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Original Article

The relationship of serum adiponectin and leptin levels with pain, function and intervertebral disc degeneration in patients with chronic low back pain

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ABSTRACT

Objectives: The aim of this study was to investigate the relationship between serum adiponectin and leptin levels, which are cytokines released from fatty tissue, and pain, function and intervertebral disc degeneration (IVDD).

Patients and methods: Between January 2018 and November 2019, a total of 85 patients (34 males, 51 females; mean age: 42.1±10.7 years; range, 18 to 62 years) who were diagnosed with IVDD and 84 healthy volunteers (34 males, 50 females; mean age: 41.9±10.7 years; range, 22 to 64 years) were included in this cross-sectional study. The Visual Analog Scale (VAS, 0-10 cm) and Oswestry Disability Index (ODI) scales were used in the patient group. Serum adiponectin and leptin levels were measured in all participants. The grading of IVDD was determined using the Pfirrmann Classification.

Results: There was no significant difference in serum adiponectin (p=0.35) and leptin (p=0.19) levels between the patient group and the control group. No relationship was found between serum adiponectin and leptin levels and pain intensity (VAS), pain duration, and disability (ODI) in patients with low back pain. No relationship was found between the severity of IVDD as evidenced by magnetic resonance imaging (MRI) and adiponectin (p=0.18) and leptin (p=0.11) levels. There was a positive correlation between the severity of disc degeneration and body mass index (r=0.35, p=0.008) and waist circumference (r=0.34, p=0.01).

Conclusion: Serum adipokine levels were not associated with low back pain symptoms and IVDD severity as evidenced by MRI. These findings suggest that the effects of obesity on chronic low back pain and disc degeneration cannot be explained by systemic inflammatory effects alone.

Keywords: Adiponectin, chronic low back pain, intervertebral disc degeneration, leptin, obesity.

Low back pain (LBP) is defined as pain confined between the 12th rib and the inferior gluteal fold, with or without leg pain. Low back pain is now the leading cause of disability worldwide, despite the huge healthcare expenditure devoted to this area worldwide.[1] Intervertebral disc degeneration (IVDD) is one of the most important causes of LBP. Overweight and obesity are among the causes of IVDD.[2] It has been suggested that the effect of obesity on LBP may be related to some molecules secreted from adipose tissue, as well as mechanical loading.[3] Studies have shown that some mediators associated with adipose tissue contribute to joint degeneration. Adipose tissue is an endocrine organ that secretes many bioactive molecules called adipokines.[4,5] Adiponectin and leptin are adipokines secreted from adipose tissue, which have been found to be involved in inflammatory processes. It has been reported that adiponectin plays a role in physiological and pathophysiological processes in bone and cartilage diseases.[6-8] It has also been shown that leptin plays a role in the reorganization of nucleus pulposus (NP) and causes changes in the disc structure.[9]

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Many studies have demonstrated the presence of low-level systemic inflammation in patients with LBP.[3,10,11] There are conflicting results in the literature regarding the effects of serum adiponectin, leptin and other adipokine levels on pain and function in chronic LBP.[2,12-14] It is still unclear whether circulating cytokines cause degenerative changes and pain in the intervertebral disc (IVD) or whether elevated cytokine levels are a result of IVDD and painful condition.

The high prevalence of IVDD among asymptomatic individuals leads to questioning the clinical significance of this condition in patients with LBP. However, the severity of degeneration is correlated with the severity of LBP.[15] Therefore, studies on disc degeneration are clinically important to identify risk factors for preventive measures.

In the present study, the primary objective was to compare serum adiponectin and leptin levels in patients with chronic LBP with a healthy control group, and to investigate the relationship between serum adiponectin and leptin levels and pain, function and IVDD. By examining the relationship between obesity-related anthropometric measurements and serum adipokine levels, the secondary objective was to investigate the effects of obesity on serum cytokine levels and its relationship with chronic LBP and disc degeneration.

PATIENTS AND METHODS

Study design and subjects

This cross-sectional, case-control study was conducted at Ankara University Faculty of Medicine, Department of Physical Medicine and Rehabilitation (PMR) between January 2018 and November 2019. Patients who were admitted with chronic LBP lasting longer than three months were screened. A total of 85 patients (34 males, 51 females; mean age: 42.1±10.7 years; range, 18 to 62 years) and 84 healthy volunteers (34 males, 50 females; mean age: 41.9±10.7 years; range, 22 to 64 years) were included in the study. Patients with magnetic resonance imaging (MRI) or computed tomography (CT) findings supporting degenerative disc disease within the last six months and normal complete blood count, biochemistry, erythrocyte sedimentation rate, and C-reactive protein (CRP) values were included in the chronic LBP group. Cardiovascular disease (New York Heart Association [NYHA] Class III-IV), chronic kidney disease, chronic liver disease, presence of active inflammatory or infectious systemic disease, pregnancy, diagnosis of diffuse pain syndrome (fibromyalgia, myalgia, chronic pain syndrome), presence of malignancy and patients who underwent lumbar surgery within the last three months were excluded. A written informed consent was obtained from each participants. The study protocol was approved by the Ankara University Faculty of Medicine Clinical Research Ethics Committee (date: 28.01.2018, no: 02-62-18). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Demographic and clinical characteristics

Sociodemographic data (age, sex, education, occupation, comorbidities, medications) and pain duration of the patients were recorded. Physical examination of the patients was performed. The CT and MRI images of the chronic LBP group, which were taken for diagnosis within the last six months, were evaluated for the presence of disc degeneration. Body weight (kg), height (m), body mass index (BMI) (kg/m^2), waist circumference (cm), hip circumference (cm) and waist/hip ratio measurements of all participants included in the study were recorded.

Questionnaires

The Visual Analog Scale (VAS) was used for pain assessment. The VAS consists of a 10 cm line, with two end points representing 0 (no pain) and 10 (pain as bad as it could possibly be). Functional status assessment was performed using the Oswestry Low Back Disability Index (ODI) version 2.0.[16] The validity and reliability studies of the Turkish version of the ODI were conducted by Yakut et al.[17]

Biochemical analysis

Blood samples of all participants were taken from the antecubital vein as 5 mL between 8.00 and 10.00 A.M. after an average of 8 to 10 h of fasting during the evaluation. The blood samples were centrifuged at 3,600 rpm for 5 min in the Heraeus brand centrifuge device (Heraeus Labofuge Centrifuge, Thermo Scientific, Germany) After centrifugation, the serum portion was separated and stored in a Haier brand freezer (Haier DW-86L628-86 Ultra, Haier, Qingdao, China) at –80 degrees. Samples and reagents were brought to room temperature and vortexed on the day of use, then pipetted and included in the study. Hemolyzed samples were not used.

Adiponectin was studied in human serum with BioVendor kits (BioVendor RD191023100, Brno-Řečkovice a Mokrá Hora, Czech Rebuplic)

using enzyme-linked immunosorbent assay (ELISA) method. Concentrations of the samples were calculated as µg/mL using the standard graph. Of note, 0.47 µg/mL is the lowest value that the kit can detect. The intra-assay coefficient of variation of the adiponectin kit was 4.4% and the inter-assay coefficient of variation was 5.8%.

Leptin was studied in human serum using the ELISA method with Diasource brand kits (DiaSource KAP2281, Louvain-la-Neuve, Belgium). The reference range of leptin specified in the package insert varies according to age and sex. The concentrations of the samples were calculated as ng/mL by using the standard chart. Of note, 0.04 ng/mL is the lowest value that the kit can detect. The intra-assay coefficient of variation of the leptin kit is 10% and the inter-assay coefficient of variation is 12.7%.

Adiponectin and leptin levels were analyzed and interpreted by the Department of Biochemistry Faculty Members.

Radiological evaluation

Eighty-five patients with disc degeneration detected by CT or MRI were included in the study. However, since it was aimed to use the Pfirrmann Classification to determine the severity of IVDD, 57 patients with MRI images were evaluated for the Pfirrmann Classification. In this classification, rating system is based on signal intensity, disc structure, distinction between NP and annulus fibrosus (AF), and disc height on MRI.[18] This evaluation was made by a PMR resident and the senior professor. First, each case was evaluated separately. Then, the results of all cases were reviewed together. For those who were different, the shared decision was recorded. The score sums of disc degeneration degrees obtained from five lumbar levels in each patient were determined based on the study by Takatalo et al.[19] In line with the scores given, six groups (0,1,2,3,4,5 points) were formed.

Statistical analysis

Using power analysis, the number of participants in the chronic LBP and healthy control groups was determined. Sample size calculation was made using R version 3.2.3 (2015-12-10) (R Foundation for Statistical Computing, Vienna, Austria). The power analysis parameters used to determine the number of participants were as follows: n1=85, n2=84, d=0.5 (effect size 0.5 medium, [conventional effect size from Cohen 1982]), significance level=0.05, power=0.8981773, alternative=two sided. Study groups were formed by simple random sampling method, considering the percentage that all participants had an equal chance of participating in the study.

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were presented in mean ± standard deviation (SD), median (min-max) or number (n) and frequency (%), where applicable. Normality assumption was evaluated using the Shapiro-Wilk test and homogeneity was evaluated using the Levene test. For continuous variables, whether the differences between the groups were statistically significant was tested with the Independent sample t-test if the number of groups was two (patient group-control group, female-male, etc.) in cases where normal distribution was achieved. In cases where there is a deviation from the normal distribution, it was tested with the non-parametric Mann-Whitney U test. Whether there was a statistically significant relationship between continuous variables was determined by Spearman rho correlation. A p value of <0.05 was considered statistically significant.

TABLE 1
Comparisons of patient and control groups in terms of anthropometric measurement values

	Patient group (n=85)			Control group (n=84)			
	Mean±SD	Min-Max	95% CI	Mean±SD	Min-Max	95% CI	p†
Height (cm)	165.9±9.3	143-191	163.9-167.9	166.4±9.5	148-187	164.4-168.5	0.71
Body weight (kg)	75.5±11.4	53.5-104	73.0-77.9	74.6±12.6	45-108	71.9-77.4	0.65
Body mass index (kg/m^2)	27.4±4.2	19.1-40.7	26.6-28.4	26.9±3.8	20.0-35.5	26.1-27.7	0.37
Waist circumference (cm)	90.0±9.6	72 -113	87.9-92.0	90.2±9.8	70-115	88.1-92.3	0.90
Waist/hip ratio	0.8±0.1	0.7-1.1	0.8-0.9	0.9±0.1	0.7-1.0	0.8-0.9	0.36

CI: Confidence interval; SD: Standard deviation; † Mann Whitney U, statistically significant p<0.05.

RESULTS

There was no statistically significant difference between the patient and control groups in terms of anthropometric characteristics (Table 1).

The mean VAS (0-10 cm) of the patients was 5.6±1.9, pain duration (month) was 57.3±69.8, and ODI (0-100) was 33.8±15.8, respectively.

In the patient group, a low positive correlation was found between pain duration and body weight (r=0.23, p=0.03) and waist circumference (r=0.24, p=0.03). A moderate positive correlation was found between pain duration and BMI (r=0.36, p=0.01) (Table 2).

There was no statistically significant difference in serum adiponectin and serum leptin values between the patient and control groups (Table 3).

In the patient group, serum adiponectin and leptin levels were not statistically significantly correlated with pain severity, pain duration, and ODI scores (Table 4).

The relationship between anthropometric measurements and serum adiponectin and leptin levels in the patient group is presented in Table 5. A low positive correlation was found between leptin and body weight (r=0.25, p=0.02) and waist circumference (r=0.29, p=0.01), and a moderate positive correlation was found between leptin and BMI (r=0.48, p<0.001). However, a low negative correlation was found between waist/hip ratio and serum adiponectin levels (r=0.24, p=0.03).

Lumbar IVDD severity of the patients was determined using the Pfirrmann Classification. Of the 57 patients whose MRI findings were obtained, three

TABLE 2
The relationship of patient group anthropometric measurement values with VAS, pain duration and ODI

	VAS (0-10 cm) (n=85)		Pain duration (month) (n=85)		ODI (0-100) (n=85)	
	rho	*p*†	rho	*p*†	rho	*p*†
Height (cm)	−0.14	0.19	−0.20	0.07	−0.29	0.01
Body weight (kg)	−0.20	0.07	0.23	0.03	−0.07	0.52
BMI (kg/m^2)	−0.06	0.58	0.36	0.01	0.20	0.07
Waist circumference (cm)	−0.12	0.26	0.24	0.03	0.06	0.60
Waist/hip ratio	−0.07	0.50	0.08	0.45	0.01	0.97

VAS: Visual Analog Scale; ODI: Oswestry Disability Index; BMI: Body mass index; † Spearman correlation analysis, statistically significant p<0.05.

TABLE 3
Comparison of patient and control groups in terms of serum adiponectin and serum leptin values

	Patient group					Control group					
	n	Mean±SD	Median	Min-Max	95% CI	n	Mean±SD	Median	Min-Max	95% CI	*p*†
Serum adiponectin (µg /mL)	85	7.52±2.65	6.86	1.62-15.06	6.95-8.10	84	8.26±3.60	7.57	2.74-17.56	7.48-9.04	0.35
Serum leptin (ng/mL)	85	3.97±4.57	2.07	0.004-19.57	2.98-4.96	84	4.78±5.26	2.61	0.020-25.40	3.64-5.92	0.19

SD: Standard deviation; † Mann Whitney U, statistically significant p<0.05.

TABLE 4
The relationship of serum adiponectin and leptin levels in the patient group with VAS, pain duration and ODI values

	VAS (0-10 cm)		Pain duration (month)		ODI (0-100)		
	n	rho	*p*†	rho	*p*†	rho	*p*†
Serum adiponectin (µg /mL)	85	0.04	0.69	−0.10	0.35	0.16	0.14
Serum leptin (ng/ mL)	85	−0.03	0.82	0.14	0.20	0.04	0.69

VAS: Visual Analog Scale; ODI: Oswestry Disability Index; † Spearman correlation analysis, statistically significant p<0.05.

TABLE 5
Relationship between anthropometric measurement values and serum adiponectin and leptin levels in the patient group

	Serum adiponectin (µg/L) (n=85)		Serum leptin (ng/mL) (n=85)	
	rho	*p*†	rho	*p*†
Height (cm)	−0.29	0.01	−0.33	<0.001
Body weight (kg)	−0.15	0.16	0.25	0.02
Body mass index (kg/m^2)	−0.06	0.58	0.48	<0.001
Waist circumference (cm)	−0.13	0.22	0.29	0.01
Waist/hip ratio	−0.24	0.03	−0.09	0.42

† Spearman correlation analysis, statistically significant p<0.05.

(5.3%) received 0 points, eight (14.0%) scored 1 point, 17 (29.8%) scored 2 points, 12 (21.1%) scored 3 points, seven (8.2%) scored 4 points, and 10 (17.5%) scored 5 points. The relationship of these groups with all other measurements (anthropometric measurements, VAS, pain duration, ODI, serum adiponectin, serum leptin) was evaluated. Accordingly, there was a moderate positive correlation between the severity of disc degeneration and BMI (r=0.35, p=0.008), a moderate positive correlation between the severity of disc degeneration and waist circumference (r=0.34, p=0.01) and a low positive correlation between the severity of disc degeneration and ODI (r=0.28, p=0.04). However, no significant relationship was found between disc degeneration severity and adiponectin (r=0.12, p=0.39) and leptin (r=0.16, p=0.24) values.

DISCUSSION

In the present study, we primarily compared serum adiponectin and leptin levels in patients with chronic LBP with a healthy control group, and investigated the relationship between serum adiponectin and leptin levels and pain, function and disc degeneration. Secondly, we investigated the effects of obesity on serum cytokine levels and its relationship with chronic LBP and disc degeneration. Our study results showed that there was no significant relationship between the serum adiponectin and leptin levels of patients with chronic LBP and IVDD, and pain severity, pain duration, and loss of function. However, anthropometric measurements were found to have some relationship with serum adiponectin and leptin levels, pain duration and severity of disc degeneration.

Intervertebral disc degeneration is one of the most important causes of LBP. Although some histopathological stages of IVDD have been identified, its etiology and underlying mechanisms have not been clearly elucidated yet. Obesity contributes to IVDD by changing mechanical loading and biomechanical properties of the spine. Joints, such as the hand, are not mechanically affected by body weight. However, degenerative changes in the hand joints have been shown to be more common in obese or overweight individuals.[20] In some studies, it was found that high levels of inflammatory cytokines and catabolic mediators were isolated from degenerative discs.[21,22]

Adipokines secreted by white adipose tissue, such as adiponectin and leptin, are associated with low-grade inflammation, extracellular matrix disruption, and fibrosis.[23] Studies have shown that adiponectin and leptin play a role in IVDD. Khabour et al.[12] found higher levels of adiponectin in the circulation of patients with lumbar disc degeneration compared to healthy controls. On the contrary, Yuan et al.[13] reported decreased expression of adiponectin in degenerated human IVD NP cells compared to healthy NP tissues. In addition, a negative correlation was found between adiponectin levels and IVDD severity. Similarly, the relationship between leptin and LBP is controversial.[24-28] Lippi et al.[24] showed that serum leptin levels in patients with LBP were lower than in healthy individuals. On the contrary, Shiri et al.[25] reported that high serum leptin levels were associated with LBP. In addition, Segar et al.[26] showed that the addition of leptin to the inflammatory disc environment has a deleterious synergistic effect by increasing NO, matrix metalloproteinase (MMP) production and pro-inflammatory cytokine production.

In the current study, we observed no statistically significant difference in serum adiponectin and

leptin values between the patient and control groups. In addition, there was no statistically significant relationship between adiponectin and leptin levels in the patient group and VAS (pain intensity), pain duration, ODI and IVDD levels as evidenced by MRI.

Studies on osteoarthritic joints show that local leptin concentrations may be significantly higher than those detected in serum.[29] Similarly, adipokine levels in the IVD may be higher than in serum. Since the relationship between LBP and loss of function with serum adipokine levels was examined in our study, study samples were obtained by taking peripheral venous blood and IVD tissue analysis was not performed. Local adipokine concentrations may originate predominantly from adipokine-producing IVD cells and adipose tissue adjacent to the disc. These adipokines may cause degeneration of adjacent disc cells with local paracrine effect. However, as IVD is an avascular tissue, serum adipokine concentration may be weakly correlated with adipokine levels in IVD tissue. Since serum adipokines levels were studied in this study, changes in adipokine expression at the IVD tissue level may not have been detected in the peripheral blood circulation, or the effects of adipocytokine levels in the peripheral blood circulation on IVDD may be limited.

In the current study, a positive correlation was found between body weight, BMI, waist circumference and leptin, while a negative correlation was found between waist/hip ratio, and serum adiponectin. The relationship between adipokines and anthropometric measurements, which we found in our study, is similar to the studies in the literature.[30,31] A positive correlation was found between pain duration and body weight, BMI and waist circumference in the patient group. Additionally, there was a positive correlation between IVDD severity as assessed by MRI and waist circumference and BMI. These findings indicate that the effects of obesity on chronic LBP and disc degeneration cannot be directly explained by its systemic inflammatory effects. Various factors such as obesity-related spinal biomechanical changes, endothelial inflammation (atherosclerosis, etc.) and local inflammation in the disc tissue can cause LBP.

This study has some strengths. The number of subjects was determined by power analysis. There are limited studies in the literature investigating the relationship between adipokine and IVDD.[32] Studies in the literature mostly focused on *in vitro* IVD tissue examination, but adequate evaluation was not made in terms of the clinical correlation of adipocytokines. In our study, the severity of IVDD was determined by MRI and its correlation with the clinical status of the patients was evaluated. In addition, the patient and control groups were equalized in terms of BMI. In this way, the possible misleading effect of obesity on serum cytokine levels was eliminated and the relationship between IVDD and serum cytokine levels could be accurately evaluated.

On the other hand, the main limitation to our study is its cross-sectional design. Therefore, the effect of participants' serum adipokine levels on the onset and progression of LBP is unknown.

In conclusion, serum leptin and adiponectin levels were not associated with LBP symptoms and IVDD severity as evidenced by MRI. However, obesity-related anthropometric measurements were associated with the duration of pain and the severity of disc degeneration. These findings suggest that the diagnostic value of systemic adipokine levels in LBP is limited. We believe that the effects of obesity on chronic LBP and disc degeneration are not related to systemic adipokine levels. Finally, although the inflammatory processes in the etiology of LBP are important in terms of creating pharmacological intervention opportunities, it should be considered that LBP is a multi-etiology, multifactorial disease.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Concept, design, literature search, writing manuscript, critical review: N.D.T., B.S.T.; Supervision: B.S.T.; Resources, materials, data collection and/or processing, analysis and/or interpretation: N.D.T., B.S.T., B.İ.E., M.D.

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