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Relationship between atherosclerosis risks and lipoprotein-dependent phospholipase a2 activity in type 2 diabetic patients

Tip 2 diyabetli hastalarda ateroskleroz riski ile lipoprotein-bağımlı fosfolipaz a2 aktivitesi arasındaki ilişki

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Abstract

Aim: Atherosclerosis is the most common macro-complication of diabetes and the most common cause of coronary artery disease. We aimed to investigate the relationship between the risk of atherosclerosis and lipoprotein-dependent phospholipase A2 activity in patients with type 2 diabetes.

Methods: The study was enrolled on 48 subjects: Group I: control group consisting of 20 healthy participants. Group II: 28 patients of type 2 diabetes mellitus before statin (rosuvastatin 10 mg/day) therapy. Group III: 28 patients of type 2 diabetes mellitus after statin (rosuvastatin 10 mg/day) therapy. Lp-PLA_2 activity was measured with immuno-turbidimetric method (plac test kit), HDL-C (High-Density Lipoprotein Cholesterol), LDL-C (Low-Density Lipoprotein Cholesterol), triglyceride, cholesterol and fasting blood glucose (FBG), levels were measured by spectrophotometric method using autoanalyzer (Architect C16000). LDL-C levels were measured by an assay for the direct quantification of LDL-C. Carotid intima-media thickness (IMT) was measured by B-mode ultrasonography method.

Results: Serum Lp-PLA_2 activity, serum LDL-C, triglyceride, cholesterol levels and IMT values of Group II (before 10 mg/gün rosuvastatin therapy) and Group III (after rosuvastatin therapy) patients were statistically significant higher than Group I (control group) ($p<0.01$) Serum Lp-PLA_2 activity, serum LDL-C, triglyceride, cholesterol levels and IMT values of Group II patients were statistically significant higher than Group III patients ($p<0.01$) and HDL-C levels only were lower than Group III (after 10 mg/gün rosuvastatin therapy) but It was not statistically significant ($p=0.198$).

Conclusion: According to our results, Increased Lp-PLA_2 activity is associated with risk of atherosclerosis in diabetic patients and plays an important role in the progression of atherosclerosis.

Keywords: Atherosclerosis, Diabetes, Statin therapy, Lp-PLA_2, Intima-media thickness

Öz

Amaç: Ateroskleroz diyabetik en sık makro komplikasyonudur ve koroner arter hastalığının en temel nedenidir. Çalışmamızda tip 2 diyabetli hastalarda ateroskleroz riski ile lipoprotein bağımlı fosfolipaz A_2 (Lp-PLA_2) aktivitesi arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Çalışmaya 48 kişi dahil edildi. Grup I: sağlıklı katılıcılardan oluşan kontrol grubu, Grup II: Statin (Rosuvastatin 10 mg/gün) tedavisi öncesi tip 2 diyabetli 28 hasta. Grup III: Statin (Rosuvastatin 10 mg/gün) tedavisi sonrası 28 tip 2 diyabetli hasta. Hiperlipidemisi olan diyabetik hastaların ve sağlıklı gönüllülerin serum örneklerinden, Serum Lp-PLA_2 aktivitesi immünotürbidimetrik yöntem (plac test kit) ile ve Serum HDL-C (Yüksek Dansiteli Lipoprotein Kolesterol), LDL-C (Düşük Dansiteli Lipoprotein Kolesterol), trigliserid, kolesterol ve açlık glikoz seviyeleri otoanalizör kullanılarak (Architect C16000) spektrofotometrik yöntemle ölçüldü. LDL-C ölçümü direct LDL kiti ile gerçekleştirildi. Karotis intima-media kalınlığı (IMK) B-mode ultrasonografi metodu ile ölçüldü.

Bulgular: Grup II (rosuvastatin (10 mg/gün) tedavisi öncesi) and Grup III (rosuvastatin (10 mg/gün) tedavisi sonrası) hastalarının serum Lp-PLA_2 aktivitesi, serum LDL-C, trigliserid, kolesterol düzeyleri ve IMK değerleri Grup I'e (kontrol grubu) göre istatistiksel olarak anlamlı düzeyde yüksek bulundu ($p<0,01$). Grup II'nin serum Lp-PLA2 aktivitesi, serum LDL-C, trigliserid, kolesterol düzeyleri ve IMK değerleri Grup III'e göre istatistiksel olarak anlamlı düzeyde yüksek bulunurken ($p<0,001$), serum HDL-C düzeylerinde istatistiksel olarak anlamlı bir fark elde edilemedi ($p=0,198$).

Sonuç: Sonuçlarımıza göre, artan serum Lp-PLA_2 aktivitesi diyabetik hastalarda ateroskleroz riski ile ilişkilidir ve ateroskleroz gelişiminde önemli role sahiptir.

Anahtar kelimeler: Ateroskleroz, Diyabet, Statin tedavisi, Lp-PLA_2, İntima-media kalınlığı

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Introduction

Diabetes increases the clinical risk of cardiovascular morbidity and mortality. This risk remains elevated with conventional low-density lipoprotein cholesterol (LDL-C) lowering therapies, such as statins [1]. Atherosclerosis is a major cause of coronary artery disease and most common macro complication of diabetes [2]. Atherosclerosis is a disease of the arterial wall, initiated by dyslipidemia and exacerbated by inflammation. An early event in the progression of the disease is the accumulation of LDL-C in subintima of arterial wall where it may become oxidized (oxLDL). Subclinical atherosclerosis precedes cardiovascular disease (CVD) and an increased intima-media thickness (IMT), measured by ultrasonography, and is regarded as an early indicator of generalized atherosclerosis [3]. Inflammation plays an important causal role in the initiation and progression of atherosclerosis lesion by promoting sustained plaque inflammation, large necrotic cores, thin fibrous caps, and thrombosis [4].

Lipoprotein-associated phospholipase A2 (Lp-PLA_2), known as a novel inflammatory biomarker, is involved in the pathophysiology of atherosclerosis [5]. Lp-PLA_2 is produced by monocyte, macrophage and T lymphocytes on the atherosclerotic process [6-8]. Lp-PLA_2 also is known as platelet-activating factor acetylhydrolase (AH) that carry out hydrolysis of platelet activating factor (PAF) [9,10]. Meanwhile, Lp-PLA_2 also hydrolyzes the modified phospholipids, lysophosphatidylcholine and oxidized fatty acid on the oxidized LDL-C that accumulate on the arterial wall during the atherosclerotic process [11]. Almost all prospective and nested case-cohort studies suggested that Lp-PLA_2 is proatherogenic [12]. Especially, Lp-PLA_2 enlightens about inflammation that occurs in the vascular area on the atherosclerotic process. That's why, expression of Lp-PLA_2 increase in necrotic core, rupture-prone plaque, atherosclerotic plaque. Due to these features, Lp-PLA_2 is referred to as a mediator of plaque progression [7].

Carotid atherosclerosis is a major risk factor for ischemic stroke [13,14]. While lipid metabolism and inflammation have been the major focus of atherosclerosis research for many years, there has been growing interest in Lp-PLA_2 due to it is a key enzyme both in lipid metabolism and in stimulating inflammation [15,16]. Development of the B-mode ultrasound technique has made it possible to noninvasively study the atherosclerotic process. IMT of the carotid artery has been used as a noninvasive indicator of the atherosclerotic process in the coronary arteries [17,18].

In our current study, we purposed to investigate the association between the Lp-PLA_2 activity and atherosclerosis risk in diabetic patients. Therefore we also aimed to find a possible link between lipid-lowering treatment (10 mg/day Rosuvastatin) and IMT.

Materials and methods

28 (14 male, 14 female) patients having applied to Gazi University Medical Faculty Hospital Diabetes and Obesity Clinic, between the ages of 18-65 with type-2 diabetes, diagnosed with hyperlipidemia and would receive an anti-hyperlipidemic treatment for the first time; and 20 (10 male, 10 female) healthy participants volunteering for the control group were included in this study. Carotid IMT of the patients and of the control group was measured in the same day. Then, an antihyperlipidemic treatment started to be applied to the patients by the Department of Obesity and Diabetes in Gazi University (standard 10 mg/day Rosuvastatin). Following the 3-month-Rosuvastatin treatment, the patients were recalled to the clinic. Carotid intima-media thickness was measured the same day in addition to routine examinations. While determining the groups, the control group was classified as Group I; patients before the Rosuvastatin treatment as Group II; and patients after the rosuvastatin treatment as Group III. Group II and Group III were two dependent groups having the same patients. They were named differently in order to indicate that they represent the results at different times and to compare these results. Following 10-12 hours fasting of the patients and of the control group, venous blood was taken and centrifuged at 4000 rpm for 10 minutes. After completing routine biochemistry tests, the venous blood was stored at -80^0 until the day of study. Patients were informed regarding the study and consent forms were signed. In addition, this study was approved by the Ethics Committee of Gazi University Medical Faculty. This study was funded by Gazi University Scientific Research Projects (SRP) unit (Project No: 01/2009-04).

While determining the patients to be included in the study; those who previously received an antihyperlipidemic treatment, those using drugs affecting lipid metabolism, those who had cardiovascular disease, cigarette and alcohol users, those having BMI>30, those who had an infection recently and those who disrupted the antihyperlipidemic treatment were excluded from the study. Moreover, the control group was entirely composed of healthy volunteers not using alcohol and cigarette, not taking any medication and not having any previous cardiovascular medical record. All participants were informed about the study and the consent forms were received.

Lp-PLA_2 measurement and routine biochemistry tests

Lp-PLA_2 activity was measured in serum samples with the PLAC Test (diaDexus Inc) reagent kit on Olympus AU 400 clinical chemistry analyzer. The PLAC test is a turbidimetric immunoassay using two highly specific monoclonal antibodies (2C10 and 4B4) against Lp-PLA_2. Lp-PLA_2 concentrations were given as ng/ml. Clinical and analytical sensitivities of the assay are 7 ng/ml and 4 ng/ml respectively. Reference intervals suggested by the reagent manufacturer are 120-342 ng/ml for females and 131-376 ng/ml for males. HDL-C (High-Density Lipoprotein Cholesterol), LDL-C (Low-Density Lipoprotein Cholesterol), triglyceride, cholesterol and fasting blood glucose (FBG), levels were measured by spectrophotometric method using autoanalyzer (Architect C16000). LDL-C levels were measured by an assay for the direct quantification of LDL-C.

Carotid ultrasonography

All participants were examined in the supine position (head turned 45°) by the same trained operator with a high-resolution B-mode ultrasonography equipped with a 10 MHz linear array transducer (GE LOGIQ 9). In our study, IMT values of right and left carotid arteries were measured by ultrasonography and then, measured values were divided into

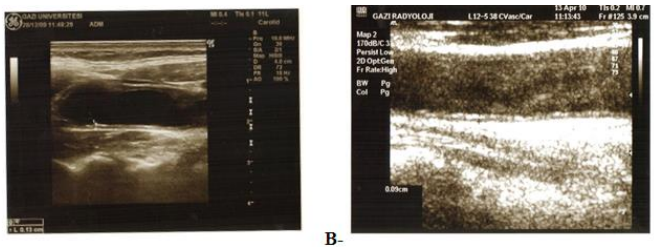
two average values were found and recorded by IMT value. IMT>0.9 mm values were considered to be pathological.

Statistical analysis

SPSS 15.0 for Windows program was used for the statistical analysis. Descriptive statistics were expressed as numbers and percentages for categorical variables; and as means, standard deviation, minimum, maximum and median for numeric variables. Normal distribution was determined by examining the distribution of skewness and kurtosis values, Kolmogorov-Smirnov (Lilliefors Significance Correction), Shapiro-Wilk tests and histogram graphs. Comparison of two independent groups not fulfilling the normal distribution requirement for numeric variables was performed by "Mann Whitney U" test; and the comparison of two dependent groups not fulfilling the normal distribution requirement was performed by Wilcoxon test. Statistical alpha significance level will be accepted as $p<0.05$. Due to the fact that the relations between numerical values did not meet parametric test requirement, it was examined by Spearman Correlation Analysis.

Results

Overall, the median age for the patients (n=28 (50% female, 50% male)) was 52.17 (39, 63) years and the median age for the control group (n=20 (50% female, 50% male)) was 48.02 (37-60) years. The baseline characteristics of all groups are shown in Table 1. The Lp-PLA2 activity levels were significantly higher in Group II than in Group III who receiving statin therapy (rosuvastatin 10 mg/day) ($p<0.01$). Moreover, the serum LDL-C, triglyceride and cholesterol levels were significantly higher in Group II than in Group III ($p<0.01$). Serum HDL-C levels were higher in Group III than Group II. However, it was not significant ($p<0.01$). IMT values were significantly lower in Group III than Group II ($p<0.01$). Pre and post-therapy results of IMT values which belong to a study patient were shown in Figure 1. According to the correlation results of Group II, exclusively, Lp-PLA2 activity was negatively correlated with HDL-C in Group II (r: -0.452, $p=0.016$). Lp-PLA_2 activity was not significantly correlated with LDL-C, triglyceride, cholesterol, IMT, FBG, BMI and age in Group II ($p>0.05$). According to the correlation results of Group III, Lp-PLA_2 activity was not significantly correlated with HDL-C, LDL-C, triglyceride, cholesterol, IMT, FBG, BMI and age in Group III ($p>0.05$). The correlation results of Group II and Group III are shown in Table 2.



A- B-

Figure 1: IMT (mm) measurement before statin (rosuvastatin 10 mg/dose) treatment (IMT: 1.13 mm (0.13 cm)) (A). IMT measurement after statin (rosuvastatin 10 mg/dose) treatment (IMT: 0.9 mm) (B) (*patient carotis IMT (mm) measurement from our study)

Table 1: Median and IQR values of all groups

Variable	Group I (n=20)		Group II (n=28)		Group III (n=28)	
	Median	IQR	Median	IQR	Median	IQR
Age (year)	48.02	37-60	52.17	39-63	52.17	39-63
Lp-PLA_2 activity (ng/ml)	172.4	44-293	304.9 [a]	171-553	213.6 [a,b]	91.7-500.7
Fasting glucose (mg/dl)	85.5	60-97	161 [a]	95-322	136 [a,b]	79-262
Total cholesterol (mg/dl)	163.5	115-220	225.5 [a]	148-332	200.5 [a,b]	100-293
Triglycerides (mg/dl)	99.5	35-237	168.5 [a]	79-376	146 [a,b]	55-464
HDL-C (mg/dl)	47.5	35-60	42	32-65	168.5	30-70
LDL-C (mg/dl)	89.5	52-124	137 [a]	73-235	119.5 [a,b]	45-211
Baseline maximal IMT (mm)	0.65	0.5-0.9	0.85 [a]	0,5-1.35	0.72 [a,b]	0.6-1.15
Body mass index (kg/m^2)	24.5	18-27	28 [a]	22-45	26.5 [a,b]	19-39

Abbreviations: Lp-PLA_2: Lipoprotein-associated phospholipase A_2, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, IMT: intima-media thickness, IQR: interquartile range, Group I (control), Group II (before rosuvastatin therapy), Group III (after rosuvastatin therapy), a: $p<0.01$ vs control (p values obtained Man-Whitney U test), b: $p<0.01$ vs Group II (p values obtained Wilcoxon test)

Table 2: Correlations between the Lp-PLA_2 activity and cardiovascular risk factors and carotid IMT values

Variable	Group II (n=28)		Group III (n=28)	
	r	p	r	p
Age (year)	0.127	0.518	0.290	0.135
Fasting glucose (mg/dl)	-0.044	0.823	0.090	0.648
Total cholesterol (mg/dl)	0.094	0.634	-0.213	0.275
Triglycerides (mg/dl)	0.162	0.412	-0.004	0.986
HDL-C (mg/dl)	-0.452	0.016*	-0.185	0.345
LDL-C (mg/dl)	0.263	0.177	-0.163	0.406
Baseline maximal IMT (mm)	-0.009	0.966	0.025	0.901
Body mass index (kg/m^2)	0.415	0.463	-0.141	0.474

Abbreviations: Lp-PLA_2: Lipoprotein-associated phospholipase A_2, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, IMT: intima-media thickness, r: Spearman's correlation coefficient, $p<0.05$*, $p<0.01$**

Discussion

In this study, we discussed whether Lp-PLA_2 enzyme activity, as an indicator of potential cardiovascular disease risk, has relevance with atherosclerosis being one of the major complications of diabetes. In the pre-treatment group (Group II) Lp-PLA_2 levels were significantly higher than the healthy volunteer control group (Group I) ($p<0.01$) and post-treatment group (Group III) ($p<0.01$). Furthermore, the IMT values of patients before the rosuvastatin treatment were significantly lower than the post-treatment IMT values ($p<0.01$). According to the acquired results, serum Lp-PLA_2 levels were associated with the risk of atherosclerosis progress especially in diabetic patients.

Our first finding concerning the relation between Lp-PLA_2 and the risk/progress of atherosclerosis is supported by the fact that carotid IMT values of the patients having increased Serum Lp-PLA_2 levels are high. The fact that diabetic patients' cholesterol and LDL-C levels are as high as to pose a risk for coronary artery diseases may lead to high serum Lp-PLA_2 levels and increased carotid IMT values. 80% of Lp-PLA_2 is dependent upon LDL-C; and the remaining 20% is dependent upon HDL-C. Along with dyslipidemia in diabetic patients, LpPLA_2-LDL-C levels increase and Lp-PLA_2-HDL-C levels decrease [19]. Lp-PLA_2-LDL-C levels decrease and they are rearranged with statin therapy. Lp-PLA_2-HDL-C levels are not affected by statin therapy [20]. The second finding of our study was that the diabetic patients who developed dyslipidemia had a statistically significant decrease in serum LDL-C, Lp-PLA_2 levels and in IMT values; and no statistically difference in serum HDL-C levels was found after 3 months of regular rosuvastatin treatment. These findings confirm the information given above.

Previous studies have revealed that there was a relation between Lp-PLA_2 and atherosclerosis. Okamura et al. [21] suggested that even the Lp-PLA_2 having an important function in

atherogenesis, its association with HDL-C plays the opposite role, as observed by high LDL-C-Lp-PLA_2 to the HDL-C-Lp-PLA_2 ratio in patients with atrial fibrillation. Allison et al. [22] demonstrated that an increment of one standard deviation in Lp-PLA_2 activity was associated with a higher risk of CVD in five years, however, not with mortality. Accordingly, Sabatine et al. [23] observed that an elevated level of Lp-PLA_2 is a predictor of adverse cardiovascular outcomes, independently of the traditional clinical risk factors in patients with stable coronary artery disease. Persson et al. [24] observed that this enzyme was strongly correlated with lipid fractions and the degree of carotid artery atherosclerosis; this study showed that the association with cardiovascular risk is stronger for activity than for mass, reinforcing the impact of activity in atherogenesis [24]. Lp-PLA_2, known as a novel inflammatory biomarker, is involved in the pathophysiology of atherosclerosis [5]. Lp-PLA_2 plays a role as a novel predictor of cardiovascular risk in a population at high risk for future CVD events [25-29]. In the study by Liu et al. examining the relation between subclinical atherosclerosis progress and Lp-PLA_2 activity, the carotid plaque status was determined by measuring the IMT thickness, and it was concluded that IMT and carotid plaque progress were significantly related to the increased Lp-PLA_2 activity. It was also reported that Lp-PLA_2 was a useful indicator for early prevention of cardiovascular diseases [30]. The results specified below were consistent with our findings.

However, Blake et al. [31] did not find any relevance between potential cardiovascular risks and Lp-PLA_2 contrary to our findings. Furthermore, it was reported by O'Donogheu et al. [33] that Lp-PLA_2 was not useful for risk classification following an acute coronary syndrome. It was reported that serum Lp-PLA_2 levels significantly decreased following the high-dose statin therapy and these levels may be associated with cardiovascular events independently of LDL-C.

Regarding that Lp-PLA_2 is associated with cholesterol and oxidized lipids in LDL-C and HDL-C, it is probable that drugs and environmental factors, capable of modulating the lipid metabolism, may change the mass and the activity of this enzyme. Schaefer et al. [32] compared the effect of atorvastatin with placebo in coronary heart disease patients, and observed a reduction of Lp-PLA_2 under therapy. In this way, O`Donoghue et al. [33] found that an intensive statin therapy was responsible for 20% of reduction in LDL-C-Lp-PLA_2, in average, the report by Saougos et al [34] the report by Joseph et al. [35], the report by White et al. [36].

Statin therapy is the first-stage therapy for the regulation of lipid profile for high-risk groups; but for patients with diabetic dyslipidemia, treatment with a single statin may not be effective enough on LDL-C. LDL-C and Lp-PLA_2 levels in patients who received statin therapy (10 mg Ezetimibe / 20 mg simvastatin, double dose 40 mg simvastatin or 20 mg atorvastatin and 10 mg rosuvastatin) at different doses for 6 months were examined by Le et al. Moreover, it has been found that 10 mg Ezetimibe / 20 mg Simvastatin treatment provides statistically more reduction in LDL-C and Lp-PLA_2 levels compared to other treatment options [37]. In another study conducted by Lee et al., the effect of the combination of 20 mg atorvastatin monotherapy and low dose 5 mg atorvastatin / 5 mg ezetimibe on LDL-C and Lp-PLA_2 activity was examined. While LDL-C levels decreased at similar rates with both treatments, it was concluded that Lp-PLA_2 levels decreased more effectively with 20 mg/day atorvastatin monotherapy [38]. Rosuvastatin (10 mg/day) monotherapy known to be more effective than atorvastatin treatment in decreasing HDL-C levels is almost as effective as atorvastatin in decreasing LDL-C [39] and causing [40] less rhabdomyolysis than other statin group drugs was administered for 3 months. A statistically significant decrease was found in serum LDL-C, Lp-PLA_2 and IMT levels ($p < 0.01$). However, no statistically significant increase was found in HDL-C levels ($p = 0.198$).

Limitation of the study

Although the research has reached its aim, there are some unavoidable limitations, First of all, to generalize the result for larger groups, the study should have involved more participants according to gender and different age ranges. Second, due to the lack of previous studies in the research area, the adequate comparison in discussion section was not achieved. Therefore, more regional researches which belong to the Turkish population should be done.

Conclusions

In our study, patients with type 2 diabetes (n=28) were treated with 10mg/gün Rosuvastatin monotherapy during the three months and at the same time, IMK values were measured in after and before treatment. According to our results, serum Lp-PLA_2 activity, serum LDL-C, triglyceride, cholesterol levels and IMT values of Group II (before rosuvastatin therapy) patients were statistically significantly higher than Group III (after rosuvastatin therapy) patients and HDL-C levels only were lower than Group III (after rosuvastatin therapy) however, It was not statistically significant (p=0.198). According to our results, Increased Lp-PLA_2 activity is associated with risk of atherosclerosis in diabetic patients and plays an important role in the progression of atherosclerosis.

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