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Original research-Orijinal araştırma

PAI-1 4G/4G gene polymorphism is associated with higher serum lipid level in Turkish population.

PAI-1 4G/4G gen polimorfizmi Türk popülasyonunda yüksek serum lipid düzeyleri ile ilişkilidir.

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Abstract

Aim. PAI-1 gene is a member of prothrombotic gene group. The 4G allele of the PAI-1 4G/5G polymorphism is associated with higher plasma levels of PAI-1 and increase the risk for thrombosis. Besides, there are some studies in the literature claiming an association between the 4G allele and the atherogenic lipid profile in certain populations. However, there is no detailed information about the effect of 4G on lipid levels in Turkish population. In this study, we aimed to investigate correlation between the PAI-1 4G/4G gene polymorphism and plasma lipid levels in healthy Turkish subjects. **Method.** Medical genetic department and hospital database were used in this retrospective study. Over 55 years old subjects were excluded. None of these subjects was receiving any type of medication. Fifty subjects (Group 4G) which had isolated 4G/4G homozygote PAI-1 gene polymorphism and 59 subjects (Group 5G) which had normal (5G/5G) PAI-1 gene variant were included in the study. Body mass index (BMI), age, sex, blood pressure (BP), high-density lipid levels (HDL), low-density lipid levels (LDL), triglyceride and cholesterol levels were investigated in each group. Obtained data were evaluated statistically. **Results.** The groups were similar about age, sex, BMI and BP. The difference was not significant between each groups, were compared for HDL. However, the levels of LDL (p=0.01), triglyceride (p=0.001) and cholesterol (p=0.02) were significantly higher in Group 4G. **Conclusions.** PAI-1 is a characteristic biological example of how complicated and unpredictable could be the influence of the same enzyme on different tissues or organs. Our findings suggest that the 4G/4G polymorphism of the PAI-1 gene might be associated with higher serum of LDL and triglyceride in healthy Turkish population. Therefore, evaluation of the PAI-1 gene in hyperlipidemic population will help clarify etiology and prognosis of the disease.

Keywords: Gene polymorphism , PAI-1, serum lipid level

Özet

Amaç. PAI-1 geni protrombotik gen grubunun bir üyesidir. PAI-1 4G/5G polimorfizmindeki 4G alleli yuksek plazma PAI-1 düzeyi ve artmış tromboz riski ile birliktedir. Diğer yandan literatürde bazı popülasyonlarda, 4G alleli ile aterojenik lipid düzeyleri arasında ilişki bulunduğunu iddia eden makaleler bulunmaktadır. Ancak, Türk popülasyonunda lipid düzeyleri üzerine 4G allelinin etkileri hakkında detaylı bilgi bulunmamaktadır. Bu çalışmada, sağlıklı Türk bireylerinde plazma lipid düzeyleri ile PAI-1 4G/5G gene polimorfizminin korelasyonunu araştırmayı amaçladık. **Yöntem.** Retrospektif olan bu çalışmada, hastanemizin ve tıbbi genetik bölümünün veri tabanı kullanıldı. 55 yaşından büyük bireyler çalışmaya alınmadılar. Katılımcılardan hiç biri herhangi bir tedavi almamaktaydı. İzole PAI-1 4G/4G gen polimorfizmi bulunan 50 kişi (Grup 4G) ve PAI-1 5G/5G Polimorfizmi saptanan 59 kişi (Grup 5G) çalışmaya dâhil edildi. Her grupta olguların vücut kitle indeksi, yaş, cinsiyet, kan basıncı, HDL, LDL, trigliserid ve total kolesterol düzeyleri araştırıldı. Elde edilen veriler istatistiksel olarak değerlendirildi. **Bulgular.** Gruplar yaş, cinsiyet, vücut kitle indeksi ve kan basıncı yönünden benzerdi. HDL yönünden gruplar arasındaki fark önemsiz bulundu. Ancak, LDL (p=0.01), trigliserid (p=0.001) ve kolesterol (p=0.02) Grup 4G'de anlamlı olarak yüksek bulundu. **Sonuç.** PAI-1, aynı enzimin değişik doku ve organlar üzerindeki etkilerinin ne kadar karmaşık ve beklenmedik olabileceğinin karakteristik biyolojik bir örneğidir.

Bizim bulgularımız PAI-1 gen 4G/4G polimorfizminin sağlıklı Türk popülasyonunda yüksek LDL ve trigliserid düzeyleri ile ilişkili olabileceğini desteklemektedir. Bu nedenle, hiperlipidemik popülasyonda PAI-1 geninin değerlendirilmesi bu hastalığın prognozu ve etiyolojisinin açığa çıkarılması konusunda yardımcı olabilir.

Anahtar sözcükler: Gen polimorfizmi, PAI-1, serum lipid düzeyi

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Introduction

Hyperlipidemias are important risk factors for cardiovascular disease. Especially, increased low-density lipoprotein (LDL) cholesterol is a well-known major risk factor for cardiovascular disease. Particularly in the developed countries, most of the hyperlipidemias are usually related with diet and lifestyle. However, serum lipid levels are strongly influenced by genetic factors, although heritability has been observed to vary widely (20-80%) in different studies [1]. Plasminogen activator inhibitor-1 (PAI-1) is the major physiological inhibitor of the tissue plasminogen activator and uroplasminogen activator in the regulation of fibrinolytic balance. Disorders are associated with increased thrombosis, such as coronary heart disease, deep-vein thrombosis, and obesity. PAI-1, a risk marker of atherosclerosis, is the most important endogenous inhibitor of tissue plasminogen activator and uroplasminogen activator, and is a main determinant of fibrinolytic activity. Besides, it was reported that PAI-1 4G/5G gene polymorphism affects serum cholesterol levels in different populations. However, there is not any detailed information about whether 4G affects lipid levels in Turkish population. In this study, we aimed to investigate correlation between PAI-1 4G/4G gene polymorphism and plasma lipid levels in healthy Turkish subjects.

Material and methods

Our hospital's medical genetic department and hospital database were used in this retrospective study. Between 2008-2010 all results regarding above stated genetic polymorphism were extracted from the database. Subjects without overt health problem according to hospital records were considered. Subjects over 55 years old, and those taking any chronic medication were excluded. Hence, consecutive fifty subjects (Group 4G) who had isolated 4G/4G homozygote PAI-1 gene polymorphism and 59 subjects (Group 5G) which had normal (5G/5G) PAI-1 gene variant were included in the study. None of these subjects was taking any type of medication. Body mass index (BMI), age, sex, blood pressure (BP), high-density lipid levels (HDL), low-density lipid levels (LDL), triglyceride and cholesterol levels were investigated in each group. Obtained data were evaluated statistically.

Statistical analysis

Statistical analysis was performed by using the SPSS statistical package, version 16.0 (SPSS Inc., Chicago, IL, USA) for Windows. Data are presented as mean values ± SD. Gender of the subjects was evaluated by $\chi 2$-test. Parametric data such as age, body mass index, systolic blood pressure, total cholesterol, triglyceride, HDL, and LDL cholesterol were compared with independent sample t-tests. A P-value of <0.05 was considered as statistically significant.

Results

The groups were similar according to demographic and clinical data. In the 4G Group,

mean age was 35.1±8.6 years and there were 23 male (46%). In the 5G group, mean age was 36.6±8.7 years and there were 28 male (48%) (p=0.32 and p=0.88), (Table 1). The systolic blood pressures were 123.7±16.8 mmHg in 4G group and 122.2±16.5 mmHg in 5G group (p=0.65).

Table 1. Demographic and clinical data of the study groups

	Group 4G (n: 50) (n, %)	Group 5G (n: 59) (n, %)	p
Male Gender	23 (46%)	28 (48%)	0.88
Age (mean ± SD)	35.1±8.6	36.6±8.7	0.32
Body mass index	25.1±3.7	26.4±3.9	0.28
Systolic blood pressure (mmHg)	123.7±16.8	122.2±16.5	0.65

In the 4G group, triglyceride was 185.6±50.1 mg/dL, LDL cholesterol was 132.2±31.7 mg/dL, and total cholesterol was 184.5±45.3 mg/dL. When comparison was made, the levels of total cholesterol, triglyceride, and LDL cholesterol were significantly higher in the 4G Group than those of the 5G Group (p=0.002, p=0.001, p=0.01). However, the level of HDL cholesterol was similar in study groups. Table 2 presents cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol level of the Groups.

Table 2. Serum lipid levels of the study groups

	Group 4G (n: 50) (mg/dl)	Group 5G (n: 59) (mg/dl)	p
Cholesterol	184.5±45.3	165±37.9	0.02
Triglyceride (mg/dL)	185.6±50.1	154.7±37.2	0.001
HDL (mg/dL)	30.8±3.1	31.5±4.2	0.33
LDL (mg/dL)	132.2±31.7	117.7±28.1	0.01

Discussion

Hyperlipidemia often occurs because of diet and lifestyle. Besides, it is well known that serum lipid levels are also strongly influenced by genetic factors, although heritability has been observed to vary widely (20-80%) in different studies [1]. Although, main role of the PAI-1 is to be a major component of the fibrinolytic system [2], there are some studies claiming that PAI-1 is positively associated with serum lipid levels in the literature [3, 4]. As far as we know, there is no study in the literature that has investigated the relationship between the PAI-1 4G/5G gene polymorphism and serum lipid parameters in Turkish population. PAI-1 is a major component of the fibrinolytic system, and the changes in plasma PAI-1 levels lead to corruption of the balance between the fibrinolytic and procoagulant systems [5]. However, this balance is directly affected by the genetic situation [6]. PAI-1 gene is located at chromosome 7q22 [7]. The PAI-1 4G/5G polymorphism is the deletion or addition of one guanosine in the promoter region of the PAI-1 gene [8]. The 5G allele has an additional binding site for a repressor, responsible for lower transcription rates and less PAI-1 activity. The deletion of the allele (4G) has been linked with the increased PAI-1 messenger RNA expression and increased serum PAI-1 levels [8, 9]. There are some studies in the literature claiming that PAI-1antigen levels are correlated with the lipid profile [10]. Moreover, Juhan-Vague et al. [3] reported that PAI-1 is positively associated with cholesterol, LDL-cholesterol, VLDL and triglyceride levels and negatively with HDL cholesterol. In addition, Boncoraglio et al. [4] suggested that the 4G/4G genotype itself has been reported to be associated with high cholesterol levels. Similarly, we found positive association between PAI-1 4G/4G gene polymorphism and LDL cholesterol, triglyceride, and total cholesterol in our study population. Although, several studies have claimed an increase in PAI-1 levels resulting from the activation of renin–angiotensin system and hypertension in subjects with the 4G/4G genotype, we could not find blood pressure difference related with 4G/4G

genotype [11]. In addition, obesity is associated with increased PAI-1 levels [12], however, in this study, no significant difference was found about body mass index between study groups. Our study has some limitations. Firstly, we did not study plasma PAI-1 levels but the relationship between PAI-1 4G genotype and high PAI-1 level is well known in both adults and children [8, 9]. Secondly, due to the small number of individuals with the 4G/4G genotype analyzed, the genotype effect observed in our Turkish population does not guarantee a rigid conclusion. Different results from other reports might be due to racial differences. Further research, including the consideration of additional genetic differences in the study populations, is needed to clarify these discrepancies and the mechanism by which this polymorphism influences the serum lipid profile. PAI-1 is a characteristic biological example of how complicated and unpredictable could be the influence of the same enzyme on different tissues or organs. Our findings suggest that the 4G/4G polymorphism of the PAI-1 gene might be associated with higher serum levels of LDL and triglyceride in healthy Turkish population. Therefore, evaluation of the PAI-1 gene in hyperlipidemic population will help clarify etiology and prognosis of the disease.

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