The association between clinically suspect arthralgia and adipokines in obese patients

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ABSTRACT

Objective: Obesity is a moderate low-grade chronic inflammatory condition. The cause of low-grade inflammation in obese patients who have clinically suspect arthralgia (CSA) may be the subject of debate in clinical practice. Our aim is to determine whether inflammation is associated with obesity or rheumatic disease, and the association between leptin, chemerin, visfatin and inflammatory markers in obese patients with/without musculoskeletal symptoms.

Methods: Seventy-four obese patients who admitted to our rheumatology clinic with CSA were enrolled. The control group consisted of 40 obese patients who have no rheumatic symptoms. Body mass index (BMI) was calculated in kg/m^2 with body weight ratio to height squared, and obesity was defined as BMI 30 or above. Age, gender, BMI, waist and hip circumferences, waist-to-hip ratio (WHR), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), leptin, chemerin, and visfatin were evaluated. The relationship between all parameters was assessed by Spearman correlation, Wilcoxon Signed--rank, and paired t-tests.

Results: There were no significant differences for age, gender, ESR and CRP between obese patients with CSA and control group. The mean TNF-α, IL-1β, IL-6 concentrations were 60.8 pg/mL, 39.9 pg/ml, and 26.2% in obese patients with CSA, respectively. ESR, CRP, TNF-α, IL-6, and IL-1β concentrations were higher in these patients compared to obese patients without any rheumatic symptoms. The mean WHR and waist circumference were 0.8±0.1 and 107.1±13.4 cm, respectively in patients with CSA. IL-6 correlated with WHR and waist circumference, positively. There were significant differences for adipokines such as chemerin, visfatin, but not for leptin between both group. Moreover, a significant correlation was found between pro-inflammatory cytokines and visfatin, chemerin.

Conclusion: Visfatin and chemerin correlated with inflammation and may be useful indicators of undifferentiated inflammatory arthritis in obese patients with CSA.

Keywords: Obesity; Adipokines; Rheumatic disease; Clinically suspect arthralgia

INTRODUCTION

Obesity is a global health problem that has increased prevalence in the last 50 years over worldwide. The World Health Organization defined overweight and obesity as abnormal or excessive fat accumulation that may impair health[1]. Obesity has been proven to be a major risk factor associated with type 2 diabetes mellitus, cardiovascular diseases, cancers, and musculoskeletal diseases[2-4]. Obesity and overweight have also been shown to be a risk factor associated with inflammatory rheumatic diseases, seronegative inflammatory polyarthritis, and psoriatic arthritis[5,6]. Arthritis may not be present in patients with clinically suspicious arthralgia (CSA). These patients constitute only 7% of all arthralgia patients who applied to the rheumatology clinics[7]. European League Against Rheumatism (EULAR) defined parameters for patients with arthralgia without clinical arthritis and other explanation for the arthralgia[7]. In this situation, acute phase reactants (APR) may help to the clinicians for distinguishing arthralgia and arthritis. However, in case there are some confounder factors that affect APRs such as obesity, age etc., it may limit the use of APRs.

Acute phase response includes metabolic, endocrinological, neurological and immunological reactions. Acute phase proteins are mostly released from the liver

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and are stimulated mainly by cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) in acute or chronic inflammatory conditions[8]. Proinflammatory cytokines are major stimulators of APR and the increase of these cytokines in obese adipose tissue has been reported[9,10].

Obesity is a moderate low-grade chronic inflammatory condition. The function of adipose tissue in obesity becomes pathological and the altered release and expression of cytokines shift in the proinflammatory direction[11]. Many cytokines such as TNF-α, IL-6, IL-1β, IL-8, and adipokines such as chemerin, leptin, and visfatin are released from adipose tissue. In recent years, adipokines have been thought to play a role in the development and progression of rheumatic diseases and may be used as a biomarker or even a therapeutic target[12-14].

According to adipose tissue distribution, two types of obesity are mentioned. In the case of fat accumulation mainly around the trunk and abdomen, is named abdominal or central obesity while in the hip or lower extremities is named gynecoid obesity[15]. Central obesity has more risk for many chronic diseases than gynecoid obesity. Body Mass Index (BMI) is a method of predicting increasing total body fat mass, however, does not reflect the proportion of body adipose tissue distribution. In the evaluation of obesity, different anthropometric measurements such as waist circumference, waist-to-hip ratio (WHR), waist-to-height ratio were developed beside BMI. It has been shown that the waist circumference is most sensitive for abdominal adipose tissue mass among these measurements[16]. Despite the wide variety of measurement techniques for waist circumference reported in the literature, there is no consistent evidence of the superiority of a measurement field over others for assessment and measurement[17].

The aim of the study is to determine whether inflammation in obese patients is associated with obesity or any underlying inflammatory rheumatic disease. Also, we evaluate the association between leptin, chemerin, visfatin and inflammatory markers in obese patients with/without CSA.

MATERIALS AND METHODS

Seventy-four obese patients with CSA (4 male, 70 female, with the mean age of 47.09±10.7 years) who admitted to rheumatology clinic between March 2017 and January 2018 were enrolled. The control group consisted of 40 obese patients (5 male, 35 female, with the mean age of 44.9±10 years) who admitted to endocrinology and metabolism clinic without any rheumatic symptoms.

We excluded patients who fulfilled classification criteria for any rheumatic diseases, disorders of the thyroid and parathyroid, soft tissue rheumatism like fibromyalgia, electrolyte imbalance, malignancies, infections, and patients with gynecoid obesity. There was no medical history about using any drugs such as non-steroidal anti-inflammatory drug or statins regularly in the population included in the study. Age, gender, BMI, waist and hip circumferences, WHR, acute-phase reactants (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]), serology (anti-cyclic citrullinated peptide [anti-CCP], rheumatoid factor [RF], antinuclear antibodies [ANA]) as well as IL-1β, TNF-α, IL-6, leptin, visfatin, and chemerin serum levels were evaluated. BMI clinically approximates body fat percentage and was calculated in kg/m^2 with body weight ratio to height squared, and the obesity was defined as BMI 30 or above[1,15]. Waist circumference was measured at the level of the superior iliac crest and hip circumference from the widest part of the pelvis. WHR was obtained by calculating the ratio of the waist circumference to hip circumference[18]. The cut-off levels of waist circumference for visceral obesity were defined as 100 cm in males and 90 cm in females, respectively[16].

Blood samples were taken in gell tubes used in routine biochemical tests, centrifuged at 4000 g for 10 minutes. After centrifugation, each sample was separated into two Eppendorf tubes and stored in deep freeze (-85 °C) until experiments were performed. In sera, adipokine levels determined via commercial human ELISA kit (Elabscience Biotechnology Co., Lt), and test results were calculated by Bioelisa Reader Elx800 using standard curve. The sensitivity of IL-1β and TNF-α were indicated 4.69 pg/mL, and their detection range was 7.81-500 pg/mL. The calculated overall intra-assay coefficient of variation for IL-6 was given as 3.4-5.2%. The sensitivity of leptin, chemerin and visfatin were indicated as 46.88 pg/mL, 0.1 ng/mL, and 0.19 ng/mL, respectively. The detection range of these adipokines were 78.13-5000 pg/mL, 0.16-10 ng/mL, and 0.31-20 ng/mL, respectively. The normal reference range for ESR and CRP were as follows: 0-20 mm/h and 0-5 mg/dl.

The study protocol was approved by Adnan Men-

deres University Faculty of Medicine Ethics Committee (approval number 2017/1057). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The distribution of normality was examined with the Kolmogorov-Smirnov test. The statistical data were presented as the number, percentage, mean±standard deviation, and median (minimum-maximum). Wilcoxon test and Mann Whitney U test were used for non-parametric tests for variables without normal distribution. If the variables were in normal distribution, student t-test and paired t-test were used to evaluate the parameters. The correlation between the parameters was assessed by Spearman and Pearson correlation coefficient. The value of r 0.0-0.19 was accepted as very weak, 0.2-0.39 as weak, 0.4-0.59 as moderate, 0.6--0.79 as strong, and 0.80-1.0 as very strong. The Statistical Package for Social Sciences version 17.0 (SPSS for Windows Inc., Chicago, IL, USA) was used to analyze the data. $p<0.05$ was accepted as statistically significant.

RESULTS

One hundred and fourteen obese patients were included in the study. Most of the patients were female, with the mean age of 46.7±11.1 years. The mean age of obese patients with CSA was 47.09±10.7 years. The control group consisted of 40 obese patients without any rheumatic symptoms and the mean age was 44.9±10 years. The mean BMI was 37.6±7.2 kg/m^2 for obese patients with CSA. It was 36.9±4.8 kg/m^2 for obese patients without any rheumatic symptoms. There were no significant differences for sex, age, and BMI between both groups. Autoantibodies of the all obese patients included in the study were negative. The demographic and clinical features of the patients are summarized in Table I.

The levels of ESR and CRP were higher in obese patients with CSA compared to control group. The mean ESR levels were 32.9±15.1 mm/h, 27.5±16.1 mm/h, and the median CRP levels were 8.4 mg/dL and 7.6 mg/dL, respectively for both groups. There were no significant differences in acute phase reactants between obese patients with CSA and patients without any rheumatic symptoms.

The median serum TNF-α, IL-1β, IL-6 concentrations were 60.8 pg/mL, 39.9 pg/ml, and 26.2% in obese patients with CSA and significantly higher than the control group. The median serum levels of chemerin and visfatin were found higher in obese patients with CSA ($p<0.001$). There were significant differences for

TABLE I. DEMOGRAPHIC CHARACTERISTICS AND LABORATORY VALUES OF OBESE PATIENTS WITH CLINICALLY SUSPECT ARTHRALGIA AND WITHOUT ANY RHEUMATIC SYMPTOMS

	With clinically suspect artralgia	Without any rheumatic symptoms	p-value
Obese patients (n)	74	40	-
Age (years)	47.09±10,7	44.9±10	NS
Gender (female/male)	70/4	35/5	NS
Body Mass Index (kg/m^2)	37.6±7.2	36.9±4.8	NS
ESR (mm/h)	32.9±15.1	27.5±16.1	NS
CRP (mg/dL)	8.4 [0.1-35.3]	7.9 [1-54.7]	NS
IL-1β (pg/mL)	39.9 [4-347.5]	20.4 [0.7-266.1]	0,04*
IL-6 (%)	26.2 [3.8-350.9]	13.2 [3-63]	0,001*
TNF-α (pg/mL)	60.8 [11.3-301.6]	36.2 [5.6-243.3]	<0,001*
Visfatin (ng/mL)	4.8 [0.2-48.9]	1.5 [0.1-19.5]	<0,001*
Chemerin (ng/mL)	4.2 [0.1-39.5]	1.3 [0.1-20.4]	<0,001*
Leptin (pg/mL)	3460.8±510.9	3285.2±696.6	NS

NS: not significant, [minimum-maximum], ESR: erthyrocyte sedimentation rate, CRP: C-reactive protein, IL-1β: Interleukin-1β, IL-6:Interleukin-6, TNF-α: Tumor necrosis factor-α, *significant difference

chemerin, visfatin, but not for leptin between both group (Table I).

The mean of waist and hip circumferences in patients with CSA were 107.1±13.4 cm and 122.8±14.0 cm, respectively. The mean level of waist circumference was higher in patients with CSA than the control group, but there was no statistical difference between these groups (107.1±13.4 cm vs 106.8±14.6 cm, respectively). We noted a positive moderate correlation between waist circumference and BMI, hip circumference and IL-6, and strong correlation between waist circumference and IL-6. The mean WHR was 0.8±0.1, and WHR moderately correlated with waist circumference and IL-6. Correlations between parameters (waist circumference, WHR, cytokines, adipokines) in patients with CSA are shown in Table II.

In obese patients with CSA, there was a weak correlation between BMI and leptin. When visfatin and chemerin were assessed, there was no correlation between BMI and these adipokines. Also, no correlation was found between BMI and pro-inflammatory cytokines (TNF-α, IL-1β). There was a moderate correlation between BMI and IL-6. But, chemerin and visfatin were correlated with pro-inflammatory cytokines. The correlation between BMI, proinflammatory cytokines, and adipokines of obese patients with CSA are shown in Table III.

TABLE II. CORRELATIONS BETWEEN COMPARED PARAMETERS IN OBESE PATIENTS WITH CLINICALLY SUSPECT ARTHRALGIA

	Waist Circumference (cm)	Waist-to-Hip Ratio
IL-1β (pg/mL)	0.131	0.047
IL-6 (%)	0.751*	0.439*
TNF-α (pg/mL)	0.405	0.041
Visfatin (ng/mL)	0.204	0.017
Chemerin (ng/mL)	0.146	0.068
Leptin (pg/mL)	0.149	0.075

*significant difference, BMI: Body Mass Index, IL-1β: Interleukin-1β, IL-6:Interleukin-6, TNF-α: Tumor necrosis factor-α

DISCUSSION

In our study, the mean ESR and median CRP levels were higher in obese patients with CSA than obese patients without any symptoms. However, there was no statistically significant difference between both groups for acute phase reactants. Proinflammatory cytokines (IL--1β, IL-6, and TNF-α) were significantly higher in patients with CSA. There was no correlation between BMI and proinflammatory cytokines, visfatin, and chemerin except for IL-6 and leptin in obese patients with CSA. Waist circumference correlated only with IL-6. Visfatin and chemerin were significantly higher in obese patients with CSA and correlated with proinflammatory cytokines. Therefore, increased levels of these cytokines may be associated with undifferentiated arthritis rather than obesity-related adipose tissue. Leptin levels were higher in the patient group compared to control group without any significant difference.

As of 2016, more than 1.9 billion adults are overweight and over 650 million of those are obese. The prevalence of overweight and obesity is 39% and 13%, respectively[1]. By gender differences, 23.9% of women were obese and 30.1% were overweight. Recently, the relationship between obesity and rheumatic diseases has been reported[5,6]. However, it may be difficult to distinguish between inflammation of rheumatic diseases and obesity.

In practice, the most commonly used APRs are ESR

TABLE III. CORRELATION BETWEEN BMI, PROINFLAMMATORY CYTOKINES, AND ADIPOKINES IN OBESE PATIENTS WITH CLINICALLY SUSPECT ARTHRALGIA

	BMI (kg/m²)	IL-1β (pg/mL)	IL-6 (%)	TNF-α (pg/mL)
BMI (kg/m²)	1,0	0,14	0,438*	0,025
Leptin (pg/mL)	0,321*	0,092	0,084	0,029
Chemerin (ng/mL)	0,049	0,499*	0,040	0,427*
Visfatin (ng/mL)	0,017	0,402*	0,171	0,550*

*significant difference, BMI: Body Mass Index, IL-1β: Interleukin-1β, IL-6:Interleukin-6, TNF-α: Tumor necrosis factor-α

and CRP. In inflammatory conditions increased fibrinogen and immunoglobulin cause increased ESR, of note, ESR may be affected by physiological conditions such as pregnancy, age, sex, and technical errors[8]. ESR and CRP are used to diagnose and assess the activity of rheumatic diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), spondyloarthritis, vasculitis. However, the activity of the disease does not always correlate with APR[19]. In our study, the inflammation may be associated with undifferentiated arthritis rather than obesity in patients with CSA. ESR and CRP levels were higher in obese patients than the control group, but there was no statistically significant difference between both groups. Therefore, ESR and CRP may not be useful to distinguish suspect arthralgia or arthritis in this group of patients due to the fact that obesity itself is an inflammatory process.

It was shown that IL-6 production increased in omental and subcutaneous adipose tissue in obese subjects and omental adipose tissue secretes 3-fold more IL-6 than subcutaneous adipose tissue[20]. Additionally, it was determined that the source of up to 30% of the systemic IL-6 level was subcutaneous abdominal adipose tissue and IL-6 positively correlated with BMI[20]. Authors also found that TNF-α is not released mainly from subcutaneous fat depot, thus, they speculated that IL-6 levels increases with adiposity and IL-6 may have synergistic role with leptin for regulating energy and lipid metabolism[21]. In our study, there was a moderate positive correlation between BMI and IL-6 ($p<0.05$, $r=0.438$). No correlation was found between IL-1β, TNF-α, and BMI. We believe that IL-6 is strongly associated with visceral adipose tissue and may have metabolic effects as well as proinflammatory effects that stimulate acute phase responses.

In a study investigating immunological mechanisms in overweight RA patients, IL-1β and IL-21 showed a positive correlation with BMI in overweight patients[22]. In a large population-based study, the association with BMI, waist circumference and IL-1β, IL-6, TNF-α, and high sensitive CRP were evaluated. Participants with abdominal obesity had higher levels of IL-6 and TNF-α, also TNF-α levels positively correlated with waist circumference in men, and with BMI in female, on the contrary, no differences were found in IL-1β levels associated with obesity markers, only % body fat negatively associated with IL-1β on multivariate analysis and authors considered it might be related to reduced adipocyte differentiation[23]. When cytokine levels were evaluated with WHR and waist circumference; IL-6 and waist circumference strongly, IL-6 and WHR moderately correlated. Furthermore, a positive correlation was found between waist circumference and BMI, waist circumference and WHR. There was no correlation between IL-1β, TNF-α and waist circumference. WHR is an anthropometric measure of abdominal obesity that seems to have a close correlation with BMI like waist circumference. The ratio was reported as a promising factor to predict cardiometabolic risk, myocardial infarcts, and death events[24]. In clinical practice, waist circumference measure and WHR which reflect visceral adiposity may be more practical than BMI.

Adipokines are a group of peptides that synthesized mostly from adipocytes but also from immunocytes such as macrophages. They have various metabolic and immunological functions and include many hormones such as leptin, adiponectin, visfatin, apelin, vaspin, hepcidin, chemerin, omentin[25]. One of the most important and the most studied among adipokines is leptin, the first discovered adipokine is a non-glycolyse 16 kDa protein and belongs to type 1 cytokine superfamily mainly released from white adipose tissue and positively correlates with BMI[25]. We found a weak correlation between BMI and leptin in patients with CSA. Generally, leptin levels in serum of patients with RA were found higher than in healthy controls[12,13,26]. Nevertheless, it has not been clearly associated with RA pathogenesis and there is still no consensus. Leptin levels were higher in obese patients with CSA than the control group. However, there was no statistically significant difference between both groups. Rho et al. found that serum leptin levels were higher in patients with RA than in the control group and positively correlated with Disease Activity Score-28 (DAS28), CRP, IL-6, and BMI[12]. Targonska *et al.* found a positive correlation between leptin with DAS28, ESR and the number of tender joints[26]. On the other hand, Mirfeizi *et al.* compared plasma leptin and visfatin levels in 29 RA patients who had erosion on radiographic studies and 25 with no erosion and showed leptin correlated positively with BMI, but did not correlate with inflammatory markers and erosive course in RA patients[13]. Also, no correlation was reported between disease activity of RA and serum leptin levels in another study[27]. There was no correlation between leptin and proinflammatory cytokines (IL-1β -IL-6, and TNF-α) in our study. We consider that leptin has no proinflammatory effects, thus it can not be a marker for inflammatory diseases.

Visfatin is synthesized from the liver, bone marrow, skeletal muscle, and white adipose tissue, as well as

produced by many immune system cells and synovial fibroblasts and involved in inflammation[26]. In contrast to leptin, there are controversial results with the association of visfatin and obesity. There are reports of increased visfatin levels in obesity, nevertheless, some have suggested that visfatin is not associated with obesity and BMI[12-14,28]. In Rho *et al.* study, visfatin was significantly higher in RA patients compared to controls, positively correlated with TNF-α, IL-6, CRP, and neutrophil count but not correlated with BMI[12]. In our study, visfatin levels were statistically significantly higher in obese patients with CSA compared to control group. In Mirfeizi *et al.* study, visfatin significantly associated with erosive RA and had a positive correlation with CRP level, but no correlation with BMI[13]. In another study by Sglunda *et al.*, serum visfatin levels of 40 early RA patients were measured both before treatment and three months after starting treatment and compared them with 30 healthy controls aged and gender--matched[14]. Serum visfatin level was significantly higher in untreated patients with early RA, correlated positively with CRP and DAS28 but not with BMI. Furthermore, the decrease in visfatin levels after treatment correlated with the improvement in disease activity, hence, visfatin has been reported to be an independent predictor of disease activity[14]. We found a moderate correlation between visfatin and IL-1β, visfatin, and TNF-α, but no correlation between visfatin and BMI, visfatin and waist circumference. Based on these findings we come to the conclusion that visfatin is a pro-inflammatory molecule, may play an independent role in the pathogenesis of rheumatologic diseases and may be a marker of undifferentiated arthritis.

Chemerin is an 18 kDa peptide released predominantly from the visceral adipose tissue and has both inflammatory and metabolic effects. It has been shown that chemerin and its receptor chemerinR23 are highly expressed in obese adipose tissue and associated with BMI, blood pressure and plasma triglyceride level[29]. Additionally, chemerin and its receptor are excreted by synovial fibroblasts and chemerin has been found to be increased in RA synovium and triggered the release of IL-6, chemokine ligand 2 and matrix metalloproteinase 3 from fibroblast-like synoviocytes[30]. In a study by Ha *et al.*, it was found chemerin levels were significantly higher in RA patients compared to normal subjects and positively correlated with RA disease activity and negatively correlated with BMI[31]. Thus, they suggested chemerin is indicative of systemic inflammation rather than obesity in RA. The median chemerin levels were higher in patients with CSA compared to obese patients without any rheumatic symptoms, in our study. There was no correlation between BMI and chemerin, waist circumference and chemerin, however, significant correlation was found between chemerin and IL-1β, TNF-α in obese patients with CSA (Table III).

The highlights of the study is that adipokines may be used in rheumatology practice in obese patients with CSA in order to distinguish arthritis. We evaluated waist circumference, WHR with adipokines and cytokines in a large population. However, our study has some limitations. We are not able to evaluate non-obese patients with clinically suspect arthralgia and sex-dependent differences due to few male patients.

In conclusion, it may be difficult to distinguish CSA whether it is a non-inflamatuary rheumatic disease or undifferentiated/early arthritis in obese patients. The differential diagnosis is important for management and treatment of the rheumatic diseases. The moderate elevation of ESR and CRP levels leads to confusion, especially in obese patients. Visfatin and chemerin may be biomarkers in order to differentiate inflammatory arthritis in obese patients with CSA, rather than leptin which is more associated with obese adipose tissue.

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REFERENCES

1. World Health Organization. 2017. WHO Fact Files: Ten facts on obesity. Geneva: WHO. Available from: http://www.who.int/features/factfiles/obesity/en
2. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444:860-867.
3. Anandacoomarasamy A, Fransen M, March L. Obesity and the musculoskeletal system. Curr Opin Rheumatol. 2009; 21(1): 71-77.
4. Hu FB. Obesity and Mortality: Watch Your Waist, Not Just Your Weight. Arch Intern Med. 2007; 167(9): 875-876.
5. Gremese E, Tolusso B, Gigante MR, et al. Obesity as a risk and severity factor in rheumatic diseases (autoimmune chronic inflammatory diseases). Front Immunol. 2014; 5: 576.
6. Daïen CI, Sellam J. Obesity and inflammatory arthritis: impact on occurrence, disease characteristics and therapeutic response. RMD Open. 2015; 1: 12.
7. van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJ, et al. EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. Ann Rheum Dis. 2017; 76(3): 491-496.
8. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999; 340(6): 448--454. Review. Erratum in: N Engl J Med 1999; 340(17): 1376.
9. Zeyda M, Farmer D, Todoric J, et al. Human adipose tissue

macrophages are of an anti-inflammatory phenotype but capable of excessive pro-inflammatory mediator production. Int J Obes (Lond). 2007; 31(9): 1420-1428.
10. Mauer J, Chaurasia B, Goldau J, et al. Signaling by IL-6 promotes alternative activation of macrophages to limit endotoxemia and obesity-associated resistance to insulin. Nat Immunol. 2014; 15(5): 423-430.
11. Hauner H. Secretory factors from human adipose tissue and their functional role. Proc Nutr Soc. 2005; 64(2): 163-169.
12. Rho YH, Solus J, Sokka T, et al. Adipocytokines are associated with radiographic joint damage in rheumatoid arthritis. Arthritis Rheum. 2009; 60(7): 1906-1914.
13. Mirfeizi Z, Noubakht Z, Rezaie AE, et al. Plasma levels of leptin and visfatin in rheumatoid arthritis patients; is there any relationship with joint damage? Iran J Basic Med Sci. 2014; 17(9): 662-666.
14. Sglunda O, Mann H, Hulejová H, et al. Decreased circulating visfatin is associated with improved disease activity in early rheumatoid arthritis: data from the PERAC cohort. PLoS One. 2014; 9(7): 103495.
15. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res. 1998; 6 (Suppl 2): 51-209. Review. Erratum in: Obes Res 1998; 6(6): 464.
16. Sonmez A, Bayram F, Barcin C, et al. Waist circumference cut-off points to predict obesity, metabolic syndrome, and cardiovascular risk in Turkish adults. Int J Endocrinol. 2013;2013: 767202.
17. Pinho CPS, Diniz ADS, Arruda IKG, et al. Waist circumference measurement sites and their association with visceral and subcutaneous fat and cardiometabolic abnormalities. Arch Endocrinol Metab. 2018;62(4):416-423.
18. TEMD Obesity, Lipid Metabolism, Hypertension Study Group. Guidelines of obesity Diagnosis and Treatment. Turkey Endocrinology and Metabolism Association. 6th Edition: April 2018. ISBN: 978-605-4011-31-5
19. Keenan RT, Swearingen CJ, Yazici Y. Erythrocyte sedimentation rate and C-reactive protein levels are poorly correlated with clinical measures of disease activity in rheumatoid arthritis, systemic lupus erythematosus and osteoarthritis patients. Clin Exp Rheumatol. 2008; 26(5): 814-819.
20. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab. 1998; 83(3): 847-850.
21. Mohamed-Ali V, Goodrick S, Rawesh A, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J Clin Endocrinol Metab. 1997; 82(12): 4196--4200.
22. Shoda H, Nagafuchi Y, Tsuchida Y, et al. Increased serum concentrations of IL-1 beta, IL-21 and Th17 cells in overweight patients with rheumatoid arthritis. Arthritis Res Ther. 2017; 19(1): 111.
23. Marques-Vidal P, Bochud M, Bastardot F, et al. Association between inflammatory and obesity markers in a Swiss population--based sample (CoLaus Study). Obes Facts. 2012; 5(5): 734--744.
24. Cao Q, Yu S, Xiong W, Li Y, Li H, Li J, Li F. Waist-hip ratio as a predictor of myocardial infarction risk: A systematic review and meta-analysis. Medicine (Baltimore). 2018; 97(30) :11639.
25. Wozniak SE, Gee LL, Wachtel MS, et al. Adipose tissue: the new endocrine organ? A review article. Dig Dis Sci. 2009; 54(9): 1847-1856.
26. Targonska-Stepniak B, Majdan M, Dryglewska M. Leptin serum levels in rheumatoid arthritis patients: relation to disease duration and activity. Rheumatol Int. 2008; 28(6): 585-591.
27. Oner SY, Volkan O, Oner C, et al. Serum leptin levels do not correlate with disease activity in rheumatoid arthritis. Acta Reumatol Port. 2015; 40(1): 50-54.
28. Catalán V, Gómez-Ambrosi J, Rodríguez A, et al. Association of increased visfatin/PBEF/NAMPT circulating concentrations and gene expression levels in peripheral blood cells with lipid metabolism and fatty liver in human morbid obesity. Nutr Metab Cardiovasc Dis. 2011; 21(4): 245-253.
29. Bozaoglu K, Bolton K, McMillan J, et al. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology. 2007; 148(10): 4687-4694.
30. Kaneko K, Miyabe Y, Takayasu A, et al. Chemerin activates fibroblast-like synoviocytes in patients with rheumatoid arthritis. Arthritis Res Ther [Internet]. 2011; 13: 158.
31. Ha YJ, Kang EJ, Song JS, et al. Plasma chemerin levels in rheumatoid arthritis are correlated with disease activity rather than obesity. Joint Bone Spine. 2014; 81(2): 189-190.