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Increased epicardial fat thickness in rheumatoid arthritis patients.

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Abstract

Objective: Rheumatoid arthritis (RA) is the most common inflammatory arthritis. Known risk factors, along with inflammation and autoimmunity, contribute to the development of coronary artery disease in RA patients. Epicardial adipose tissue (EAT) is a strong risk factor for coronary artery disease. The present study aimed to compare EAT thickness in RA patients with a healthy control group.

Methods: The study included 31 RA patients (female: 25, male: 6; mean age: 52.74 ± 11.30) and 33 healthy individuals (female: 29, male: 4; mean age: 48.55 ± 9.27) as the control group. Patients with cardiovascular disease and other comorbid diseases were not included. The EAT thickness of patient and control groups was measured using transthoracic echocardiography. Demographic, clinical and laboratory findings of all the subjects were recorded. The EAT thickness, demographic, clinical and laboratory findings of RA patients were compared with those of control group.

Results: The epicardial fat thickness was significantly higher in the patient group than the control group (0.68 ± 0.16 cm; 0.40 ± 0.11 cm, respectively, p<0.000). There was no correlation between epicardial fat thickness and the duration of the disease, rheumatoid factor, C-Reactive protein and erythrocyte sedimentation rate in the patient group (p>0.05). There was no correlation between epicardial fat thickness and age, gender, body mass index, glucose, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, systolic blood pressure and diastolic blood pressure in the patient group (p>0.05).

Conclusion: The present study showed a significant increase in the EAT thickness in RA patients compared to healthy control subjects, which is an indicator of subclinical atherosclerosis.

Keywords: Epicardial fat thickness, Rheumatoid arthritis, Inflammation.

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology, which is characterized by symmetrical erosive synovitis, and multisystem organ involvement in some cases. [1] RA is most common inflammatory arthritis in the world. The incidence of RA is about 0.5-1%. [2] In the other hand, RA is associated with high cardiovascular morbidity and mortality. [3] There are many cardiac manifestations associated with the RA such as pericarditis, coronary arteritis, myocarditis and pulmonary hypertension [4]. The other mechanism responsible for the development of coronary artery disease in RA patients is inflammation and autoimmunity [3]. Epicardial adipose tissue (EAT) is the visceral adipose tissue of the heart [5-9] and located between the visceral pericardium and myocardium [5,6]. This metabolically active adipose tissue releases several proinflammatory and proatherogenic cytokines [10]. When compared to the adipose tissues located in other parts of the body, epicardial adipose tissue is a strong risk factor for coronary artery disease and may play a significant role in the development of coronary artery disease [11,12]. A study with ankylosing spondylitis patients found increased epicardial adipose tissue and carotid artery intima-media thickness and determined that this is a risk factor for subclinical atherosclerosis and cardiovascular disease [13]. EAT is easily visualized by echocardiography and which remains the attractiveness for researchers. The present study aimed to evaluate EAT measured by echocardiography in patients with rheumatoid arthritis compared to healthy control subjects.

Materials and Methods

This study conducted in Mevlana University Medical Faculty Hospital Internal Medicine and Physical Medicine and Rehabilitation Department. Total 64 participants enrolled to study including 31 RA patients were admitted to Internal Medicine and Physical Medicine and Rehabilitation Department and 33 were healthy individuals accepted as a control group. The study was approved by the Mevlana University Medical Faculty Ethics Committee and followed the Declaration of Helsinki. The study included patients whose diagnoses were based on the criteria of the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) [14] and were receiving disease-modifying anti-rheumatic drugs (DMARDs) for a minimum of six months. The control group consisted of healthy subjects without rheumatic diseases and chronic diseases. Patients with heart disease, cerebrovascular disease, chronic renal failure, primary hyperlipidaemia and diabetes mellitus, hypothyroidism, Cushing syndrome and acromegaly were excluded from the study. Medical history was taken from all patients. Demographic data were also recorded. The patients' weight and height measured on an empty stomach and with light clothes. Body Mass Index (BMI) calculated by dividing weight by the square of height in meters. Blood pressure measured from the arm, using an aneroid sphygmomanometer, in a sitting positing following a 10 minute rest. Echocardiographic measurements made using Vivid 5 Pro (GE Vingmed Ultrasound, Horten, Norway). The thickness of epicardial adipose tissue measured on the free wall of the right ventricle in the parasternal long axis view. Epicardial adipose tissue identified as an anechoic space between the epicardial layers on a two-dimensional echocardiography and its thickness measured vertically on the free wall of the right ventricle at the diastolic end [15]. For biochemical tests, a blood sample was taken from the antecubital vein in the morning after a minimum eight hours fasting. Fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), rheumatoid factor (RF), C-reactive protein and erythrocyte sedimentation rate (ESR) were recorded in the patient and control groups.

Statistical analysis

The statistical analyses made using SPSS for Windows v.16.0 (SPSS Inc., Chicago, IL). The distribution of the data providing the parametric condition was expressed in X ± SD. The normality analysis of the data made using the Kolmogorov-Smirnov Test. For normally distributed data, the statistical difference between two groups determined using an Independent Sample Test. The Mann-Whitney U test used for non-normally distributed data. The correlation between epicardial adipose tissue and other parameters in patient and control groups evaluated using Pearson's coefficient. $P<0.05$ was considered statistically significant.

Results

The study enrolled 31 patients with rheumatoid arthritis and 33 healthy individuals. The average patient age was 52.74 ± 11.3 years and control group age was 48.55 ± 9.27 years. The study population included 10 (15.6%) men. Disease duration was 5.98 ± 6.16 years in patient group. There was no statistically significant difference in age, gender, weight, height, body mass indices, and systolic and diastolic blood pressures between patient and control groups. The demographic, anthropometric and clinical data of the both study groups are summarized in Table 1.

The patients with rheumatoid arthritis had a significantly greater ESR (26.71 ± 18.59 mm/h *vs.* 9.12 ± 4.44 mm/h; p=0.000), RF (69.96 ± 113.54 IU/ml *vs.* 9.45 ± 3.47 IU/ml; p=0.003), CRP (13.65 ± 11.25 mg/l *vs.* 3.85 ± 1.41 mg/l; p=0.000) and epicardial fat thickness (0.68 ± 0.16 cm; 0.40 ± 011 cm; p<0.000) when compared to the control group, respectively. There was no correlation between epicardial fat thickness and the duration of the disease, RF, CRP and ESR in the patient group (Table 2). There was no correlation between epicardial fat thickness and age, gender, BMI, glucose, total cholesterol, triglycerides, HDL-C, LDL-C, systolic blood pressure and diastolic blood pressure in the patient group.

Table 1. *The demographic, anthropometric and clinical data of the both study groups.*

	Patient Group	Control Group	P
Age (years)	52.74 ± 11.30	48.55 ± 9.27	0.111
Gender (female/male)	29/4	25/6	0.429
Weight (kg)	78.77 ± 8.18	76.97 ± 7.02	0.349
BMI (kg/m^2)	30.02 ± 2.94	28.88 ± 2.75	0.114
Height (cm)	1.62 ± 0.07	1.63 ± 0.04	0.437
SBP	128.90 ± 7.04	126.61 ± 9.20	0.265
DBP	82.42 ± 5.83	79.58 ± 9.22	0.144
Glucose (mg/dl)	99.94 ± 19.19	103.39 ± 25.39	0.809
Cholesterol (mg/dl)	198.16 ± 48.38	190.30 ± 46.04	0.509
Triglycerides (mg/dl)	162.29 ± 73.11	140.64 ± 62.15	0.208
HDL-C (mg/dl)	48.94 ± 12.87	48.76 ± 12.28	0.955
LDL-C (mg/dl)	117.10 ± 39.82	118.45 ± 42.76	0.896
Epicardial fat thickness (cm)	0.68 ± 0.16	0.40 ± 0.11	**0.000**
CRP (mg/l)	13.65 ± 11.25	3.85 ± 1.41	**0.000**
RF (IU/ml)	69.96 ± 113.54	9.45 ± 3.47	**0.003**
ESR (mm/h)	26.71 ± 18.59	9.12 ± 4.44	**0.000**

CRP: C-reactive protein, DBP: Diastolic blood pressure, ESR: Erythrocyte sedimentation rate, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, RF: rheumatoid factor, SBP: Systolic blood pressure.

Bolded data are statistically significant.

Table 2. *Correlation between epicardial fat thickness and study parameters in patient group.*

	r	p
Age (years)	0.313	0.087
Gender (female/male)	0.049	0.795
BMI (kg/m^2)	0.034	0.857
Glucose (mg/dl)	0.0170	0.362
Cholesterol (mg/dl)	-0.040	0.829
Systolic blood pressure	0.196	0.291
Diastolic blood pressure	0.249	0.177
Triglycerides (mg/dl)	0.235	0.203
HDL-C (mg/dl)	-0.309	0.091
LDL-C (mg/dl)	-0.239	0.195
Disease duration	0.224	0.226
CRP (mg/l)	0.225	0.223
RF (IU/ml)	-0.53	0.777
ESR (mm/h)	-0.56	0.766

CRP: C-reactive protein, DBP: Diastolic blood pressure,

ESR: Erythrocyte sedimentation rate,

HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, RF: rheumatoid factor, SBP: Systolic blood pressure.

Discussion

A high cardiovascular morbidity is reported in individuals with RA. However, it is not known whether this is caused by risk factors, or the inflammatory process underlying the disease [16]. This study is investigated the importance of the increased EAT in RA patients who have not more information about this field. The present study found significantly increased thickness of epicardial adipose tissue in RA patients when compared with the healthy control group. There was no correlation between the EAT thickness, the duration of the disease, RF, sedimentation, CRP levels, blood pressures and biochemical parameters. EAT is located under the visceral pericardium. It is more closely associated with visceral fat than total body fat [21]. EAT is an indicator of visceral adiposity and this visceral fat may suggest that it is an independent indicator of metabolic risk factors [17]. EAT is currently defined as the source of varied bioactive molecules [18,19], and it is believed to have effects on the coronary arteries [20,21]. There is evidence reported that the increased thickness of epicardial adipose tissue is significantly associated with anthropometric and clinical parameters and BMI, systolic blood pressure and diastolic blood pressure [22,23]. In our study found that there was an increased EAT thickness in RA patients compared to control group, regardless of the systolic and diastolic blood pressures. The study by Torres et al. [23] found statistically significantly higher BMI, systolic and diastolic blood pressures in patients with metabolic syndrome, whereas the present study did not find any difference between the patient and control groups. Moreover, the present study did not establish any correlation between the EAT thickness and these parameters. The cause of increased epicardial fat thickness in RA patients is a reflection of potential visceral fat accumulation independent from obesity and metabolic syndrome. EAT, which is a reflection of high visceral adiposity, may be associated with the diffuse accumulation of glucocorticoids in the visceral adipose tissue, and used during the treatment of RA patients [24]. Recently, several studies have been conducted to determine the cause of increased cardiovascular disease. In fact, traditional atherosclerotic risk factors play a significant role in the development of cardiovascular disease. However, these factors do not fully explain the cardiovascular disease burden in RA. Negative risk profiles associated with systemic inflammation and autoimmunity contribute to the development of cardiovascular disease in RA [3]. We included RA patients without any distinct heart disease or comorbidity, as well as control subjects. There was no significant difference in cardiovascular data and demographic characteristics between the healthy controls and RA patients. We found significantly increased EAT thickness in RA patients compared with the healthy controls. The association of RA and increased EAT may be related to permanent inflammation and autoimmunity [3,25]. Tumour necrosis factor alpha (TNF-a) is a cytokine with a key role in the inflammatory process in RA. Several clinical studies have proven that the use of TNF-a inhibitors to treat RA reduces the clinical signs of the inflammation [26,27]. Additionally, it has been found that treatment with TNF-a inhibitors reduces the risk of cardiovascular events [28]. The study by Lima-Martínez MM et al. with RA patients, found that the EAT thickness was significantly increased compared with the healthy controls. The authors found that the EAT thickness significantly lower in the group receiving TNF-a inhibitors than the patient group receiving non-biological DMARDs. When the RA patients and the control group compared, they found no any significant difference in serum levels of glucose, total cholesterol, HDL-L, LDL-C and triglycerides. When the group receives TNF-a inhibitors and the group receiving DMARDs compared, they found lower plasma levels of total cholesterol, LDL-C and triglycerides, and higher levels of HDL-C, but they found no any statistically significant difference [29]. The present study also showed no any significant difference in plasma levels of glucose, total cholesterol, LDL-C, triglycerides and HDL-C when the RA patient group and the control group compared. Pollono et al. evaluated the lipid profiles of RA patients receiving TNF-a antagonists and found significantly increased levels of total cholesterol and HDL-C. However, they only observed these changes in the group with a good response to treatment and suggested that such lipid changes might have developed due to their not receiving treatment specifically for decreased inflammation [30]. Resorlu et al. [13] found increased EAT thickness in the patient group with ankylosing spondylitis compared to the control subjects and they showed that this is a risk factor for cardiovascular disease and

subclinical atherosclerosis. The study by Lipson et al. which conducted with SLE (systemic lupus erythematosus) patients, found increased EAT thickness. Additionally, there was a significant correlation between hsCRP (high sensitive C-reactive protein) and EAT thickness, whereas the authors could not find any correlation between other disease-related markers and disease activity scores [31] The present study showed no correlation between CRP, sedimentation, RF and epicardial fat thickness. We believe that this is due to the regression of systemic inflammation since the patients received treatment. The study by Lima-Martinez MM et al. determined no significant difference in blood pressure between the patient group with RA and the control group [29]. The present study also found similar finding. The present study did not include patients with DM and HT. Furthermore, there was no correlation between systolic and diastolic bloods pressures and EAT thickness, in this study.

Limitation

Although this study identifies important findings, it has some limitations. The study has a relatively small sample size, but there was a sufficient statistical significance between the study and control groups. Another limitation is the lack of Multi Slice Computed Tomography (MDCT) or Magnetic Resonance (MR) imaging is the gold standard evaluation methods of EAT thickness. MR imaging and computed tomography used to evaluate the EAT thickness; however, these are not always available and expensive. EAT measurements with echocardiography is the current practical method that is objective, non-invasive and easy to perform. In the literature there were not significant differences between measurements of EFT obtained with echocardiography vs. MDCT [32]. Echocardiography represents an easily accessible, and easy to use, diagnostic tool in terms of its functionality and cost-effectiveness.

Conclusion

In conclusion, the present study showed a significant increase in the EAT thickness in RA patients compared with the healthy control subjects, which is an indicator of subclinical atherosclerosis. No correlation was established between EAT thickness and the duration of the disease and other biochemical parameters. Further studies are required for EAT and RA.

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