Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Clinical Research

J. Exp. Clin. Med., 2020; 37(3): 87-95
doi: 10.5835/jecm.omu.37.03.005

Association of anteroseptal hypokinesia after myocardial infarction with LDLR variation: A cross-sectional case-control study

Pegah Pourzargham[a], Mahboobeh Azadi[a], Monireh Ataollahi[a], Hamed Fouladseresht[a], Shahdad Khosropanah[b], Mehrnoosh Doroudchi[a*]

[a] *Department of Immunology, Faculty of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*
[b] *Department of Cardiology, Faculty of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*

ARTICLE INFO

Article History
Received 03 / 02 / 2020
Accepted 02 / 04 / 2020
Online Published 30 / 04 / 2020

*** Correspondence to:**
Mehrnoosh Doroudchi
Department of Immunology,
Faculty of Medicine,
Shiraz University of Medical Sciences,
Shiraz, Iran
e-mail: mdoroud@sums.ac.ir

Keywords:
Hypokinesia
Low density lipoprotein receptor
Myocardial infarction
Polymorphism
Single nucleotide

ABSTRACT

Cholesterol-rich LDL (LDL-C) is a major atherogenic lipoprotein. Elevated content of LDL-C in serum is associated with the higher risk of atherosclerosis. The plasma LDL-C level is regulated by LDL receptor. The T allele of rs2228671 in LDLR may be associated with decreased LDL-C levels. We investigated the association of rs2228671 of LDLR with myocardial infarction (MI) in people from Fars province of Iran. In this study 248 cases with MI and 256 healthy blood donors were tested for their rs2228671 LDLR polymorphism by PCR-RFLP method. The CC genotype of the rs2228671 single nucleotide polymorphism tended to be more common in patients while TT showed a higher frequency in the control group. Patients with anteroseptal hypokinesia had a significantly higher frequency of the CC genotype compared with other patients (p=0.04, OR 8.217 and 95% CI 0.4755 to 142). Also frequency of C allele was increased as compared with that of the T allele in patients with anetroseptal hypokinesia (p=0.05, OR 7.637 and 95% CI 0.4367 to 124.6). There was also a significant increase of CT genotype in patients with abnormal heart rate (p=0.014). A significantly higher frequency of the CC genotype in patients with anetroseptal hypokinesia and its decrease in patients with abnormal heart rate suggest a complex relationship between LDLR variants and complications of MI.

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1. Introduction

Cardiovascular diseases (CVDs) have been categorized as a main health problem in Middle East and Iran in recent years (Hadaegh et al., 2013; Jahangiri-Noudeh et al., 2014; Kheirandish et al., 2014; Moghaddam et al., 2014; Hadaegh et al., 2015; Lotfaliany et al., 2015; Hadaegh et al., 2017; Mohseni et al., 2017). Coronary Artery Diseases (CADs) are the most common CVDs with a greater frequency in men compared to women which appear less frequently in younger people (Nicolini et al., 2017). On average, a first heart attack for men happens at the age of 65 years but the average age of a first heart attack in women is 72 years (Harvard).

Acute myocardial infarction (AMI), also known as heart attack, represents a leading cause of hospital admissions and mortality around the world (Moran et al., 2014). The prevalence of AMI in Iran is high and is increasing (Mohseni et al., 2017). AMI occurs

in case of a mismatch between myocardial oxygen supply and demand. Therefore, damage happens as heart encounters the inability of oxygenation (Boyette and Manna, 2019). AMI is a complex multifactor condition of familial and environmental nature (Rose, 1964). Generally, atherosclerotic plaque rupture and subsequent thrombosis of advanced atherosclerotic lesion cause partial or complete blockade in the artery (Libby, 2006), which in case of coronary arteries it can cause AMI (Boyette and Manna, 2019). It is widely accepted that the elevation of low density lipoprotein (LDL) content, as a result of hereditary or life style risk factors, causes embolism (Gofman and Lindgren, 1950; Krenz and Korthuis, 2012).

Moreover, one of the major atherogenic lipoproteins is the cholesterol-rich LDL (LDL-C). The content of cholesterol in serum is carried by LDL-C, where high levels of LDL-C accumulate and accelerate atherosclerosis (Soutar, 2001; Rafieian-Kopaei et al., 2014). The plasma LDL-C level is regulated by LDL receptor (LDLR). Therefore, variations in LDLR may lead to abnormal levels of LDL-C (van Zyl et al., 2014). LDLR is a type I transmembrane protein that is encoded by a gene located in the 19p13.2 region and is 45 kb in length, including 18 exons and 17 introns. Thirteen of the 18 exons encode sequences of protein which are similar to sequences in other proteins: five of these exons encode sequences similar to the sequences in the C9 component of complement; three exons encode sequences similar to those in the precursor of epidermal growth factor (EGF) and in three proteins of the blood clotting system (factor IX, factor X, and protein C); and five other exons encode sequences that are shared with the EGF precursor and are not repeated (Sudhof et al., 1985).

The LDLR pathway is mostly limited to tissues in which there are high interactions for cholesterol such as liver, adrenal gland and reproductive organs (Soutar, 2001). An in vivo study in mice showed that LDLR expression is differently regulated in liver and intestine by dietary cholesterol and dietary saturated fat. Dietary cholesterol regulates LDLR at the transcriptional level, while dietary fatty acids do not (Srivastava et al., 1995). Changes caused by mutation in the LDLR may decrease expression or function of LDL receptors and consequently defected LDL-C uptake (Leigh et al., 2017). Therefore, the perturbed catabolism of LDL-C may lead to an increase in its content (Motulsky, 1989). The more intensely a homozygote is affected, the less they have competent receptors and consequently they show higher levels of cholesterol (Punzalan et al., 2005). The association of elevated LDL cholesterol levels with the higher risk of atherosclerosis is already shown but there seems to be inter-population differences (Ference et al., 2017). A recent genome-wide association study (GWAS) represented various single nucleotide polymorphisms (SNPs) at the LDLR locus that provide inter-individual variations in serum lipid concentrations (Sandhu et al., 2008). Among these variations, the minor variant of rs688 (Asn591 ACC_ ACT), which is located within exon 12, is reported to be associated with a 4–10% elevation in plasma cholesterol levels (Jha et al., 2018). Backing this, another study on rs688 reported its association with LDL-C and total cholesterol in a gender-dependent manner (Zhu et al., 2007). The rs1122608 SNP is reported to be associated with lower serum levels of LDL-C and the lower risk of coronary artery disease (Martinelli et al., 2010). However, a meta-analysis established that rs1122608 of LDLR was not associated with the risk of Coronary Heart Disease (CHD) (Zhang et al., 2013). It is shown that in German and British populations, the T allele at SNP site of rs2228671, which is located in exon 2, is associated with decreased LDL-C levels and CHD risk (Linsel-Nitschke et al., 2008). By contrast, no association between this SNP and cardiovascular diseases in Chinese population is seen (Ye et al., 2014). It is also suggested that the T allele of rs2228671 is associated with LDL-C levels but no association has been found with the risk of CAD (Martinelli et al., 2010).

Given the importance of LDLR in CAD, and the inter-population differences of association of rs2228671 with CAD, the objective of this study was to investigate the frequency of this SNP in a sample of patients in southwestern Iran and controls from the same region, to determine the importance of this LDLR variant in our population.

2. Material and methods

Study population

All approved MI cases (n=248, mean age=59.64 ± 12.44 y) included in this study, were referred to the affiliated hospitals of Shiraz University of Medical Sciences in southwest of Iran, between 2014 and 2017. The sample size was calculated based on the minor allele frequency of 8% and CI of 95% and the DEFF of 1.8 using EPI info statistical analysis software (https://www.openepi.com/SampleSize/SSPropor.htm). MI diagnosis was confirmed by the collaborating cardiologist, on the basis of typical ECG variations and changes in cardiac markers. All individuals had evidences in favor of acute MI and sampling and data recording were done in less than 24 hours as of progression of symptoms. Confirmation of MI was based on more than 50% stenosis in one or more of the coronary arteries in coronary angiography. The clinical data of patients who underwent echocardiography was also recorded.

The patients' clinical criteria are shown in Table 1. Based on the criteria defined by American Heart

Association, systolic blood pressure more than 140 mmHg and diastolic blood pressure more than 90 mmHg were considered as high systolic and high diastolic blood pressure, respectively (https://www.heart.org/en/health-topics/arrhythmia/about-arrhythmia). BMI was calculated by division of weight in kilograms to the square height in meters for each patient.

Table 1. Demographical criteria of patients with AMI.

Characteristics	
Number of subjects	248
Age(mean ± SD)	59.64 ± 12.44
Sex (male/female)	183/65
BMI (129)	no. (%)
<25	68 (27.42)
25-30	48 (19.35)
30-35	12 (4.84)
>35	1 (0.40)
Missing	119 (47.98)
Familial history (157)	
Yes	45 (18.15)
No	112 (45.16)
Missing	91 (36.69)
Hypertension (157)	
Yes	48 (19.35)
No	109 (43.96)
Missing	91 (36.69)
Diabetes mellitus (156)	
Yes	38 (15.32)
No	118 (47.58)
Missing	92 (37.1)
Smoking (157)	
Yes	76 (30.65)
No	81 (32.66)
Missing	91 (36.69)

Control individuals (n=256, mean age=45.45 ± 9.26 y) were recruited from among healthy blood donors between 2014 and 2017 who referred to Fars Blood Transfusion Center and resided in the same geographic region as of patients. The blood donors were also examined by a physician and were assessed for systemic diseases, including: hypertension, dyslipidemia, stroke, coronary artery disease and also they were approved of not being cured with drugs for related disorders. Also the individuals in control group were all non-smokers, -alcoholics or -drug addicts. The potential sources of bias between patients and controls was the mean age differences between the two groups, as the patients had a significantly greater age ($p<0.001$).

Blood samples and DNA extraction

Ten ml venous blood was collected from all individuals in tubes containing ethylene diamine tetra acetic acid (EDTA) 5% w/v (weight/volume) anticoagulant. DNA extraction was further performed by salting out method. DNA quality and quantity was evaluated using Eppendorf Biophotometer. Also DNA concentration and protein contamination were determined by means of spectrophotometer (Agilent) in 260 and 280 nm wavelength. Samples were kept in -40°C until used. Samples with 1.6 to 1.9 optical densities (O.D.) were used for polymerase chain reaction (PCR).

Genotyping

PCR and RFLP methods were used for genotyping of coding rs2228671 polymorphism in LDLR gene. PCR procedure was performed in a 25 µL total reaction volume containing 0.75 µL of dNTP, 2 µL genomic DNA (50 ng/ml), 0.75 µL of $MgCl^2$, 2.5 µL10X PCR Buffer, 2 µL Taq DNA polymerase, 16 µL distilled water, and 1.0 µL of each of the forward and reverse primers. Mentioned components were mixed in each single tube and 40 µL mineral oil was added to each one. After 10 seconds of centrifugation, tubes were placed in the thermocycler (Techne Flexigene).

For RFLP, the required restriction enzyme was added to PCR products and incubated at 37°C for 6-10 hours in a dry block. The enzymatically cleaved products were electrophoresed on a 3.5% agarose gel containing 2.5 µL safe stain and visualized by UV light at 254 nm (Fig. 1). The rs2228671-T allele was identified as a 194 bp band and the rs2228671-C allele as a 174 bp band in the gel. Due to their small fragment size, the 20 bp bands were not clearly defined on the gel. The primer sequences, required restriction enzyme, recognition site of the restriction enzyme, and the length of cleaved products are represented in Table 2. All the experiments were performed in our laboratory in the Department of Immunology, Faculty of Medicine, Shiraz University of Medical Sciences.

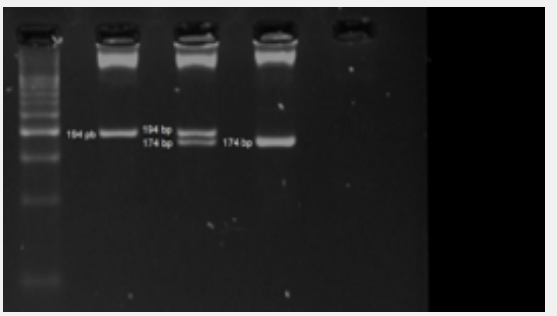

Fig. 1. PCR-RFLP products corresponding to the LDLR rs2228671 polymorphism.

Table 2. Primer sequences, restriction endonucleases, PCR product lengths, and restriction patterns.

SNP	**Primer sequences**	**Restriction enzyme**	**Product length (bp)**	**Length of final fragments (bp)**
LDLR rs2228671	Forward-5'CTCTCAGTGGGCGACAGACG-3' Reverse-5'-CAACATGGCGAGACCCTGTC-3'	BstUI 5' CG↓CA 3' 5' GC↑GC 3'	194	CC: 20, 174 CT: 20, 174, 194 TT: 194

Statistical analyses

SPSS software (Version 19) was used to perform statistical analysis. $\chi 2$ test and Fisher's exact test were performed to investigate the differences in the frequencies of genotype and allele between patients and controls as well as the correlation of clinical manifestations with genotypes and alleles. Also binary and multinomial logistic regression analyses were performed to confirm the primary $\chi 2$ results, where applicable. Odds ratios and relative risks were calculated using online EPI info statistical analysis software (www.openepi.com/TwobyTwo/TwobyTwo.htm). The significance level was set at and below 0.05. We used the STREGA reporting guidelines for reporting this study (Little et al., 2009).

3. Results

Genotype and allelic distribution

SNP analysis was performed in a population of 248 MI cases (65 females and 183 males) and 256 controls (18 females and 238 males). Table 3 illustrates the distribution of genotypes and allelic frequencies of the LDLR (rs2228671 C/T) polymorphism in MI patients and healthy control group. As shown in Table 3, rs2228671 alleles ($\chi 2$ p=0.07, OR 1.4) and genotypes ($\chi 2$ p= 0.06, OR: CC VS TT= 0.098, CT VS TT= 0.117, TT= 1) had no significant difference between MI patients and healthy controls. Hardy-Weinberg Equilibrium was tested for each group and genotypes in both patients (p=0.38) and controls (p=0.47) were in equilibrium. The proportion of genotypes among patients increased progressively from rare homozygous genotype, TT (0%) to heterozygotes, CT (16.13%) to common homozygous genotype, CC (83.87%). Compared with the control group, CC was more common in patients while TT showed a higher frequency in the control group. Accordingly, the decrease in frequency of the rs2228671-T allele in patients was notable (Table 3). The relative risk for rs2228671-C and -T alleles showed that the C allele has a greater non-significant risk for myocardial infarction (p=0.07, RR=1.219; Table 3). The CC genotype of the rs2228671 SNP also showed a higher non-significant relative risk in comparison with other genotypes (p=0.06, RR=1.162; Table 3).

Association of LDLR polymorphism with clinical manifestations of the disease

Cross-tabulation was performed to determine the association of genotypes/alleles with clinical manifestations in patients. Genotype was significantly correlated with anteroseptal hypokinesia. Of 131 (100%) cases with known echocardiography data, 18 (13.74%) individuals were positive for anteroseptal hypokinesia who all (100%) had CC genotype, however, of 113 (86.26%) negative cases of anteroseptal hypokinesia, 92 (81.42%) had CC and 21 (18.58%) had CT genotype. Individuals with anteroseptal hypokinesia had a significantly higher frequency of the CC genotype in comparison with other genotypes (p=0.046, OR 8.217 and 95% CI 0.4755-142). Also frequency of C allele was increased as compared with that of the T allele in patients with anteroseptal hypokinesia (p=0.057, OR 7.637 and 95% CI 0.4367-124.6).

We also investigated the association of high systolic or diastolic blood pressure with genotypes and alleles of LDLR (rs2228671 C/T) polymorphism. There were no significant association between genotype and systolic blood pressure in $\chi 2$ test (p=0.19; Table 4), or regression analysis (p=0.23; Table 4). However, there was a significant increase ($\chi 2$ p=0.075, regression p=0.014, OR 2.242; Table 4) in the CT genotype in patients with abnormal heart rate (i.e., the heart rate below 60 BPM or over 100 BPM). By inclusion of age in the regression analysis and after correction for age the difference in the genotype frequencies based on rate, stayed significant (p=0.009). Similarly, a significant increase in T allele was observed in patients with abnormal heart rate (p=0.02; Table 5). No association was observed for BMI with genotypes (p= 0.10) and alleles (p=0.12). The genotypes and alleles of LDLR (rs2228671 C/T) polymorphism did not show any significant differences in other wall motion abnormalities (Table 6, Table 7).

Table 3. The distribution of rs2228671 of LDLR in MI patients and control group.

Genotype and Allele	Patients N (%)	Controls N (%)	p value	OR (95%CI)	Relative Risk
Genotypes			0.06		
CC	208 (83.87)	204 (79.69)		CC VS TT: 0.098 (0.005-1.806)	1.162
CT	40 (16.13)	47 (18.36)		CT VS TT: 0.117 (0.006-2.217)	0.918
TT	0 (0)	5 (1.95)		TT: 1 (Reference)	0.183
Alleles			0.07	1.4000 (0.9143-2.1436)	
C	456 (91.94)	456 (89.06)			1.219
T	40 (8.06)	56 (10.94)			0.82

Table 4. The association of clinical features with LDLR rs2228671 genotypes.

Clinical manifestations	LDLR rs2228671 N (%)		P Chi²	P Regression	OR (95%CI)
	CC	CT			
Arrhythmia			0.44	0.15	2.621 (0.702-9.784)
Positive	70 (81.4)	16 (18.6)			
Negative	138 (85.19)	24 (14.81)			
Rate			0.075	0.014	2.971 (1.245-7.088)

Normal	110 (88)	15 (12)			
Abnormal	98 (79.67)	25 (20.33)			
SBPA *			0.19	0.23	2.242 (0.599-8.392)
Positive	14 (73.68)	5 (26.32)			
Negative	129 (85.43)	22 (14.57)			
DBPA **			0.36	0.89	1.102 (0.268-4.533)
Positive	13 (76.47)	4 (23.53)			
Negative	130 (84.97)	23 (15.03)			
QT			0.41	0.74	1.39 (0.566-3.414)
Normal	71 (86.59)	11 (13.41)			
Abnormal	137 (82.53)	29 (17.47)			

*Systolic blood pressure on admission
**Diastolic blood pressure on admission

Table 5.The association of clinical features with LDLR rs2228671 alleles.

Clinical manifestations	**LDLR rs2228671 N (%)**		**P Chi²**	**P Regression**	**OR (95%CI)**
	C	T			
Arrhythmia			0.46	0.17	2.267 (0.699-7.359)
Positive	156 (90.7)	16 (9.3)			
Negative	300 (92.59)	24 (7.41)			
Rate			0.09	0.02	2.626 (1.163-5.927)
Normal	235 (94)	15 (6)			
Abnormal	221 (89.84)	25 (10.16)			
SBPA *			0.21	0.25	2.029 (0.600-6.863)
Positive	33 (86.84)	5 (13.16)			
Negative	280 (92.72)	22 (7.28)			
DBPA **			0.38	0.98	1.095 (0.296-4.053)
Positive	30 (88.24)	4 (11.76)			
Negative	283 (92.48)	23 (7.52)			
QT			0.43	0.50	1.341 (0.575-3.130)
Normal	153 (93.29)	11 (6.71)			
Abnormal	303 (91.26)	29 (8.73)			

*Systolic blood pressure on admission
**Diastolic blood pressure on admission

Table 6. The association of Wall Motion Abnormalities with LDLR rs2228671 genotypes.

Wall Motion Abnormalities	**LDLR rs2228671 N (%)**		**P Chi²**
	CC	CT	
Apicoseptal Akinesia			
Positive	12 (80)	3 (20)	
Negative	98 (77.78)	18 (22.22)	0.66
Missing	117		
Apicoseptal Hypokinesia			
Positive	6 (100)	0 (0)	
Negative	100 (82.65)	21 (17.35)	0.24
Missing	121		
Apicolateral Akinesia			
Positive	16 (88.89)	2 (11.11)	
Negative	94 (83.2)	19 (16.8)	0.54
Missing	117		
Apicolateral Hypokinesia			
Positive	11 (84.62)	2 (15.38)	
Negative	96 (76.80)	19 (23.20)	0.92
Missing	120		
Anterior Hypokinesia			
Positive	4 (100)	0 (0)	
Negative	103 (83.06)	21 (16.94)	0.37
Missing	117		
Anterolateral Akinesia			
Positive	3 (75)	1 (25)	
Negative	107 (84.25)	20 (15.75)	0.62
Missing	117		
Anterolateral Hypokinesia			
Positive	4 (100)	0 (0)	
Negative	106 (83.46)	21 (16.54)	0.37
Missing	117		
Anteroseptal Akinesia			
Positive	8 (100)	0 (0)	
Negative	102 (82.93)	21 (17.07)	0.20
Missing	117		
Anteroseptal Hypokinesia			
Positive	18 (100)	0 (0)	
Negative	92 (81.42)	21 (18.58)	0.046
Missing	117		
Inferior Akinesia			

Positive	4 (66.67)	2 (33.33)	
Negative	103 (84.43)	19 (15.57)	0.25
Missing	120		
Inferior Hypokinesia			
Positive	6 (66.67)	3 (33.33)	
Negative	101 (84.87)	18 (15.13)	0.155
Missing	120		
Inferoseptal Akinesia			
Positive	3 (75)	1 (25)	
Negative	103 (83.74)	20 (16.26)	0.64
Missing	121		
Inferoseptal Hypokinesia			
Positive	6 (75)	2 (25)	
Negative	101 (81.17)	19 (15.83)	0.50
Missing	120		
Dyskinesia			
Positive	4 (80)	1 (20)	
Negative	106 (84.13)	20 (15.87)	0.80
Missing	117		

Table 7. The association of Wall Motion Abnormalities with LDLR rs2228671 alleles.

Wall Motion Abnormalities	**LDLR rs2228671 N (%)**		**P Chi²**
	C	T	
Apicoseptal Akinesia			
Positive	27 (90)	3 (10)	
Negative	214 (92.24)	18 (7.76)	0.67
Missing	234		
Apicoseptal Hypokinesia			
Positive	12 (100)	0 (0)	
Negative	221 (91.32)	21 (8.68)	0.29
Missing	121		
Apicolateral Akinesia			
Positive	34 (94.44)	2 (5.56)	
Negative	207 (91.59)	19 (8.41)	0.56
Missing	117		
Apicolateral Hypokinesia			
Positive	24 (92.31)	2 (7.69)	
Negative	211 (91.74)	19 (8.26)	0.92
Missing	240		
Anterior Hypokinesia			
Positive	8 (100)	0 (0)	
Negative	227 (91.53)	21 (8.47)	0.39
Missing	234		
Anterolateral Akinesia			
Positive	7 (87.5)	1 (12.5)	
Negative	234 (92.13)	20 (7.87)	0.63
Missing	234		
Anterolateral Hypokinesia			
Positive	8 (100)	0 (0)	
Negative	233 (91.73)	21 (8.27)	0.40
Missing	234		
Anteroseptal Akinesia			
Positive	16 (100)	0 (0)	
Negative	225 (91.46)	21 (8.54)	0.22
Missing	234		
Anteroseptal Hypokinesia			
Positive	36 (100)	0 (0)	
Negative	205 (90.71)	21 (9.29)	0.057
Missing	234		
Inferior Akinesia			
Positive	10 (83.33)	2 (16.67)	
Negative	225 (92.21)	19 (7.79)	0.27
Missing	240		
Inferior Hypokinesia			
Positive	15 (83.33)	3 (16.67)	
Negative	220 (92.44)	18 (7.56)	0.17
Missing	240		
Inferoseptal Akinesia			
Positive	7 (87.5)	1 (12.5)	
Negative	226 (91.87)	20 (8.13)	0.66
Missing	242		
Inferoseptal Hypokinesia			
Positive	14 (87.5)	2 (12.5)	
Negative	221 (92.08)	19 (7.92)	0.52
Missing	240		
Dyskinesia			
Positive	9 (90)	1 (10)	
Negative	232 (92.06)	20 (7.94)	0.81
Missing	234		

4. Discussion

In the current study we found that the frequency of rs2228671 SNP at LDLR locus was non-significantly different between patients with AMI and healthy blood donors in southwest of Iran. Our results are in line with the finding of a study in northern Italy (Martinelli et al., 2010), however, due to the lower number of cases in our study, the difference did not reach a significant level. A potential source of bias between patients and controls was the mean age differences between the two

groups, as the patients had a significantly higher age ($p<0.001$). However, this difference was inevitable due to the higher age of MI incidence in which age finding healthy volunteers is less likely.

Our most important finding was an increase in the frequency of the CC genotype in patients with anteroseptal hypokinesia, which may suggest the association of CC genotype with this type of wall motion abnormality (WMA). The relation of segmental WMA to cardiovascular events is shown in acute myocardial infarction (Peels et al., 1996; Fleischmann et al., 1997; Stein et al., 1998; Carluccio et al., 2000). WMAs have been shown to increase the re-polarization time of the heart and also cause inhomogencity of re-polarization, which results in myocardial arrhythmia. Similarly, abnormal heart rate increases the re-polarization time (Han and Moe, 1964; Kuo et al., 1983; Zareba and Moss, 1995; Opthof et al., 2012). In our analysis, however, there was a significant decrease in the CC genotype among patients with abnormal heart rate. Also a significant increase in the T allele was also observed in patients with abnormal heart rate (Table 5). Therefore, individuals with T allele were less likely to show anteroseptal hypokinesia but were more likely to have increased heart rate. All but one patient had heart rates less than 140 beats per minute and it is possible that the increased heart rate had maintained blood pressure and/or contractility, therefore resisting hypokinesis. Whether the increased heart rate in these individuals has a compensatory effect for lower contractility of the heart muscle through "Treppe phenomenon" needs to be investigated (Mulieri et al., 1992). Of note, despite expectations, we did not find any correlation between anteroseptal hypokinesia and arrhythmia in our patients (Opthof et al., 2012).

The limitations of this study were the relatively low number of cases, missing values and the age difference between cases and controls, as well as lack of clinical and paraclinical data of controls, which may have hampered the clear conclusion on the differences of cases ad controls.

Our study showed an association between rs2228671 CC genotype of LDLR and anteroseptal hypokinesia, while this genotype decreased in patients with abnormal heart rate. Further investigation of this SNP along with haplotypic combinations of LDLR polymorphisms may provide information on the part these variants and their products play in mechanical complications of heart after MI.

Acknowledgement: The authors thank all the individuals (patients, blood donors, and hospital staff) who participated in this study. This work was supported by grants from Shiraz University of Medical Sciences (grant numbers: 94-9301 and 93-7326), Shiraz, Iran. The codes of ethical approval of these projects are: IR.SUMS.REC.1394.s96 and IR.SUMS. REC.1393.7326. I had full access to all of the data in this study and I take complete responsibility for the integrity of the data and accuracy of the data analysis.

Conflict of interest: The authors declare no conflict of interest.

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