Is there a relationship between serum paraoxonase level and epicardial fat tissue thickness?

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Abstract

Objective: This study aimed to show the relationship between serum paraoxonase 1 level and the epicardial fat tissue thickness.
Methods: Two hundred and seven patients without any atherosclerotic disease history were included in this cross-sectional observational study. Correlation analysis was performed to determine the correlation between epicardial fat tissue thickness, which was measured by echocardiography and serum paraoxonase 1 level. Also correlation analysis was performed to show correlation between patients' clinical and laboratory findings and the level of serum paraoxonase 1 (PON 1) and the epicardial fat tissue thickness. Pearson and Spearman test were used for correlation analysis.
Results: No linear correlation between epicardial fat tissue thickness and serum PON 1 found (correlation coefficient: -0.127, p=0.069). When epicardial fat tissue thickness were grouped as 7 mm and over, and below, and 5 mm and over, and below, serum PON 1 level were significantly lower in ≥7 mm group (PON1 : 168.9 U/L) than <7 mm group (PON 1: 253.9 U/L) (p<0.001). Also hypertension prevalence was increased in ≥7 mm group (p=0.001). Serum triglyceride was found to be higher in ≥7 mm group (p=0.014), body mass index was found higher in ≥5 mm group (p=0.006).
Conclusion: Serum PON 1level is not correlated with the epicardial fat tissue thickness. But PON 1 level is lower in patients with epicardial fat tissue thickness 7 mm and over. Therefore, increased atherosclerosis progression can be found among patients with 7 mm and higher epicardial fat tissue thickness. *(Anadolu Kardiyol Derg 2014; 14: 115-20)*
Key words: echocardiography, epicardial fat tissue, serum paraoxonase 1 level

Introduction

Despite all the advances in the diagnosis and treatment of cardiovascular disease (CVD), deaths due to atherosclerotic vascular disease today is still the leading cause of death in the world (1-3).

It has been shown that there is a relationship between the distribution of visceral adipose tissue with coronary artery disease (CAD) and CVD (4-8). Epicardial fat tissue (EFT) is defined as visceral adipose tissue that is located between myocardial and the visceral pericardium.

Paraoxonase 1 (PON 1) shows its effect by suppressing the receipt of the oxidized low-density lipoprotein (LDL) cholesterol with macrophages, preventing the oxidation of the lipid peroxides, providing the increase of flow of the cholesterol out of the cell, and by preventing foam cell formation (9). In many studies, it has shown that low PON 1 level and activity are risk factors for CVD, and for patients who have CVD, low levels of PON 1 and low activity of PON1 were associated with the severity of the disease.

The level of EFT can be measured most accurately with magnetic resonance imaging (MRI) and computerized tomography (CT). The thickness of EFT can also be measured by transthoracic echocardiography (TTE) (10).

In the literature, there were no study about relationship of PON 1 level and EFT thickness. In this study, we investigated whether PON 1 levels correlated with the degree of EFT thickness in patients without atherosclerotic disease.

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Methods

Study design

An observational cross-sectional study.

Study population

Two hundred and seven patients were included to the study, who did not have atherosclerotic disease and admitted to the Department of Cardiology at Atatürk Education and Research Hospital in Ankara between April 2011 and May 2012. The study protocol was in accordance with the Declaration of Helsinki and approved by the local Ethics Committee. Informed consent was obtained in all patients before enrolment.

Study protocol

Exclusion criteria were listed as; the existence of CAD, the presence of moderate- severe aortic and/or mitral valve disease, coronary artery bypass surgery history, aorta and/or valve surgery history, heart failure with low ejection fraction (EF) <50%, positive exercise electrocardiogram (ECG) or perfusion test, history of prior stroke, angina or symptoms of atherosclerotic vascular disease, such as angina or claudication, liver failure. Body mass indexes (BMI) (kg/m^2) were obtained by kilograms (kg) of body weight divided by the square of height in length in meters (m). In addition, the presence of the metabolic syndrome according to the criteria ATP3 is investigated for patients (11).

Study variables

Age, sex, body mass index, hemoglobin, platelet count, total cholesterol, HDL cholesterol, triglyceride (TG), LDL cholesterol levels and cardiovascular risk factors of study participants were recorded as baseline variables. PON levels of the study participants were measured as outcome variable. EFT was accepted as a predictor variable as shown in Table 1 and 2.

Blood sampling protocol

Serum samples were obtained by venipuncture with vacationer tubes after 12 hours fasting to measure the serum lipid and biochemical profile. Serum creatinine, serum total cholesterol, LDL cholesterol, high density lipoprotein (HDL) cholesterol, and serum triglyceride levels were measured by automated enzymatic methods.

Assessment of PON levels

Paraoxonase assays were performed in the absence of sodium chloride (NaCl) (basal activity) and in the presence of 1 mol/L NaCl (NaCl-stimulated activity). Initial rates of hydrolysis of paraoxon (O,O-diethyl-O-p-nitrophenylphosphate; Sigma Chemical Co, London, UK) were determined by measuring liberated p-nitrophenol at 405 nm at 37 C on a Technicon RA-1000 autoanalyzer (Bayer, Milan, Italy). The basal assay mixture included 2.0 mmol/L paraoxon and 2.0 mmol/L of calcium chloride (CaCl2) in 0.1 mol/L Tris-HCl buffer, pH 8.0. To 350 L of the reagent mixture 10 L of serum was added.

Echocardiography

Transthoracic echocardiography (Vivid 7, Vingmed Ultrasound, GE, Horten, Norway) was performed in the left lateral decubitus position. The epicardial fat thickness (EFT) was identified as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium, and its thickness was measured perpendicularly on the free wall of the right ventricle at end-systole in three cardiac cycles. Parasternal long- and short-axis views were used. The average value of three cardiac cycles from each echocardiographic view was considered (12, 13). In previous studies, there were no consensus about EFT thickness cut-off values. Several values are postulated for this condition (10, 11, 13).

Statistical analysis

Statistical Package for Social Sciences 17.0 (SPSS 11.0, Chicago, IL, USA) program was used for evaluating the data. In order to evaluate the suitability to the normal distribution parameters Kolmogrov-Smirnov test was applied. For normally distributed data Pearson and for the data non- normally distributed data Spearman correlation coefficient were used for correlation analysis. Student's t-test was used for comparing the negative two groups of data that fits normal distribution. Mann-Whitney U test was used for comparing the non-normally distributed data. A $p<0.05$ was considered as statistically significant.

Results

Baseline characteristics

Clinical and demographical characteristics of the study population is shown in Table 1. The average age was 48.2±9.7 years. Eighty one (39.1%) of the patients were male. Forty-three patients (20.8%) were smokers, BMI was 29.5±5.2 (18.3%).

Relationship between PON 1 levels and EFT

Serum PON 1 level were 250.4±144.6 IU/dL, EFT levels were 5.2±1.7 mm, respectively. There were not statistically significant correlation between serum PON 1 and the level of EFT thickness (correlation coefficient: -0.127, p=0.069) (Fig. 1).

Relationship between variables and EFT and PON 1 level

There was found statistically significant relationship between PON 1 levels and the presence of diabetes mellitus (DM), age, LDL cholesterol, and serum creatinine levels (correlation efficient/p value: -0.182/0.009; -0.172/0.013; 0.145/0.037; -0.192/0.006, respectively), and also statistically significant relationship between EFT thickness and age, BMI, HT, and fasting glucose (correlation efficient/p value: 0.508/<0.001); 0.214/0.002); 0.319/<0.001); 0.264/<0.001, respectively) (Table 2).

As shown in Table 3, there were significant relation between EFT thickness ≥7 mm and serum PON 1 level, age, fasting glucose, serum trigliseride level, hypertension (p<0.001, p<0.001, p=0.013, p=0.014, p=0.001, respectively). Also, there were significant relation between EFT thickness ≥5 mm and age, fasting glucose, BMI, HT (p<0.001, p=0.002, p=0.006, p<0.001, respectively).

Discussion

In the present study, we investigated that relation between EFT thickness and serum PON 1 levels. We have demonstrated that there were no relation between serum PON 1 level and EFT thickness, but there were significant relation between EFT thickness (≥7 mm) and serum PON 1 level.

Visceral adipose tissue has been recognized as a risk factor for the occurrence of CVD (14, 15). Previous studies showed that epicardial adipose tissue is responsible for the production of many proinflammatory and proatherogenic bioactive adipokines: such as tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1, interleukin-6, nerve growth factor (NGF), resistin, visfatin, omentin, leptin, plasminogen activator inhibitor-1 (PAI-1), and angiotensinogen (16-21). Determining the amount of visceral adipose tissue helps to the determination of high-risk patient group. As shown in previous studies, metabolic syndrome, EFT thickness, and insulin resistance is associated with subclinical atherosclerosis and CVD (22-38).

PON 1 is an enzyme that consists of 355 amino acids with a molecular mass of 43 kDa. Majority of this enzyme of which almost all of it is associated with HDL cholesterol in humans, is produced in liver (39, 40). It is found that serum PON 1 levels in patients with CVD were lower than the normal control group. At patients with low serum PON1 level and CAD, it has been found to be associated with the severity of the disease (41). Zama et al. (42) showed that at patients with low serum PON 1 activity level and CAD, during the follow-up, more major cardiovascular events occurred in.

Previous studies demonstrated that there is a correlation between age and EFT thickness (43, 44). In this study, we demonstrated that there is a strong correlation between EFT thickness and age. When the participants' age were older, the correlation value became stronger between EFT thickness and age.

Iacobellis et al. (12) found that the incidence of insulin resistance is higher in patients whose EFT thickness is higher than 9.5 mm. In addition, there were relation between fasting glucose and EFT (45). In this study, we showed that there were correlation fasting glucose and EFT thickness, and when EFT thickness increased, relation became stronger.

Previous studies showed that there is a linear correlation between thickness of EFT and triglyceride levels (46). In our study, unlike previous studies, no linear correlation could be found between thickness of EFT and triglyceride levels. However, serum triglyceride levels in patients with ≥7 mm EFT thickness were found significantly higher.

Table 1. Clinical and demographic characteristics of the study population

Male/ female, n, %	81 (39.1%)/126 (60.9%)
Age, years±SD	48.2±9.7
Body mass index, kg/m^2±SD	29.5±5.2
Smoking, n, %	43 (20.8%)
Metabolic syndrome, n, %	70 (33.8%)
Hypertension, n, %	72 (34.8%)
Hyperlipidemia, n, %	14 (6.8%)
Diabetes mellitus, n, %	17 (8.2%)
LDL cholesterol, mg/dL±SD	123.6±34.4
HDL cholesterol, mg/dL±SD	53.5±14.1
Trygliceride, mg/dL±SD	152.3±145.5
Fasting glucose, mg/dL±SD	96.5±25.2
Serum creatinine, mg/dL±SD	0.79±0.20
(n)	207

Table 2. Correlation between epicardial fat tissue thickness and serum paraoxonase 1 levels and variables

	Paraoxonase	EFT thickness
Age	-0.172 (p=0.013)	0.508 (p<0.001)
Diabetes mellitus*	-0.182 (p=0.009)	0.035 (p=0.61)
Smoking*	0.010 (p=0.89)	-0.037 (p=0.59)
Metabolic syndrome*	-0.124 (p=0.08)	0.106 (p=0.13)
Hypertension*	0,037 (p=0.60)	0.319 (p<0.001)
Hyperlipidemia*	-0.098 (p=0.16)	0.074 (p=0.29)
Body mass index**	0.055 (p=0.43)	0.214 (p=0.002)
LDL cholesterol**	0.145 (p=0.037)	0.091 (p=0.19)
HDL cholesterol**	0.123 (p=0.08)	0.003 (p=0.97)
Trygliseride**	-0.110 (p=0.12)	0.148 (p=0.034)
Fasting glucose**	-0.050 (p=0.47)	0.264 (p<0.001)
Serum creatinine**	-0.192 (p=0.006)	0.085 (p=0.25)

EFT - epicardial fat thickness; HDL - high density lipoprotein; LDL - low density lipoprotein;
*For non-parametric variables: Spearman correlation test were used
**For parametric variables: Pearson correlation test were used

Study limitations

This study has some limitations. This study is a single center, and nonrandomized study. The sample size was relatively small and there were no control group in this study. Although previous studies have detected the relationship with HL, in this study it couldn't be demonstrated. It may be due to the fact that using antihyperlipidemic drug has been affecting the level of PON 1 and in this study the patients newly diagnosed hyperlipedemia (HL) and hyperlipedemic (HL) patients with using antihyperlipidemic drug were not evaluated separately.

Table 3. Relation between variables and epicardial fat tissue thickness (after thickness adjustment)

	<7 mm	≥7 mm		<5 mm	≥5 mm	
	Mean value		*P*	Mean value		*P*
Number of patients	163	44		86	121	
Age*	45.9	56.5	<0.001	43.5	51.5	<0.001
Paraoxonase**	253.9	168.9	<0.001	250.8	225.2	0.69
Fasting glucose**	95.2	101.1	0.013	91.1	100.2	0.002
HDL cholesterol**	53.8	52.4	0,425	53.6	53.5	0.8
Trygliseride**	137.1	208.2	0.014	136.5	163.4	0.31
LDL cholesterol**	123.7	123.2	0.614	117.8	127.8	0.09
Creatinine**	0.77	0.84	0.106	0.77	0.8	0.71
Body mass index**	29.3	30.1	0.095	28.7	30	0.006
Male/female*	60/103	23/21	0.19	32/54	49/72	0.63
Hypertension (+/-)*	47/116	25/19	0.001	17/69	55/66	<0.001
Diabetes mellitus (+/-)*	12/151	5/39	0.392	7/79	10/111	0.97
Hyperlipidemia (+/-)*	10/153	4/40	0.489	5/81	9/112	0.64
Smoking (+/-)*	35/128	8/36	0.634	20/66	23/98	0.46
Metabolic syndrome (+/-)*	51/112	19/25	0.140	26/60	44/77	0.36

HDL - high density lipoprotein; LDL - low density lipoprotein;
*For normally distributed variables: Student's t test were used
**For non-normally distributed variables Mann-Whitney U test were used

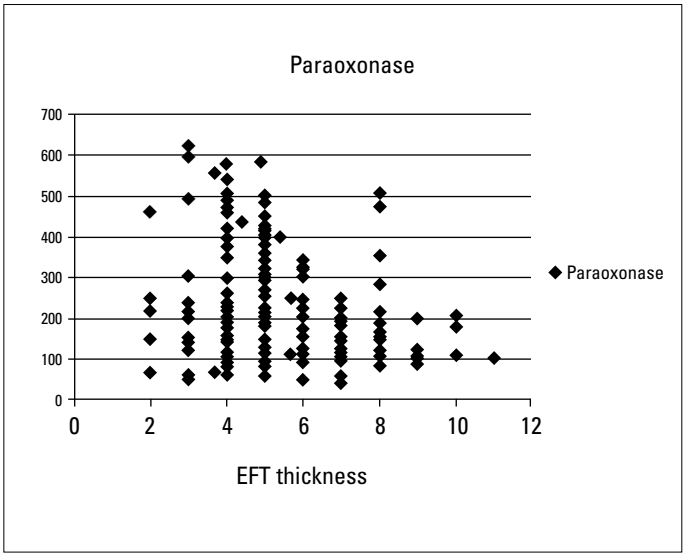

Figure 1. Correlation between epicardial fat tissue thickness and serum paraoxonase levels. (Correlation coefficient: -0.127, p=0.069)

Conclusion

In this study, there were no relation between serum PON 1 levels and EFT thickness. If we set the EFT thickness as ≥7 mm, there were significantly relation between serum PON1 levels and EFT thickness. There were also relation between EFT thickness (≥7 mm) and age, fasting glucose, serum trygliseride level, and hypertension (HT).

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