ATP-Binding Cassette Cholesterol Transporter–1 (ABC1) G1051A, and G2706A Gene Polymorphism in patients with primary hyperlipidemi

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Abstract

Objective: we aimed to investigate the effects of ABCA1 G2706A and G1051A gene polymorphisms on glycemic levels, and inflammatory markers as hs-CRP, and fibrinogen in patients with primary hyperlipidemia.

Material, and Method: Sixty male and 78 female patients participated in the study. DNAs of white blood cells were isolated, and ABCA1 G2706A, and G1051A gene polymorphisms were analyzed using PCR.

Results: Among patients included in the study, systolic blood pressures of the patients carrying AA genotype in ABCA-1 2706 gene polymorphism were lower relative to those having AG, and GG genotypes. (p=0.027). Statistical analysis performed between ABCA1 G1051A (R219K) gene polymorphism, and HDL-cholesterol levels revealed that HDL-cholesterol level was statistically significantly higher in patients with GG genotype when compared with those having AA, and AG genotypes (p=0.047). The presence of metabolic syndrome did not differ statistically significantly among patients carrying ABCA1 G2706A polymorphism. [GA genotype *vs* GG genotype (p=0.321, OR: 0.364), AA genotype *vs* GG genotype (p=0.438, OR: 0.534)]. Incidence of metabolic syndrome in ABCA1 gene G1051A polymorphism in patients carrying GG genotype was significantly more frequently detected in those having GA (p=0.001, OR: 5.816) or AA (p=0.039, OR: 3.619) genotype. On the other hand, the individuals with AA genotype had lower systolic blood pressures.

Conclusion: ABCA1 gene polymorphism has been seen to be correlated with hypertension, and metabolic syndrome apart from HDL-cholesterol metabolism

Introduction

These kinds of changes emerging due to genetic alterations are classified as primary disorders of the lipid metabolism. Among these modifications, variations in *ABCA1* gene may play an important role. Firstly, *ABCA1* gene has been held responsible as an etiological agent of Tangier disease. In this disease HDL-related cholesterol transport between the tissue,and the liver is impaired (1–3).

Macrophages, hepatocytes, and fibroblasts, intake lipid-deficient polyproteins, remnants of HDL, and chylomicrons into cell, load them with lipid, and can secrete them back. This phenomenon is termed as retroendocytosis. Mutation occurring in ATP binding cassette transporter 1 (ABC1) which enables exit of cholesterol from the cell with resultant decrease in the levels of lipid-rich HDL-lipoprotein in the circulation decrease. (4–5). Mutations present in both of the alleles constituting ABC 1 gene decrease HDL-cholesterol, and consequently increase the risk of coronary artery disease.

In this study we aimed to investigate the effects of ABCA 1 gene on lipid levels, and patient's clinical parameters under various polymorphic conditions in patients with primary hyperlipidemia.

Materyal-metod

Selection of patients, and control subjects

The patients participated in this study consisted of primary dyslipidemia patients who consulted to the outpatient clinics of Department of Endocrinology, and Diseases of Metabolism of Ege University. Faculty of Medicine. Sixty male (mean age, 45.96 ± 15.19 years), and 78 female (48.30 ± 11.56 years) patients participated in the study. Body weights, heights, body mass indices, waist circumferences, systolic, and diastolic blood pressures, smoking status, presence of familial diabetes, dyslipidemia, and coronary disease were questioned, and recorded. Control group consisted of age-, and gender –matched healthy individuals without any past or present evidence of any disease or drug use (n = 114) (Table 1).

Table 1
Relationship between clinical, and biochemical parametres in the patient, and control groups

Groups	Patients (n = 138)	Control Group (n = 114)	*P*-value
Age (year)	47.55 ± 12.90	46.76 ± 7.16	> 0.05
Male/female	60/78	50/64	> 0.05
Bodyweight (kg)	77.23 ± 12.44	78.67 ± 22. 66	> 0.05
BMI (kg/m2)	27.404 ± 3.94	26.43 ± 10.22	> 0.05
Waist circumference (cm)	91.24 ± 8.75	94.82 ± 7.957	> 0.05
Systolic blood pressure (mmHg)	126.00 ± 10.70	120.77 ± 3. 265	> 0.05
Diastolic blood pressure (mmHg)	80.64 ± 6.5	83.24 ± 8.62	> 0.05
Baseline insulin level (mIU/ml)	9.799 ± 6.5 9	7.82 ± 2.56	> 0.05
Fasting blood sugar (mg/dl)	99.45 ± 20.633	92.89 ± 3,96	> 0.05
Postprandial glycemic level (mg/dl)	123.73 ± 42.37	118.57 ± 70.45	> 0.05
Total-cholesterol (mg/dl)	283.21 ± 62.62	185.2 ± 14.6	< 0.05
Triglyceride (mg/dl)	310.41 ± 484.50	128.9 ± 23.7	< 0.05
LDL-cholesterol (mg/dl)	184.87 ± 66.24	117,4 ± 11.5	< 0.05
HDL-cholesterol (mg/dl)	54.59 ± 14.97	57.6 ± 5.76	> 0.05

Biochemical, And Hormonal Evaluation

From all patients blood samples were drawn under normal conditions at 8:00 AM for the measurement of the levels of fasting blood sugar, LDL-cholesterol, triglyceride, HDL-cholesterol, and total cholesterol. In patients with dyslipidemia, in order to rule out secondary dyslipidemia, TSH measurement, oral glucose

loading test using 75 gram glucose, urea, creatinine, liver function tests, and also routine urinalysis were performed, and drug use was re-questioned (Causes of secondary dyslipidemia: chronic liver disease, diabetes mellitus, hypothyroidism, chronic renal failure, drugs increasing levels of LDL-cholesterol, and decreasing HDL-levels, progestin, anabolic steroids,and corticosteroids). Patients with secondary dyslipidemia were excluded from the study.

The indicators of cardiovascular disease including fibrinogen, hs-CRP, lp-a were analyzed. Lipoprotein electrophoresis was performed for the classification of hyperlipidemia.

Genetic Analyses

ANALYSIS OF ABCA 1 G1051A (R219K), G2706A (V771M) GENE POLYMORPHISMS

DNA isolation was performed using blood samples drawn from the patient, and the control group selected in compliance with the objective of our study. Then method of Polymerase Chain Reaction (PCR) was used to analyze (R219K), G2706A (V771M) gene polymorphisms in ABCA 1 gene. Statistical analyses of the biochemical,and demographic data of the patient, and the control groups were performed in consideration of their genotype, and allele status.

Statistical Analyses

For statistical analyses of the results SPSS 14.0 for windows (SPSS Inc. Chicago USA) program was used. Characteristic features, mean plasma glucose, insulin, dehydroepiandrosterone sulphate, estrogen HOMA-IR, total cholesterol, HDL- cholesterol, LDL- cholesterol, triglyceride, T-cholesterol /HDL- cholesterol ratio, sensitive CRP, fibrinogen, Apolipoprotein A, Apolipoprotein B, and TSH levels of primary dysipidemia patients were compared one by one for each gene polymorphism of different genotypes using ANOVA statistical analysis method. All results were expressed as mean ± SD. Parameters with p value less than 0.05 were considered to be statistically significant.

Results

Evaluation Of General Characteristics Of The Control, And Study Groups

Sixty male (mean age, 45.96 ± 15.19 years), and 78 female (48.30 ± 11.56 years) patients with primary hyperlipidemia participated in the study. Mean body weights of the patients, and the control group were 77.23 ± 12.44 kg, and 78.67 ± 22. 66 kg, respectively. A statistically significant difference was detected

between the patient, and the control groups as for the levels of total cholesterol, LDL-cholesterol, and triglyceride (Table 1).

Evaluation of clinical, and biochemical parameters of the patient, and the control groups based on the results of genetic analysis

ABCA1 G2706A (V771M) polymorphism in AA genotype was associated with statistically significantly different (higher) systolic blood pressures when compared with other genotypes (p = 0.027) (Table 2). High-sensitivity CRP (hs-CRP) (p = 0.001) levels, and total cholesterol /HDL-cholesterol ratios (p = 0.047) were statistically significantly higher when compared with other genotypes (Table 3).

Table 2
The relationships between ABCA-1 G2706A gene polymorphism,and clinical, and biochemical parametres in patients with primary hyperlipidemia

	Patients with primary hyperlipidemia			P value
ABCA-1 G2706A Genotype	**AA**	**GA**	**GG**	
(%)	**3**	**16.0**	**81.0**	**0.125**
Age (year)	44.67 ± 17.61	44.0 ± 11.16	48.53 ± 13.52	0.473
Bodyweight (kg)	77.23 ± 12.44	76.63 ± 12.165	73.11 ± 10.1	0.408
Body mass index (kg/m2)	27.98 ± 3.68	27.98 ± 3.68	27.98 ± 3.68	0.510
Waist circumference (cm)	97.00 ± 9.849	92.38 ± 8.469	90.53 ± 8.330	0.337
Systolic blood pressure (mmHg)	110.00 ± 17.321	126.88 ± 13.525	126.50 ± 9.325	0.027
Diastolic blood pressure (mmHg)	73.33 ± 11.547	80.94 ± 8.606	80.56 ± 5.953	0.171
Baseline insulin (mIU/ml)	7.55 ± 4.038	11.05 ± 5.545	10.92 ± 12.158	0.914
Fasting blood sugar (mg/dl)	100.00 ± 7.000	98.19 ± 14.307	100.53 ± 22.6	0.923
HOMA-IR	2.57 ± 1.49	2.26 ± 1.64	2.32 ± 2.32	0.502
Postprandial 2. hour glycemic level (mg/dl)	143.50 ± 26.16	121.25 ± 37.825	123.0 ± 45.48	0.800
Homocysteine (mmol/L)	14.47 ± 6.555	11.37 ± 4.945	9.67 ± 2.535	0.143
Fibrinogen (mg/dl)	365.0 ± 125.86	462.17 ± 73.98	463.58 ± 129.43	0.552
Total cholesterol (mg/dl)	290.67 ± 23.79	278.73 ± 52.29	284.0 ± 65.91	0.938
Triglyceride(mg/dl)	269.33 ± 265.71	384.60 ± 503.96	307.53 ± 518.64	0.857
LDL –cholesterol (mg/dl)	188.00 ± 61.147	167.93 ± 51.395	186.09 ± 70.884	0.640
HDL-cholesterol (mg/dl)	50.00 ± 13.115	53.47 ± 13.038	56.10 ± 15.218	0.670
Total cholesterol / HDL kolesterol ratio	5.32 ± 2.03	6.24 ± 2.18	5.83 ± 7.26	0.124
Lipoprotein (a) (mg/dl)	11.00 ± 7.071	62.00 ± 56.104	47.84 ± 60.2	0.557

Metabolic syndrome was statistically significantly more frequent in ABCA1 gene G1051A polymorphism in individuals with GA (p = 0.001, OR: 5.816), and AA (p = 0.039, OR: 3.619) genotypes, when compared with those carrying GG genotype (Table 4). A statistically significant correlation was not detected between the presence of metabolic syndrome, and the patients having ABCA1 G2706A polymorphism according to different genotypes. [GA genotype *vs* GG genotype (p = 0.321, OR: 0.364), and AA genotype *vs* GG genotype (p = 0.438, OR: 0.534)] (Table-5).

Table 3

The relationship between ABCA-1 G1051A gene polymorphism, clinical, and biochemical parameters in patients with primary hyperlipidemia

	Primer Hiperlipidemi Hastaları			P değeri
ABCA-1 G1051A Genotype	**AA**	**AG**	**GG**	
(n, %)	15 14.9	27 26.7	59 58.4	0.062
Age (year)	44.67 ± 17.61	44.0 ± 11.16	48.53 ± 13.52	0.473
Bodyweight (kg)	76.84 ± 12.10	74.20 ± 11.63	73.04 ± 9.5	0.287
Body mass index (kg/m2)	27.98 ± 3.68	27.12 ± 3.96	27.56 ± 3.56	0.773
Waist circumference (cm)	93.50 ± 7.419	90.62 ± 8.6	90.0 ± 8.48	0.491
Systolic blood pressure (mmHg)	127.14 ± 10.69	127.59 ± 11321	125.34 ± 10,45	0.624
Diastolic blood pressure (mmHg)	81.79 ± 7.74	82.04 ± 5.59	79.49 ± 6.80	0.194
Baseline insulin (mIU/ml)	9.30 ± 4.107	11.11 ± 5.034	11.19 ± 13.8	0.818
Fasting blood sugar (mg/dl)	107.87 ± 17.74	103.17 ± 19.69	96.6 ± 21.88	0.125
HOMA-IR	2.57 ± 1.49	2.26 ± 1.64	2.32 ± 2.32	0.886
Postprandial 2. hour glycemic level (mg/dl)	143.54 ± 53.93	129.06 ± 52.34	114.40 ± 33.67	0.083
Homocysteine (mmol/L)	9.04 ± 2.25	9.67 ± 3.186	11.00 ± 3.971	0.521
Fibrinogen (mg/dl)	447.43 ± 116.38	438.58 ± 199.141	467.88 ± 94.837	0.819
Total cholesterol (mg/dl)	288.71 ± 69.83	277.18 ± 64.51	283.38 ± 60.472	0.860
Triglyceride(mg/dl)	460.00 ± 589.228	270.33 ± 231.402	298.5 ± 558.260	0.507
LDL –cholesterol (mg/dl)	168.14 ± 62.215	188.95 ± 67.53	183.75 ± 68.74	0.660
HDL-cholesterol (mg/dl)	53.79 ± 17.125	49.29 ± 13.027	58.40 ± 13.95	0.047
Total cholesterol / HDL kolesterol	5.32 ± 2.03	6.24 ± 2.18	5.83 ± 7.26	0.885
Lipoprotein (a) (mg/dl)	32.33 ± 35.69	59.80 ± 50.31	47.80 ± 65.63	0.667
Apolipoprotein A1 (mg/dl)	139.67 ± 17.24	118.0 ± 31.12	135.07 ± 32.61	0.523
Apolipoprotein B (mg/dl)	135.0 ± 38.23	174.33 ± 139.8	117.28 ± 48.16	0.280

	Primer Hiperlipidemi Hastaları			P değeri
ABCA-1 G1051A Genotype	**AA**	**AG**	**GG**	
hs-CRP	0.64 ± 0.82	0.50 ± 0.532	1.00 ± 3.34	0.001

Table 4
The relationships between the frequency of metabolic syndrome, and ABCA-1 G1051A and G2706A gen polymorphisms in patients with primary hyperlipidemia

Polymorphism	Genotype	Normal	Metabolic Syndrome	OR	95% CI	P
G1051A	GG	38	14	**R**		0.003
		73.1%	26.9%			
	GA	7	15	5.816	1.963 - 17.238	0.001
		31.8%	68.2%			
	AA	6	8	3.619	1.065–12.296	0.039
		42.9%	57.1%			
G2706A	GG	42	27	**R**		0.595
		60.9%	39.1%			
	GA	8	7	0.321	0.028–3.720	0.364
		53.3%	46.7%			
	AA	1	2	0.438	0.032–5.926	0.534
		33.3%	66.7%			

Table 5: Frequency of genotypes as a result of ABCA-1 G1051A , and G2706A gene polymorphism analyses in patients with hyperlipidemia, and controls

	ABCA1 G1051A (%)			
	AA	GA	GG	*p* -value
Patient	15.2	44.2	40.6	0.085
Control	15.8	27.2	57	
	ABCA1 G2706A (n, %)			
	AA	GA	GG	*p* -value
Patient	4.5	28.4	67.2	0.054
Control	3.5	16.8	79.6	

Discussion

ABCA1 is expressed from β cells of the pancreas, and controls transcription network of various drugs, and proteins (6). However glucose upregulates in vivo ABCA1 expression from leukocytes, while insulin suppresses in vitro ABCA1 expression. (7, 8). Various studies have demonstrated that inactivation of ABCA1 in pancreatic β cells induces intracellular accumulation of cholesterol which progressively impairs insulin secretion leading to impaired glucose tolerance (9–11). Individuals with RR homozygous genotype carrying R219K polymorphism of the the ABCA1 gene are more sensitive to insulin relative to those conveying K minor alleles (106). In our study different G1051A (R219K) gene polymorphisms of ABCA1 G2706A (V771M), and ABCA1 genes were analyzed in consideration of diverse genotypes, and statistically significant difference was not detected among AA, AG, and GG genotypes as for fasting insulin, 2. hour postprandial blood sugar, fasting blood sugar, and HOMA-IR levels. Daimon et al. demonstrated the role played by ABCA1 genotype in the pathophysiology of type 2 DM independent from the levels of HDL cholesterol (12). Besides relationship between ABCA-1 lower HDL levels, obesity, and metabolic syndrome have been also displayed (13–15). R230C variant of ABCA1 is associated with low HDL cholesterol, obesity, and metabolic syndrome in Mexican population. Statistically significantly higher incidence (24.6%) of R230C/C230C genotype has been detected in Type 2 diabetics (16).

However in our study, statistically significantly higher rates of metabolic syndrome were detected in ABCA1 gene G1051A polymorphisms in patients with GA (p = 0.001, OR: 5.816) or AA (p = 0.039, OR: 3.619) genotype relative to GG genotype. Rates of metabolic syndrome did not statistically significantly differ among patients carrying ABCA1 G2706A polymorphism regarding GG, GA, and AA genotypes [GA *vs* GG genotype GG (p = 0.321, OR: 0.364), AA *vs* GG genotype (p = 0.438, OR: 0.534)].

In a study performed on 2752 healthy, and 1276 hypertensive patients in Japan, the correlation between ABCA 1 gene-14 C—> T polymorphism, and hypertension prevalence was detected. In separate analyses

on both systolic, and diastolic blood pressures, statistically significant results have been found (17).

In our study, any difference was not found between genotypes regarding G1051A polymorphism of ABCA1 gene of the patients participated in our study, However in individuals carrying AA genotype, ABCA-1 2706 gene polymorphism was associated with lower systolic blood pressures when compared with those having AG, and GG genotypes ($p = 0.027$).

ABCA1 expression stimulates transformation of 3T3-L1 preadipocytes into mature adipocytes (120). Disruption of this process can effect lipid levels, increase in the secretion of some cytokines (IL-6, and TNF), fluctuate levels of regulatory adipocytokines as adinopectin, and resistin subsequently leading to development of atherosclerosis which is an inflammatory process. This change involving ABCA1 gene may increase levels of the markers of inflammation, and atherosclerosis.

In our study we analyzed both ABCA1 G2706A, and ABCA G1051A (R219K) gene polymorphisms, and demonstrated lack of any statistically significant difference among genotypes, when levels of hs-CRP, fibrinogen, and homocysteine levels were compared in dyslipidemic patients having different genotypes.

These results might be obtained because of the impact of diverse ABCA1 gene polymorphisms in different ethnic groups on hypertension, metabolic syndrome, and chronic diseases as type 2 diabetes through pathways dependent or independent on HDL-cholesterol. In a study performed in American population, in individuals with AA genotype, ABCA 1 G1051A (R219K) polymorphism was found to be associated with moderately high HDL levels, and lower prevalence of coronary artery disease (18).

However in our study, statistical analysis was performed between ABCA1 G1051A (R219K) gene polymorphism, and HDL –cholesterol levels, and statistically significantly higher HDL-cholesterol levels were detected in patients with GG genotype, when compared with those having AA, and AG genotypes ($p = 0.047$). In a previous study performed in a different population (Jerome I. Rotter et al.) the correlation between ABCA1 G1051A polymorphism, and increased HDL-cholesterol levels was stated. The same researchers indicated moderate LDL-cholesterol decrease in ABCA1 G1051A gene polymorphism (19, 20). In our study a statistically significant correlation was not detected between ABCA1 G2706A gene polymorphism, and HDL cholesterol levels ($p = 0.670$). This inverse outcome between ABCA1 G1051A gene polymorphism, and HDL cholesterol may be related to ethnic differences.

Conclusion

we found ABCA1 gene polymorphism has been seen to be correlated with hypertension, and metabolic syndrome apart from HDL-cholesterol metabolism. Despite higher blood triglyceride, LDL-cholesterol levels in glucose metabolism, inability to detect any correlation is one of the interesting aspects of this study. In this study the relationship of ABCA 1 gene polymorphism with hypertension, and metabolic syndrome was seen independent from HDL-cholesterol metabolism.

Abbreviations

ABC1	ATP-Binding Cassette Cholesterol Transporter–1
HDL	High density lipoprotein
LDL	Low density lipoprotein
CRP	C-reactive protein

Declarations

Compliance with ethical standards

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

Ethical approval: Consent forms and protocols were approved by the ethics committee of the Ege University Medical School. All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee, as well as the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies on animals performed by any of the authors.

Informed consent: An informed consent was obtained from all individual participants included in the study.

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Author Contributions Statement

In this study, ATV, VBC, ZE carried out the molecular genetic studies, MK, AGO, ME conceived of the study, and participated in its design and coordination. MK, ME participated in the sequence alignment and drafted the manuscript. MK, ME participated in the design of the study and performed the statistical analysis and participated in the sequence alignment. All authors read and approved the final manuscript.

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Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the findings of this article are available from the Ege University Medical School, Department of Medical Biocemistry.

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