ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Investigation of *Scavenger Receptor Class B Type I* gene variants in patients with coronary heart disease with a history of early myocardial infarction

Erken miyokart enfarktüs geçmişi olan koroner kalp hastalarında *Çöpçü Reseptör Sınıf B Tip I* gen varyantlarının araştırılması

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ABSTRACT

Objective: The scavenger receptor class B type 1 (*SR-BI,* SCARB1), which is a high-density lipoprotein (HDL) receptor that mediates selective cholesteryl ester uptake, plays an important role in reverse cholesterol transport. This study investigated the distribution of polymorphic variants of the *SR-BI* gene in patients with coronary heart disease (CHD) with a history of early myocardial infarction (MI) at an early age and their effects on their serum lipid levels.

Methods: *SR-BI* rs5888(T>C), rs4238001(C>T), and rs10846744(G>C) were analyzed in 100 male patients with CHD with a history of MI (MI+) who were younger than 50 years and 89 male control subjects without MI history (MI–) using real-time polymerase chain reaction (PCR) and mutant-allele–specific PCR techniques.

Results: *SR-BI* rs4238001 common-CC genotype was found to be more frequent in patients with MI+ than in control subjects (MI–; odds ratio 4.046, p<0.001). The rs10846744 rare-C allele showed a significant association with increased total cholesterol (p=0.014) and triglyceride (p=0.009) levels in the MI+ CHD group. Logistic regression analysis confirmed that there may be an association between the rs4238001-CC genotype (p=0.002), smoking (p=0.026), and MI+ CHD in the presence of other risk factors associated with CHD, whereas haplotype analysis confirmed that patients with MI+ CHD (rs5888-C, rs10846744-G, and rs4238001-C alleles) and CCC (rs5888-C, rs10846744-C, and rs4238001-C alleles) haplotypes were highly frequent (p<0.01 and p=0.027, respectively).

Conclusion: These results indicated that *SR-BI* gene variants show different distribution in patients with MI+ CHD compared with that in MI– control subjects, and these variants may have effects in favor of dyslipidemia.

ÖZET

Amaç: Kolesterol esterin selektif alımına aracılık eden bir yüksek yoğunluklu lipoprotein (HDL) reseptörü olan Çöpçü reseptör sınıfı-B tip-1 (*SR-BI*, SCARB1), ters kolesterol taşınmasında önemli bir rol oynar. Bu çalışmada *SR-BI* geninin polimorfik varyantlarının erken yaşta miyokart enfarktüsü (MI) hikayesi olan koroner kalp hastalarındaki (KKH) dağılımı ve bunların serum lipidlerine etkisi incelenmiştir.

Yöntemler: *SR-BI* rs5888(T>C), rs4238001(C>T) ve rs10846744(G>C), 50 yaşından önce MI öyküsü olan (MI (+)) 100 erkek KKH hastasında ve MI öyküsü olmayan (MI (–)) 89 erkek kontrolde real time-PCR ve mutant allel spesifik PCR teknikleri ile analiz edildi.

Bulgular: MI(+) Hasta grubunda *SR-BI* rs4238001 atasal-CC genotipi frekansı MI(–) kontrol grubundan istatistiksel olarak anlamlı yüksek bulunmuştur (OR:4.046, p<0.001). Rs10846744 nadir-C alleli, MI(+) KKH grubunda artmış toplam kolesterol (p=0.014) ve trigliserit (p=0.009) seviyeleri ile anlamlı bir ilişkili iken, MI(–) grupta düşük ApoA1 düzeyleriyle ilişkiliydi (p=0.021). Lojistik regresyon analizi, diğer ilişkili KKH risk faktörlerinin varlığında rs4238001-CC genotipi (p=0.002), sigara (p=0.026) ve MI(+) KKH arasında bir ilişki olabileceğini doğrularken, haplotip analizinde ise MI(+) KKH hastalarında CGC (rs5888-C, rs10846744-G, rs4238001-C allelleri) ve CCC (rs5888-C, rs10846744-C, rs4238001-C allelleri) haplotiplerinin yüksek sıklıkta olduğu bulundu (sırasıyla p<0.01 ve p=0.027).

Sonuç: Bu sonuçlar, *SR-BI* gen varyantlarının MI(+) KKH hastalarında MI(–) kontrollere göre farklı dağılım gösterdiğini ve bu varyantların dislipidemi lehine etkileri olabileceğine işaret etmektedir.

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Cardiovascular diseases (CVDs) are the leading cause of the death worldwide,[1] and early myocardial infarction (MI) is one of the serious conditions among CVDs. Regarding the definition of early MI or MI in young ages, in the literature, the term "young" refers to age ranging between ≤40[2-5] and ≤55.[6] The mean age for young age group is accepted as 45 years in some of the studies.[7,8] Because there is no universally accepted mean age for the occurrence of early MI and 50 years has been accepted as the one in the recently published studies,[9,10] we chose the same mean age for this study.

The scavenger receptor class B type 1 (*SR-BI*, SCARB1), which is a cell-surface glycoprotein with a molecular weight of 82 kD and 509 amino acid residues, is a high-density lipoprotein (HDL) receptor that binds to HDL-cholesterol (HDL-C) with a high affinity and plays an important role in selective cholesterol uptake of HDL-C and reverse cholesterol transport.[11,12] *SR-BI* is expressed predominantly in hepatic and steroidogenic tissues.[13] It is reported that *SR-BI* is protective against the early onset of atherosclerosis in the *SR-BI/apolipoprotein E* double homozygous knockout mice,[14] and the loss of *SR-BI* expression causes occlusive atherosclerotic coronary artery disease (CAD), spontaneous MIs, severe cardiac dysfunction, and early death. Thus, *SR-BI* is considered as an anti-atherogenic receptor.[15,16]

SR-BI gene, which consists of 13 exons and 12 introns, is localized on chromosome 12.[17,18] It is a multiligand receptor because it functions as a receptor for Apo-B–containing low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) transport. Based on the effects of *SR-BI* gene variations on serum HDL-C, LDL-C, VLDL-C, and triglyceride (TG) levels, it was suggested that *SR-BI* gene variations may be responsible for individual differences in lipid metabolism.[12,13,19-23] In addition, some previous studies,[24-26] attribute the development of CHD or tendency to CHD to deficient receptor-mediated uptake and catabolism of plasma LDL and consequent hypercholesterolemia. Although many studies have been conducted to show the association between *SR-BI* mutations and CHD, the results remain controversial.[19,27-29]

Constantineau et al.[30] reported that the rs5888 variant of the *SR-BI* gene, a silent mutation in exon 8, affects the secondary structure of the RNA, with the protein translation causing reduced *SR-BI* protein expression and function. Furthermore, it was reported that *SR-BI* rs5888 is associated with atherogenic lipid profile,[20,21] peripheral arterial disease,[31] and cardiovascular risk in an age- and gender-specific manner.[25,29,32] A missense rs4238001 mutation of the *SR-BI* gene in exon 1, which results in an amino acid change from Gly to Ser at position 2, was found to be associated with altered cholesterol levels.[19,33] In addition, rs10846744, an intronic mutation in the *SR-BI* gene, has been reported to affect the transcriptional regulation of *SR-BI*.[22,34]

Abbreviations:

BMI	*Body mass index*
CAD	*Coronary artery disease*
CIs	*Confidence intervals*
CVDs	*Cardiovascular diseases*
DBP	*Diastolic blood pressure*
ECG	*Electrocardiography*
ERα	*Estrogen receptor alpha*
ERβ	*Estrogen receptor beta*
gnomAD	*Genome Aggregation Database*
HALP	*Hyperalphalipoproteinemia*
HDL	*High-density lipoprotein*
HDL-C	*HDL-cholesterol*
HWE	*Hardy-Weinberg equilibrium*
LAG3	*Lymphocyte activation gene 3*
LD	*Linkage disequilibrium*
LDL-C	*Low-density lipoprotein cholesterol*
LIPAD	*Linz peripheral artery disease*
LR	*Logistic regression*
MAF	*Minor allele frequency*
MASA-PCR	*Mutant allele-specific amplification PCR*
MI	*Myocardial infarction*
OR	*Odds ratio*
PXR	*Pregnane X receptor*
SBP	*Systolic blood pressure*
SCORE	*Systematic COronary Risk Evaluation*
SNP	*Single nucleotide polymorphism*
SR-BI, SCARB1	*Scavenger receptor class B type 1*
TG	*Triglyceride*
Total-C	*Total cholesterol*
VLDL-C	*Very low-density lipoprotein cholesterol*
YY1	*Yin Yang 1*

Acton et al.[19] suggested that the effects of genetic variations in the *SR-BI* gene locus on lipid metabolism are gender specific. Indeed, the effects of *SR-BI* gene variations on lipid levels may depend on sex hormones. *SR-BI* is highly expressed in steroidogenic tissues, including adrenal glands, placenta, ovaries, and testis. Cholesterol is used as the precursor of steroidogenesis in steroidogenic cells. One of the cholesterol sources used for steroidogenesis in these tissues is selective cellular uptake of cholesterol through *SR-BI*.[35] Estrogen is a powerful regulator that affects the expression of *SR-BI* isoforms.[22] The promoter region of *SR-BI* is positively regulated by the estrogen receptor alpha (ERα) and estrogen receptor (ERβ), while pregnane X receptor (PXR), DAX-1, and Yin Yang 1 (YY1) are negatively regulated by transcription factors.[36] Ghaffari et al.[37] reported that estrogen

significantly reduces LDL transcytosis and leads to decreased endothelial *SR-BI* expression. Velasco et al.[38] also showed that baseline and peak E2 levels were significantly lower in patients with low *SR-BI* RNA expression than those in patients with high *SR-BI* expression. Moreover, it is well known that estrogen has important effects on serum lipid levels as it lowers the serum levels of LDL-C and TG, which results in the protection of premenopausal women against CAD. Therefore, the design of this study includes only age-matched male patients and control subjects to investigate the effects of *SR-BI* variants on the development of CHD excluding the effects of estrogen and age.

Because of the important role of *SR-BI* in the cellular uptake of VLDL, LDL, and HDL and in reverse cholesterol transport, we hypothesized that rs5888, rs4238001, and rs10846744 variations of the *SR-BI* gene may have effects on serum lipid profile and early MI in patients with CHD. To identify the exact effects of *SR-BI* gene variants on serum lipid/lipoprotein levels by eliminating estrogen effect on HDL-C, only men were included in this study. The purpose of this study was to investigate the individual and combined effects of rs5888, rs4238001, and rs10846744 variations of the *SR-BI* gene on the development of CHD and early MI, and their dyslipidemic effects on serum lipid profiles.

METHODS

Patient selection and clinical investigation

In this study, we included 100 male patients with CHD with first MI who were aged 50 years or younger and 89 healthy male control subjects without any history of MI. All study participants were questioned for CHD risk factors such as smoking and cardiometabolic risk factors such as the family history of CHD, hyperlipidemia, hypertension, and diabetes mellitus. The smoking habits were assessed from a questionnaire. Participants were identified as nonsmokers or smokers. Individuals who had never smoked in their lifetime were defined as nonsmokers; otherwise, they were defined as smokers (smokers who stopped smoking for >1 year were also defined as smokers).

The diagnosis of CHD was made by analysis of medical history, symptoms of angina pectoris, electrocardiography (ECG), and changes in angiography, which was also used to identify the severity of CHD. The inclusion criteria for angiography were at least one major coronary vessel with ≥50% stenosis due to atherosclerosis, and a vascular event, such as MI, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty. Although 90% of the patients in the CHD group were on atorvastatin monotherapy, 10% of them did not use the statin group or any other lipid-lowering medication. Of the patients who received atorvastatin treatment, 67 were using moderate-high–dose (≥20 mg) atorvastatin, and 23 were receiving low-dose (10 mg) atorvastatin treatment. Control subjects did not have any symptoms of CHD and a history of vascular events or a family history of CVD and metabolic diseases such as diabetes, kidney/liver failure, and lipid disorders.

Ethics committee approval was received for this study from the Clinical Researches Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (Approval Date: March 15, 2021; Approval Number: 591). Each individual in this study gave written informed consent prior to physical examination and blood sample collection.

Lipid measurement

After the collection of blood samples from participants who had fasted overnight, the serum samples were obtained from whole blood and immediately frozen at -20 °C. The enzymatic techniques were used to measure serum total cholesterol (Total-C), HDL-C, and TG levels. Serum LDL-C level was calculated using the Friedewald formula. The lipid profile typical for dyslipidemia is characterized by low HDL-C and increased TG levels and the prevalence of small, dense LDL particles.[39] In this study, the dyslipidemia phenotype was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria. Accordingly, LDL-C ≥130 mg/dL, HDL-C <40 mg/dL, and TG ≥150 mg/dL were used as dyslipidemic values.[40]

Genotyping

High Pure PCR Template Preparation Kit (Roche Diagnostics GmbH, Germany) was used for isolating genomic DNA from peripheral blood samples. Genotypes of *SR-BI* rs5888 (T>C) (Figure 1) and rs10846744 (G>C) (Figure 2) were determined by a real-time PCR method using LightSnip primer-probe sets (TIB Molbiol GmbH, Germany) and Light Cy-

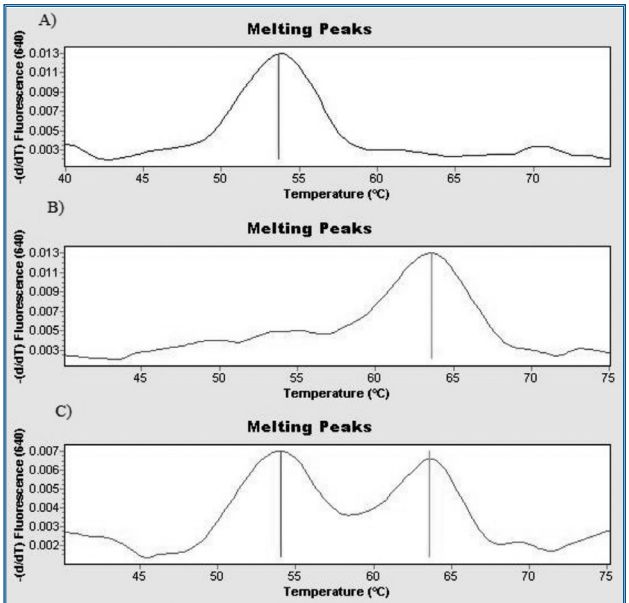

Figure 1. Genotypes of rs5888 were determined by RT-PCR according to melting curve analysis. **(A)** wild-type CC genotype, **(B)** mutant TT genotype, and **(C)** heterozygous CT genotype.
RT-PCR: real-time transcription polymerase chain reaction.

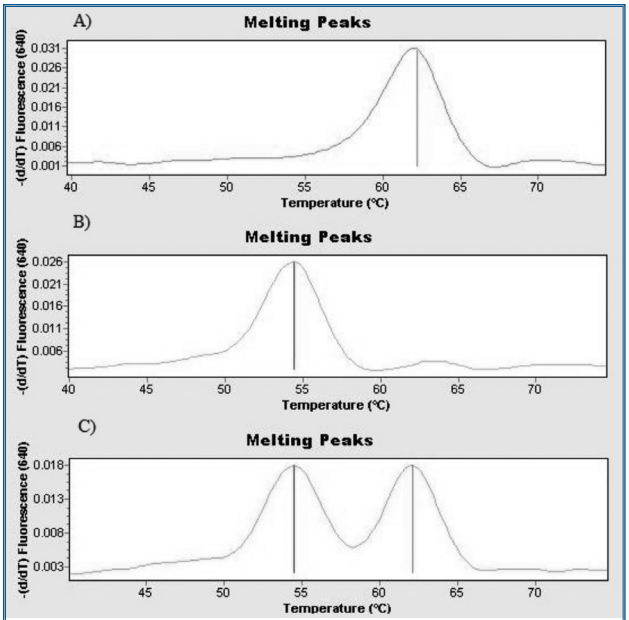

Figure 2. Genotypes of rs10846744 were determined by RT-PCR according to melting curve analysis. **(A)** wild-type GG genotype, **(B)** mutant CC genotype, and **(C)** heterozygous GC genotype.
RT-PCR: real-time transcription polymerase chain reaction.

cler FastStart DNA Master Hyprobe kit (Roche Diagnostics GmbH, Germany). PCR conditions were as follows: an initial denaturation of 10 minutes at 95 °C; annealing step at 95 °C for 10 seconds, at 60 °C for 10 seconds, and at 72 °C for 15 seconds (40 cycles); and a melting curve step at 95 °C for 30 seconds and at 40 °C for 2 minutes (1 cycle). The mutant allele–specific amplification PCR (MASA-PCR) method was used to detect the rs4238001 (Gly2Ser) polymorphism.[41] Forward primer-1 (5′-GCTTTGGCGGA GCAGCC-3′) was used to amplify the wild-type allele, and forward primer-2 (5′-CCCAGCGC GCTTTGGCGGAGCAGCT-3′) was used to amplify the mutant allele of the *SR-BI* gene. The reverse primer (3′-GTCCCCGTCTCCTGCCA-5′) was the same for both wild-type and mutant alleles. PCR conditions for amplification of wild-type allele of the *SR-BI* gene were as follows: an initial denaturation step of 3 minutes at 95 °C followed by 35 cycles of denaturation at 95 °C for 45 seconds, annealing at 63 °C for 30 seconds, and extension at 72 °C for 45 seconds. PCR conditions for amplification of mutant allele of the *SR-BI* gene were as follows: an initial denaturation step of 3 minutes at 95 °C followed by 35 cycles of denaturation at 95 °C for 45 seconds, annealing at 69.5 °C for 30 seconds, and extension at 72 °C for 45 seconds with a final extension step for 10 minutes at 72 °C. The sizes of PCR products were 83 bp with wild-type (Gly) and 91 bp with mutant (Ser) alleles (Figure 3). When the test was repeated by taking 15% of the objects randomly, there was no misapprehension in genotyping. The findings were similar to a replicative study, with the results being 100% concordant.

Statistical analysis

We performed sample size calculation using the PS software, Power and Sample Size Calculation package program (version 3.0, Dupont and Plummer, 2018), with inputs of p0 *(*probability of exposure in controls*)* and p1 (probability of exposure in cases) from the Ensemble genome browser. The type I error probability (α) was used as 0.05. As a result, the statistical power of the relationship between *SRBI*, rs4238001 variation, and CHD risk was obtained as 99.7% in our study.

The findings of the study were evaluated using the SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Normal distribution of continuous variables was tested using the Kolmogorov–Smirnov (K-S) test, and the equality of variances between groups was tested using the Levene test. Continuous

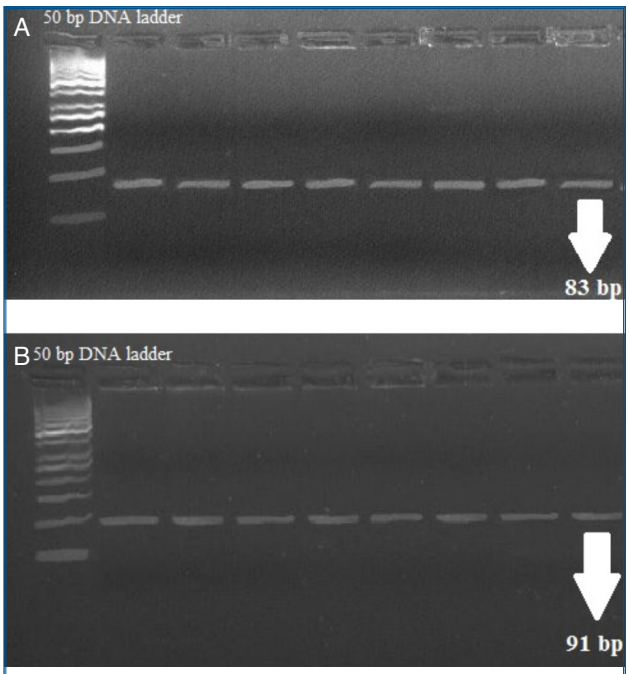

Figure 3. The sizes of PCR products for rs4238001. **(A)** 83 bp wild-type allele and **(B)** 91 bp mutant allele.
PCR: polymerase chain reaction.

variables were compared between the groups using the Student *t* test when normally distributed and nonparametric Mann–Whitney *U* test in cases of deviation from normal distribution. Relative risk was determined by calculating the odds ratios (ORs) and 95% confidence intervals (CIs). Allele frequencies of *SR-BI* gene variations were calculated using the gene counting method. The distribution of the genotypes in the study groups was examined by the chi-square test. Estimation of the effects of risky *SR-BI* genotype/alleles on MI+CHD group was also evaluated by univariate logistic regression (LR) models. Bonferroni correction was applied using the formula pc=p/n (pc: corrected p value, p: original p value, n: number of comparisons made). Because of the small number of individuals with homozygous minor genotype, heterozygotes and homozygotes were combined for the minor allele. In this case, the corrected p value was calculated as 0.025, and the results were interpreted according to this value (pc=0.05/2=0.025).

Binary logistic regression analysis was performed to determine the CHD risk factors by the backward LR method. The linkage disequilibrium between *SR-BI* gene variants was assessed using D' and r^2 values determined through the Haploview Program (www.broad.mit.edu/mpg/ haploview/documentation.php).

RESULTS

Clinical investigation

The participants in the study groups were age matched. Characteristics of patients with CHD with MI+ were as follows: 17.4% had type 2 diabetes, 96% had hypertension, 85.9% had a stent (70.8% in 1 artery, 10.8% in 2 arteries, and 4.6% in 3 arteries), and 92.5% were receiving continued statin therapy. Therefore, patients with CHD with early MI history had a lower frequency of traditional cardiovascular risk factors compared with MI– control subjects. A lower level of total-C (p=0.017) was found in patients with CHD MI+ group than that in control subjects, whereas smoking (p=0.006) was higher in patients than in MI– control subjects. There was no significant difference between the study groups in terms of systolic blood pressure (SBP) and diastolic blood pressure (DBP), alcohol consumption, body mass index (BMI), and the serum levels of apoprotein-A1 (ApoA1), TG, HDL-C, LDL-C, fasting glucose levels, and VLDL-C (p>0.05) (Table 1).

SR-BI rs5888, rs10846744, and rs4238001 genotypes and allele distribution

The frequency of wild-type CC genotype of *SR-BI* rs4238001 was higher in CHD with early MI history group than in control subjects without any history of MI or CHD (control subjects: 31.5% vs CHD: 65.0%; OR: 4.046, 95% CI: 2.204–7.427, p<0.001). It was found that minor rs4238001 TT genotype was lower in the patient group; however, this difference did not reach statistical significance (control subjects: 29.2% vs CHD: 17.0%, p=0.068). In the univariate LR analysis, only the *SR-BI* rs4238001 CC genotype showed a significant association with MI+ CHD (p<0.001) (Table 2). In fact, the *SR-BI* rs5888 minor CC genotype was also found to be higher in patients (30.0%) than in controls (16.9%) (p<0.05), but this association was not confirmed after the Bonferroni correction (p>0.025) was made. However, rs10846744 single nucleotide polymorphism (SNP) of the *SR-BI* gene was not found to be statically significant between study groups (p>0.05) (Table 2).

There was no significant deviation from the Hardy-Weinberg equilibrium (HWE) for *SR-BI* rs5888 and rs10846744 polymorphisms in the MI+ CHD group and the MI– control subjects (p>0.05), while a significant deviation from the HWE was detected for the rs4238001 polymorphism in the study groups (p<0.05).

Table 1. Demographic, biochemical, and clinical data

	Control (MI– CHD) (n=89)	MI+ CHD (n=100)	*p*
Age (year)	55.91±4.69	57.07±7.3	0.203
First MI age (year)	-	48.96±0.63	
SBP (mmHg)	129.36±18.92	125.26±13.92	0.109
DBP (mmHg)	70 [16.25]	80 [10]	0.180
BMI (kg/m^2)	25.17±4.28	25. 39±3.76	0.715
Apoprotein A1 (g/L)	1.34±0.25	1.26±0.19	0.103
TC (mg/dL)	188.80±44.40	173.36±44.40	**0.017**
TG (mg/dL)	144 [70]	112.5 [112]	0.793
LDL-C (mg/dL)	121.5 [30]	82.5 [61]	0.078
HDL-C (mg/dL)	45.17±11.97	42.08±10.04	0.060
VLDL-C (mg/dL)	31.9 [14]	22.5 [21]	0.381
Fasting blood glucose (mg/dL)	93.5 [17]	89 [16.25]	0.127
Smoking (%)	43.1	66.3	**0.006**
Alcohol use (%)	36.8	42.7	0.534

Variables are presented as number (%), mean±SD or median [interquartile range]. Statistical analysis were performed by chi-square test, Student t test, and Mann–Whitney U test. Bold values indicate statistical significance.
BMI: body mass index; CHD: coronary heart disease; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low density lipoprotein-cholesterol; MI: myocardial infarction; n: subsample of study population; SBP: systolic blood pressure; TC: total cholesterol; TG: triglyceride; VLDL-C, very low-density lipoprotein cholesterol.

Table 2. Genotype distributions of *SR-BI* rs5888, rs10846744, and rs4238001 in the study groups

SR-BI polymorphism		Control (MI– CHD) (n=89)	MI+ CHD (n=100)	Statistical analysis
rs5888 genotypes	TT	29 (32.6%)	19 (19.0%)	Chi-square
	CC	15 (16.9%)	30 (30.0%)*	*χ^2=3.791, p=0.05
	TC	45 (50.6%)	51 (51.0%)	(OR: 2.11, 95% CI: 1.049-4.260)
rs5888 alleles	T	103 (57.87%)	89 (44.5%)	Univariate analysis
	C	75 (42.13%)	111 (55.5%)	CC vs TT+TC
	HWE	p>0.05	p>0.05	**p=0.036** (OR: 2.114, 95% CI: 1.049-4.260)
rs10846744 genotypes	GG	48 (53.9%)	50 (50.0%)	Chi-square
	CC	10 (11.2%)	10 (10.0%)	NS
	GC	31 (39.3%)	40 (40.0%)	
rs10846744 alleles	G	127 (71.35%)	140 (70.0%)	Univariate analysis
	C	51 (28.65%)	60 (30.0%)	CC+GC vs GG
	HWE	p>0.05	p>0.05	p=0.589 (OR: 0.854, 95% CI: 0.482-1.514)
rs4238001 genotypes	CC	28 (31.5%)	65 (65.0%)†	Chi-square
	TT	26 (32.9%)	17 (17.0%)	†: χ^2=21.194, p<0.001 (OR: 4.046,
	CT	35 (39.3%)	18 (18.0%)	95% CI: 2.204-7.427)
rs4238001 alleles	C	91 (51.12%)	148 (74.0%)	Univariate analysis
	T	87 (48.88%)	52 (26.0%)	CC vs. TT+TC
	HWE	p<0.05	p<0.05	**p<0.001** (OR: 4.046, 95% CI: 2.204-7.427)

Statistical analysis was performed by chi-square test and univariate logistic regression analysis. Bold values indicate statistical significance.
CHD: coronary heart disease; CI: confidence interval; HWE: Hardy-Weinberg Equilibrium; n, subsample of study population; NS: not significant; OR: odds ratio.
*p<0.05; †p<0.001.

Table 3. Effects of *SR-BI* genotypes on metabolic parameters (level of significance: p=0.025)

Group	Parameter	*SR-BI* gene variations					
		rs5888		rs10846744		rs4238001	
Control		TT (n=24)	CC/TC (n=52)	GG (n=42)	CC/GC (n=33)	TT (n=26)	CC/TC (n=53)
(MI– CHD)	Apo A1	1.36±0.22	1.29±0.24	1.38±0.21	**1.21±0.23***	1.32±0.22	1.37±0.28
	Glucose	91.64±17.48	91.62±13.89	93.14±18.13	89.76±10.38	91.71±17.09	89.72±14.24
	Total-C	200.0±45.95	186.10±47.10	200.0±45.17	**174.90±38.99†**	180.69±30.12	192.66±51.74
	TG	130.09±44.25	149.56±70.80	142.48±75.22	138.94±43.36	131.86±42.48	144.25±69.91
	HDL-C	45.17±12.36	44.79±11.97	47.49±10.42	41.70±13.51‡	45.17±12.74	44.79±30.50
	LDL-C	3.14±1.01	2.83±0.72	2.98±0.75	2.66±0.62	2.73±0.52	3.03±0.85
	VLDL-C	0.70±0.30	0.76±0.35	0.73±0.36	0.71±0.23	0.68±0.21	0.75±0.37
	BMI	25.98±3.64	24.85±4.58	25.31±2.60	24.89±5.94	25.45±3.45	25.17±4.79
	SBP	125.59±17.30	130.91±20.03	125.94±17.66	132.67±20.24	132.59±17.10	128.94±20.31
	DBP	72.90±12.63	76.19±14.12	74.00±12.06	76.22±15.18	75.45±13.84	75.70±14.12
MI+ CHD		(n=18)	(n=74)	(n=47)	(n=42)	(n=14)	(n=66)
	Apo A1	1.25±0.28	1.26±0.18	1.24±0.21	1.29±0.19	1.33±0.25	1.27±0.19
	Glucose	88.5 [9.75]	94.25 [24.75]	90.5 [19.75]	95.5 [22]	94.5 [92.75]	90 [20]
	Total-C	167.95±49.42	172.20±42.08	161.78±41.31	**185.33±46.72§**	184.94±55.60	173.75±45.17
	TG	114.5 [108]	130 [101]	107 [100]	**131 [134]‖**	103 [101]	131 [122]
	HDL-C	41.70±8.11	41.70±10.42	41.69±10.42	42.47±9.27	45.95±12.74	41.70±9.27
	LDL-C	119 [47]	83.5 [47]	89.5 [44]	108 [62]¶	92.5 [60]	99 [45]
	VLDL-C	25.87±10.04	26.64±8.88	25.10±9.65	27.41±8.87	26.25±12.35	26.25±9.27
	BMI	23.23±6.19	25.89±3.02‡	25.95±2.77	24.87±4.90	24.51±7.75	25.44±2.74
	SBP	124.11±9.39	125.75±14.99	125.10±13.81	123.65±13.73	120.83±12.40	126.51±14.51
	DBP	75 [10]	80 [10]	80 [10]	70 [10]	75 [10]	80 [10]

All the p values were calculated using the Student t test and Mann–Whitney U test. Bonferroni-corrected significance cut-off value was .025 for allele frequency (statistical significance: p<pc=0.025). Bold values indicate statistical significance after Bonferroni correction.
BMI: body mass index; CHD: coronary heart disease; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; SBP: systolic blood pressure; TC: total-cholesterol; TG: triglyceride; VLDL-C: very low-density lipoprotein-cholesterol.
*p=0.021; †p=0.015; ‡p=0.05; §p=0.014; ‖p=0.009; ¶p=0.037.

Table 4. Evaluation of CHD risk factors with binary LR analysis (backward LR method) in MI+ CHD group

Independent variables	p	OR	95% CI for OR
rs4238001 CC genotype	**0.002**	3.136	1.522-6.464
Smoking	**0.026**	2.274	1.105-4.678

Dependent variable: group. Bold values indicate statistical significance.
CHD: coronary heart disease; CI: confidence interval; LR: logistic regression; MI: myocardial infarction; OR: odds ratio.

Association of *SR-BI* gene variants with metabolic parameters

It was observed that patients from the MI+ CHD group with the Rs5888-C allele (CC+CT genotypes) had higher BMI values (p=0.05) than patients with the common TT genotype, but this p value was not statistically significant after the Bonferroni correction (p>0.025). In addition, no significant effect of rs5888 genotypes on metabolic parameters was observed in MI– control subjects as in MI+ CHD group (p>0.05).

MI+ CHD group with rs10846744 minor C allele had higher TC (p=0.014), LDL-C (p=0.037), and TG (p=0.009) levels than patients with the GG genotype. The statistically significant difference between LDL-C and rs10846744 was lost after the Bonferroni correction (p>0.025). In contrast, control subjects with rs10846744-C allele (CC+GC genotypes) had lower ApoA1 (p=0.021), TC (p=0.015), and HDL-C (p<0.05) levels than those with the common GG genotype, and the latter significance was lost after the

Table 5. The frequencies of haplotypes of *SR-BI* gene variants in the study groups

Haplotypes	Frequency			Chi-square	p
	Total	Control (MI– CHD)	MI+ CHD		
TGC	0.241	0.211	0.266	1.393	0.237
CGC	**0.193**	**0.132**	**0.243**	**6.607**	**0.010**
TGT	0.180	0.269	0.105	3.268	0.075
CCC	**0.124**	**0.080**	**0.160**	**4.869**	**0.0273**
CGT	0.120	0.129	0.113	0.178	0.673
TCC	0.069	0.070	0.068	0.004	0.950
CCT	0.052	0.075	0.032	3.055	0.080
TCT	0.022	0.035	0.012	1.978	0.159

The order of haplotypes of the *SR-BI* gene variants is rs5888, rs10846744 and rs4238001.
Bold values indicate statistical significance.
CHD: coronary heart disease; MI: myocardial infarction.

Bonferroni correction (p>0.025).

As for rs4238001, no significant effect on metabolic and clinical parameters was detected in the study groups (p>0.05) (Table 3).

Multivariate regression analysis

The evaluation of CHD risk factors with multivariate regression analysis (binary LR, backward LR method) is shown in Table 4. MI+ CHD was used as a dependent variable, and rs4238001-CC genotype and smoking were used as independent variables. Multivariate LR analysis revealed that the rs4238001-CC genotype and smoking were associated with MI+ CHD (p=0.002 and p=0.026, respectively) (Table 4).

Haplotype analysis

No significant linkage disequilibrium (LD) was found among the 3 SNPs (for rs5888 and rs10846744 D'=0.314, r^2=0.036; for rs10846744 and rs4238001 D'=0.261, r^2=0.015; and for rs5888 and rs4238001 D'=0.056, r^2=0.002). All r^2 values were below 0.1, indicating a weak LD among these 3 SNPs.

The distribution of rs5888, rs4238001, and rs10846744 haplotypes as sets of 3 alleles together was analyzed between the study groups for determining the association with MI+ CHD. It was found that CGC (rs5888-C, rs10846744-G, and rs4238001-C alleles) and CCC (rs5888-C, rs10846744-C, and rs4238001-C alleles) haplotype frequencies were higher in MI+ CHD group than MI– control subjects (p<0.001 and p=0.027, respectively) (Table 5).

DISCUSSION

In this study, the frequency of rs5888 common T allele in MI– control subjects was 57.87%, whereas it was 44.5% in the MI+ CHD group Furthermore, it was found that the *SR-BI*- rs5888 (T>C) homozygous mutant CC genotype was significantly higher in the patient group than the control group (p<0.05). Lipid levels were not affected by *SR-BI* rs5888 variation in this study, as observed in the study by Zeng et al.;[42] however, many studies have shown that *SR-BI* rs5888 (T>C) variation is associated with serum lipids and CHD. Wu et al.[28] reported that the TT genotype is associated with lower HDL-C and ApoA1 levels (p<0.05) in Bai Ku Yao and Han populations of China. In another study, it was suggested that *SR-BI* rs5888 SNP influenced serum lipid levels and was associated with the risk of CAD.[32] Stanislovaitiene et al.[25] reported a lower frequency of *SR-BI* rs5888 TT genotype in the oldest male MI group (65–74 years) and altered lipid levels including elevated serum HDL-C and decreased risk of MI in older Lithuanian men (65–75 years) possessing rs5888 TT genotype. Rejeb et al.[23] showed that the carriers of T allele of *SR-BI* rs5888 had elevated HDL-C and ApoA1 levels and reduced risk of coronary stenosis and that individual atherogenic effect as exon1 (G/A) and intron5 (C/T) and combined effect as CAT haplotype of exon8, exon1, and intron5 on coronary stenosis. Smalinskiene et al.[36] reported a significantly lower risk of having elevated TG levels (>1.7 mmol/L) in *SR-BI* rs5888 CT genotype carrier men than in those with CC genotype in a random sample of Lithuanian

population, thus suggesting an atheroprotective effect of *SR-BI* rs5888 CT genotype. Cerda et al.[43] found that individuals with hypercholesterolemia with rs5888 C allele had a lower change of total cholesterol and lower levels of LDL-C, ApoB, and ApoB/ApoA1 ratio ($P<.05$) than in those with the TT genotype carriers in response to atorvastatin in a Brazilian population. Morabia et al.[20] found the overall mean levels of HDL-C in CC, CT, and TT genotype carrier men as 1.17, 1.22, and 1.24 mmol/L (p=0.0062), respectively, and reported the atheroprotective role of rs5888 in men (OR=0.36, p<0.05).

Few studies have indicated no significant association of *SR-BI* rs5888 (T>C) variation with the risk of CHD.[19,28] No significant effect of rs5888 SNP was found on serum lipid levels and CHD or cerebral infarction risk in the Chinese population.[42] In a Turkish population, Ayhan et al.[44] also reported 2-fold lower CVD risk of TT genotype *SR-BI* gene rs5888 (p=0.04) and 2-fold higher CVD risk of TC genotype carriers of rs5888 variation (p=0.03). They also reported elevated serum levels of big-sized HDL subfraction (p=0.02) in *SR-BI* rs5888 TT genotype carriers of the study group. Thus, they concluded that while *SR-BI* rs5888 TT genotype decreased the risk of CHD, the TC genotype, and especially C allele, increased the risk of CHD development.[44] In this study, rs5888 rare C allele was found to be associated with high BMI values in MI+ CHD group (P<0.05). Moreover, our findings were somehow different from previously obtained data.[20,23,26,28,43] The observed differences can be attributed causally to differences in the statin treatment. In the study of Morabia et al.,[20] patients with CHD did not use statins; however, Cerda et al.[43] included patients with CHD who were receiving statin therapy in their study. In our study, 92.5% of patients with CHD received lipid-lowering statins and only 7.5% of patients with CHD did not receive any antihyperlipidemic treatment. Moreover, the difference might be because of the study population with different number and ethnicity.

SR-BI rs4238001 (Gly2Ser), one of the SNPs we analyzed, is associated with lower *SR-BI* receptor expression as a result of the altered *SR-BI* RNA secondary structure and inefficient protein translation.[19] This mutation was reported to be associated with higher plasma TG concentrations in patients with hypercholesterolemia in the studies of Tai et al.[45] and Morabia et al.[46] Acton et al.[19] reported the association of rs4238001 SNP with higher HDL and lower LDL levels in men, but not in women. In contrast, McCarthy et al.[47] suggested that the exon1 rs4238001 SNP was not associated with HDL-C in men or women from any of the 3 populations examined (Finland, Sweden, and Israel). In this study, similar to the study by McCarthy et al.,[47] we did not observe the effect of rs4238001 variation on serum lipids, blood pressure, and BMI in our study groups (p>0.05). However, rs4238001 (Gly2Ser) minor homozygous TT genotype (T) was lower in the MI+ CHD patient group than in the MI– control group (p=0.046), and the frequency of common CC genotype was higher in MI+ CHD patient group than in MI– control group (p<0.001). According to our rs4238001 SNP distribution results, we suggest that *SR-BI* rs4238001 CC genotype might be associated with CHD and MI independent of serum lipid levels in the Turkish population. The multivariate LR analysis also showed that rs4238001 CC genotype might be associated with MI+CHD in the presence of other CHD risk factors (p=0.002, OR=0.220, 95% CI: 0.129-0.572). On the other hand, compared with the Genome Aggregation Database (gnomAD), the minor allele frequency (MAF) of the rs4238001 variant was found to be higher in our study (0.1 vs 0.49 [for MI– control subjects] and 0.26 [for MI+ CHD patient group]). It has been shown that the MAF value for numerous SNPs varies widely between ethnic groups.[48,49] Regarding rs4238001, T allele frequencies (hypertension group, 50.68% and control subjects, 53.73%) in this study were also found similar to the data in our previous study.[50] When we consider that the allele frequencies might change from population to population and that only very limited studies have investigated the effect of rs4238001 in Turkish population, we believe that the discrepancy will be explained better when more studies are performed with rs4238001 in the Turkish population. However, the frequencies of other *SR-BI* SNPs (rs5888 and rs10846744) were found to be similar to those in gnomAD.

There are few studies investigating the effects of rs10846744 polymorphism that resides within the first intron of the *SR-BI* gene on atherosclerotic CVD development. A significant association of rs10846744 with the incident subclinical atherosclerosis,[34] MI, and CVD was reported in men in a multiethnic study of 7936 participants with ath-

erosclerosis (Multi-Ethnic Atherosclerosis Study, MESA study) (p=0.01).[33] They suggested that the association of rs10846744 polymorphism with subclinical atherosclerosis was not dependent on lipids and other cardiovascular risk factors. On the other hand, Chiba-Falek et al.[22] did not find any effects of rs10846744 polymorphism on *SR-BI* expression in liver and lipid levels in their population-based study. In their study in patients with hyperalphalipoproteinemia (HALP) and participants from MESA, Golden et al.[51] found that the *SCARB1* intronic rs10846744 CC genotype was significantly associated with a higher concentration of small HDL particles and lymphocyte activation gene 3 (LAG3) protein, both of which are known to contribute to CHD risk. In this study, we also found that the rs10846744 polymorphism was associated with mild dyslipidemia in MI + CHD patient group.

Those in the MI+CHD patient group with rs10846744 minor C allele had higher serum total-C (C: 185.3 vs GG: 161.8, p=0.01) and TG (C: 131 vs GG: 107, p=0.009) levels than those with GG genotype. However, we could not find a relationship between rs10846744 and MI+CHD. These findings indicated that the rs10846744-C allele might be associated with dyslipidemia in the MI+CHD patient group. Besides, the effects of rs10846744 polymorphism in favor of dyslipidemia in patients with MI+ CHD may also be due to lipid-lowering statin therapy. In our study, the use of low-dose atorvastatin (10 mg) was high in patients with MI+ CHD carrying rs10846744 C allele (CC+GC) due to the dose preference of physicians according to the patient's lipid profile. Of the patients using 10-mg atorvastatin, 15 had the rs10846744 C allele and 5 had the rs10846744 GG genotype. In other words, the rate of receiving >10 mg atorvastatin treatment was 3 times higher in patients with rs10846744 C allele than that in those with rs10846744 GG genotype (p=0.003). Liu et al.[52] demonstrated that the variant for rs4238001 (c.4G>A) SNP was associated with TG change after fenofibrate treatment in GOLDN study participants, while Cerda et al.[43] suggested that *SCARB1* rs5888 SNP was associated with individual response to lipid-lowering atorvastatin therapy in the Brazilian population. In this case, it can be suggested that lipid levels may be lower if patients with rs10846744 C allele receive more than 10 mg of atorvastatin. Therefore, it is essential to investigate these findings in a larger group of patients with CHD treated with different doses of statin therapy to obtain more precise results. Consistent with our findings, previous studies have also reported that *SR-BI* polymorphisms can alter the effectiveness of lipid lowering.

In some reports that previously investigated *SR-BI* gene polymorphisms, LD between *SR-BI* genetic variants has been demonstrated, and therefore, it has been suggested that some *SR-BI* variants are inherited together as a haplotype.[31,43,53] McCarthy et al.[53] suggested that there is a strong, significant linkage imbalance between the exon 8 (rs5888), intron 5, and intron 10 variants of the *SR-BI* gene. In their study with the Linz peripheral artery disease (LIPAD) study population, Ritsch et al.[31] found that *SR-BI* polymorphisms in exon 8 (rs5888) and intron 5 (c.795+54 C>T) were in strong LD in both the total study group and in the female/male subgroups (p<0.0001). Cerda et al.[43] showed that there is a significant LD between C.726 + 54 C> T (rs61932577) and c.1050C> T (rs5888) (D'=0.781). In this study, we also evaluated the effects of *SR-BI* rs5888, rs10846744, and rs4238001 genotypes on the risk of CHD using haplotype analysis, but we could not find any significant LD among these SNPs (r^2<0.1). On the other hand, CGC (rs5888-C, rs10846744-G, and rs4238001-C alleles) (P=0.01) and CCC (rs5888-C, rs10846744-C, and rs4238001-C alleles) (p=0.0273) haplotypes were found to be in high frequency in patients with MI+ CHD.

Limitations

This study has some limitations. First, the study group was relatively small. Second, the young age of the control group may have negatively affected the results and reliability of the study, which constitutes a bias in the study. There is no guarantee that the control group will not have MI after including them into the study, and the expected frequency of events at young ages is relatively low as discussed by Kayıkçıoğlu.[54] Third, the SCORE (Systematic COronary Risk Evaluation) risk estimation was not prepared in the study groups. Patients with MI can be considered as the "very high risk group." Since there was no any history of CHD symptoms or vascular events, hypertension and metabolic disorders, which were questioned in detail in the control group, it can be considered that those in the control group have a low risk for CHD. As coronary angiography was

not performed in the control group due to the study design, the presence of asymptomatic (subclinical) coronary artery disease could not be excluded in this group. Finally, smoking was higher in patients than in control subjects. Therefore, future studies with larger groups including more selective controls both with and without using lipid-lowering drugs are required to obtain more reliable results on the *SR-BI* expression and its effects on serum lipid levels.

Conclusion

Understanding the effects of genetic variants underlying the atherosclerosis process would have important implications for the prevention and treatment of atherosclerosis and related diseases. Because of the limitations in our study design, it is not yet apparent that *SR-BI* gene variations are associated with early cardiovascular events. However, our study provides additional evidence for the contribution of genetic variations of the *SR-BI* gene to the development of dyslipidemia. In this context, further investigation of *SR-BI* gene variations that may affect the individual response to statins is valuable in establishing individual treatment protocols for CHD and related diseases. Most importantly, our findings lay the groundwork for investigating the relationship between *SR-BI* gene variations and early cardiovascular events such as MI in our future well-designed and larger sample size studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Researches Ethics Committee of İstanbul University İstanbul Faculty of Medicine (Approval Date: March 15, 2021; Approval Number: 591).

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