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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Adipocyte fatty acid binding protein levels in patients with coronary artery disease and its relationship to alternative biomarkers

Dilara Kaman, Necip Ilhan, Mehmet Akbulut

University Firat Medical Centre, Elazığ, Turkey

Abstract

Background and aim: An association between circulating adipocyte fatty acid-binding protein (A-FABP) levels and coronary artery disease (CAD) has been reported. In this case-control study, we investigated the relationship between plasma levels of A-FABP and the severity of CAD in Turkish subjects. We also assessed its relationship to alternative biomarkers.

Methods: Two hundred and eighty patients undergoing coronary angiography were enrolled in the study. By means of coronary angiography, the study population was divided into subjects without any angiographically detectable CAD (no vessel disease; n = 88) and individuals with single-vessel disease (n = 65), or double- or triple-vessel disease (n = 127). Lipid concentrations were measured by an autoanalyser and A-FABP, lipoprotein associated phospholipase A_2 (Lp-PLA_2), oxidised-low density lipoprotein (ox-LDL) and high-sensitivity C-reactive protein (hsCRP) levels by a commercial enzyme-linked immunosorbent assay (ELISA) kit.

Results: In our study population, total cholesterol and LDL cholesterol levels did not differ significantly between the groups. Levels of high density lipoprotein cholesterol, A-FABP, Lp-PLA_2, ox-LDL and hsCRP were significantly different among groups. The higher levels of A-FABP, Lp-PLA_2, ox-LDL and hsCRP levels were shown in patients with double/triple-vessel disease. There was not a significant correlation between A-FABP and other biomarkers in CAD patients.

Conclusions: Initially, plasma levels of A-FABP were significantly elevated in CAD patients with double/triple-vessel disease. Our results demonstrated alterations in A-FABP levels with severity of CAD and, therefore, indirectly support the hypothesis of an active role for A-FABP in the pathogenesis of CAD.

Key words: adipocyte fatty acid-binding protein (A-FABP), coronary artery disease, lipoprotein associated phospholipase A_2 (Lp-PLA_2), oxidised-low density lipoprotein (ox-LDL), high-sensitivity C-reactive protein (hsCRP)

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INTRODUCTION

Cardiovascular (CV) diseases are the leading cause of death and disability in developed countries. Several factors have been hypothesised as participating in the development of atherosclerosis; however, the precise mechanisms remain unclear.

Fatty acid binding proteins (FABPs) are small, highly expressed cytoplasmic proteins and they bind fatty acids, eicosanoids, and other lipids reversibly [1–3]. Adipose tissue FABP (A-FABP, also known as AP2 and FABP4) gene has been carefully examined and it has been shown that A-FABP plays an important role in plasma lipid levels, insulin sensitivity, and coronary heart disease risk [4]. It is also present in macrophages and possesses similar functions to adipocytes. It has been suggested that A-FABP is modulated by proliferator-activated receptor-γ agonists and oxidised low density lipoproteins (ox-LDL) [5]. Both the biomarker and functional properties of A-FABP have been studied in relation to atherosclerotic disease. Data from animal studies also supports that A-FABP deficiency results in a marked reduction of atherosclerotic lesions in apolipoprotein E-deficient mice [6]. By using an antagonist, the inhibition of A-FABP resulted in a significant protection against atherosclerotic plaque formation in mice [7]. Effects of A-FABP on atherosclerotic disease progression seem to be specific for macrophage-derived A-FABP. Human and animal studies show that A-FABP functions at the interface of lipid metabolism and inflammatory responses and acceler-

Address for correspondence:
Dilara Kaman, MD, Associate Professor, Department of Biochemistry, University Firat Medical Centre, Elazığ, Turkey, tel: +90 424 2333555 ext. 2260, fax: +90 424 2388096, e-mail: drdilara_76@hotmail.com

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ates CV disease. A-FABP antagonists can be used to combat atherosclerotic disease in further studies. Although human studies showed that the plasma A-FABP level predicted the development of type II diabetes [8] and was independently associated with carotid intima–media thickness in Chinese women [9] and the number of stenotic coronary arteries in Korean adults [10], another report in Caucasians reported that plasma A-FABP was not associated with clinical and subclinical atherosclerosis [11].

Lipoprotein associated phospholipase A_2 (Lp-PLA_2) is a risk factor associated with a higher incidence of CV events. It is also an important pathogenic factor participating in the progression of atherosclerosis [12]. Lp-PLA_2 is an enzyme produced by inflammatory cells as well as T-lymphocytes in atherosclerotic plaques and by liver cells [13]. Lp-PLA_2 hydrolysis the oxidised phospholipids, and leads to the production of pro-inflammatory products (lysophosphatidylcholine and oxidised non-esterified fatty acids) [13]. It has been shown that Lp-PLA_2 is associated with LDL [13]. Significantly higher concentration of Lp-PLA_2 has been reported in vulnerable and ruptured plaques. The correlation between elevated Lp-PLA_2 levels and increased risk for CV events has been demonstrated in studies [14, 15]. Lp-PLA_2 is positively correlated with LDL cholesterol and triglyceride levels, and is inversely associated with high-density lipoprotein (HDL) cholesterol [15].

Oxidised-LDL has a prominent role in the pathogenesis of atherosclerosis [16]. The oxidative conversion of LDL to ox-LDL is considered to be a key factor in the development of early atherosclerotic lesions [17]. The elevation of ox-LDL levels in atherosclerotic plaques is an important event in the development of atherosclerosis [18]. Circulating ox-LDL could be a predictor of coronary artery disease (CAD) patients [19, 20].

Although debate persists regarding the precise physiologic role of C-reactive protein (CRP), the prognostic value of high-sensitivity CRP (hsCRP) as a marker of CV risk is now firmly established. Prospective epidemiologic studies with follow-up periods ranging from three to 20 years have found that a single hsCRP measurement is a strong predictor of myocardial infarction or coronary heart disease mortality, stroke, peripheral vascular disease, congestive heart failure, atrial fibrillation, and sudden cardiac death in individuals without a history of CV disease [21–29].

In this case-control study, we investigated the relationship between plasma levels of A-FABP and the severity of CAD in Turkish subjects. We also assessed its relationship to alternative biomarkers such as Lp-PLA_2, ox-LDL, and hsCRP.

METHODS

The patient population and documentation of CAD severity

This was a case-control study. The cases and controls were angiographically confirmed. The study sample comprised 280 persons who underwent coronary angiography for diagnostic purposes. The angiograms were assessed by two cardiologists who were unaware that the patients were to be included in the study. No patient was treated with thrombolytics, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers. The extent of coronary lesions was estimated visually by comparing the reduction in the diameter of the narrowed vessel to a proximal assumed normal arterial segment. The three main arteries (left anterior descending artery, left circumflex artery, or right coronary artery) were classified as free of disease, or presenting ≥ 50% stenosis. Patients having a normal angiogram with no atherosclerosis or lesions in coronary arteries were considered as CAD control subjects (n = 88). Patients with coronary artery stenosis were classified into two categories: CAD patients with ≥ 50% stenosis in one vessel (n = 65), or CAD patients with ≥ 50% stenosis in two or three vessels (n = 127) (Table 1).

Table 1. Clinical characteristics of individuals with single, double/triple-vessel disease and controls

	Control (n = 88)	Single-vessel (n = 65)	Double/triple-vessel (n = 127)	P
Age [years]	58.03 ± 8.06	60.01 ± 12.05	60.87 ± 8.34	0.92
Gender (female/male)	53%/47%	48%/24%	95%/43%	0.055
Hypertension	27.3%	32.3%	41.7%	0.08
Smoking	30.7%	33.8%	32.3%	0.92
Creatinine [mg/dL]	0.82 ± 0.21	1.08 ± 0.59	1.07 ± 0.39	< 0.001
$eGFR_{MDRD}$ [mL/min/1.73 m^2]	98.33 ± 53.77	80.09 ± 27.89	77.80 ± 28.11	< 0.001
Total cholesterol [mg/dL]	205.11 ± 51.62	200.67 ± 50.28	202.50 ± 55.79	0.87
Triglyceride [mg/dL]	149.21 ± 95.48	175.29 ± 78.10	174.40 ± 74.95	0.059
HDL-cholesterol [mg/dL]	46.61 ± 9.50	42.81 ± 11.27	41.19 ± 9.75	< 0.001
LDL-cholesterol [mg/dL]	132.47 ± 41.55	126.98 ± 39.44	130.77 ± 49.32	0.75
hsCRP [ng/mL]	2.81 ± 1.15	4.40 ± 2.10	5.50 ± 2.55	< 0.0001

eGFR — estimated glomerular filtration rate; LDL — low density lipoprotein; HDL — high density lipoprotein; hsCRP — high-sensitivity C-reactive protein

Written informed consent was obtained from all subjects, and the local ethics committee approved the study protocol.

Blood sample collection

Patients were fasted for at least 6 h before venous blood samples were drawn into 5 mL EDTA vacuum tubes and blood samples were separated in a refrigerated centrifuge within 15 min of collection for determination of plasma A-FABP, Lp-PLA$_2$, ox-LDL and hsCRP. Plasma was divided into small aliquots, stored at –20°C until analysis. For determination of serum lipids and creatinine, a blood sample was obtained from the cubital vein of each participant and the samples were sent for detection within 1 h. by using the Advia 1800 (Siemens Diagnostics, Tarrytown, NY, USA) autoanalyser and reactives. The creatinine method is based on the reaction of picric acid with creatinine in an alkaline medium as described in the original procedure of Jaffe.

Based on the serum creatinine level on admission, estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula [175 × (serum creatinine)$^{1.154}$ × (age)$^{0.203}$ × (0.742 if patient is female)] [30].

Determination of plasma levels of A-FABP, Lp-PLA$_2$, ox-LDL and hsCRP

Plasma levels of A-FABP (Adipo bioscience, USA; Cat no: SK00030-09), hsCRP (DRG®, USA; Cat no: EIA3954), Lp-PLA$_2$ (Cusabio biotech, China, Cat No: CSB-E08319h) and ox-LDL (Biomedica Medizinprodukte GmbH & Co KG, Austria; Cat no: BI-20022) were measured by enzyme-linked immunosorbent assay.

Statistical analysis

All of the statistical analyses were performed using the SPSS 12.0 statistical package. We have presented normally distributed data as mean ± standard deviation. ANOVA was used to test for overall differences in mean levels of total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, A-FABP, Lp-PLA$_2$, ox-LDL and hsCRP between the groups. When we analysed the quantitative relationships between A-FABP and alternative biomarkers, bivariate correlation coefficients were calculated, using Pearson's for parametric data. Two-tailed p values are reported. For the comparisons of the values of different groups, $p < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of patients with single/double/triple-vessel disease and controls

The clinical characteristics of the patients with single/double/triple-vessel disease and controls are shown in Table 1. Total cholesterol, triglyceride and LDL cholesterol levels did not differ significantly between the groups. Levels of HDL cholesterol, creatinine, eGFR and hsCRP were significantly different among groups ($p < 0.001$, $p < 0.001$, $p < 0.001$ and $p < 0.0001$, respectively). The higher level hsCRP and the lowest level of HDL cholesterol were shown in patients with double/triple-vessel disease. Fasting plasma levels of A-FABP, Lp-PLA$_2$ and ox-LDL according to groups are presented in Figures 1–3. There was a tendency for increased fasting levels of A-FABP, Lp-PLA$_2$ and ox-LDL as the number of stenotic coronary arteries increased. The highest fasting level of A-FABP, Lp-PLA$_2$ and ox-LDL occurred with double/triple-vessel in CAD patients and the lowest values were observed in controls. There were no statistical significances in A-FABP concentrations between double- and triple-vessel disease ($p = 0.71$, data not shown). There was no statistically significant difference in fasting levels of A-FABP, Lp-PLA$_2$ and ox-LDL between control subjects and single-vessel disease.

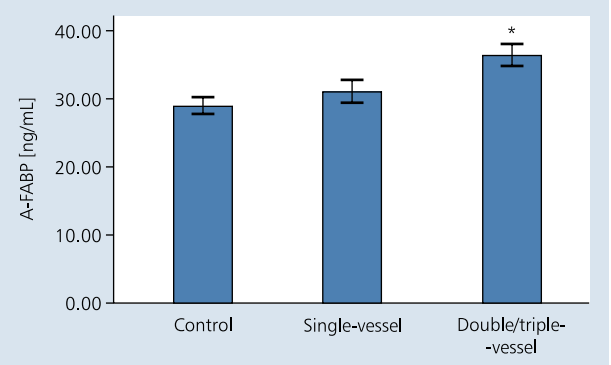

Figure 1. Fasting plasma levels of plasma adipocyte fatty acid-binding protein (A-FABP) in control and coronary artery disease patients. Data was analysed by ANOVA; *$p < 0.0001$, compared to control and single-vessel disease

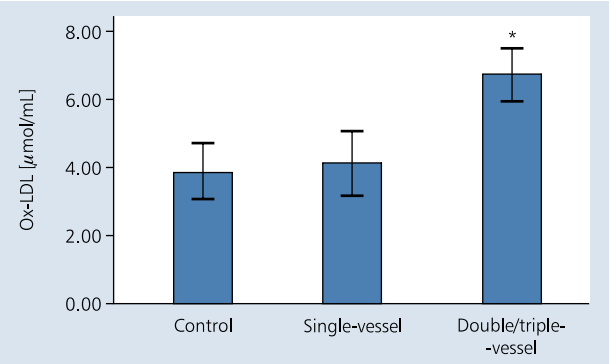

Figure 2. Fasting plasma levels of oxidised-low density lipoprotein (ox-LDL) in control and coronary artery disease patients. Data was analysed by ANOVA; *$p < 0.0001$, compared to control and single-vessel disease

Correlation of A-FABP with other biomarkers

Table 2 shows the correlations between A-FABP levels and alternative biomarkers in patients with CAD. There was no significant correlation between A-FABP and other biomarkers.

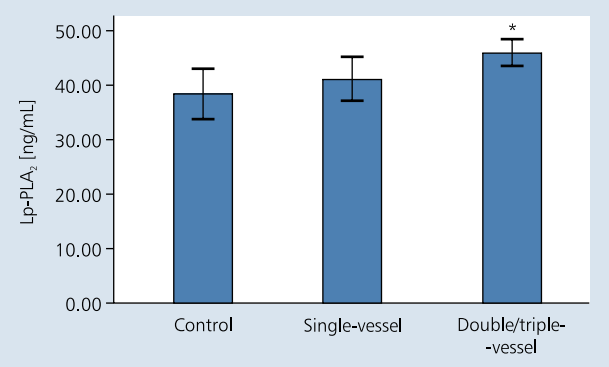

Figure 3. Fasting plasma levels of lipoprotein associated phospholipase A_2 (Lp-PLA_2) in control and coronary artery disease patients. Data was analysed by ANOVA; *$p < 0.005$, compared to control

Table 2. Pearson correlations for plasma adipocyte fatty acid-binding protein (A-FABP) with the other clinical variables in patients with coronary artery disease

	r	P
Age [years]	0.074	0.31
Ox-LDL [μmol/mL]	0.022	0.76
Lp-PLA_2 [ng/mL]	–0.024	0.74
hsCRP [ng/mL]	0.098	0.18
Total cholesterol [mg/dL]	0.016	0.82
HDL-cholesterol [mg/dL]	–0.068	0.35
LDL-cholesterol [mg/dL]	0.032	0.66
Triglyceride [mg/dL]	–0.006	0.93
Creatinine [mg/dL]	0.027	0.71

ox-LDL — oxidised-low density lipoprotein; Lp-PLA_2 — lipoprotein associated phospholipase A_2; hsCRP — high-sensitivity C-reactive protein; LDL — low density lipoprotein; HDL — high density lipoprotein

Logistic regression analysis was performed to analyse the relevance of selected parameters to clinical outcomes (Table 3). Plasma hsCRP and serum triglyceride levels proved to be significantly linked with CAD patients in all vessel diseases. Plasma A-FABP, ox-LDL and Lp-PLA_2 levels were significantly linked with CAD patients only in double/triple vessel-disease ($p < 0.0001$).

DISCUSSION

In the current study, we provided clinical evidence showing that A-FABP was closely associated with the severity of CAD, and was a significant risk factor for the development of CAD. Furthermore, plasma hsCRP and serum triglyceride levels proved to be significantly linked with CAD patients in all vessel diseases and A-FABP, ox-LDL and Lp-PLA_2 levels were significantly linked with CAD patients only in double/triple-vessel disease.

CAD remains a leading cause of death, despite significant improvements in treatment and prevention of primary disease manifestations. Atherosclerosis proceeds in the presence of enhanced serum cholesterol levels and it is considered an autoimmune-like inflammatory disease [31]. Studies to understand the pathogenesis of atherosclerotic disease often focus on the role of the local inflammatory response or lipid metabolism and lipoprotein profiles.

The relationship of A-FABP with metabolic disease has been well demonstrated in several clinical studies, which might partly explain the impact of A-FABP on CAD. In a recent study, circulating A-FABP levels and CV morbidity and mortality in patients with coronary heart disease were examined [32]. This study included a ten-year follow-up with > 200 major CV events and reported that circulating A-FABP levels are associated with long-term prognosis in patients with coronary heart disease. Although the predictive value of A-FABP for the occurrence of CV events was tested, the results will have more relevance from a pathogenesis perspective. Bao et al. [33] reported that A-FABP was closely associated with the severity of coronary atherosclerosis, and was a significant risk factor for the development of CAD in Chinese women. The mechanism of the association between A-FABP and CAD has been investigated in several studies. A-FABP is capable of binding to various intracellular hydrophobic compounds such as saturated and unsaturated long-chain fatty acids, modulating cholesterol ester accumulation, and mediating intracellular lipid trafficking, thus altering cellular and systemic lipid transport and composition, as well as contributing to dyslipidaemia [34, 35].

Numerous epidemiological studies have demonstrated the correlation between increased levels of Lp-PLA_2 and increased risk for both primary and secondary CV events [14, 15]. Lp-PLA_2 has been shown to be an independent risk factor for CV events; enzyme activity and mass positively correlated with LDL cholesterol and triglyceride levels, and was inversely associated with HDL cholesterol [15].

In accordance with previously published data, we found that the total plasma Lp-PLA_2 (mass or activity) is associated positively with the severity of CAD. The level of plasma Lp-PLA_2 was higher in CAD patients with double/triple-vessel disease and the lowest level was in control subjects. Indeed, previous studies have consistently demonstrated that the total plasma Lp-PLA_2, which primarily represents the LDL-associated enzyme, is associated with CV events in subjects both with and without documented CAD, and these findings support the hypothesis that this enzyme may be a causal mediator of atherosclerosis and plaque instability.

There are many well-established factors that influence the prognosis of CAD, such as hsCRP which is the most promising biomarker in terms of clinical utility [36–38]. The current study shows that hsCRP level proved to be significantly linked with

Table 3. Logistic regression analysis of determinants of clinical outcomes

Parameters	Single-vessel		Double/triple-vessel	
	OR (95% CI)	P	OR (95% CI)	P
Age (per year)	0.73 (0.33–1.61)	0.437	0.28 (0.11–0.71)	0.007
Male (yes)	0.59 (0.24–1.50)	0.266	0.87 (0.35–2.17)	0.759
Smoking (yes)	0.66 (0.29–2.11)	0.337	0,93 (0.38–2.26)	0.875
Hypertension (yes)	0.75 (0.32–1.75)	0.507	0,27 (0.10–0.71)	0.008
Creatinine [mg/dL]	0.78 (0.29–2.11)	0.624	0.54 (0.22–1.28)	0.159
Total cholesterol [mg/dL]	1.01 (0.28–4.10)	0.930	1.42 (0.34–6.02)	0.635
Triglyceride [mg/dL]	0.25 (0.10–0.63)	0.003	0.18 (0.07–0.50)	0.001
HDL-cholesterol [mg/dL]	1.03 (0.45–2.35)	0.930	0.96 (0.38–2.41)	0.930
LDL-cholesterol [mg/dL]	0.79 (0.24–2.65)	0.705	0.80 (0.20–3.22)	0.754
A-FABP level [ng/mL]	1.48 (0.66–3.36)	0.345	0.06 (0.02–0.15)	< 0.001
hsCRP [ng/mL]	0.36 (0.16–0.81)	0.013	0.38 (0.16–0.89)	0,025
Ox-LDL [μmol/mL]	0.71 (0.32–1.58)	0.403	0.30 (0.06–0.38)	< 0.001
Lp-PLA_2 [ng/mL]	0.65 (0.30–1.45)	0.298	0.15 (0.11–0.80)	< 0.001

OR — odds ratio; CI — confidence interval; other abbreviations as in Tables 1 and 2

CAD patients in all vessel diseases. Prospective epidemiologic studies have found that a single hsCRP measurement is a strong predictor of myocardial infarction or CAD mortality, stroke, peripheral vascular disease, congestive heart failure, atrial fibrillation, and sudden cardiac death in individuals without a history of CAD [21, 22, 24, 39–41]. CRP is a component of innate immunity that actively participates in the inflammatory process. Recent studies have suggested that hsCRP has a direct pathogenic role in the atherosclerosis process and plaque formation [42–44] and that an increasing hsCRP level promotes arterial atherosclerosis. Alternatively, this may merely be an epiphenomenon and an indicator of systemic inflammation which itself is associated with atherosclerosis.

Ox-LDL plays roles in all stages of CAD. The results of various studies have shown that ox-LDL impairs endothelial progenitor cell migration [45–48]. We found that CAD patients with double/triple-vessel disease have elevated plasma ox-LDL levels.

CONCLUSIONS

Plasma levels of A-FABP, Lp-PLA_2, ox-LDL and hsCRP were significantly elevated in CAD patients with double/triple-vessel disease in a Turkish population. A-FABP levels were not correlated with alternative biomarkers in patients with CAD. Our results demonstrated alterations in A-FABP levels with severity of CAD and, therefore, indirectly support the hypothesis of an active role for A-FABP in the pathogenesis of CAD.

Conflict of interest: *none declared*

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Stężenie adipocytarnego białka wiążącego kwasy tłuszczowe u pacjentów z chorobą wieńcową i zależności między tym białkiem a innymi biomarkerami

Dilara Kaman, Necip Ilhan, Mehmet Akbulut

University Firat Medical Centre, Elazığ, Turcja

Streszczenie

Wstęp i cel: Opisano związek między stężeniem krążących białek wiążących kwasy tłuszczowe adipocytów (A-FABP) i chorobą wieńcową (CAD). W tym kliniczno-kontrolnym badaniu autorzy przeanalizowali zależności między stężeniem A-FABP w osoczu a ciężkością CAD u osób narodowości tureckiej. Autorzy ocenili również zależności między tym białkiem a innymi biomarkerami.

Metody: Do badania włączono 280 chorych poddanych koronarografii. Na podstawie jej wyników pacjentów podzielono na trzy grupy: osoby bez wykrywalnej w koronorografii CAD (bez zmian w naczyniach; n = 88), osoby z chorobą jednonaczyniową (n = 65) i osoby z chorobą dwu- lub trójnaczyniową (n = 127). Stężenia lipidów mierzono za pomocą analizatora automatycznego, a stężenia A-FABP, fosfolipazy A_2 związanej z lipoproteinami (Lp-PLA_2), utlenionych LDL (ox-LDL) i wysokoczułego białka C-reaktywnego (hsCRP) określano przy użyciu komercyjnego enzymatycznego testu immunoabsorpcyjnego (ELISA).

Wyniki: W badanej populacji ani stężenia cholesterolu całkowitego, ani stężenia cholesterolu frakcji LDL nie różniły się znamiennie między grupami. Stężenia cholesterolu frakcji LDL, A-FABP, Lp-PLA_2, ox-LDL i hsCRP różniły się istotnie między grupami. Najwyższe stężenia A-FABP, Lp-PLA_2, ox-LDL i hsCRP stwierdzono u pacjentów z chorobą dwunaczyniową/trójnaczyniową. U osób z CAD nie wykazano istotnych korelacji między A-FABP a innymi biomarkerami.

Wnioski: Stężenie A-FABP w osoczu było istotnie zwiększone u pacjentów z CAD z chorobą dwunaczyniową/trójnaczyniową. Uzyskane w tym badaniu wyniki wykazały zmiany stężenia A-FABP zależne od stopnia ciężkości CAD, co potwierdza pośrednio hipotezę o aktywnej roli A-FABP w patogenezie CAD.

Słowa kluczowe: białka wiążące kwasy tłuszczowe adipocytów (A-FABP), choroba wieńcowa, fosfolipaza A_2 związana z lipoproteinami (Lp-PLA_2), utlenione LDL (ox-LDL), wysokoczułe białko C-reaktywne (hsCRP)

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Adres do korespondencji:
Dilara Kaman, MD, Associate Professor, Department of Biochemistry, University Firat Medical Centre, Elazığ, Turkey, tel: +90 424 2333555 ext. 2260, fax: +90 424 2388096, e-mail: drdilara_76@hotmail.com
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