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The role of inflammation in the epicardial adipose tissue on coronary artery disease pathogenesis

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ABSTRACT

Objectives: In this study, we aimed to investigate the potential relationship between inflammation of the epicardial adipose tissue (EAT) and coronary artery disease (CAD).

Patients and methods: Between September 2017 and March 2018, a total of 38 patients (31 males, 7 females; mean age: 55 years; range, 46 to 64 years) who underwent elective open heart surgery were prospectively analyzed. The patients were divided into two groups according to the procedure type as those without CAD (n=15) and those with CAD (n=23) as the control group. The CAD group underwent isolated coronary artery bypass grafting, while the control group underwent open heart surgery and had normal coronary arteries as assessed by coronary angiography. The EAT samples were taken intraoperatively from peri-arterial and right atrial appendage in the CAD patients, while the samples were taken from only right atrial appendage in the control group. Specimens were stained and the presence and amount of inflammatory cell infiltrates were examined. More than 50 inflammatory cell counts in the pathological examination were accepted as significant inflammation.

Results: The mean white blood cell (7.5±2.3 vs. 7.1±2.2, respectively; p=0.842) and mean C-reactive protein (0.4±1.0 vs. 0.5±0.8, respectively; p=0.755) values were similar in both groups. In the CAD group, inflammatory cell infiltration in the atrium was more frequent than the control group (43% vs. 6.6%, respectively; p=0.036). Peri-arterial infiltration was also high similar with RAA in the CAD group.

Conclusion: Our study shows that both peri-arterial and atrial EAT inflammation significantly increase in patients with CAD, suggesting that inflammation in EAT may have a significant relationship with the CAD's pathogenesis.

Keywords: Atherosclerosis, coronary artery disease, epicardial adipose tissue, inflammation.

The pathological mechanism of atherosclerosis includes certain processes such as lipid accumulation, neo-intima and fibrous cap formation, and inflammation in the arterial wall.[1] Previously, it was thought that inflammation in the arterial wall developed in response to intimal injury, and peri-arterial epicardial inflammation occurred due to a close neighborhood relationship.[2] In recent studies, it has been proposed that adipose tissues act as a paracrine organ rather than an energy store and have proinflammatory effects.[3] However, in addition to the close relationship between cardiovascular diseases and obesity, the absence of coronary artery disease (CAD) at the same level in every patient with obesity suggests that there may be another mechanism different from the amount of adipose tissue.

Some mediators called adipokines secreted from adipocytes have been shown to be responsible for inflammatory responses occurred after intimal injury.[4] Therefore, the possible relationship between inflammation levels of epicardial adipose tissue (EAT) and atherosclerosis may lead to investigate different treatment strategies for CAD. In the present study, we

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aimed to examine the presence of inflammation of the EAT and its relationship with CAD.

PATIENTS AND METHODS

This single-center, prospective cohort study was conducted at Health Science University, Kartal Koşuyolu Yüksek Ihtisas Training and Research Hospital, Department of Cardiovascular Surgery between September 2017 and March 2018. A total of 38 patients (31 males, 7 females; mean age: 55 years; range, 46 to 64 years) who underwent elective open heart surgery were included. The patients were divided into two groups according to the procedure type as those without CAD (n=15) and those with CAD (n=23) as the control group. The CAD group underwent isolated coronary artery bypass grafting, while the control group underwent open heart surgery and had normal coronary arteries as assessed by coronary angiography. Inclusion criteria were as follows: having coronary artery disease and valvular disorder scheduled for elective coronary artery bypass graft (CABG) implantation, valvular replacement, or valvuloplasty. Those undergoing acute cardiac and aortic surgical procedures and those who were unwilling to give a consent were excluded from the study. A written informed consent was obtained from each patient. The study protocol was approved by the Health Science University, Kartal Koşuyolu Yüksek Ihtisas Training and Research Hospital Ethics Committee (date/no: 2018/1-42). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Adipose tissue sampling

Due to ethical reasons, EAT samples were obtained only from routine dissection by avoiding making additional dissections which were out of procedural steps. Epicardial adipose tissue samples were taken from the right atrial appendage (RAA) in both groups before cardiopulmonary bypass (CPB). In the

Table 1
Baseline demographic and clinical characteristics of study population

	All patients (n=38)			CAD group (n=23)			Control group (n=15)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			54.1±12.9			57.8±8.9			48.3±2	0.024
Sex										
Male	31	81		19	8		12	80		0.051
Hypertension	16	42		11	47		5	33		0.060
Smoking	18	47		13	56		5	33		0.082
Diabetes mellitus	11	28		5	21		6	40		0.751
Dyslipidemia	23	60		16	69		7	46		0.671
LVEF %			56.5±9.9			56.5±10.1			56.3±10.1	0.954
Laboratory parameters										
WBC (10^3/μL)			7.3±2.3			7.5±2.3			7.1±2.2	0.842
Hg (g/dL)			13.5±1.7			13.3±1.9			13.8±1.5	0.404
Hct (%)			40.7±5.1			40.0±5.5			41.9±4.2	>0.999
Platelet (10^3/μL)			239.2±48.9			238.7±55.6			240±38.3	0.939
Glucose (mg/dL)			138.1±74.8			144.5±77.7			128.1±71.6	0.516
Urea (mg/dL)			35.7±11.2			35.5±12.5			35.9±9.1	0.913
Creatinine (mg/dL)			0.9±0.3			1.0±0.4			0.9±0.3	0.511
Uric acid (mg/dL)			5.9±1.7			6.0±2.0			5.7±1.3	0.550
TC (mg/dL)			187.3±49.1			179.9±46.0			203.2±50.3	0.149
LDL-C (mg/dL)			117.7±43.3			107.0±43.3			132.1±40.3	0.080
HDL-C (mg/dL)			37.4±9.7			35.4±5.9			40.1±13.1	0.139
Triglyceride (mg/dL)			164.3±67.4			178.7±81.2			144.3±34.6	0.130
CRP (mg/L)			0.4±1.7			0.4±1.0			0.5±0.8	0.755
ESR (h)			20±5.1			21±3.8			19±7.3	0.904

CAD: Coronary artery disease; SD: Standard deviation; LVEF: Left ventricular ejection fraction; WBC: White blood cell; Hg: Hemoglobin; Hct: Hematocrit; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

Table 2
Inflammatory grading of samples

	CAD group (n=23)				Control group (n=15)	
	Samples taken from RAA		Samples taken from peri-arterial		Samples taken from RAA	
	n	%	n	%	n	%
Grade 0	13	56	18	78	14	93
Grade 1	3	13	3	13	1	6.6
Grade 2	0	0	0	0	0	0
Grade 3	7	30	2	8	0	0

CAD: Coronary artery disease; RAA: Right atrial appendage.

CAD group, additional EAT samples were obtained from anterior interventricular sulcus during the left anterior descending (LAD) artery exploration under CPB support to explore the extent of inflammation (peri-arterial).

Histopathological examination

The tissue samples were fixed in 10% buffered formalin. Paraffin-embedded tissues were cut into 3-µm sections. A digital light microscope (Olympus BX53; Olympus Optical Co., Ltd., Tokyo, Japan) was used to evaluate the specimens by a pathologist blinded to the group allocation. Specimens were stained with hematoxylin and eosin (H-E) and the presence and amount of inflammatory cells (mainly macrophages and, lesser amount, T and B lymphocytes) infiltrates (ICIs) were examined. In the presence of more than one focus, the largest ICIs focus was taken into consideration. According to the amount of inflammatory cells, the specimens were scored as follows: (Grade 0): 0-50 cells, (Grade 1): 51-100 cells, (Grade 2): 101-200 cells, and (Grade 3): >200 cells.

Statistical analysis

Statistical analysis was performed using the GraphPad Prism version 8.4.2 software (GraphPad Software Inc., CA, USA). Continuous variables were presented in mean ± standard deviation (SD) or median (25^{th}-75^{th} percentiles), while categorical variables were expressed in n and frequency. Univariate comparisons between two groups were performed using the chi-square or Fisher's exact tests for categorical variables or Wilcoxon rank sum test for continuous variables. The Spearman or Pearson correlation test was used to assess the association between lymphocytes and other measured parameters. A p value of <0.05 was considered statistically significant.

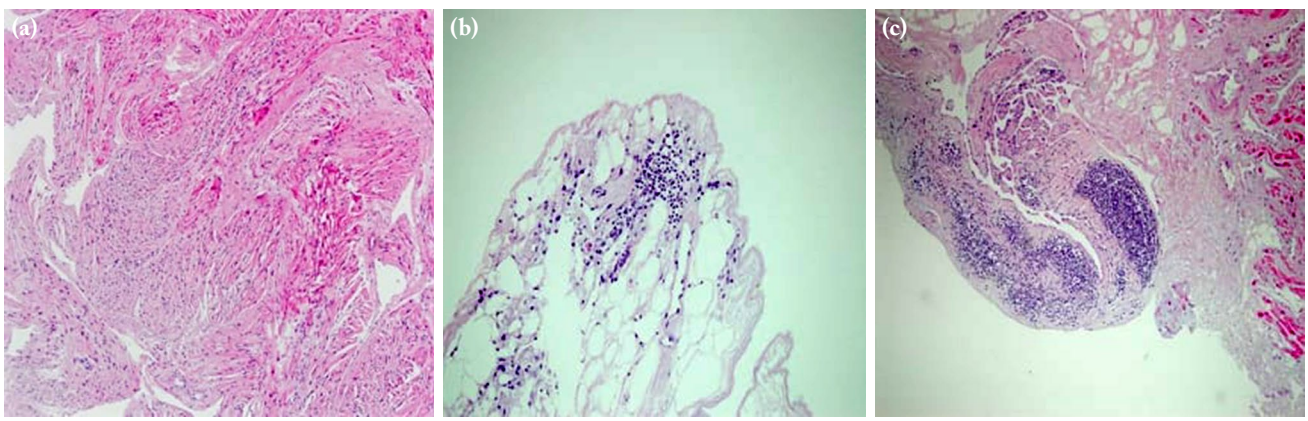

Figure 1. Histopathological examination showing inflammatory cell accumulations. Specimens were stained with H-E with ×100 magnification. Any of the specimens showed Grade 2 inflammation. **(a)** Grade 0, **(b)** Grade 1, **(c)** Grade 3.
H-E: Hematoxylin and eosin.

RESULTS

Baseline demographic and clinical characteristics of the patients with and without CAD are shown in Table 1. There were no significant differences in these characteristics between the groups (p>0.05). However, the prevalence of hypertension and smoking was higher in patients with CAD than in those without CAD. While the number of patients with dyslipidemia was significantly higher in the CAD group, the mean cholesterol levels were higher in the control group. Preoperative laboratory parameters including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were similar in both groups (p>0.05).

In the CAD group, ICI using the samples taken from the RAA was more frequent than the control group (43% vs. 6.6%, respectively; p=0.036) (Table 2). Seven patients in the CAD group demonstrated Grade 3 ICI at the RAA samples compared to two patients in the control group. Grade 2 inflammation was not detected in any of samples (Figure 1). The ICI was not statistically different between the RAA samples and peri-arterial samples in the CAD group (RAA Grade 0, n=13 vs. peri-arterial Grade 0, n=18, respectively).

There was significant correlation between inflammation grade and the existence of CAD (r=0.44, p=0.006).

DISCUSSION

The role of inflammation in atherosclerosis has been a topic of interest in recent years. Many studies have shown that inflammation in plaque formation, in addition to intimal damage and lipid accumulation, plays a key role in the mechanism of atherosclerosis. The accumulation of cellular and humoral structures involving in the mechanism of inflammation has become a guide for these studies.[1,2] Later studies have attempted to identify the proinflammatory structures having paracrine or endocrine effects on the inflammation to discover novel treatment strategies to overcome plaque formations in the arterial wall.[3] In our study, we mainly observed the numerical increase in the inflammatory cells in EAT of the patients having CAD.

Epicardial adipose tissue was initially thought to be responsible for the storage of energy substrates and behaving as a guard for myocardium; however, later studies showed several soluble products produced by adipocytes in the EAT.[5,6] During any inflammatory process, inflammatory cells and several cytokines increase in the tissues nearby the culprit lesions.[7] Mazurek et al.[8] showed in their study that inflammatory cells and markers were significantly higher in the EAT samples of patients with CAD. In our study, similarly, we found a significantly higher accumulation of inflammatory cells in the EAT tissue samples of CAD group than the control group.

In another study of İzgi,[9] EAT was described as a local player of atherosclerosis in the coronary artery walls with its neighborhood. In this study, the author emphasized by referring several studies that the increase of the inflammatory cells and markers in the EAT samples were not seen in the serum samples of the same patients. Additionally, in a study of Erdogan et al.,[10] the decrease in coronary flow was associated with the increased epicardial adipose tissue thickness, independent of serum CRP levels.[10] Similarly, in our study, the measurement of inflammatory cells and markers (CRP and ESR) in the serum samples did not show any significant increment. Moreover, in the study of Yeşilkaya,[11] no significant relationship was found between systemic inflammation and mortality after CABG. This result may suggest a consideration about the interaction of solely local inflammatory of EAT with coronary arterial atherosclerosis.

Beside the increase of inflammatory cells in the EAT taken from the RAA in the CAD patients compared to those without CAD, the increment of inflammatory cells was also similar in the peri-arterial EAT in the CAD patients. In addition to our findings, Moos et al.[12] observed the inflammatory cells accumulation in the adventitia rather than the intima. Taken together, these findings indicate that the EAT may have a proinflammatory effect on atherosclerosis, rather than the inflammatory process in the EAT occurred secondary to intimal injury.[13]

The main limitation of this study was its small sample size. In addition, although sample collections were made prospectively, preoperative data were obtained retrospectively.

In conclusion, our study showed that both peri-arterial and atrial EAT inflammation significantly increased in patients with CAD. This result may suggest that inflammation in EAT have a significant relationship with the CAD's pathogenesis. However, further large-scale, prospective studies are needed to confirm these findings.

Declaration of conflicting interests

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