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Koroner arter hastalarında insan trombosit antijen-1 gen polimorfizmi ile klopidogrel direnci ilişkisi

Relationship between human platelet antigen-1 gene polymorphism and clopidogrel resistance in patients with coronary artery disease

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ÖZET

Amaç: İnsan trombosit antijeni-1 (İTA-1) gen polimorfizminin koroner arter hastalığı (KAH) ile ilişkili olduğu ve trombosit fonksiyonlarını etkilediği öne sürülmüştür. Bu çalışmada KAH olan ve olmayan bireylerde İTA-1 gen polimorfizminin dağılımını ve KAH olan bireylerde İTA-1 gen polimorfizminin trombosit kümelenmesiyle ilişkisini incelemeyi amaçladık.

Çalışma planı: Çalışmaya perkütan koroner girişim (PKG) uygulanan 94 hasta ve kontrol grubu olarak koroner anjiyografisi normal olan 115 birey alındı. KAH grubunda PKG sonrası beşinci gün impedans agregometre ile trombosit kümelenmesi (KB) ölçüldü. Trombosit kümelenmesinin >490 KB/dakika olması klopidogrel direnci olarak tanımlandı. Tüm katılımcılardan İTA-1 gen polimorfizmini araştırmak için kan örnekleri alındı.

Bulgular: Hasta ve kontrol grubu arasında İTA-1 gen polimorfizmi yönünden fark yoktu (A aleli için %78.7 ve %78.1, p=AD; B aleli için %21.3 ve %21.9, p=AD). Klopidogrel direnci olan ve olmayan

ABSTRACT

Objectives: It has been proposed that human platelet antigen-1 (HPA-1) gene polymorphism is associated with coronary artery disease (CAD) and affects platelet function. We aimed to investigate the distribution of HPA gene polymorphism between angiographic CAD and a control group and the relation between HPA gene polymorphism and platelet aggregation.

Study design: The study population consisted of 94 patients with angiographic CAD and 115 patients without angiographic CAD. Platelet aggregation was measured with impedance aggregometry on the fifth day of percutaneous coronary intervention (PCI). Platelet aggregation >480 AU/min was defined as the clopidogrel resistance. Blood samples were obtained from all participants at discharge for the analysis of HPA-1 gene polymorphism.

Results: There was no significant difference in the distribution of HPA-1 gene polymorphism between the control and CAD groups (78.7% vs. 78.1% for A allele and 21.3% vs. 21.9% for B allele, p=NS). The analysis between groups with and without clopidogrel resistance revealed no significant difference

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gruplar arasındaki analizde İTA-1A ve İTA-1B alleleri sıklığı açısından fark tespit edilmedi (Her iki grupta, A aleline sahip hasta oranları %78.7 ve %78.9, p=AD; B aleli için %21.3 ve %21.1, p=AD). Ayrıca, KAH'da İTA-1A ve İTA-1B alellerine sahip hastalarda trombosit kümelenmesi açısından fark yoktu (294±240 ve 259±261 KB/dakika, p=AD).
Sonuç: İnsan trombosit antijeni-1 gen polimorfizmi dağılımı KAH olan ve olmayan bireylerde benzerdir. KAH'da, impedans agregometre ile değerlendirilen trombosit kümelenmesi ve klopidogrel direnci, İTA-1 gen polimorfizmi ile ilişkili değildir.

in the distribution of HPA-1A and HPA-1B alleles between the groups (A allele 78.7% vs. 78.9% and B allele 21.3% vs. 21.1%, p=NS). In the CAD group, there were no significant differences in platelet aggregation between HPA-1A and HPA-1B alleles (294±240 vs. 259±261 AU/min, p=NS).
Conclusion: Distribution of HPA-1 gene polymorphism was not different in CAD patients compared to the control group. HPA-1 gene polymorphism was not associated with platelet aggregation or clopidogrel resistance assessed by impedance aggregometry in the CAD group.

Abbreviations:

ACS Acute coronary syndrome
GP Glycoprotein
HPA Human platelet antigen
CAD Coronary artery disease
AU Aggregation unit
PCI Percutaneous coronary intervention

Platelet surface receptors play a key role in the adhesion, activation, and aggregation of platelets. These receptors are called human platelet antigens (HPA) or platelet surface glycoproteins (GP). HPA polymorphisms (ie. HPA-1,-2,-3,-4,-5,-15) are associated with variations in platelet GPs. Major GPs formed on the surface of platelets (GPIIb, GPIIIa, GPIb, and GPIa) are associated with different HPA polymorphisms.[1] GP IIb/IIIa receptors are the most prevalent receptors found on the surface of platelets. This receptor comprised of two subunits named αIIb, and βIII In the aggregation of platelets, platelet- GP IIb/IIIa receptor, and for affinity to fibrinogen, βIII subunit play important roles.[2,3] In various studies, polymorphic alterations in HPA gene have been proposed to have an impact on platelet functions, and and increase the risk of coronary artery disease (CAD), and frequency of acute thrombotic events.[4,5] However some studies reported different outcomes.[6-8] Besides, it has been demonstrated that HPA gene polymorphism has an impact on response to clopidogrel.[9-11]

In this study, we investigated distribution of HPA-1 gene polymorphism in individuals with or without CAD, and also its relationship with platelet aggregation in patients with CAD.

MATERIALS AND METHODS

A total of 94 patients who had undergone scheduled or emergency percutaneous intervention (PCI) in our hospital between January 2008, and July 2009 were enrolled in the study. Control group consisted of 115 patients age-, and gender-matched with the patient group, but without CAD as documented (coronary stenosis, < 50% or normal coronary arteries) on coronary angiograms (CAG) obtained because of exercise test positivity, ischemic findings in myocardial scanning tests or clinical probability of higher risk of CAD. All patients underwent PCI after receiving a loading dose (600 mg) of clopidogrel. For the subsequent five days its maintenance dose of 150 mg was administered till platelet aggregation values were detected. Afterwards daily maintenance doses of 75

or 150 mg was sustained at least for one year. Decision on complying with a long-term maintenance dose was based on the observance of platelet aggregation, and response to clopidogrel. Concomitant drugs received by the patients were arranged according to current guidelines. Blood samples were drawn from the patients at the time of hospitalization for the determination of HPA gene polymorphism. Patients who had declined or hadn't undergone PCI procedure were not included in the study. The patients were informed about the investigation, and their written, and undersigned consent forms were obtained. Our study was approved by the Local Ethics Committee

Evaluation of the clopidogrel resistance: Impedance aggregometre

For the evaluation of clopidogrel resistance an impedance aggrometric method (Multiplate Analyser, Dynabyte, Munich, Germany) was used. For testing, blood samples were drawn into 4-ml tubes containing hirudin, and kept for 30 minutes under room temperature before analysis. Blood samples were diluted at 1:2 ratio, and agitated at 37ºC for 3 minutes, and then 20 µl ADP was added. In the test cell using two pairs of electrodes variations in clopidogrel resistance induced by platelets aggregated, and adhered to electrodes all along the procedure were recorded. Increased resistance caused by platelets adhered to the electrodes was converted to aggregation units. (AU), and aggregation - time (AU/min) curve were drawn by the analyser. The area under the aggregation curve (AUC) which is the best parametre reflecting platelet activity was calculated. Response to clopidogrel or clopidogrel resistance was evaluated in consideration of platelet aggregation 5 days after the clopidogrel treatment. Platelet aggregation values above 480 AU/min as measured on the 5. day were evaluated as resistant or irresponsive to clopidogrel.[12]

Human platelet antigen -1 gene polymorphism

To determine gene mutations of human platelet antigens, 3 milliliters of venous blood samples were drawn into tubes with EDTA. After isolation of DNA, gene sequences were replicated in the laboratory (in vitro tests) using multiplex polymerase chain reaction. For the analysis of mutations, reverse in situ hybridization method was applied using an appropriate kit (Vienna Lab CVD StripAssay, Austria))

Statistical Analysis

Numerical data were expressed as mean ± standard deviation, and categorical variables as percentages. Distribution of numerical variables were tested using Kolmogorov-Smirnov test. $P < 0.05$ was accepted as the level of statistical significance. For numerical variables with non-normal distribution, Mann-Whitney U-test, and those demonstrating normal distribution pattern Student-t test was used. Categorical variables were evaluated using *chi*-square test. For statistical analysis SPSS 15.Version (SPSS Inc, Chicago, Ilinois) program was employed.

RESULTS

Basic clinical, and laboratory characteristics of the groups with or without angiographically documented CAD are summarized in Table 1. Genotypes, and alleles are presented in Figure 1. Since BB genotype frequency is relatively lower, assessments of A (AA genotype),and B alleles (AB, and BB genotype) were performed. Any difference between the patient, and the control group

as for the frequency of HPA -1 gene polymorphism (respective frequencies: A allele, 78.1, and 78.7 %; p=NS, and B allele, 21.9, and 21.3 %, p=NS) (Figure 1).

In the group with angiographically documented CAD, median (216 AU/min) , and mean (287±243 AU/min; range, 0-1022 AU/min) platelet aggregation values were also calculated (Figure 2). Drug-eluting or bare metal stents were implanted in 55, and 45 % of the patients, respectively. In the CAD group, clinical demographics as indications for clinical referral, age, smoking habit, diabetes mellitus (DM), hypertension (HT), hyperlipidemia, statin and aspirin use, and levels of mean platelet volume, platelet counts, lipoprotein (a), homocysteine, high-sensitivity C-reactive protein, hemoglobin, creatinine did not differ between patient groups with or without clopidogrel resistance. However platelet distribution width was significantly higher in the clopidogrel-resistant group (17.1±0.7 *vs* 16.2±1.2, p=0.03) (Table 2).

Table 1. Demographic, and clinical characteristics of the groups with or without angiographic CAD

Variable	Control group (n=115)		CAD group (n=94)		*p*
	%	Mean ± SD	%	Mean ± SD	
Age (years)		57±11		56±10	NS
Gender (male)	74		76		NS
Diabetes mellitus	17		32		0,02
Hypertension	52		58		NS
Smoking	43		38		NS
Creatinine (mg/dL)		0,90±0,23		0,93±0,20	NS
LDL-cholesterol (mg/dl)		116±22		124±25	NS
HDL-cholesterol (mg/dl)		41±12		35±8	NS
Triglyceride (mg/dl)		144±54		163±66	0,04
Lipoprotein (a) (mg/dl)		22±18		40±24	0,01
Homocysteine (µg /ml)		14,1±2,8		14,4±3,1	NS
C-reactive protein (mg/l)		0,35±0,34		0,64±0,75	0,07
HPA-1 a/b	78,7±21,3		78,1±21,9		NS
CAD, coronary artery disease; SD, standard deviation; LDL- low-density lipoprotein; HDL: high-density lipoprotein; HPA, human platelet antigen; NS, not significant					

Frequencies of HPA-1 gene polymorphism in groups with or without clopidogrel resistance were not different (respective percentages: A allele, 78.7 vs 78.9 %, p=NS, and B allele, 21.3 *vs* 21.1%, p=NS) (Figure 3). Similarly, mean platelet aggregation values in patients with HPA-1A, and HPA-1B alleles did not differ (294±240 *vs* 259±261 AU/min, p=NS) (Figure 4).

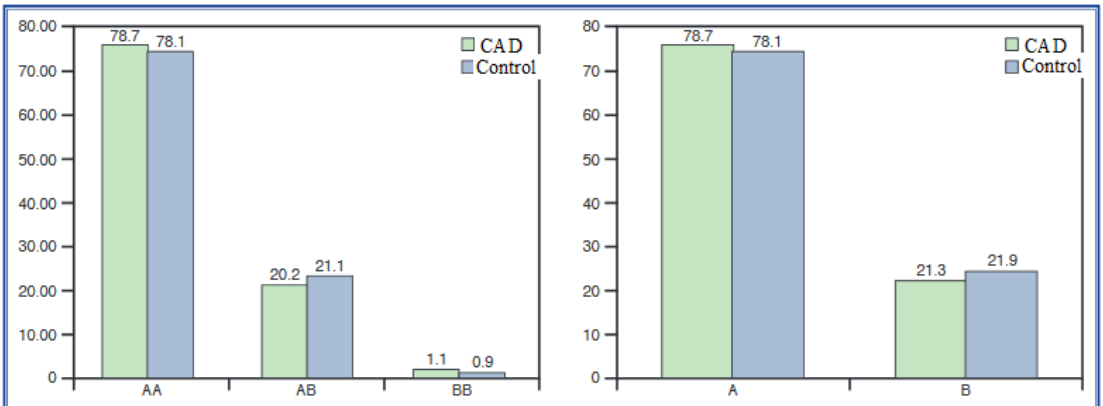

Figure 1. Distribution of HPA genotype, alleles in coronary artery disease (CAD), and control groups

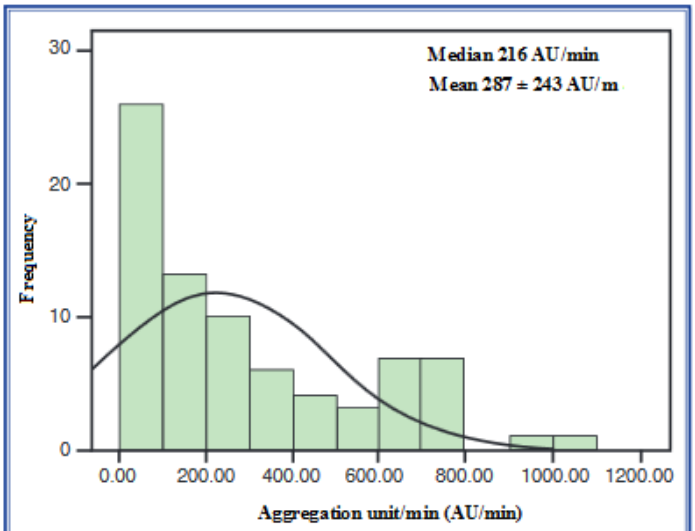

Figure 2. Distribution of platelet aggregation values among coronary artery disease patients

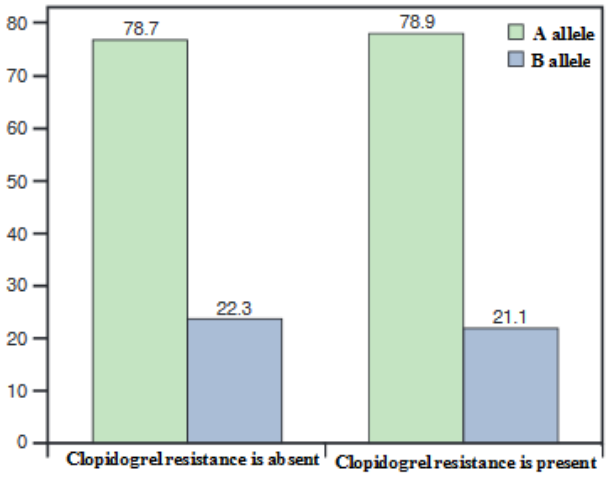

Figure 3. Distribution of human platelet antigens-1 gene alleles in groups with or without clopidogrel resistance

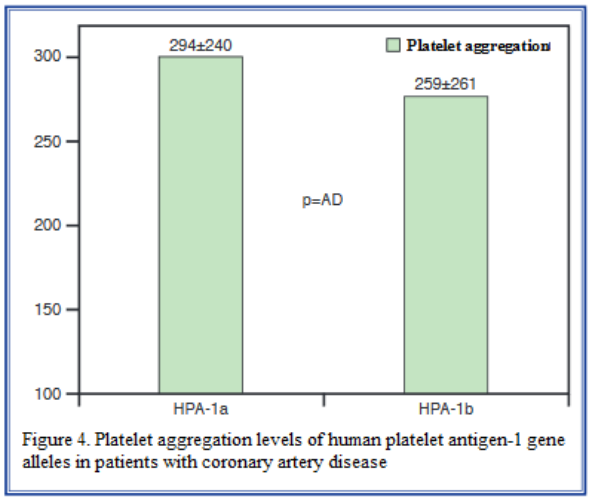

Figure 4. Platelet aggregation levels of human platelet antigen-1 gene alleles in patients with coronary artery disease

Table 2. Characteristics of the groups with or without clopidogrel resistance

Variable	Clopidogrel resistance (-)		Clopidogrel resistance (+)		*p*
	%	Mean ± SD	%	Mean ± SD	
Age (years)		57.4±10.6		54.7±8.4	**NS**
Gender (Male)	77		68		**NS**
Diabetes mellitus	32,2		33,3		**NS**
Hypertension	62,7		43,8		**NS**
Smoking	37,9		37,5		**NS**
Clinical					**NS**
Stable angina	41,0		29,4		**NS**
Non-STEMI-ACS	31,1		41,2		**NS**
STEMI	27,9		29,4		**NS**
Creatinine (mg/dl)		0.92±0.2		0.95±0.2	**NS**
Platelets (x 10^3/ml)		237±66		289±109	**NS**
Mean platelet volume (fL)		8.8±1.1		9.0±1.7	**NS**
Lipoprotein (a) mg/dl		37±20		47±46	**NS**
Homocysteine (µg /ml)		14.0±2.9		15.2±3.6	**NS**
C-reactive protein (mg/l)		0.7±0.9		0.5±0.4	**NS**
Platelet distribution width		16.2±1.2		17.1±0.7	**0.03**
Hemoglobin (g/dl)		13.8±2.3		13.4±1.9	**NS**
HPA-1 a/b	78.7 / 21.3		78.9 / 21.1		**NS**
Drugs used					**NS**
Aspirin	94		100		**NS**
Statin	85		90		**NS**
Beta blocker	82		79		**NS**
ACE-I/ARB	88		89		**NS**

SD, standard deviation; non-STEMI, non-ST segment elevation acute coronary syndrome; STEMI, ST segment elevation myocardial infarction; HPA, human platelet antigen; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; NS, not significant

DISCUSSION

In our study, distribution of HPA-1 gene polymorphisms between the control group with angiographically normal coronary arteries, and CAD patients was not different between groups Besides, any difference could not be detected in the distribution of HPA-1 gene polymorphisms, and platelet aggregation as assessed by impedance aggrometry in groups of patients with or without clopidogrel resistance.

Platelet surface receptors ensure adhesion of platelets to subendothelial layer, and ensuing aggregation when integrity of vascular epithelium is impairedActivated platelets directly bind to coagulation protein fibrinogen in the circulation. This process is mediated by receptors of an integrin, ie. GpIIb/IIIa found on the surface of activated platelets. .[2,3,13]

Numerous platelet GP gene polymorphisms have been defined in association with thromboembolic events .[14,15] Correlations between increased rate of cardiovascular events, and HPA-1 gene polymorphisms have been demonstrated. However, a clear-cut relationship between alleles of this gene, and pathogenesis of atherosclerosis, and especially acute coronary syndrome (ACS) does not exist. In our study, any difference as for the presence of HPA-1 gene polymorphisms in patients with or without CAD was not detected. In some investigations, CAD has been reported in higher frequency in individuals having HPA-1B alleles.[4,16-19] Contrarily, data refuting any association between HPA-1B allele, and coronary artery disease are also available.[6-8,20,21] Many factors might contribute to the debatable relationship between HPA-1 gene polymorphism, and CAD, especially ACS. Case-control study design might have masked an existing relationship. Besides, gene polymorphism data coming from different countries might have an impact on outcomes. Ours is also a case-controlled study, and another study performed in our country also could not detect any relationship between HPA-1 gene polymorphism, and CAD. [6] Since we enrolled both stable CAD patients, and cases with acute coronary syndrome in our study, this heterogeneity might have concealed the existing association between HPA-1 gene polymorphism, and CAD

Human platelet antigen gene polymorphism, and especially B allele regulates platelet functions, and this allele has been associated with increased platelet reactivity[22] In individuals with HPA-1B allele, inadequate platelet inhibition has been identified after administration of loading doses (330 mg or 600 mg) of clopidogrel.[9,10] In our study, any difference was not detected between groups with or without clopidogrel resistance as for distribution of HPA-1A, and ITA-1 B alleles. Besides, platelet aggregation values were not different between patients with HPA-1A, and HPA-1B allels. Our study results pertaining to the relationship between HPA-1 gene polymorphism, clopidogrel resistance, and platelet reactivity are in compliance with some literature studies.[11,23,24]

Many etiological factors might be responsible for the debatable impact of HPA gene polymorphism on platelet functions. Above all, platelet functions involve a complex process which can not be regulated by a single gene. Besides, differences in measurement techniques used for the evaluation of platelet functions might explain such diversified outcomes. In our study, we analyzed platelet functions using a multiplate impedance aggregometre. However in other investigations, different methods

such as VASP phosphorylation, light transmission aggregometry, and VerifyNow have been used. Additionally, definitions as clopidogrel resistance, and clopidogrel-related platelet inhibition are not explicit. Though cut-off values have been defined for different measurement techniques, these are far from being ideal criteria.As is in the study conducted by Sibbing et al., we divided our study population into five equal groups, and the group with the highest value was considered as clopidogrel-resistant. .[25]

Limitations of the study

One of the limitations of our study is failure to assess baseline platelet aggregation values before starting on clopidogrel therapy. However administration of identical doses of clopidogrel for 5 days till aggregation values of all patients were read, helped us to overcome this limitation to some extent. Besides, in our study, aspirin resistance was not measured. Inability to achieve clinical endpoints is another limitation of our study. During the study period only 2 patients received GP IIb/IIIa receptor inhibitor. Therefore analyses related to the use of GP IIb/IIIa receptor inhibitor could not be performed. During long-term monitorization, only one patient developed stent thrombosis. Any incident of death or myocardial infarction was not observed. Lastly, heterogeneity of the study population, in other words inclusion of patients with ACS, and stable CAD in the study, and relatively small number of the participants might have an impact on the outcomes of the study. Similarly, scarce number of clopidogrel- resistant patients might effect generalization of our outcomes.

Distribution of human platelet antigen-1 gene polymorphism in patients with CAD is not different from that of normal individuals. As assessed by impedance aggregometer, platelet aggregation, and clopidogrel resistance are not associated with HPA -1 gene polymorphism.

Conflict of interest: None declared

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Anahtar sözcükler: Anjiyoplasti, balon, koroner/yöntemler; doz-yanıt ilişkisi, ilaç; ilaç direnci; insan trombosit antijeni-1; klopidogrel; perkütan koroner girişim; polimorfizm, genetik; trombosit kümelenmesi/ilaç etkisi/genetik.

Key words: Angioplasty, balloon, coronary/methods; dose-response relationship, drug; drug resistance; human platelet antigen-1; clopidogrel; percutaneous coronary intervention; polymorphism, genetic; platelet aggregation/drug effects/genetics.