The effect of interleukin-10 gene promoter polymorphisms on early-onset coronary artery disease

Erken başlangıçlı koroner arter hastalığında interlökin-10 gen promotor polimorfizmlerinin etkisi

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ABSTRACT

Objective: We assessed the association between interleukin-10 (IL-10) -1082G/A and -592C/A polymorphisms, and coronary heart disease (CHD).
Methods: A cross-sectional, observational study included 86 patients (mean age 43.36±4.930 years) diagnosed to have CHD and 88 healthy controls (mean age 47.07±8.135 years). IL-10 -1082G/A and -592C/A polymorphisms were analyzed using restriction fragment length polymorphism (RFLP) and agarose gel electrophoresis methods in both patient and control groups. Genotype distributions of the polymorphisms between CHD patients and controls were assessed by Chi-square analysis.
Results: The genotype distribution of the -1082 G/A polymorphism was not different in premature CHD patients (GG: 38.3%; GA: 51.1%; AA: 10.6%) and controls (GG: 43.1%; GC: 43.1%; CC: 13.8%) (p=0.57). The prevalence of the A allele at -1082G/A polymorphism was 36.6% in patients and 35.3% in controls. Both allele and genotype frequencies of -592C/A polymorphism did not also differ significantly between patients with CHD and controls. We did not observe relationships between polymorphism-specific haplotypes and adverse angiographic and clinical outcomes. We have observed a significant difference of IL-10 -592C/A allelic frequency (OR=2.00 95% CI=0.9434-4.2579) between the younger CHD patients (<45 years, Group 2) and matched controls.
Conclusion: Our study suggests that IL-10-592C/A polymorphism may play a role in susceptibility to CHD in younger patients.
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Key words: Interleukin-10, promoter polymorphisms, coronary heart disease, prevalence

ÖZET

Amaç: Bu çalışmada, koroner kalp hastalığı (KKH) ve interlökin-10 (IL-10) -1082 G/A ve -592C/A promotor polimorfizmleri arasındaki ilişkinin değerlendirilmesi hedeflenmiştir.
Yöntemler: Enine-kesitli gözlemsel olarak tasarlanan bu çalışmada, koroner kalp hastalığı tanısı alan 86 hasta (ortalama yaş 43.36±4.930 yıl) KKH ve 88 sağlıklı kontrolde (ortalama yaş 47.07±8.135 yıl) interlökin-10 (IL-10) -1082 G/A ve -592C/A promotor polimorfizmleri RFLP ve jel elektroforezi yöntemi ile çalışılmıştır. KKH ve kontrol grubu arasındaki polimorfizmlerin genotip dağılımları Ki-kare analizi ile değerlendirilmiştir.
Bulgular: Hasta (GG:%38.3; GA:%51.1; AA:%10.6) ve kontrol (GG:%43.1; GC:%43.1; CC:%13.8) (p=0.57) grupları arasında IL-10, -1082 G/A polimorfizmi genotip dağılımları arasında bir fark saptanmadı. Aynı polimorfizm allel sıklığı açısından değerlendirildiğinde A alleli sıklığı hasta grubunda %36.6, kontrol grubunda %35.3 olması nedeniyle belirgin bir fark görülmedi. IL-10 -592C/A polimorfizmi hem allel, hem de genotip frekansları değerlendirildiğinde hasta ve kontrol grupları arasında istatistiksel olarak anlamlı bir farka rastlanmadı. Polimorfizmlere özgü allel ve genotip frekansları ve haplotipler ile anjiyografik ve klinik bulgular arasında istatistiksel olarak anlamlı bir fark bulunmadı. Genç KKH olan (<45 yaş), hastaların yaş uyumlu kontrolleri ile yapılan karşılaştırmada IL-10 -592C/A polimorfizmi allel sıklığı (OR=2.00 % GA=0.9434-4.2579) açısından istatistiksel olarak anlamlı bir fark saptanmıştır.
Sonuç: Bu çalışma IL-10-592 C/A polimorfizminin genç KKH'na yatkınlıkta bir rolünün olabileceğini düşündürtmektedir.
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Anahtar kelimeler: Interlökin-10, promotor polimorfizmleri, koroner kalp hastalığı, prevalans

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Introduction

Coronary heart disease (CHD) is one of the most important health problems worldwide causing the highest rate of mortality and morbidity. Extensive clinical and statistical studies have identified several factors that increase the risk of coronary heart disease and heart attack. Increasing age, gender, heredity, tobacco smoke, high blood cholesterol, high blood pressure, physical inactivity, diabetes mellitus and obesity are the predisposing factors to CHD (1).

These traditional risk factors for CHD do not yet predict the majority of new cases. CHD results from the progression of atherosclerotic plaque. Inflammation is a key component of the atherosclerotic disease and its complications (2-5). It is highly probable that genes affecting the inflammatory response promote or retard its development.

Interleukin- 10 (IL-10) has a complex and predominantly opposing roles in inflammation and plays a major role in suppressing immune and inflammatory responses (6). Its effects are directed mainly against functions of mononuclear cells, T lymphocytes and polymorphonuclear leukocytes. Furthermore, IL-10 plays a role in inhibition of cell adhesion molecules, monocyte chemotactic protein-1, tissue factor, fibrinogen, matrix metalloproteinase-9, T-lymphocyte granulocyte-macrophage colony-stimulation factor, inducible nitric oxide synthase and smooth muscle cell proliferation (7-9). Several of these functions of IL-10 are centered on inhibition of macrophage function, including cytotoxic activity and cytokine synthesis that was suggested as IL-10 may arrest and reverse the chronic inflammatory response in established atherosclerosis, as well as limit thrombotic complications (10, 11).

The human IL-10 gene is located on chromosome 1 and has been mapped to the junction between 1q31 and 1q32 (12, 13).

The inter- individual difference among individuals in their ability to produce IL-10 appears to have a genetic origin. The heritability of the endotoxin induced IL-10 production has been estimated to be 74% in studies on monozygotic or dizygotic twins and nonrelated individuals (14). The gene encoding IL-10 contains variable sites (polymorphisms and micro satellite markers) that have previously been associated with the level of IL-10 produced, indicating that they may be associated with different responsiveness to regulatory signals.

The best documented of these polymorphisms are the IL-10 gene promoter polymorphisms -1082G/A -819C/T, and -592C/A (15, 16).

This study was based on the assumption that the IL-10 gene polymorphisms may have an influence role on atherosclerotic mechanisms and contribute to the occurrence of CHD and myocardial infarction (MI).

Methods

Study design and patients

This cross-sectional and observational study was carried out among 86 CHD consecutive patients (male -60, female-26, mean age 43.36±4.930 years) who referred at Ege University Faculty of Medicine, Department of Cardiology and 88 age matched healthy controls (male - 63, female - 25, mean age 47.07±8.135 years).

Controls included in the study had no symptoms of angina or possible myocardial infarction by WHO questionnaire assessment (17) or had no history of CHD diagnosed by a cardiologist and had a resting 12- lead electrocardiogram showing no evidence of ischemia or previous MI.

As there are many studies emphasizing the importance of myocardial infarction at a young age, we have divided the patients into two groups such as >45 years old and ≤45 years old and compared to the age matched healthy controls (17, 18).

Written informed consent was obtained from the patients and controls. The study was approved by the Faculty Ethics Committee of the Ege University.

Study protocol

All subjects underwent physical examination including height, weight, and blood pressure measurement. They also provided demographic information and medical history (including CHD risk factors).

CHD was defined as the presence of a history of acute MI [as defined by WHO criteria (19)], or a history of unstable angina (typical chest pain with dynamic electrocardiographic changes or minor elevations in cardiac markers) and obstructive coronary artery disease angiographically (70% luminal stenosis).

The diagnosis of CHD was confirmed by coronary angiography performed using standard techniques. CHD was considered to be present if there was a diameter narrowing of at least 50% in at least one of the three major epicardial coronary arteries.

Genetic analysis

-1082 G/A and -592C/A polymorphisms in IL-10 gene promoter were examined in patient (n=86) and control (n=88) groups.

Genomic DNA was isolated from peripheral blood using standard techniques (DNA Isolation Blood Mini Kit, Invitek, Germany). Briefly, the PCR consisted of denaturing at 95°C for 1 min, then 30 cycles at 95°C for 15 s, 65°C for 50 s, and 72°C for 50 s, and a final extension at 72°C for 5 min. The following primers were used; IL-10 -1082 G/A: 5'-CCA AGA CAA CAC TAC TAA GGC TCC TTT- 3'and 5'-GCT TCT TAT ATG CTA GTC AGG TA -3'; IL-10 -592C/A: 5'- CAA CTT CTT CCA CCC CAT CTTT -3' and 5'- GTC GGC TAA ATA TCC TCA AAG TT- 3'. The PCR products for IL-10 -1082 G/A and IL-10 -592C/A were digested by XagI (EcoNI) (Fermentase) and RsaI (Fermentase) at 37°C overnight, respectively and were analyzed by electrophoresis on 3% agarose gel and were stained with ethidium bromide for visualization under ultraviolet light.

Statistical analysis

Statistical Program for Social Sciences (SPSS, Inc., Chicago, IL, USA) software, version v.15.0 was used for statistical analysis. The genotype distributions and allele frequencies for the polymorphisms investigated in healthy volunteers, patients with normal coronary arteries and single vessel and multivessel disease groups were compared by Chi-square analyses. Independent samples t test and Mann-Whitney U test were used for comparison of continuous variables. Statistical significance was established at $p<0.05$.

Results

The frequencies of conventional risk factors are presented in Table 1. High-density lipoprotein-cholesterol level was signifi-

cantly higher in control group, whereas triglyceride level was significantly higher in patients (p<0.001 for both).

The genotypic and allelic distributions of IL-10 gene promoter -1082G/A and -592C/A polymorphisms did not differ significantly between patients with CHD and controls (Table 2).

Combined genotypes of the two polymorphic loci of IL-10 promoter were tested. Seven out of nine different theoretically possible allele combinations were present for-1082G/A and -592C/A polymorphisms (Table 3). In our group, in essence, the frequency of each IL-10 combined genotype was not significantly different between CHD patients and matched controls.

No significant differences were also found between allelic and genotype frequencies of CHD patients with single-vessel disease (SVD) and those with multi-vessel disease.

Finally, a significant difference was observed between allelic frequencies of IL-10 -592C/A polymorphism of younger CHD patients (<45 years) and controls ((OR=2.00 95%CI=0.9434-4.2579, p=0.049) (Table 4).

The genotype distributions of the study group were consistent with those predicted by the Hardy-Weinberg equilibrium.

Discussion

The distribution of IL-10 -1082G/A and -592C/A genotypes as well as allele frequencies were not significantly different between patients with CHD and the controls in this study which was in agreement with many previous studies (20-22). There are many studies evaluating the effect of gene polymorphisms on the occurrence of CHD in younger ages (≤45 years old) (18, 19, 23, 24). Therefore when patients are divided into two groups such as >45 years old and ≤45 years old in our study, and compared to the age matched healthy controls, the -592C/A polymorphism was significantly more prevalent in younger CHD patients (p=0.049).

IL-10 is widely viewed as an anti-inflammatory mediator and is thought to play a critical role in a number of pathophysiological conditions like atherosclerosis and its acute complications. Therefore, IL-10 gene appears to be a good candidate for coronary artery disease studies.

Recent studies have shown inconsistent results on this IL-10 gene promoter polymorphisms and cardiovascular diseases (25-27).

Table 1. Conventional risk factors and their frequencies

Variables	Patients (n=86)	Controls (n=88)	*p
Age, years	43.36±4.93 43.00 (35.00-61.00)	47.07±8.14 45.00 (37.00-68.00)	0.208
Male/female, n	60/26	63/25	0.896
Smoking habit (>5 per day), n (%)	48 (55)	52 (59)	0.065
Alcohol habit, n (%)	13 (18)	18 (20)	0.658
Total cholesterol, mg/dl	209.21±55.08 201.00 (103.00-403.00)	195.74±37.84 197.50 (125.00-300.00)	0.061
HDL cholesterol, mg/dl	42.38±9.40 40.00 (20.00-68.00)	48.11±10.44 48.50 (27.00-66.00)	<0.001
LDL cholesterol, mg/dl	128.44±50.91 124.00 (40.00-315.00)	126.77±30.47 125.00 (46.00-220.00)	0.795
Triglycerides, mg/dl	236.91±241.93 171.50 (47.00-840.00)	143.98±68.16 132.50 (55.00-435.00)	<0.001

Data are presented as mean±SD, median (min-max) values and number (percentage)
*Chi-square and Mann-Whitney U tests
HDL - high density lipoprotein, LDL - low-density lipoprotein, max-maximum, min-minimum

Table 2. Genotype and allele frequencies of IL-10 -1082G/A and -592C/A polymorphisms in patient and control groups

IL-10		Patients (n=86)		Controls (n=88)		Total (n=174)		
		n	%	n	%	n	%	*p
G1082A	GG	22	25.50	23	26.10	45	25.86	0.575
	GA	44	51.10	44	50.00	88	50.57	
	AA	20	23.40	21	23.90	41	23.56	
	Total	86	100.00	88	100.00	174	100.00	
	G	109	63.40	114	64.70	223	64.08	0.836
	A	63	36.60	62	35.30	125	35.92	
	Total	172	100.00	176	100.00	348	100.00	
C592A	CC	51	59.30	58	65.90	109	62.64	0.875
	CA	29	33.80	24	27.30	53	30.46	
	AA	6	6.90	6	6.80	12	6.90	
	Total	86	100.00	88	100.00	174	100.00	
	C	130	75.60	140	79.50	270	77.59	0.287
	A	42	24.40	36	20.50	78	22.41	
	Total	172	100.00	176	176.00	348	100.00	

Data are presented as number (percentage)
* Chi-square test
IL-10 - interleukin - 10

Table 3. Combined genotype and frequencies in patients and control groups

IL-10	Patients		Controls		
1082/592	n	%	n	%	*p
GG/CC	14	16.28	21	23.86	0.206
GG/CA	13	15.12	11	12.50	0.660
GG/AA	6	6.98	6	6.82	1.000
GA/CC	30	34.88	26	29.55	0.510
GA/CA	13	15.12	12	13.64	0.830
AA/CC	8	9.30	11	12.50	0.620
AA/CA	2	2.33	1	1.14	0.610
Total	86	100.00	88	100.00	

Data are presented as number (percentage)
*Chi-square test
IL-10 - interleukin - 10

Table 4. Allele frequencies of IL-10 -1082G/A and -592C/A polymorphisms in patient and control groups and less than 45 years of age

		G		A		
IL-10	Groups	n	%	n	%	*p
1082G/A	Controls (n=43)	55	63.95	31	36.05	0.464
	Patients (n=53)	66	62.26	40	37.74	
	Total (n=96)	121	63.02	71	36.98	
		C		A		
	Groups	n	%	n	%	p
592C/A	Controls (n=43)	74	86.05	12	13.95	0.049
	Patients (n=53)	80	75.47	26	24.53	
	Total (n=96)	154	80.21	38	19.79	

Data are presented as number (percentage)
* Chi-square test
IL-10 - interleukin - 10

In the study reported by Koch et al. (20) allele frequencies, genetic distributions and frequencies of allele combinations for IL-10 -1082G/A, -819C/T and -592C/A promoter polymorphisms were similar between patients with MI, coronary artery disease patients and matched controls. Donger et al. (21) also investigated the genotypes of the same three IL-10 promoter polymorphisms and allele frequencies in 1107 patients with MI and their results suggested no association between IL-10 polymorphisms and increased risk of MI. In another study, McGlinchey et al. (22) examined polymorphisms in the promoter regions of the pro inflammatory cytokine IL-6 (-174G/C), anti-inflammatory cytokines IL-10 (-1082G/A) and TGF-β1 (-509C/T) genes in the susceptibility to ischemic heart disease (IHD). They demonstrated that the genotypes of these polymorphisms and allele frequencies were not associated with IHD in Irish population (22). In one of the latest study which was performed in the Finnish population showed conflicting results as they have found IL-10 promoter region haplotype GCC (-1082G/A, -819C/T and -592C/A) associated with decreased arterial elasticity in 24-39 years aged CHD patients. In addition to this they have also emphasized the IL10 -1082 G/A; -819 C/T; -592 C/A genotypes were significantly associated with carotid artery compliance, stiffness index and young's elastic modulus in young male CAD (28). On the other hand, no significant difference between CHD and IL-10-592 C/A polymorphism has been found in a recent study and the authors have shown an association between those polymorphisms and susceptibility to Kawasaki disease (29). Another study found an association between coronary artery disease and IL-6-174 G/C polymorphism but no association with IL-10-1082 G/A, IL-10-819 C/T, IL-10-592 C/A, TGF-β1-codon 10 T/C and TGF-β1-codon 25 G/C, IFN-γ-874 T/A, TNF-α-308 A/G polymorphisms (30). Trompet et al. (31) performed a genetic association study of four IL-10 promoter single nucleotide polymorphisms (SNPs) (4259A/G, -1082G/A, -592C/A, and -2849G/A) with coronary and cerebrovascular events in participants at risk for vascular disease. They found that the -592C/A polymorphism in the promoter region of the IL-10 gene was associated with coronary events.

Genotype -592AA was reported to reduce IL-10 production in cultures of peripheral blood mononuclear cells treated with interferon (32). The AA genotype was associated with lower IL-10 production in both patients and healthy controls (22).

There may be several potential reasons why an association between these polymorphisms and CHD was not found. First, as McGlinchey emphasized that, these promoter polymorphisms are not associated with CHD. It has been suggested that the contradictory results are due to possible differences in IL-10 regulation in different cell types (33).

Second there could be a possible relationship between IL-10 alleles and IL-10 gene expression and protein production, which was previously examined in different experimental settings (25, 32, 34). For example, Turner et al. (25) showed with the presence of allele -1082A, the stimulation of lymphocytes with concanavalin A resulted in lower IL-10 production compared to allele -1082A-negative cells. Third, conflicting results may be due to different ethnic origins in different studies. Most of the studies revealing no relationship between IL-10 polymorphisms and CAD were performed in the Western populations.

Regarding to the number of vessels involved in CHD, there was no difference in the genotype and allele frequencies of patients with single vessel disease compared with patients with multi-vessel disease in our study. In a study comparing the effects of genetic polymorphisms (-1082G/A, -819C/T, and -592C/A) on CHD, no association between these polymorphisms and number of effected vessels was found (35).

In our study, conventional risk factors such as age, gender, serum lipid levels, alcohol habit and smoking habits showed similar frequencies in our patient and control groups.

In our study, considering the genetic factors may be more effective in younger age hormonal profile that has important effects on metabolic processes related with cardiovascular diseases, CHD patients were divided into two groups: older than 45 years of age, and equal and younger than 45 years of age. In the literature there is no study evaluating the association of IL-10 polymorphisms in this age groups. -592C/A polymorphism which was significantly more prevalent in younger CHD patients in our study may be further evaluated in larger series.

Study limitations

A small cohort and the missing determination of plasma levels of IL-10 were the limitations of this study. The statistical

power increases with increasing sample size. This means that a larger sample has a greater ability to detect a clinically important effect than a smaller sample. When the sample size is very small, the test may have an inadequate power to detect a particular effect. It is well known that limitations and complexities exist in 'simple' association studies; however, as more data accumulate, a conclusion can be reached. Therefore, further larger studies are needed to investigate the relationship between the IL-10 gene polymorphisms and CHD in various populations.

Conclusion

We demonstrated a significant relation between IL-10 -592C/A polymorphism and risk of CHD in young male patients in a Turkish cohort. Functional studies of this mutation are required in order to understand the mechanisms of action. Further studies are also required to examine the relation of IL-10 -592C/A polymorphism in order to refine the identification of individuals at early risk of CHD.

Conflict of interest: None declared.

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