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Original Research

HMGCR and *ApoE* mutations may cause different responses to lipid lowering statin therapy

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Abstract: Coronary artery disease (CAD) and its complications are the major causes of death in the world. Although statins have been used to lower lipid levels in CAD patients, this goal can not be attained in 1/3 of the patients. The objective of this study was to investigate whether common variations in HMG-CoA Reductase(*HMGCR*) and Apolipoprotein E (*ApoE*) genes involved in lipid and statin metabolism modify the effect of statins on serum lipid and lipoprotein concentrations in CAD patients.A hundred CAD patients were enrolled into the study. At the beginning of the study biochemical measurements were performed to determine the baseline levels performed. Patients were treated with 40 mg atorvastatin for 2 months and biochemical measurements were repeated. According to the post-treatment, LDL-c levels, patients were divided into 2 groups as non-responders and responders, respectively. The information regarding the risk factors such as smoking, alcohol consumption etc. were also obtained. DNA was isolated from peripheral blood. The presence of rs17244841 ve rs17238540 mutations in *HMGCR* and ε2, ε3 and ε4 variants of *ApoE* were determined by using RT-PCR. Results were evaluated statistically. *HMGCR* mutatations were mostly found in responders and ε4 variant of ApoE was mostly found in non-responders. It was also found that presence of *HMGCR* mutations causes a significant reduction in total cholesterol and LDL-c levels. Also presence of ε2 variant of *ApoE* causes a statistically significant increase in trigliseride levels. Our findings should be investigated with other researchers to clarify the mechanism.

Key words: CAD; *HMGCR*; *ApoE*; Statin therapy.

Introduction

CAD is the leading cause of death in industrialized countries. The evidences from clinical trials supports the causal relation between elevated levels of LDL-c and CAD, and pharmacologic or nonpharmacologic interventions to reduce LDL-c levels (1).To reduce the risk of cardiovascular events, β-hydroxy-β-methylglutaryl Coenzyme A (HMG-CoA) reductase inhibitors, or statins are among the most prescribed drugs worldwide (2).Statins decrease LDL-c with efficacy and are able to reduce clinical outcomes in both primary and secondary prevention of CAD(3). Statins inhibit endogenous cholesterol production by competitive inhibition of HMG-CR, the enzyme that catalyzes conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol synthesis. By reducing intracellular cholesterol production, statin treatment results in upregulation of LDL receptors, leading to increased plasma clearance of LDL, primarily by the liver. In addition, statins can reduce hepatic secretion of the ApoB-containing lipoproteins, very low-density lipoprotein (VLDL) and LDL(4). Generally statin therapy is associated with a LDL-c lowering up to 55% and a reduction of cardiovascular events by 20–30% (5).Other effects of potential clinical significance include reductions in plasma triglycerides, increases in high-density lipoprotein cholesterol (HDL-c)(4).

Clinical response to statin-mediated reduction of lipid and lipoprotein parameters is highly variable. Although statin dosages are often adjusted once individual response to treatment is assessed, nearly a third of statin-treated patients do not meet their lipid-lowering goals(4). Statins are widely prescribed medications that prevent incident and recurrent CAD events primarily through the reduction of LDL-c. The goal of lipid-lowering therapy is to reduce the LDL-c cholesterol to 100 mg/dL in patients at high risk and an optional goal of 70 mg/dL for patients at highest risk. Because of these aggressive recommendations, a significantly great proportion (40%) of patients treated outside of clinical trials remain above their recommended LDL-c goal (6). Variability in response to statin therapy results from environmental and non-genetic factors, such as age, physical activity, racial ancestry, smoking status, diet, body weightand baseline plasma LDL-c concentrations. Baseline LDL-c concentrations are also under genetic influence(7). Genetic factors are also likely contributors to the variation in statin response, as suggested by several recent studies(8, 9).

The central role of *HMGCR* in hepatic regulation of plasma cholesterol makes it a primary candidate gene

for studies of genetic sequence variation associated with both basal and statin-responsive lipid and lipoprotein concentrations (7). Therefore *HMGCR* gene, encoding HMG-CoA reductase, is an important candidate gene for the pharmacogenomics of statins(2).*HMGCR* spans about 24200 base pairs on chromosome 5q13.3. rs17244841(also reported as SNP12) A>T base substitution and rs17238540 (also reported as SNP29) T>G base substitutionare detected in intron 5 and intron 18, respectively. (8, 10). These two variations were found to be associated with LDL-c response in a cohort study with pravastatin (8).

Other cholesterol pathway related genes may also be of importance for statin responsiveness(2). One of the most extensively studied genetic factors is the *ApoE* genotype. ApoE is one of the protein constituents of chylomicrons, VLDL, remnant particles, and HDL, serving as a ligand for their receptor-mediated catabolism via the LDL and the ApoE receptor (11). ApoE is a 34-kDa glycosylated polymorphic protein, its gene islocated on chromosome 19(12). Two point mutations in the exon 4 of the apoE gene account for the 3 common alleles known as ε2, ε3, and ε4, coding for the 3 major apoE isoforms(11). ε2, ε3, and ε4 variants of apolipoprotein E corresponds to ApoE SNP haplotypes T-T, T-C, and C-C, respectively, at rs429358 and rs7412 (13).Functionally, Apo ε alleles and genotypes influence lipid profile, as evidenced by the association of Apo ε2 alleles with lower and ε4 alleles consistently with higher total cholesterol and LDL-c levels (14, 15). Also it was found that ε2 carriers tended to have lower levels of total cholesterol and LDL-c compared with 3 and ε4 carriers during atorvastatin usage (11).

In this study, we studied2 important genes related to lipid homeostasis and with potential to be genetic determinants of statin responsiveness: (a) *ApoE*(ε2/ε3/ε4) responsible for the hepatic clearance of triglyceride-rich lipoproteins and*HMGCR* (rs17244841, rs17238540) which encodes HMG-CoA reductase enzyme and plays arole in hepatic regulation of plasma cholesterol . We also examined the interactions between genes and environmental factors such as smoking, alcohol intake, sex, age and family history in response to lipid-lowering therapy.

Materials and Methods

Study population

A hundred angiographically confirmed, unrelated CAD patients (44 female, 56 male) attending the Cardiology Clinic of Kartal Kosuyolu Training and Research Hospital, Istanbul, betweenJanuary 2015 and May 2016, who have not received any lipid lowering therapy so far were enrolled in the study. They were prescribed atorvastatin and both the baseline and follow up lipid level measurements were done. Subjects with a history of stroke, renal diseases, and diabetes mellitus were excluded from the study. All the patients were started on atorvastatin therapy (40mg/day) and overnight fasting blood sample was taken at baseline and at 2 months after starting therapy for measuring plasma lipid and lipoprotein concentrations. The patients were divided into two groups according to their LDL-c levels; 50 patients whose LDL-c levels were not sufficiently reduced (>100 mg/dL) and 50 patients whose LDL-c levels were sufficiently reduced (<100 mg/dL) were assigned as non-responders and responders respectively.

Inclusion criteria included age ≥30 years, total serum cholesterol concentration within the range of 4.14 to 10.36 mmol/L, serum triglyceride <4.52 mmol/L, fasting glucose <6.99 mmol/L, and no medical conditions or use of drugs known to affect lipoprotein metabolism. Exclusion criteria included: triglycerides ≥4.52 mmol/lLunstable/uncontrolled clinically significant disease, uncontrolled hypothyroidism or diabetes, and impaired hepatic or renal function.

The present study protocol complies with Declaration of Helsinki and was approved by the Institutional Ethics Committee of Yeditepe University, Istanbul, Turkey. Written informed consent was obtained from each participant at the begining of the study.

Molecular analysis

Total genomic DNA was extracted from peripheral blood leukocytes collected from each subject, into EDTA-tubes, using the High Pure PCR Template Preparation Kit (Roche, Basle, Switzerland), according to manufacturer's instructions. DNA purity and concentration were determined by NanoDrop spectrophotometer (Thermo Scientific). Real-time PCR reactions for rs17244841, rs17238540 in *HMGCR*;and for rs7412 and rs429358 in *ApoE*for identifying ε_2, ε_3 and ε_4 variants were carried out on 7500 Fast Real-Time PCR System (Applied Biosystems). For *ApoE* genotyping, subjects were classified as ε_2 allele carriers if they had the apoE2/3 or apoE2/2 genotype; ε_3 allele carriers allele carriers if they had the apoE3/3 genotype; and ε4 allele carriers allele carriers if they had the apoE4/3 or apoE4/4 genotype. The presence of the "T" allele at rs7412 and "T" allele at rs429358 represents ε2 variant; the presence of the "C" allele at rs7412 and "T" allele at rs429358 represents ε3 variant; and the presence of the "C" allele at rs429358 and "C" allele at rs7412 represents ε4 variant (13). The reactions were performed according to the manufacturer's instructions.

Biochemical investigations

Blood samples, at baseline and 2 months after the beginning of the treatment, were collected after 12hours from the fasting subjects. Total cholesterol (TC), HDL-c, LDL-c, triglycerides (TG), glucose and other relevant biochemical parameters were determined by using standard enzymatic kits (Accurex Pvt. Ltd.). Body mass index was calculated as weight (kg) divided by height squared (m^2).

Statistical Analysis

SPSS 24.0 was performed for statistical analysis. Continuous variables are expressed as mean ± standard deviation (SD) and discrete variables are expressed as counts or percentages. Normal distribution assumption was checked with Kolmogorov-Smirnov test. Two independent samples t test was used to compare continuous variables' means between two groups which arenormally distributed. If the variables are not normally distributed, Mann-Whitney U test was used to compare the groups. The Chi-Square and Fisher's exact test, where appopriate, was used to compare the proportions of the

Table 1. LDL cholesterol and total cholesterol levels of groups.

Parameters	Responders (n=50) Baseline levels	Non-responders (n=50) Baseline levels	p values	Responders (n=50) Post-treatment levels	Non-responders (n=50) Post-treatment levels	p values	% change of responders	% change of non-responders	p values
LDL-cholesterol	160.58 ± 32.42	175.54 ± 33.04	**0.03***	85.74 ± 32.73	152.77 ± 34.46	**<0.001****	47.37 ± 10.33	14.45 ± 11.28	**<0.001****
Total cholesterol	240.36 ± 38.66	255.4 ± 40.02	0.06	160.98 ± 34.39	232.84 ± 43.01	**<0.001****	34.66 ± 8.84	9.85 ± 9.99	**<0.001****

p<0.05*, p<0.001**.

groups. p values less than 0.05 (p<0.05) were considered to be statistically significant.

Results

Study population

The baseline, post-treatment and mean percent reductions of total cholesterol and LDL-c concentrations are shown in Table 1. Treatment with 40 mg per day of atorvastatin significantly reduced the plasma concentrations of total cholesterol and LDL-c in responders whereas reductions of total cholesterol and LDL-c are insufficient in non-responders. According to the significant differences between baseline LDL-c level and post-treatment LDL-c levels, study population were divided into two as non-responders and responders. 50 patients whose LDL-c levels were not sufficiently reduced (>100 mg/dl) and 50 patients whose LDL-c levels were sufficiently reduced (<100 mg/dl) were assigned as non-responders and responders respectively. Table 1 shows LDL-c and total cholesterol levels of groups.

Table 2 shows the characteristics of the study population. When characteristics were compared between groups; no significant association wasfound except post-treatment levels of trigliseride (p<0.05*).

HMGCR and ApoE genotyping

Table 3 shows genetic analyses of non-responders and responders. Any significant associations were not found between groups (p>0.05).

Association of genotypes and risk factors

Some statistically significant relations were detected betweengenotypes and risk factors. Statistically significant associations are shown in Table 4.

Discussion

Statins are considered one of the most effective classes of drugs for reducing total cholesterol and LDL-c. Eventhough statin treatment efficacy is very high, there are important differences in treatment effectiveness among individuals. It is thought that genetic backround plays an important role in these differences, but the contribution of individual and combination of mutations are poorly understood(16).

In this study, we examined *ApoE* and *HMGCR* mutations which are involved in lipid and statin metabolism with the changes in total cholesterol, LDL-c, HDL-c and trigliseride

Table 2. Characteristics of the study population.

Characteristics	Groups (number of participants)		p values
	Responders (n=50)	Non-responders (n=50)	
Age (years)	58.24 ± 10.12	60.8 ± 10.53	0.22
Weight (kg)	78.82 ± 11.89	79.78 ± 9.11	0.65
Height (cm)	169.86 ± 29.05	166.26 ± 7.94	0.40
BMI (kg/m^2)	28.97 ± 4.04	28.89 ± 3.18	0.91
Dyslipidemia (%)	50 (100%)	50 (100%)	1
Hypercholesterolemia (%)	50 (100%)	50 (100%)	1
Diabetes mellitus (%)	10 (20%)	10 (20%)	1
Hypertension (%)	27 (54%)	31 (62%)	0.42
Current smoking (%)	11 (22%)	14 (28%)	0.59
Alcohol consumption (%)	4 (8%)	4 (8%)	1
CVD (%)	50 (100%)	50 (100%)	1
Family history of CAD (%)	31 (62%)	25 (50%)	0.23
Trigliseride (baseline levels) (mg/dL	159.56 ± 52.65	188.98 ± 124.49	0.13
Trigliseride (post-treatment levels) (mg/dL)	125.9 ± 36.59	172.74 ± 120.09	**0.01***
HDL-c (baseline levels) (mg/dL	46.16 ± 11.03	46.24 ± 10.14	0.97
HDL-c (post-treatment levels) (mg/dL	49.64 ± 10.51	48.06 ± 10.0	0.44
Glucose (baseline levels) (mg/dl)	115.4 ± 31.37	120.35 ± 54.31	0.64
Glucose (post-treatment levels) (mg/dL)	104.30 ± 28.17	130.10 ± 55.01	0.06

*p<0.05.

Table 3. Genetic analyses of responders and non-responders.

Genes and variations	Responders (n=50)			Non-responders (n=50)			p values
	Wild type	Homozygous mutation	Heterozygous mutation	Wild type	Homozygous mutation	Heterozygous mutation	
HMGCR							
rs17244841	46	0	4	49	0	1	0.36
rs17238540	45	0	5	49	0	1	0.20
ApoE							
ε_2	47	3	0	48	2	0	1
ε_3	11	39	0	13	37	0	0.64
ε_4	42	8	0	39	11	0	0.44

Table 4. Statistically significant relations between genotypes and risk factors.

Genes, variations and risk factors	Wild type	Homozygous mutation	Heterozygous mutation	p values
***HMGCR* (rs17244841)**				
Total cholesterol (post-treatment levels)	199.82 ± 51.98	-	141.6 ± 43.68	**0.017***
LDL-c (post-treatment levels)	120.58 ± 47.08	-	74.8 ± 32.89	**0.012***
***HMGCR* (rs17238540)**				
Total cholesterol (baseline levels)	249.9 ± 39.83	-	216.17 ± 26.06	**0.032***
Total cholesterol (post-treatment levels)	200.27 ± 52.07	-	144.33 ± 39.64	**0.014***
LDL-c (baseline levels)	169.61 ± 33.30	-	141.83 ± 24.75	**0.045***
LDL-c (post-treatment levels)	121.0 ± 47.16	-	76 ± 29.56	**0.008***
***ApoE* (ε_2)**				
Trigliseride (baseline levels)	165.24 ± 68.59	345.8 ± 282.70	-	**0.032***
Trigliseride (post-treatment levels)	142.58 ± 75.50	277.4 ± 226.29	-	**0.041***

*$p<0.05$.

levels in response to atorvastatin. Treatment with 40 mg per day of atorvastatin significantly reduced the plasma concentrations of total cholesterol and LDL-c in 50 patients (responders). Triglyceride concentrations were also reduced in responders, while HDL-c did not reach statistically significant value.

In this study it was also found that presence of rs17244841 or rs17238540 mutations in *HMGCR* caused a statistically significant reduction in total cholesterol and LDL-c levels. Similarly Chasman et al. found that the presence of rs17244841 or rs17238540 cause a reducton in total cholesterol and LDL-c levels (8). Contrary to these findings Poduria et al. found that rs17238540 mutation was significantly and independently associated with a poor response to atorvastatin in terms of LDL-C lowering (16). In another study it was found that individuals carrying genetic variant in *HMGCR* experienced significantly smaller LDL-C reductions, for rs17244841 (8). Also in some studies no statistically significant relation was detected. Krauss et al. found no significant associations between rs17244841 mutation and change in total cholesterol, triglycerides and HDL-c levels(7). Similarly Polisecki et al. found no association with the presence of rs17238540 mutation in the *HMGCR* gene locus and baseline lipid, baseline vascular disease, LDL-C lowering response to pravastatin or on trial coronary heart disease or cardiovascular disorders(17). The mechanism underlying the association of the *HMGCR* haplotypes with LDL-c concentrations or LDL-c response to statin treatment has not yet been determined. Because statins mediate LDL-c reduction by inhibiting HMGCR activity through competitive enzymatic binding, a dual association of this genetic variation with both baseline LDL-c concentrations and LDL-c response could result from structural modifications to the HMGCR active site that change binding affinities for both statins and HMG-CoA. Although all of the involved SNPs are intronic, they may promote changes in protein sequence by affecting mRNA splicing (7).

*ApoE*is another candidate gene to understand the regulation of cholesterol level in our body. ApoE is involved in intestinal cholesterol absorption, is a ligand for the LDL receptor (LDL-R), and, as a component of HDL, plays a role in reverse cholesterol transport(18).It has been shown in many studies that the *ApoE* ε4 and ε2 alleles associate with higher and lower concentrations of total cholesterol, LDL-c and ApoB, respectively, compared with the ε3 allele (19, 20). Several studies report less effect of statins in ε4 carriers for lowering total cholesterol and LDL-c levels, compared with ε3 carriers, whereas carriers of the ε2 allele have a larger reduction of total cholesterol and LDL-c levels during statin therapy compared with ε3 carriers. (5, 9, 21). These results occur because ε2 shows defective, whereas the ε4 shows higher receptor binding ability compared with the ε3 variant (22). These differences determine lipoprotein clearance rates; lipoproteins with the ε4variant are taken up with greater affinity than those with the common 3variant, which in turn are cleared more efficiently than lipoproteins with the ε2variant. Accelerated ε4 variant containing lipoprotein clearance by the liver leads to an increase in hepatic cholesterol and downregulation of hepatocyte LDL receptors, therefore increasing serum total cholesterol, LDL-c, and apoB levels which is associated with a higher risk of atherosclerosis and cardiovascular mortality. (22, 23, 24). The opposite condition is observed with the ε2variant. ε2 containing lipoproteins display attenuated plasma clearance resulting in upregulation of HMG-CoA synthesis. Thus, statins may be less effective in reducing cholesterol levels in ε4 carriers, as they already have low HMG-CoA reductase levels. Contrary to these findings, patients with the ε2 genotype may especially profit from statin therapy (21). Nevertheless, several studies found no si-

gnificant associations for ApoE SNPs and lipid levels during statin therapy (25, 26, 27).Furthermore, ameta-analysis did not confirm the association between *ApoE*mutations and lipid response during statin therapy(28).Similarly in our study no significant relation was not found between *ApoE* genotypes, LDL-c and total cholesterol levels however statistically significant relation was found between ε2 genotype and trigliseride levels. Trigliseride levels were found high in individuals who had ε2 genotype.Similarly Christidis et al. found that, after atorvastatin therapy, ε2 carriers had greater triglyceride levels followed by ε4 and ε3 carriers(11).Although these studies add to the growing body of literature relating apoE variation to statin response, they do not help in providing a definitive description of this relationship(29).

Basic research is required to explain the mechanisms governing the association of *HMGCR* and *ApoE* genotypes and response to hypolipidemic medication, whereas clinical studies with larger numbers of patients will answer the question of whether it is meaningful to incorporate *HMGCR* and *ApoE* polymorphisms in the individualization of hypolipidemic treatment in CAD patients.

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Conflict of interest
All of the authors have no conflict of interest to declare.

References

1. Kajinami K, Akao H, Polisecki E, Schaefer J. Pharmacogenomics of statin responsiveness.Am J Cardiol 2005;96(9A):65-70.
2. Peters BJ, Pett H, Klungel OH, Stricker BH, Psaty BM, Glazer NL, et al. Genetic variability within the cholesterol lowering pathway and the effectiveness of statins in reducing the risk of MI. Atherosclerosis 2011;217(2):458-64.
3. Fiegenbaum M, da Silveira FR, Van der Sand CR, Van der Sand LC, Ferreira ME, Pires RC, et al. Pharmacogenetic study of apolipoprotein E, cholesteryl ester transfer protein and hepatic lipase genes and simvastatin therapy in Brazilian subjects. Clin Chim Acta 2005;362(1-2):182-8.
4. Mangravite LM, Thorn CF, Krauss RM. Clinical implications of pharmacogenomics of statin treatment. Pharmacogenomics J 2006;6(6):360-74.
5. Postmus I, Verschuren JJ, de Craen AJ, Slagboom PE, Westendorp RG, Jukema JW, et al. Pharmacogenetics of statins: achievements, whole-genome analyses and future perspectives. Pharmacogenomics 2012;13(7):831-40.
6. Voora D, Shah SH, Reed CR, Zhai J, Crosslin DR, Messer C, et al. Pharmacogenetic predictors of statin-mediated low-densitylipoprotein cholesterol reduction and dose response. Circ Cardiovasc Genet 2008;1(2):100-6.
7. Krauss RM, Mangravite LM, Smith JD, Medina MW, Wang D, Guo X, et al. Variation in the 3-hydroxyl-3-methylglutaryl coenzyme a reductase gene is associated with racial differences in low-density lipoproteincholesterol response to simvastatin treatment. Circulation 2008;117(12):1537-44.
8. Chasman DI, Posada D, Subrahmanyan L, Cook NR, Stanton VP Jr, Ridker PM. Pharmacogenetic study of statin therapy and cholesterol reduction. JAMA 2004;291:2821–27.
9. Thompson JF, Man M, Johnson KJ, Wood LS, Lira ME, Lloyd DB, et al. An association study of 43 SNPs in 16 candidate genes with atorvastatin response. Pharmacogenomics J 2005;5:352–58.
10. Thompson JF, Hyde CL, Wood LS, Paciga SA, Hinds DA, Cox DR, et al. Comprehensive whole genome and candidate gene analysis for response to statin therapy in the Treating to New Targets (TNT) cohort. Circ Cardiovasc Genet 2009;2(2):173-81.
11. Christidis DS, Liberopoulos EN, Kakafika AI, Miltiadous GA, Cariolou M, Ganotakis ES, et al. The effect of apolipoprotein E polymorphism on the response to lipid-lowering treatment with atorvastatin or fenofibrate. J Cardiovasc Pharmacol Ther 2006;11(3):211-21.
12. Saidi S, Slamia LB, Ammou SB, Mahjoub T, Almawi WY. Association of apolipoprotein E gene polymorphism with ischemicstroke involving large-vessel disease and its relation to serum lipidlevels. J Stroke Cerebrovasc Dis 2007;16(4):160-6.
13. Deshmukh HA, Colhoun HM, Johnson T, McKeigue PM, Betteridge DJ, Durrington PN, et al. Genome-wide association study of genetic determinants of LDL-cresponse to atorvastatin therapy: importance of Lp(a). J Lipid Res 2012;53(5):1000-11.
14. Yamauchi K, Tozuka M, Nakabayashi T, Sugano M, Hidaka H, Kondo Y, et al. Apolipoprotein E in cerebrospinal fluid: Relation to phenotype and plasma apolipoprotein E concentrations. Clin Chem 1999;45(4):497-504.
15. Luc G, Bard JM, Arveiler D, Evans A, Cambou JP, Bingham A, et al. Impact of apolipoprotein E polymorphism on lipoproteins and risk of myocardial infarction. The ECTIM Study. Arterioscl, Thromb Vas 1994;14:1412-19.
16. Poduri A, Khullar M, Bahl A, Sehrawat BS, Sharma Y, Talwar KK. Common variants of HMGCR, CETP, APOAI, ABCB1, CYP3A4, and CYP7A1 genes as predictors of lipid-lowering response to atorvastatin therapy. DNA Cell Biol 2010;29(10):629-37.
17. Polisecki E, Muallem H, Maeda N, Peter I, Robertson M, McMahon AD, et al. Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) Investigators. Genetic variation at the LDL receptor and HMG-CoA reductase geneloci, lipid levels, statin response, and cardiovascular diseaseincidence in PROSPER. Atherosclerosis 2008;200(1):109-14.
18. Kajinami K, Takekoshi N, Brousseau ME, Schaefer EJ. Pharmacogenetics of HMG-CoA reductase inhibitors: exploring the potential for genotype-based individualization of coronary heart disease management. Atherosclerosis 2004;177(2):219-34.
19. Lehtimaki T, Moilanen T, Nikkari T, Solakivi T, Porkka K, Ehnholm C, et al. Regional differences in apolipoprotein E polymorphism in Finland. Ann Med 1991;23(1), 61–66.
20. Ilveskoski E, Loimaala A, Mercuri MF, Lehtimaki T, Pasanen M, Nenonen A, et al. Apolipoprotein E polymorphism and carotid artery intima–media thickness in a random sample of middle-aged men. Atherosclerosis 2000;153(1):147–53.
21. Schmitz G, Langmann T. Pharmacogenomics of cholesterol-lowering therapy. Vascul Pharmacol 2006;44(2):75-89.
22. Utermann G. Apolipoprotein E polymorphism in health and disease. Am Heart J 1987;113:433-40.
23. Mahley RW. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. Science 1988;240:622-30.
24. Liberopoulos E, Siamopoulos K, Elisaf M. Apolipoprotein E and renal disease. Am J Kidney Dis 2004;43:223-33.
25. Nieminen T, Kahonen M, Viiri LE, Gronroos P, Lehtimaki T. Pharmacogenetics of apolipoprotein E gene during lipid-lowering therapy: lipid levels and prevention of coronary heart disease. Pharmacogenomics 2008;9(10):1475–86.
26. Pena R, Lahoz C, Mostaza JM, Jimenez J, Subirats E, Pinto X, et al. Effect of apoE genotype on the hypolipidaemic response to pravastatin in an out patient stetting. J Inter Med 2002;251:518–25.
27. Sanllehy C, Casals E, Rodriguez-Villar C, Zambon D, Ojuel J, Ballesta AM, et al. Lack of interaction of apolipoprotein E phenotype with the lipoprotein response to lovastatin or gemfibrozil in patients

with primary hypercholesterolemia. Metabolism 1998;47:560-65.
28. Zintzaras E, Kitsios GD, Triposkiadis F, Lau J, Raman G. APOE gene polymorphisms and response to statin therapy. Pharmacogenomics J 2009;9(4):248–57.
29. Mangravite LM, Krauss RM. Pharmacogenomics of statin response. Curr Opin Lipidol 2007;18(4):409-14.