELISA Kit, R&D Systems, Minneapolis, MN, USA), following the procedure according to the manufacturer's instructions.

All measurements were performed the same way for the control group.

Volunteers were divided into three groups:

1 Group 1 (n = 30) were low or normal weighted OA patients with BMI < 24.9.
2 Group 2 (n = 30) were obese OA patients with BMI > 29.9.
3 Group 3 (n = 25) was the control group which was consisted of healthy volunteers.

Assessment scales

Pain

Patients' pain intensity was evaluated with a visual analogue scale (VAS). VAS scale is a 100 mm linear line with the two ends described as 'no pain' and 'the worst pain'. Patients were asked to put a mark on the line between the two extremes where their current pain was represented. Pain was evaluated as patients' current pain assessment (VAS1) and patients' global assessment (VAS2), respectively.

Disability

The functional capacities of patients were assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) functional capacity index which has Turkish reliability and validity. The Likert scale version of the index was used. The functional capacity index included 17 questions and the scores ranged between 0–68 (0 no disability, 68 severe disability).

Quality of life

Quality of life was assessed with Turkish version of the Short Form-36 (SF-36). This is a self-administered

questionnaire with 36 questions divided into eight categories. The subgroups of SF-36 questionnaire are bodily pain, physical functioning, social functioning, physical role functioning, emotional role functioning, vitality, mental health and general health.

Radiology

Radiographs of the patients were obtained in both antero-posterior and lateral semi-flexed positions while patients were standing. Radiological findings were evaluated and graded by two clinicians according to the Kellgren–Lawrence (KL) radiological scale. KL scoring method is used widely to assess severity of knee OA. There are four grades (0–4) according to the KL scoring method; grade 0 indicates normal knee joint, grade 1: doubtful narrowing of joint space; grade 2: definite osteophytes and possible joint space narrowing (JSN); grade 3: multiple osteophytes, definite JSN, sclerosis and possible deformity of bone ends; grade 4: large osteophytes, marked JSN, severe sclerosis and definite bony deformity. The KL scoring system was found to have moderate intra- and inter-observer reliability.[26]

Unlike the patient groups, VAS, WOMAC, SF-36 measurements and radiological grading were not performed for the control group due to lack of symptoms and radiological findings.

Statistical analysis

Data evaluation was conducted with SPSS software 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Kruskall–Wallis test was used for comparison of more than two groups and Mann–Whitney *U*-test was used for pairwise comparisons. Analysis of covariance was performed for the comparison of groups after controlling for the effects of covariates. Spearman's correlation analysis was performed to assess the correlation between the two variables. On the basis of the knowledge that adiponectin blood levels are affected by age, gender and BMI, the relationship between adiponectin levels and other variables were calculated by partial correlation. The correlation coefficient (*r*-value) between 0.25–0.49 was considered as weak, 0.5–0.74 as moderate and 0.75–1 as strong relation. $P < 0.05$ was considered as statistically significant.

RESULTS

Sixty patients with diagnosis of knee OA (57 female; three male) and 25 healthy volunteers (13 female, 12 male) were included in the study.

There were no significant differences in age, gender and disease duration between the two patient groups ($P > 0.05$). The mean age of the control group was lower compared to the patient groups. Also, male gender ratio was significantly higher in the control group than the patient groups ($P < 0.001$).

The socio-demographic characteristics of patient and control groups are given in Table 1.

There were no statistically significant correlations between adiponectin levels and ESR, CRP or RF levels among all three groups. There was a weak and statistically significant positive correlation between adiponectin and VAS values in Group 1. In Group 2 no statistically significant correlation was found (Table 2).

There were weak–moderate positive correlations between adiponectin plasma levels and WOMAC total scores in both patient groups ($r = 0.541$; $P = 0.002$, $r = 0.409$; $P = 0.025$, respectively).

In Group 1, there was weak–moderate negative correlation between adiponectin plasma levels and all SF-36 subscores ($r = 0.30$–0.69 $P < 0.05$) which was also statistically significant, except physical functioning and physical role functioning subscores ($P = 0.056$). In Group 2, a moderate and statistically significant negative correlation was seen only between adiponectin levels and the social functioning subscore of SF-36. The correlation analysis results between plasma adiponectin levels, WOMAC total score and SF-36 subscores are shown in Table 3.

Adiponectin levels and radiological deterioration of disease were positively correlated in Groups 1 and 2 ($r = 0.607$; $P < 0.001$, $r = 0.589$; $P = 0.001$). When patients in both groups were analyzed together, the positive correlation was maintained between adiponectin levels and radiological grading ($r = 0.572$, $P < 0.001$).

Additionally, intergroup comparisons of plasma adiponectin and adiponectin median levels according to KL grades were performed.

As the patient and control groups were heterogeneous for age, gender and BMI, plasma adiponectin levels were compared after adjustment for these and only gender was found to be significant. Although plasma adiponectin concentrations were higher in patient groups than the control group (Group 1 = 11.96 ± 6.34 μg/mL, Group 2 = 9.16 ± 6.60 μg/mL, Group 3 = 8.11 ± 7.04 μg/mL), there was no significant difference among groups ($P = 0.078$).

When the adiponectin median levels were analyzed according to KL grades, there was no statistically significant difference between Groups 1 and 2 ($P > 0.05$). The numbers of patients and the adiponectin median levels

Table 1 Comparison of socio-demographic characteristics of the groups

	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 25)	P-value
Age (years), mean ± SD	67.03 ± 12.71	64.56 ± 10.60	43.08 ± 14.60	< 0.001
Gender, n (%)				
Female	27 (90)	30 (100)	13 (52)	< 0.001
Male	3 (10)	0 (0)	12 (48)	
Duration of disease (months), mean ± SD	103.66 ± 75.85	128.13 ± 85.03	–	0.248
BMI (kg/m^2), mean ± SD	23.39 ± 1.77	33.61 ± 3.42	27.45 ± 5.55	< 0.001
Educational level, n (%)				
Illiterate	0 (0)	9 (30)	0 (0)	< 0.001
Primary school	19 (63.3)	15 (50)	6 (24)	
Secondary school	4 (13.3)	3 (10)	1 (4)	
High school	5 (16.7)	2 (6.7)	12 (48)	
College	2 (6.7)	1 (3.3)	6 (24)	
Employment status, n (%)				
Yes/No	6 (20)/24 (80)	1 (3.3)/29 (96.7)	14 (56)/11 (44)	0.046
Occupation, n (%)				
Housewife	21 (70)	29 (96.7)	6 (24)	0.000
Goverment official	3 (10)	1 (3.3)	7 (28)	
Employee	3 (10)	0 (0)	3 (12)	
Private sector	3 (10)	0 (0)	2 (8)	
Labor	0 (0)	0 (0)	2 (8)	
Student	0 (0)	0 (0)	5 (20)	
Job characteristics, n (%)				
Sedantary	14 (46.7)	20 (66.7)	6 (24)	0.001
Mild	10 (33.3)	10 (33.3)	7 (28)	
Moderate	6 (20)	0 (0)	12 (48)	

Group 1, low/normal weight patients; Group 2, obese patients; Group 3, control; SD, standard deviation; BMI, body mass ındex.

Table 2 The correlation between adiponectin and ESR, CRP, RF, VAS1, VAS2

Adiponectin level	Group 1 r/P	Group 2 r/P	Group 3 r/P
ESR	0.207/0.273	0.283/0.130	0.345/0.091
CRP	−0.109/0.565	−0.026/0.891	−0.237/0.254
RF	−0.024/0.899	−0.090/0.635	−0.054/0.798
VAS1	0.472/0.008	0.030/0.874	–
VAS2	0.404/0.027	0.096/0.612	–

Group 1, low/normal weight patients; Group 2, obese patients; Group 3, control.
ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; VAS, visuel analogue scale.

along with the minimum and maximum values in each KL grade are given in Table 4.

Adiponectin level comparison between KL grades showed statistically significant difference in Group 1 (P = 0.001). In order to determine the grades creating the difference; multiple comparison tests were performed. According to the pairwise comparisons of KL grades by adiponectin levels, there was a statistically significant difference between grades 2 and 4 (P = 0.001); however, no statistically significant difference was observed between grades 2 and 3, and grades 3 and 4 (P = 0.216, P = 0.439; respectively) (Fig. 1a).

In Group 2, there were also statistically significant differences between adiponectin levels in KL grades (P = 0.002). According to pairwise comparison results, there were statistically significant differences between KL grades 2 and 4, and KL grades 3 and 4 (P = 0.002, P = 0.007; respectively). No statistically significant difference in adiponectin levels was seen between KL grades 2 and 3 (P = 1.000) (Fig. 1b).

DISCUSSION

Obesity is known to be a biomechanical risk factor for OA. Further, high levels of various adipokines and the positive correlation with inflammatory markers in obese OA patients suggest possible involvement of the metabolic pathways in the pathophysiology of the disease. Adiponectin hormone is believed to play a role in

Table 3 Correlation analysis between plasma adiponectin levels, WOMAC total scores and SF-36 subscores

Adiponectin level	Group 1 *r*/*P*	Group 2 *r*/*P*	Groups 1 + 2 *r*/*P*
WOMAC total	0.541/0.002	0.409/0.025	0.477/0.001
SF-36 Bodily pain	−0.584/0.001	−0.177/0.351	−0.373/0.003
SF-36 Physical functioning	−0.352/0.056	−0.127/0.502	−0.268/0.038
SF-36 Social functioning	−0.605/0.001	−0.433/0.017	−0.534/0.001
SF-36 Physical role func.	−0.352/0.056	−0.043/0.821	−0.275/0.033
SF-36 Emotional role func.	−0.526/0.003	−0.010/0.957	−0.290/0.025
SF-36 Vitality	−0.424/0.019	−0.210/0.265	−0.296/0.021
SF-36 Mental health	−0.597/0.001	−0.254/0.176	−0.427/0.001
SF-36 General health	−0.458/0.011	−0.274/0.142	−0.356/0.005

Group 1, low/normal weight patients; Group 2, obese patients; Group 3, control.
WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; SF-36, Short Form-36.

Table 4 Comparison of intergroup plasma adiponectin levels in each KL grade

KL grade/adiponectin level	Group 1	Group 2	*P*-value
Grade 2, *n* (%)	16 (53.3)	8 (26.7)	0.597
Median ± (min–max) (μg/mL)	7.52 (12.17–26.17)	6.64 (2.47–25.92)	
Grade 3, *n* (%)	6 (20.0)	14 (46.7)	0.076
Median ± (min–max) (μg/mL)	14.20 (2.47–23.53)	9.79 (2.35–12.90)	
Grade 4, *n* (%)	8 (26.7)	8 (26.7)	0.097
Median ± (min–max) (μg/mL)	23.53 (13.29–32.02)	16.92 (11.19–19.79)	

Group 1, low/normal weight patients; Group 2, obese patients; min–max, minimum - maksimum values; KL=Kellgren-Lawrence Scale.

this pathophysiology. However, studies that have investigated the role of adiponectin hormone in disease etiopathology are in conflict with each other.

In this study, we aimed to determine plasma adiponectin concentrations in patients with knee OA and to investigate the relationship between adiponectin levels and clinical and radiological disease severity. Patients were divided into two subgroups as lean and obese to observe adiponectin hormone levels in individuals whose biomechanical loading on knees were relatively different. Thus, we have provided a more objective perspective with a chance to compare low and high biomechanical loaded osteoarthritic knees with a separate control group. As far we know, this is the first study that investigates the correlation between adiponectin hormone levels and all clinical, laboratory and radiological evidence of severity of OA with a group design that allows determining hormone levels in patients with a relatively low mechanical loading.

In obese people plasma adiponectin concentrations are lower than the normal population. Also, plasma adiponectin levels are inversely related to BMI and directly related to age.[27] In our study, while the control group has an inverse correlation between adiponectin levels and BMI; both patient subgroups have shown no correlation between these two parameters. This may be explained by the fact that arthritis itself would increase adiponectin levels, ending with the loss of correlation in patient subgroups.

The exact mechanism which involves adiponectin in the pathophysiology of OA still remains unknown. Previous studies have shown positive correlation between serum levels of cartilage oligomeric matrix protein (COMP), matrix metalloproteinase-3 (MMP-3) and adiponectin hormone.[18] There are also studies that showed the catabolic effect of adiponectin on cartilage by increasing expression of interleukin (IL)-6 and nitric oxide synthase 2.[19–21] Recently, a study performed by Chen *et al.* showed an increment of intracellular adhesion molecule-1 (ICAM-1) production with adiponectin leading to adhesion of monocytes in osteoarthritic synovial fluid.[22] In contrast, there is evidence that adiponectin may have a protective role on cartilage by increasing the level of tissue inhibitor of metalloproteinase-2 (TIMP-2) and reducing MMP-13.[28] Also, the studies searching for the association between adipo-

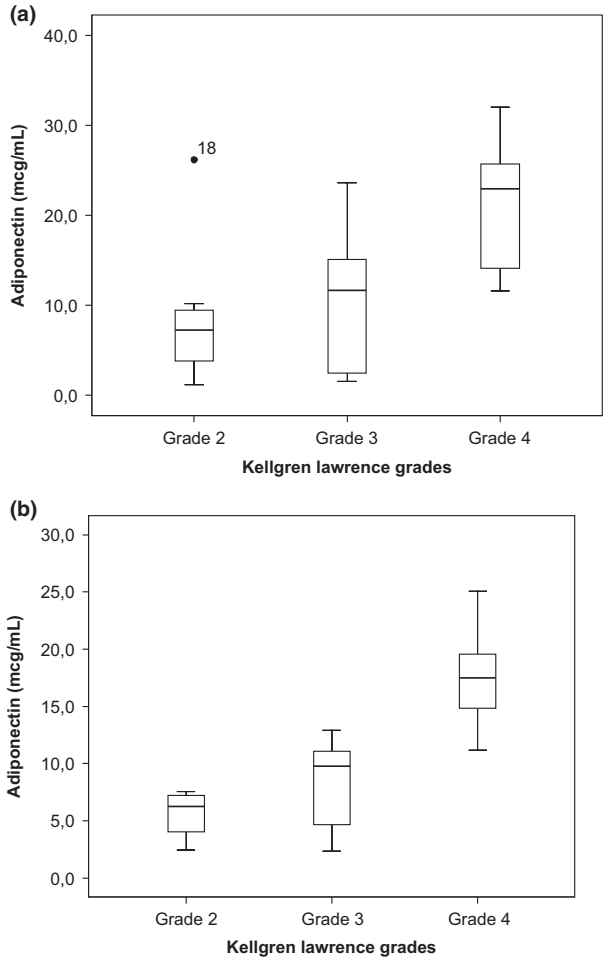

Figure 1 (a) Adiponectin level comparison between Kellgren–Lawrence (KL) grades (Group 1); (b) adiponectin level comparison between KL grades (Group 2).

nectin, ESR and CRP are in conflict with each other. In one study, lower adiponectin levels were associated with higher levels of CRP in obese women.[29] Also, increased adiponectin levels were correlated with ESR and RF in Chen's study in rheumatoid arthritis (RA) patients. However, in the study of Senolt *et al.*,[30] no correlation was observed between circulating adiponectin and ESR, CRP in both RA and OA patients. Similar to the latter study, we were not able to find any relation between adiponectin, ESR, CRP and RF levels.

Synovial fluid adiponectin levels and pain were correlated positively in OA patients in the study of Gandhi *et al.*[31] In contrast, Massangale *et al.* found no correlation between adiponectin and chronic pain in OA patients.[32] In our study, pain assessment showed weak correlation with adiponectin levels in the lean patient subgroup. Pain is a complex mechanism in which many factors play a role. The pain in knee OA is believed to originate from inflammation in synovium, tensing of nerve endings, ligaments and joint capsule by osteophytes and deformations in subchondral bone.[33] For these reasons, pain assessment cannot be directly correlated to a single hormone or mechanism in OA. However, in our study, adiponectin levels were weakly correlated with pain in lean patients whose biomechanical loading were relatively low. These results must be noteworthy in terms of its role in inflammatory pathways.

Higher adiponectin levels were associated with higher WOMAC scores (which indicate worse pain, stiffness, and functional limitations) in the present study with a weak correlation. Also, SF-36 subscores were inversely correlated with circulating adiponectin levels. According to our literature search, there is only one study which investigated the association between adiponectin and WOMAC pain score, which failed to show any correlation between these two parameters.[32] As far we know, the association between quality of life and adiponectin levels has not been studied. Quality of life may be affected by many conditions, such as pain, disease activity and presence of comorbidities, for which we were not able to control at a time. Even if the negative correlation between adiponectin levels and health quality indexes can not be directly linked to catabolic effect of adiponectin; these findings may support a relation between disease severity and adiponectin levels when considered with radiological deterioration.

In our study radiological severity graded by KL scale was positively correlated with adiponectin concentrations in both patient subgroups. Likewise, higher adiponectin concentrations were seen in erosive hand OA patients compared to non-erosive hand OA in the study by Filkova *et al.*[34] Also, Giles *et al.* observed a weak positive correlation between radiographic deterioration and plasma levels of adiponectin in RA patients.[35] In contrast, recently some studies have shown inverse or no correlation between plasma adiponectin levels and radiological disease severity.[15] Also Yusuf *et al.* found a negative correlation between hand OA progression and adiponectin values.[14] The controversy among all these studies may be due to the differences in patient populations, study protocols, radiological grading scales and involved joint regions.

According to the pairwise comparisons of each KL grade by adiponectin levels, we observed a statistically significant difference between KL grade 4 and the other KL grades. There was no statistically significant

difference between KL grades 2 and 3 in both patient groups. Our findings were supported by the studies of Giles *et al.*,[35] Filkova *et al.*,[34] Koskinen *et al.*[18] and Olcyzk-Wrochna *et al.*[13] in which higher plasma concentrations of adiponectin were associated with later stages of OA. Also Boer *et al.* found higher adiponectin levels in OA patients with severe radiological findings compared to a control group.[36] By means of the results of all these studies, we can conclude that the contribution of adiponectin hormone to etiopathology may be more prominent in the later stages of disease than the earlier stages.

Plasma adiponectin levels were higher in both patient groups compared to the control group in the current study. However, the difference did not reach statistical significance after the adjustments for gender, BMI and age. Similar to our results, Honsawek *et al.* observed higher concentrations of adiponectin hormone levels in OA patients when compared with the control group without a statistically significant difference.[12] Additionally, the studies of Boer *et al.*[36] and Laurberg *et al.*[37] showed higher hormone levels in OA patient groups compared to controls with significant difference. According to the results of aforementioned studies, including ours, adiponectin hormone has higher plasma concentrations in OA patients when compared with healthy controls. However, further studies with more homogenous groups and with a better control of covariates should be performed for more accurate results.

Our study has some limitations. First, our control group was relatively young and male-dominant. Thus, the results of intergroup analysis were gender-dependent. Second, we did not measure the low and high molecular weight oligomeric forms of adiponectin hormone separately, which were thought to have different pathophysiological mechanisms in OA. Lastly, by calculating only BMI, visceral adipose tissue from which adiponectin can be secreted might have been overlooked. However, the observation of high adiponectin levels in both patient groups and marked increase of hormone levels in later stages of the disease support the additional role of adiponectin in the disease process.

CONCLUSION

According to the results of our study, we observed higher levels of circulating adiponectin hormone in particularly later stages of OA in lean patients as well as obese patients. Also, adiponectin hormone levels were positively correlated with clinical and radiological disease severity. Further studies investigating hormone levels throughout the disease course of OA would provide a better insight about the potential clinical usefulness of adiponectin hormone.

ACKNOWLEDGEMENT

This study was funded by Turkish League Against Rheumatism (TLAR).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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