The relationship between interleukin-6 polymorphism and the extent of coronary artery disease in patients with acute coronary syndrome

Akut koroner sendromlu hastalarda koroner arter hastalığının ciddiyeti ile interlökin-6 polimorfizmi arasındaki ilişki

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Objectives: We investigated plasma fibrinogen and interleukin-6 (IL-6) levels and the frequency of IL-6 polymorphism in patients with acute coronary syndrome.

Study design: A case-control study was conducted in 115 patients who underwent coronary angiography for suspected ischemic heart disease. The patients were classified into two groups according to angiography findings: 65 patients (49 males, 16 females; mean age 61±10 years) had less extensive coronary artery disease (CAD) (1-vessel stenosis), and 50 patients (36 males, 14 females; mean age 61±9 years) had extensive CAD (≥2-vessel stenosis). Fasting blood samples were taken to determine serum lipids, high sensitivity C-reactive protein, IL-6, and fibrinogen levels. The genotypic distribution and the IL-6 C/G-174 polymorphism were determined by polymerase chain reaction.

Results: Patients with less extensive CAD had a significantly lower prevalence of positive familial CAD and significantly lower plasma IL-6 and fibrinogen levels compared to those with extensive CAD ($p<0.05$). IL-6 polymorphism was detected in 20 patients (17.4%), its frequency being significantly higher in patients with extensive CAD (32% *vs* 6.2%; $p<0.001$).

Conclusion: Our results suggest that the presence of the IL-6 C/G-174 polymorphism and increased IL-6 and fibrinogen levels are strongly associated with the inflammatory system and hemodynamical significance of CAD.

Key words: Coronary arteriosclerosis; genotype; inflammation mediators; interleukin-6/blood/genetics; polymorphism, genetic; risk factors.

Amaç: Bu çalışmada akut koroner sendromlu hastalarda plazma fibrinojen ve interlökin-6 (IL-6) düzeyleri ile IL-6 polimorfizmi sıklığı araştırıldı.

Çalışma planı: İskemik kalp hastalığı şüphesiyle koroner anjiyografi ile incelenen 115 hasta üzerinde olgu-kontrol çalışması yapıldı. Anjiyografi bulgularına göre hastalar iki grupta değerlendirildi: 65 hastada (49 erkek, 16 kadın; ort. yaş 61±10) sınırlı koroner arter hastalığı (KAH) (1 damar daralmış), 50 hastada (36 erkek, 14 kadın; ort. yaş 61±9) yaygın KAH (≥2 damar daralmış) vardı. Hastalardan açlık kan örnekleri alınarak serum lipidleri, yüksek duyarlıklı C-reaktif protein, IL-6, ve fibrinojen düzeyleri ölçüldü. İki grupta genotipik dağılım ve IL-6 C/G-174 polimorfizmi varlığı polimeraz zincir reaksiyonuyla belirlendi.

Bulgular: Sınırlı KAH bulunan grupta KAH için pozitif aile öyküsü anlamlı derecede düşük oranda bulundu; ayrıca, plazma IL-6 ve fibrinojen düzeyleri de yaygın KAH bulunan gruba göre anlamlı derecede düşük idi ($p<0.05$). IL-6 polimorfizmi toplam 20 hastada (%17.4) saptandı; sıklığı yaygın KAH bulunan grupta anlamlı derecede yüksek bulundu (%32 ve %6.2; $p<0.001$).

Sonuç: Bulgularımız, IL-6 C/G-174 polimorfizminin varlığı ve artmış IL-6 ve fibrinojen düzeyleri ile inflamatuvar sistem ve hemodinamik olarak KAH'nin yaygınlığı arasında güçlü bir ilişki olduğunu göstermektedir.

Anahtar sözcükler: Koroner arteriyoskleroz; genotip; inflamasyon mediatörü; interlökin-6/kan/genetik; polimorfizm, genetik; risk faktörü.

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Coronary artery disease (CAD) is a complex multifactorial disorder exhibiting interactions with environmental and multiple genetic factors. Despite many studies on the relationship between atherosclerosis and genetics, this relationship has not been clarified. Today, it is known that inflammation plays an important role in the development of atherosclerosis. Being present in arterial lesions, Inflammatory cells present in arterial lesions are believed to play a key role in several processes such as atherosclerotic plaque progression, plaque disruption, and thrombosis.[1]

Serum markers of inflammation such as interleukin-6 (IL-6), fibrinogen, and C-reactive protein (CRP) play a major role in atherosclerotic disease. Interleukin-6 may play a direct role in endothelial activation,[2] or an indirect role when fibrinogen synthesis is stimulated.[3] These inflammation markers are also associated with the incidence of CAD[4-6] and a worse prognosis after an acute coronary syndrome (ACS).[7-9] It was in the early 1980s that Meade et al.[10,11] first reported that the subjects for whom the cause of death was myocardial infarction had had significantly higher fibrinogen plasma levels at recruitment, namely five years earlier, than the survivors or subjects whose death was due to some other causes.

Increased levels of IL-6 have been reported among patients with acute coronary syndromes,[12] and are associated with increased risk for future myocardial infarction in apparently healthy men.[5] A polymorphism within the 5' flanking region of the IL-6 gene locus (C/G-174) has been shown to regulate gene transcription.[13] Interleukin-6 gene transcripts were found in human atherosclerotic lesions.[14]

Acute coronary syndrome is characterized by the presence of erosion or ruptured fibrous capsule of vulnerable plaque. The aim of this study was to investigate the relationship between several markers of inflammation and the involvement of the IL-6 C/G-174 variant in different hemodynamic characteristics of patients with ACS.

PATIENTS AND METHODS

Selection of the study population. The study group consisted of patients who underwent coronary angiography between October 2004 and April 2006 because of chest pain or noninvasive tests suggesting myocardial ischemia, and were found to have stenosis of ≥50% in one of the coronary arteries. The patients were then classified into two groups according to their coronary angiographic findings, namely, less extensive CAD (group 1: 1-vessel stenosis), and extensive CAD (group 2: ≥2-vessel stenosis). Acute coronary syndrome included unstable angina and acute myocardial infarction. A total of 115 patients were evaluated in the final analysis. Of these, 65 patients had angiographically proven less extensive CAD (49 males, 16 females; mean age 61±10 years), and 50 patients (36 males, 14 females; mean age 61±9 years) had extensive CAD.

Diagnosis of unstable angina pectoris was defined as the presence of one or more of the following features: *(i)* angina at rest (or with minimal exertion) and usually lasting more than 20 minutes; *(ii)* angina of increased frequency or duration or refractory to nitroglycerin administration; *(iii)* new onset of severe and frank pain (i.e., within the last two months); *(iv)* the presence of chest pain of ischemic type within the first two weeks after acute myocardial infarction.

Acute myocardial infarction was identified based on the presence of two or more of the following criteria:[15] *(i)* clinical history of ischemic type chest pain suggestive of myocardial ischemia lasting ≥30 minutes; *(ii)* changes in serial ECG tracings showing the development of Q-waves and/or ST-T changes lasting ≥48 hours (ST-segment elevation ≥1 mm in at least two subsequent derivations on a 12-lead ECG); *(iii)* increases in serum cardiac enzymes (increased serum creatine kinase of ≥2 times the normal level with an increase in creatine kinase-MB isoenzyme of >5%, and increased troponin T levels).

The extent of the stenosis was determined based on the consensus opinion of two cardiologists who were blinded to the history and lipid profile of the patients. The diagnosis was made by two cardiologists blinded to the IL-6 findings.

Exclusion criteria were age above 75 years, acute infection, acute state of chronic infection or inflammation, use of lipid-lowering drugs and aspirin, or a history of coronary bypass surgery and/or angioplasty.

All the patients came from the same geographical area (Northeast Turkey). The patients were interviewed about histories of diabetes, hypertension, hyperlipidemia, smoking, and body mass index. Ethical clearance was obtained from the local ethical committee.

Collection of blood samples. After obtaining informed consent, 12-hour fasting blood samples were taken to be analyzed for serum lipids including total cholesterol, triglyceride, low-density lipoprotein (LDL) choles-

Table 1. Comparison of all characteristics of patients with less extensive and extensive coronary artery disease (CAD)

	Less extensive CAD (n=65)			Extensive CAD (n=50)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			61±10			61±9	0.825
Gender							0.395
Male	49	75.4		36	72.0		
Female	16	24.6		14	28.0		
Family history of CAD	16	24.6		28	56.0		<0.05
Smoking	28	43.1		21	42.0		0.706
Diabetes	15	23.1		11	22.0		0.986
Hypertension	22	33.9		18	36.0		0.185
Body mass index (kg/m^2)			27.4±4.2			27.8±4.6	0.144
Total cholesterol (mg/dl)			206±50			208±51	0.760
HDL cholesterol (mg/dl)			38±9			37±8	0.681
LDL cholesterol (mg/dl)			136±43			137±42	0.936
Triglycerides (mg/dl)			174±93			169±88	0.775
High sensitivity CRP (mg/dl)			8.7±7.2			7.6±4.6	0.373
Fibrinogen (mg/dl)			284±114			366±157	<0.05
IL-6 levels (pg/ml)			5.7±16.6			8±7.4	<0.05
IL-6 C/G-174 polymorphism	4	6.2		16	32.0		<0.001

terol, high-density lipoprotein (HDL) cholesterol, high sensitivity C-reactive protein (hs-CRP). For fibrinogen analysis, samples were taken into ethylenediaminetetraacetate (EDTA) tubes.

DNA preparation. A 10-ml venous blood sample from the antecubital vein was collected in EDTA-treated vacutainers and DNA was extracted from these samples using Qiagen DNA elution columns.

Analysis of IL gene mutations. After DNA extraction, IL-6 C/G-174 polymorphism was investigated by means of polymerase chain reaction and subsequent Nla III restriction enzyme analysis. Polymerase chain reaction was carried out in a 50-µl volume sample on a Perkin Elmer-9700 thermal cycler (Perkin-Elmer Applied Biosystems, Foster City, CA, USA). Each sample contained 0.5 µg of genomic DNA, 15 pmoles of each primer, 100 mM of dNTP, 10 mmol/l Tris HCl (pH 8.3), 50 mmol/l KCl, 1.5 mmol/l $MgCl_2$, and 1 U thermostable Taq DNA polymerase. The cycles were carried out 30 times, consisting of steps at 95 °C for 60 seconds, at 58 °C for 50 seconds, and at 72 °C for 100 seconds. Then, 20 µl volumes of the amplification products were digested for 2.5 hours at 37 °C with 2 U of the Nla III restriction enzyme. After separation by 4% agarose gel electrophoresis, the fragments were visualized under ultraviolet light.

Statistical analysis. Data analyses were conducted using SPSS 11.0 software. The results were expressed as means ± standard deviation. Dichotomous variables were compared using the chi-square test, and continuous variables were compared using Student's t-test. A *p* level of <0.05 was accepted as statistical significance.

RESULTS

Patients with less extensive CAD had a significantly lower prevalence of positive familial CAD and significantly lower plasma IL-6 and fibrinogen levels compared to those with extensive CAD (p<0.05; Table 1). Less extensive CAD was associated with higher triglyceride, HDL-cholesterol, and hs-CRP levels, and lower total cholesterol and LDL-cholesterol levels, and body mass index; however, these differences were not significant.

IL-6 polymorphism was detected in 20 patients (17.4%). The frequency of IL-6 polymorphism was significantly higher in patients with extensive CAD (p<0.001; Table 1).

The genotypic distribution in group 1 was as follows: 61 patients (93.9%) were GG homozygous, four patients (6.2%) were GC heterozygous. In group 2, 34 patients (68%) were GG homozygous, and 16 patients (32%) were GC heterozygous. There was no CC homozygous patient.

DISCUSSION

Inflammation has an important role in determining the process of atherosclerosis.[8,16] In this study, we analyzed the effect of the IL-6 C/G-174 genetic variants and inflammatory markers (IL-6, CRP, fibrino-

gen) on the extent of coronary artery disease assessed by coronary angiography in patients with acute coronary syndrome.

Discrepant results have been reported concerning the relationship between IL-6 C/G-174 polymorphism and CAD. In some studies, a higher cardiovascular risk was reported in middle-aged subjects who carry the C allele.[17-19] In another study, a similar association was observed in elderly men and women.[20] By contrast, a large study found no association between the IL-6 C/G-174 polymorphism and the risk for coronary artery disease or myocardial infarction.[21] Chapman et al.[22] reported an independent association between the IL-6 C/G-174 variant and carotid plaque formation in the whole population, and an increased carotid intimal-medial wall thickness in elderly subjects in a randomly-selected, cross-sectional Australian population. In another study by Burzotta et al.[23] the IL-6 G/G-174 genotype was found to be associated with increased IL-6 levels and with prolonged stays in the hospital and intensive care unit than C allele carriers following surgical coronary revascularization.

In our study, the frequency of the IL-6 C/G-174 variant was significantly higher in patients with extensive CAD. In addition, the frequency of the C allele was found in two patients (3.1%) in group 1, and in eight patients (16%) in group 2.

IL-6 plays a major role in upregulating the synthesis of acute-phase proteins including fibrinogen and CRP from hepatocytes.[24,25] IL-6 is released from endothelial cells, fibroblasts, and macrophages activated by infection or inflammation in the vascular wall.[26] However, increased IL-6 levels may also be seen in the absence of an infection.[27] Mohamed-Ali et al.[28] showed that IL-6 was released by adipose tissue.

The relationship between CAD and IL-6 and fibrinogen levels has been examined in many studies. In some studies, the prognostic role of IL-6 was reported in the development of CAD both in healthy and cardiac populations.[5,29] In patients with ACS, IL-6 is released into the coronary circulation and it is believed that the vascular endothelium or unstable coronary plaque is the predominant source of IL-6 release.[30,31] In some prospective epidemiological studies, an independent and significant association was shown between plasma fibrinogen and development of arterial ischemic episodes, myocardial infarction, and stroke.[32]

The relationship between CRP and the extent of CAD is still controversial.[33-36] Zebrack et al.[34] reported a poor correlation between CRP and the extent of CAD. Niccoli et al.[36] failed to find a correlation between serum CRP levels and coronary atherosclerosis in patients with unstable angina. In our study, there was no significant difference between the two groups with respect to serum CRP levels.

It is also known that various external factors play a role in the levels of inflammatory markers. In this context, Tappia et al.[37] analyzed the relationship between smoking and inflammation and demonstrated that smoking affected cytokine production by exerting an inflammatory stimulus on lung macrophages. Smoking was associated with a compromised antioxidant status and high concentrations of tumor necrosis factor and IL-6. It was also found that plasma CRP and IL-6 levels increased following percutaneous coronary intervention.[38]

In our study, many factors that might influence IL-6 and fibrinogen levels were similar between the two patient groups having less extensive and extensive CAD, including age, gender, and smoking; in addition, all blood samples were taken before percutaneous coronary intervention. It was found that patients with angiographically extensive CAD (≥2-vessel stenosis) had significantly higher IL-6 and fibrinogen levels.

In conclusion, considering a significantly higher frequency of family history of CAD in patients with extensive CAD, atherosclerotic plaque may play a basic role in CAD, but the presence of different hemodynamic responses and alterations in the severity of disease from one patient to another might be attributable to the genetic variability of inflammatory system. However, there is still a need for further studies in different and larger populations to confirm these results.

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