The relationship between rheumatoid arthritis and epicardial fat thickness, and serum levels of chemerin, adropin, and betatrophin

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Conflict of interest
None declared

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Abstract

Background. Cardiovascular diseases (CVDs) are highly prevalent among patients with rheumatoid arthritis (RA). Epicardial adipose tissue, serum betatrophin, chemerin, and adropin levels are factors associated with atherosclerosis and cardiovascular involvement.

Objectives. This study aimed to investigate the relationship between RA and epicardial fat thickness (EFT), as well as serum betatrophin, chemerin and adropin levels.

Materials and methods. This cross-sectional study included 80 patients (62 women and 18 men) diagnosed with RA according to the American College of Rheumatology/The European Alliance of Associations for Rheumatology (ACR/EULAR) 2010 RA classification criteria and 80 healthy controls (64 women and 16 men). Exclusion criteria comprised other autoimmune diseases, CVDs, diabetes mellitus, other endocrine disorders, acute or chronic pancreatic disorders, malignancy, pregnancy, breastfeeding, or antihyperlipidemic drug usage. Serum betatrophin, chemerin and adropin concentrations were measured. Epicardial fat thickness was evaluated with transthoracic echocardiography.

Results. Adropin levels were significantly lower in the RA group compared to the control group ($p < 0.001$). Chemerin levels and EFT were significantly higher in the RA group than in the control group ($p = 0.016$, $p < 0.001$, respectively). When assessing the relationship between biomarkers and EFT in RA patients, a strong positive correlation was observed between chemerin and EFT ($r = 0.73$, $p = 0.046$) in patients with high disease activity.

Conclusions. Epicardial fat thickness, as an indicator of cardiovascular involvement, is higher in patients with RA. Moreover, high chemerin levels and low adropin levels in these patients may be indicative of cardiovascular involvement.

Key words: rheumatoid arthritis, chemerin, epicardial fat thickness, betatrophin, adropin

Background

Rheumatoid arthritis (RA) is a degenerative chronic rheumatic disease that affects the small peripheral synovial joints symmetrically, resulting in joint abnormalities and loss of function.[1] According to traditional cardiovascular risk factors, the prevalence of cardiovascular disease (CVD) is higher in RA patients than in the general population.[2] Patients with RA have a limited understanding of the factors associated with their condition that place them at increased risk of CVD.[3] The increased mortality associated with RA is due to severe comorbidities that frequently induce inflammation and are inadequately treated.[4] Numerous studies have demonstrated that RA is associated with a higher risk of death from cardiovascular causes.[5,6]

Up to 80% of the heart's surface is covered with epicardial fat tissue, which is located between the visceral pericardium and myocardium.[7] Visceral adipose tissue plays a significant role in the pathophysiology of coronary artery disease (CAD).[8] This disease may develop due to factors such as epicardial fat tissue being adjacent to the coronary vessels or sharing the same microcirculation as the myocardium, local inflammation or paracrine effects.[9]

Betatrophin (also known as C190RF80, RIFL, ANGPTL8, or lipasin) is a newly discovered circulatory hormone synthesized in the human liver that promotes glucose and lipid metabolism.[10,11] Betatrophin, which is thought to play a role in lipid metabolism and glucose homeostasis, may be associated with high cardiovascular risk and dysfunctional lipid metabolism.[10] Chemerin is a recently discovered adipokine that regulates inflammation, angiogenesis and adipogenesis. It is a chemoattractant adipokine identified in immune cells and white adipose tissue, potentially triggering multiple proinflammatory processes in RA, possibly by stimulating synovial fibroblasts.[12] Adropin is a newly identified peptide consisting of 76 amino acids with a molecular weight of 4,499.9 Da. It has been studied for its hormonal role in preserving endothelial cell function. It has been found in the brain and liver of rats, and its expression is associated with a gene that regulates energy homeostasis.[13] Adropin has been shown to independently suppress atherosclerosis, irrespective of glucose and lipid metabolism and blood pressure.[14]

Objectives

The objective of this study was to investigate the relationship between RA and epicardial fat thickness (EFT), as well as betatrophin, chemerin and adropin levels in the blood of study participants.

Materials and methods

Study population

The study was conducted with patients admitted to the Physical Medicine and Rehabilitation outpatient clinic of Mengucek Gazi Training and Research Hospital (Erzincan, Turkey) between June 2020 and June 2021. Eighty RA patients (62 women and 18 men) diagnosed according to the ACR/EULAR 2010 RA classification criteria and 80 healthy controls (64 women and 16 men) were included in the study. The ACR/EULAR RA classification criteria included duration of symptoms, joint involvement, anti-cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF) positivity, and acute phase reactants.[15] Patients' gender, age, waist circumference, and body mass index (BMI) were recorded. Informed consent was obtained from all subjects, and permission to conduct the study was granted by the Clinical Research Ethics Committee of Erzincan Binali Yildirim University, Turkey (dated March 3, 2020, No. 11665).

The DAS-28 remission criteria, including C-reactive protein (CRP), swollen and tender joint counts, and assessments of general health, were used to determine disease activity.[16] The Steinbrocker classification of functional capacity was used to assess functional status.[17] The healthy controls consisted of outpatients with acute musculoskeletal pain but no chronic inflammatory disease. They had no clinical history, laboratory or examination findings suggestive of RA. Both groups completed the Short Form-36 Health Survey Questionnaire (SF-36) to assess quality of life, and the visual analogue scale (VAS) to measure pain intensity.

Measurement of EFT

Epicardial fat thickness was measured from the echolucent area between the epicardial surface in front of the free wall of the right ventricle and the parietal pericardium. Measurements were taken at the end-diastole. During EFT measurement, each patient was placed in the left lateral decubitus position to obtain an optimal parasternal long-axis view. The aortic root and the interventricular septum were used as reference points for measurement from the parasternal long-axis view. Measurements were made by placing the aortic annulus and right ventricular free wall on the midline of the ultrasound waves and using the aortic root as a reference.[18,19] All measurements were performed transthoracically using a Philips HD 11XE echocardiography device (Koninklijke Philips N.V., Eindhoven, the Netherlands). According to a systematic review by Bertaso et al., a cutoff value of >5 mm was accepted for EFT.[18]

Patients with other autoimmune diseases, CVD, diabetes mellitus, endocrine disorders, acute and chronic pancreatic disorders, malignancy, pregnancy, breastfeeding, and those using antihyperlipidemic drugs were excluded from the study.

Measurement of plasma adropin, chemerin and betatrophin levels

After 8 h of fasting, blood samples were obtained from the antecubital vein in the morning and collected into vacuum gel tubes. The serum was separated by centrifugation of the samples at 5,000 rpm for 20 min at 4°C within 1 h of collection. Samples were stored at –80°C until analysis and were thawed only once before the analysis. Complete blood count, CRP, erythrocyte sedimentation rate (ESR), triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, and glucose levels were assessed from fresh blood samples. The levels of plasma adropin, chemerin and betatrophin (USCN, human adropin, chemerin, betatrophin ELISA kit) were determined using an enzyme-linked immunosorbent assay (ELISA). The absorbances of standards and samples were read at 450 nm (with correction at 540 nm) using an Epoch spectrophotometer (BioTek Instruments, Inc., Winooski, USA).

Statistical analyses

The statistical analyses were performed using IBM SPSS for Windows, v. 22.0 (IBM Corp., Armonk, USA). Results for categorical data are presented as numbers and percentages, and for continuous variables as mean ± standard deviation (±SD). The χ^2 test was used for the analysis of categorical data. The assumption of normality for continuous variables was checked using the Kolmogorov–Smirnov test. Depending on the normality of the variables, either the Mann–Whitney U test or Student's t-test was applied. Pearson's or Spearman's correlation tests were used to evaluate the relationship between variables. A p-value less than 0.05 was considered statistically significant.

Results

Table 1 displays the baseline characteristics of 80 RA patients and 80 healthy controls. The RA patients and healthy controls did not differ significantly in terms of age, gender, BMI, waist circumference, and smoking status.

The RA group had a mean disease duration of 120.5 ±98.6 months, with a mean RF value of 70.7 ±127.5 months. Anti-CCP was positive in 44 (55%) patients and negative in 36 (45%) patients. The mean DAS-28 score was 3.81 ±0.66. According to their DAS-28 scores, 18 patients (22.5%) had low disease activity, 54 patients (67.5%) had moderate disease activity and 8 patients (10%) had high disease activity.

Compared to the control group, the RA patients had significantly higher platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, CRP, ESR, monocytes, and neutrophils. The RA group also had significantly lower red blood cell counts and mean platelet volume compared to the control group. There were no significant differences between the 2 groups for glucose, total cholesterol, HDL, LDL, triglycerides, white blood cell count, hemoglobin, hematocrit, platelet count, and lymphocytes (Table 2).

There was no difference between RA patients and the control group in terms of betatrophin serum levels (0.28 ±0.24 vs 0.23 ±0.20, respectively; p = 0.466). Adropin

Table 1. Demographic and clinical features of patients

Parameters		Group		p-value
		RA	control	
Sex	female	62 (77.5)	64 (80.0)	0.699
	male	18 (22.5)	16 (20.0)	
Age [year]		51.9 ±11.3	49.7 ±9.9	0.215
Weight [kg]		70.1 ±8.6	69.8 ±10.8	0.279
Height [cm]		162.2 ±6.7	163.6 ±7.5	0.346
BMI [kg/m^2]		26.7 ±3.0	26.0 ±3.1	0.680*
Waist circumference [cm]		91.4 ±8.3	87.4 ±10.2	0.793*
Smoking status	non-smoker	74 (92.5)	78 (97.5)	0.147
	smoker	6 (7.5)	2 (2.5)	
VAS [mm]		61.9 ±17.6	46.0 ±14.4	<0.001*
SF-36		73.8 ±9.7	93.7 ±5.2	<0.001

RA – rheumatoid arthritis; BMI – body mass index; VAS – visual analogue scale; SF-36 – short form-36; *independent samples Student's t-test; otherwise, Mann–Whitney U-test was performed.

Table 2. Laboratory findings of study groups

Parameters	Group		p-value
	RA	control	
CRP [mg/L]	10.5 ±12.2	3.7 ±1.1	<0.001
ESR [mm/h]	23.0 ±19.2	8.2 ±5.7	<0.001
Glucose [mg/dL]	99.8 ±30.9	95.2 ±13.5	0.618
Total cholesterol [mg/dL]	192.7 ±35.9	186.8 ±35.9	0.092
HDL [mg/dL]	51.7 ±10.9	53.1 ±11.2	0.235
LDL [mg/dL]	122.5 ±28.6	120.8 ±29.9	0.706
Triglyceride [mg/dL]	134.0 ±72.1	113.3 ±53.9	0.090
WBC [×10^3/uL]	7.3 ±2.0	6.8 ±1.4	0.128
RBC [×10^6]	4.7 ±0.5	4.8 ±0.4	0.044*
Hb [g/dL]	13.3 ±1.4	13.7 ±1.5	0.063
Hct [%]	40.6 ±3.9	40.9 ±3.6	0.608*
Mpv [fl]	10.2 ±0.9	10.4 ±0.9	0.026
Plt [×10^3]	276.8 ±64.4	263. 0 ±50.3	0.134*
Lymphocytes [×10^3]	2.1 ±0.8	2.3 ±0.6	0.087
Monocytes [×10^3]	0.58 ±0.16	0.51 ±0.13	0.010
Neutrophils [×10^3]	4.5 ±1.6	3.8 ±1.1	0.008
NLR	2.4 ±1.7	1.8 ±0.7	0.002
PLR	146.5 ±60.9	122.0 ±36.7	0.024

RA – rheumatoid arthritis; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; WBC – white blood cells count; RBC – red blood cells count; Hb – hemoglobin; Hct – hematocrit, Mpv – mean platelet volume; Plt – platelets; NLR – neutrophils/lymphocytes rate; PLR – platelets/lymphocytes rate; *independent samples t-test; otherwise, Mann–Whitney U test was performed.

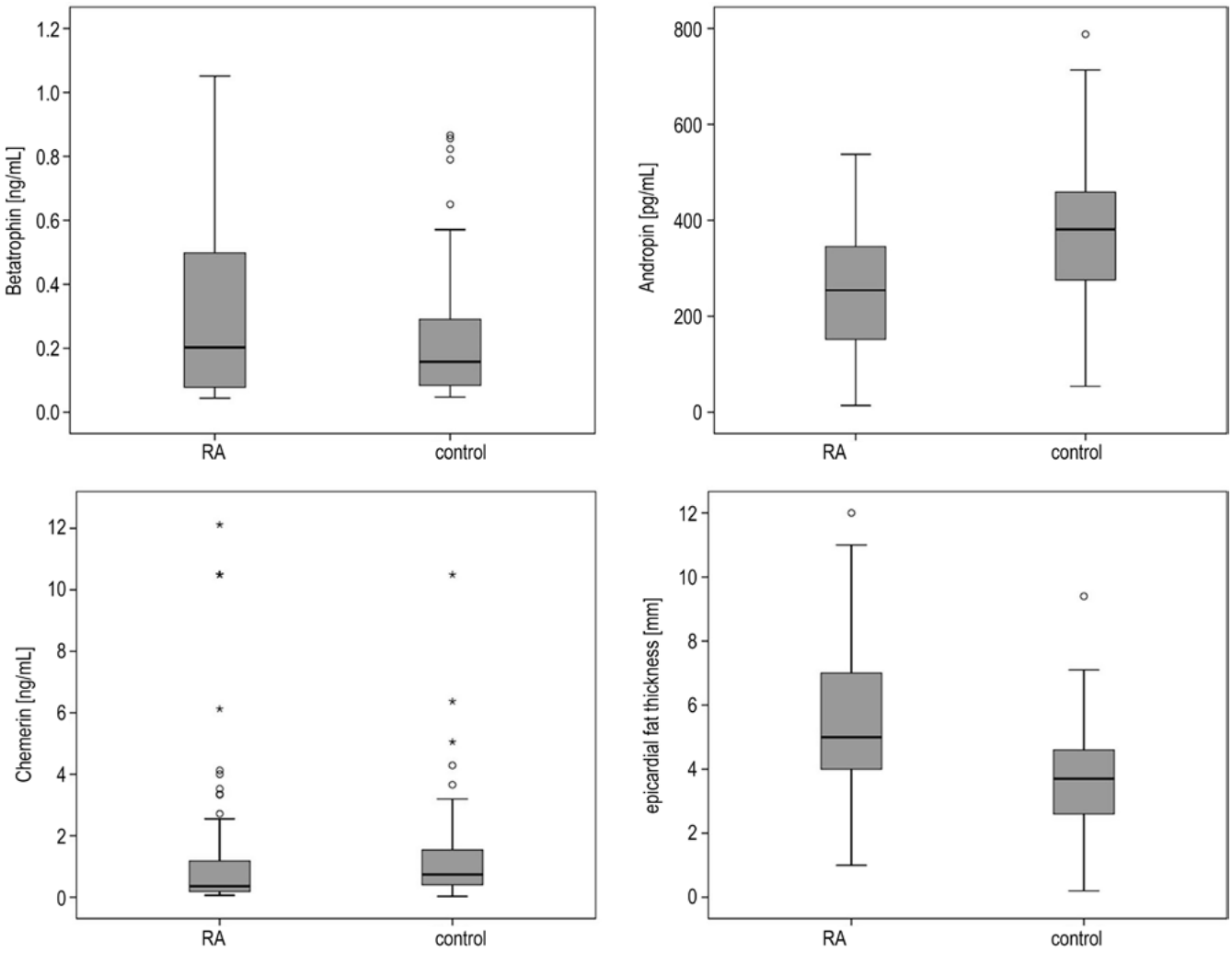

Fig. 1. Betatrophin, adropin, chemerin, and epicardial fat thickness (EFT) levels in the study groups

RA – rheumatoid arthritis.

Table 3. The serum values of biomarkers and EFT in study groups

Parameters	Group		p-value
	RA	control	
Betatrophin [ng/mL]	0.28 ±0.24	0.23 ±0.20	0.466
Adropin [pg/mL]	253.3 ±132.5	384.3 ±152.0	<0.001*
Chemerin [ng/mL]	1.37 ±2.48	1.25 ±1.55	0.016
EFT [mm]	5.7 ±2.6	3.7 ±1.6	<0.001

EFT – epicardial fat thickness; RA – rheumatoid arthritis; *independent samples Student's t-test; otherwise, Mann–Whitney U test was performed.

levels were lower in the RA group compared to controls ($p < 0.001$). Chemerin levels and EFT were higher in the RA group compared to the control group ($p = 0.016$, $p < 0.001$, respectively) (Table 3, Fig. 1).

In the RA group, patients with low disease activity according to the DAS-28 had lower EFT (4.4 ±1.76 mm) compared to those with moderate/high disease activity (6.0 ±2.7 mm; $p = 0.040$). Levels of betatrophin, adropin and chemerin did not differ significantly based on disease activity.

The study groups were also compared according to the median value of EFT (EFT < 5 mm or EFT ≥ 5 mm). The proportion of patients with high EFT (EFT ≥ 5 mm) was 57.5% in the RA group and 20% in the control group. The proportion of patients with EFT ≥ 5 mm was significantly higher in the RA group compared to the control group ($p < 0.001$).

A weak positive correlation was found between BMI and betatrophin in the RA group ($r = 0.28$, $p = 0.011$). Both the RA and control groups showed a weak positive correlation between BMI and EFT (for RA: $r = 0.24$, $p = 0.029$; for control: $r = 0.27$, $p = 0.016$). There was no correlation between CRP and the biomarkers. There was a moderate positive correlation between age and EFT ($r = 0.49$, $p < 0.001$) in the RA group, whereas this correlation was weak ($r = 0.29$, $p = 0.010$) in the control group.

When evaluating the relationship between biomarkers and EFT in RA patients, a strong positive correlation was found between chemerin and EFT ($r = 0.73$, $p = 0.046$) in patients with high disease activity.

Discussion

In this study, EFT was higher in RA patients than in controls. Serum chemerin levels were also higher in RA patients. Conversely, serum adropin levels were lower in RA patients. There was a correlation between chemerin and EFT, and a relationship was found between disease activity and EFT.

Ormseth et al. reported that patients with RA had a higher EFT associated with cardiometabolic risk factors and metabolic syndrome compared to the control group. Similar to the present study, they also reported correlations between EFT, waist circumference and BMI.[20] On the other hand, Kitagawa et al. reported that macrophage infiltration and neoangiogenesis, demonstrated with immunohistochemical staining on EFT, correlated with calcific and non-calcific plaque formation in the coronary arteries on cardiac computed tomography (CT).[21]

Karpouzas et al. evaluated epicardial fat tissue volumes (EFTVs) in RA patients and controls using CT angiography. They reported a higher plaque load and the presence of non-calcified plaques in the EFTV of RA patients, although similar EFTVs were found between RA patients and controls.[22] This demonstrates that epicardial fat tissue promotes atherogenesis through inflammation, biological dysfunction and paracrine effects through a mechanism other than traditional risk factors (e.g., metabolic syndrome, insulin resistance and abdominal visceral fat). Epicardial fat thickness may have a more pathogenic effect on the development of subclinical atherosclerosis and cardiovascular risk in RA. The relationship between severe disease activity and EFT could indicate an increased cardiovascular risk in these patients.

Chemerin, a proinflammatory adipokine, activates the chemotaxis of macrophages, natural killer cells and dendritic cells. It increases the production of tumor necrosis factor alpha (TNF-α), interleukin (IL)-6 , IL-1β, matrix metalloproteinase (MMP)-1, and MMP-8 in human chondrocytes.[23] ChemR23, or the CMKLR receptor, is expressed in macrophages, dendritic cells and fibroblast-like synoviocytes, and has been associated with both adaptive and innate immunity.[12] Tolusso et al. found that plasma chemerin values were correlated with disease activity and BMI in RA patients.[24] They also found that a reduction in BMI of at least 5% improved disease control in obese RA patients without changing the RA treatment. Vazquez-Villegas et al. demonstrated a relationship between high chemerin levels and functional disability in RA patients and found a correlation between functional disability and DAS-28.[25] Leiherer et al. demonstrated that chemerin was a strong predictor of cardiovascular events in individuals with metabolic syndrome.[26] The present study found that chemerin levels increased in patients with RA, and there was a correlation between serum chemerin levels and EFT. This suggests that patients with RA have an increased risk of CVD.

Adropin plays a role in lipid metabolism (by suppressing carnitine palmitoyl-transferase) and glucose metabolism (by activating pyruvate dehydrogenase).[27] Gao et al. reported that in a diet-dependent mouse model, adropin 34-76 suppressed cAMP-activated protein kinase A activity and reduced the phosphorylation of inositol triphosphate receptor and element-binding protein. Thus, they stated that adropin increased intracellular signaling activities in insulin-mediated glucose homeostasis.[28] Lovren et al. showed that adropin decreased the level of apoptosis caused by TNF-α in human umbilical vein endothelial cells.[29] Impaired endothelial function is the triggering factor for the development and progression of cardiovascular, metabolic, inflammatory, renal, and infectious diseases, with atherothrombosis having the most notable pathological effect. Several investigations have revealed that adropin levels are lower in the blood of people with CAD, coronary slow flow phenomenon and hypertension compared to those in control groups.[30–32]

Wu et al. included individuals with and without type 2 diabetes in a study to evaluate the link between blood adropin levels and the angiographic severity of coronary atherosclerosis. They found that serum adropin levels were lower in patients with type 2 diabetes. Furthermore, they discovered that these levels were inversely and independently associated with the angiographic severity of coronary atherosclerosis.[33] Butler et al. found that rats fed a high-fat diet had significantly elevated adiponectin levels in their blood, along with significant changes in insulin sensitivity and glucose intolerance.[34] They also stated that adropin plays a role in protecting the endothelium and maintaining its functions. Similarly, the present study revealed that adropin levels were found to be low in patients with RA.

Erman et al. reported that obese patients had low serum adropin levels, with 216.7 ng/L being the optimal cutoff point to detect insulin resistance.[35] Fujie et al. reported that adropin levels decreased with age and increased with an aerobic exercise program.[36] Tuleab et al. reported that adropin levels in the serum of RA patients were noticeably lower than in the control group.[37] Similarly, low serum levels of adropin were observed in individuals with RA in the current study.

We found that patients with RA had higher EFT levels than the control group. There was a connection between age, BMI, waist circumference, and exercise intensity. It was discovered that patients experiencing intense illness activity had higher EFT. Patients diagnosed with RA had a higher EFT, indicating cardiovascular involvement.[38] Additionally, serum chemerin levels were higher in patients with RA. Conversely, serum adropin levels were lower in RA patients. Low serum adropin levels may reduce endothelium protection and may induce or accelerate the progression of atherosclerosis.[33] Recent studies suggest that chemerin is important in the pathogenesis of CVD, particularly CAD.[39,40]

Limitations

There were 3 significant limitations to our investigation. First, this was a cross-sectional analysis focusing on the relationship between RA and EFT, serum betatrophin, chemerin, and adropin levels. Second, the sample size was somewhat limited. Third, because this was not a prospective controlled trial, causal relationships could not be inferred from our findings.

Conclusions

Measurement of EFT in patients with RA may assist in determining cardiovascular risk and enable early precautions to be taken. Given that patients with RA have a higher risk of developing CVD, it is hypothesized that elevated serum chemerin levels combined with decreased adropin levels contribute to the pathophysiology of this condition.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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