Indian Journal of Experimental Biology
Vol. 63, April 2025, pp. 285-290
DOI: 10.56042/ijeb.v63i04.11143

Early-onset myocardial infarction may be related to ApoE and CYP2C19 variations

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Received 15 May 2024; revised 31 January 2025

Myocardial infarction (MI) is among the leading causes of death in the world. While most MIs occur over the age of 65, 5-10% are detected in young individuals. This condition is known as early-onset MI. Since it is common in every population, there is a processing need of identifiying the causative factors of the disease. Genetic factors have an important effect for early-onset MI. Therefore, this study aimed to investigate the relationship between *ApoE* and *CYP2C19* variations with early-onset MI. Thirty early-onset MI patients and 30 healthy individuals were included in the study. After DNA was isolated, *CYP2C19* and *ApoE* variations were investigated by qPCR. Results were evaluated statistically. ε2 variant of *ApoE* and *CYP2C19*2* were found statistically high in control and patient group, respectively. Hypertension, diabetes mellitus, smoking, triglyceride, LDL, total cholesterol, BMI and fasting blood glucose levels were statistically high in patient group. Some statistically significant associations were detected between hypertension, fasting blood glucose, LDL, HDL, BMI, total cholesterol and triglyceride levels with ε2; and between ε4 and *CYP2C19*2* variants. *CYP2C19*2* variant may have a strong association with early-onset MI and ε2 may have a protective role for the disease. It was considered that ε4 may affect the occurrence of the disease according to the increase in some blood parameters. In conclusion, screening of *ApoE* and *CYP2C19* variations may provide information about early-onset MI.

Keywords: *CYP2C19*, *ApoE*, MI, qPCR

Cardiovascular diseases are the leading causes of mortality and morbidity in the world[1]. In our country, large-scale studies have been shown that coroner morbidity and mortality rates are quite high[2]. Although MI mostly occurs in individuals over the age of 65, approximately 5-10% of MIs occur in young individuals[3]. If the MI occurs in men under the age of 55, and women under the age of 65, this condition is known as early-onset MI. Genetic factors are also related to early-onset MI[4,5]. Variations of *ApoE* and *CYP2C19* genes may be effective in this condition[6,7]. Thus in this study, it was aimed to investigate the effects of *ApoE* and *CYP2C19* mutations to early-onset MI.

Apolipoprotein E (*ApoE*) is a macromolecular plasma protein which plays role in lipoprotein transport and homeostasis. It takes part in structural continuity of lipoprotein particles and regulation of several different lipoprotein metabolism[8]. *ApoE* gene is located at 19q13.2 chromosome region and contains 4 exons. *ApoE* encodes 299 amino acids[9]. ε2, ε3 and ε4 are mostly studied variants of *ApoE*[10]. Different combinations of two point mutations in the exon 4 cause the formation of 3 common variants known as ε2, ε3, and ε4[11]. Although many studies found relation between ApoE and MI, there are few studies about the relationship between early-onset MI and ApoE variants. Therefore, we aimed to investigate the relation between ε2, ε3 and ε4 variants of *ApoE* gene with early-onset MI.

CYP2C19 is located at 10q24.1q24.3 and contains 9 exons[12]. CYP2C19 is one of the liver cytochrome P450 enzymes. CYP2C19 plays role in drug metabolism. Moreover it is thought that mutations in *CYP2C19* gene are associated with cardiovascular diseases[13,14]. The *CYP2C19*2* and *CYP2C19*3* variants of *CYP2C19* are mostly related to cardiovascular diseases. *CYP2C19*2* (rs4244285) refers to a G681A nucleotide change in the intron 4/exon 5 junction. A nonfunctional protein occurs at a result of this variation. *CYP2C19*3* (rs4986893) causes G636A nucleotide change in exon 4. As a result of this variation, a metabolically inactive protein is formed due to the formation of the early stop codon at 212th amino acid[15]. However some studies were found about the relation between *CYP2C19* variations with

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cardiovascular diseases, any study was not found about the relation of early-onset MI and *CYPC19* variants. Therefore we also aimed to investigate the relationship between *CYP2C19*2* and *CYP2C19*3* variants with early-onset MI. Additionally, we also aimed to investigate the relationship between genotypes and other risk factors which may related to early-onset MI.

Materials and Methods

Study population

Thirty patients (Male: <45 years, Female: <55 years) who applied to Istanbul Dr.Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital and Istanbul Kartal Kosuyolu High Specialization Training and Research Hospital, Cardiology clinics and were diagnosed with early-onset MI and 30 healthy individuals (Male patient:>45 years old, Female patient:>55 years old) were included in this study as the patient and control group, respectively. Patients using oral antiplatelet or anticoagulation, confirmed coagulopathy, hematological proliferative diseases, thrombocytosis, oncological inflammatory disorders, prior coronary artery disease, treated conservatively or with thrombolysis, active infection, severe valvular disease, renal or hepatic insufficiency and patients without follow-up were excluded from the study. Clinical and demographic data related to early-onset MI were also obtained from individuals. Ethical approval was obtained from Yeditepe University, Ethics Committee of Clinical Research (Approval number: 1272, Approval date: 20.08.2020). Written informed consent was obtained from each patient.

Blood sample collection and genotyping

2 mL blood samples were collected from the participants. Total genomic DNA was extracted from peripheral blood leukocytes. PureLink DNA isolation kit (Invitrogen, CA, USA) was used for DNA isolation from peripheral blood leukocytes according to manufacturer's instructions[16].

*2 (681G>A) and *3 (636G>A) variants of *CYP2C19* gene; ε2, ε3 and ε4 variants of *ApoE* gene were investigated by qPCR[15]. The *ApoE* variants ε2, ε3 and ε4 correspond to the *ApoE* SNP haplotypes T-T, T-C and C-C at rs429358 and rs7412, respectively. The presence of the "T" allele at rs7412 and the "T" allele at rs429358 represent the ε2 variants; the presence of the "C" allele at rs7412 and "T" allele at rs429358 represent the ε3 variants; presence of the "C" allele at rs429358 and "C" allele at rs7412 represent the ε4 variants[17].

Statistical analysis

Statistical Package for the Social Science (SPSS) 25.0 was used for evaluating the data. Kolmogorov-Smirnov test was used to control normal distribution assumption. Two independent samples *t* test was used to compare continuous variables' means between two groups. Kruskal-Wallis tests were performed to investigate the difference between risk factors and genotypes. If there were statistically significant differences for pairwise comparison, Mann-Whitney U test was performed. *P* values less than 0.05 ($P<0.05$) were considered to be statistically significant.

Results

Study population

When groups were compared with each other age, hypertension, diabetes mellitus, smoking, triglyceride, total cholesterol, HDL, body mass index (BMI) and fasting blood glucose were found statistically significant ($P<0.05$). Table 1 shows the baseline characteristics of the study groups.

Table 1 — Baseline characteristics of the study population

Baseline characteristics		Control group (n=30)	Patient group (n=30)	*P* values
Age (year)		52±4.18	43.13±5.59	<0.001**
Body Mass Index (BMI)		21.98±2.04	28.05±2.8	<0.001**
Gender	Female	8 (26.7%)	9 (30%)	0.774
	Male	22 (73.3%)	21 (70%)	
Fasting blood glucose (mg/dL)		78.73±6.3	124.9±52.44	<0.001**
Total cholesterol (mg/dL)		169.91±26.45	195.8±57.58	0.031*
LDL* (mg/dL)		91.3±21.56	114.8±46.19	0.16
HDL# (mg/dL)		64.73±20.87	41.9±8.39	<0.001**
Triglyceride (mg/dL)		69.4±34.75	203.2±86.51	0.006*
Diabetes mellitus (%)		0 (0%)	10 (33.3%)	0.001*
Hypertension (%)		1 (3.3%)	21 (70%)	<0.001**
Smoking (%)		2 (6.7%)	19 (63.3%)	<0.001**
Alcohol consumption (%)		0 (0%)	2 (6.7%)	0.492

*$P<0.05$, **$P<0.001$, *Low density lipoprotein, #High density lipoprotein

***ApoE* genotyping**

When the distribution of ApoE variants were compared between the groups, ε2 variant was found statistically high in control group (P<0.05). Although the ε4 variant was detected at a high level in the patient group (23%), the difference between the groups was not found statistically significant. The distribution of ApoE variants between the groups are shown in Table 2.

***CYP2C19* genotyping**

When the distribution of *CYP2C19* variants was compared between the groups, it was found that the *CYP2C19*2* variation was statistically high in patient group (P<0.05*). CYP2C19*3* variation was not detected in both of the groups. The distribution of *CYP2C19* variants among the groups are shown in Table 3.

Relations between risk factors and variations

Statistically significant associations between alleles and risk factors are shown in Table 4. Hypertension, LDL, and fasting blood glucose levels were statistically low whereas HDL level was statistically high in patients who carry ApoE-ε2 variant. Total cholesterol, LDL, trigliseride levels were statistically high, besides these HDL level were statistically low in patients who carry ApoE-ε4 variant. BMI, fasting blood glucose and trigliseride levels were statistically high in patients who carry CYP2C19*2 variant.

Discussion

The *ApoE* gene is very polymorphic in humans. In the studies mostly three main isoforms of Apo-E (ε2, ε3, ε4) are detected[10]. The most common of these is the ε3. These three isoforms are formed as a result of changes in cysteine (Cys) and arginine (Arg) residues at positions 112 and 158 of the mature Apo-E. ApoE protein variants are expressed as Apo-ε2 (Cys112, Cys 158), Apo-ε3 (Cys 112, Arg 158), Apo-ε4 (Arg 112, Arg 158)[11]. Various studies have been carried out to show the relationship of ε2, ε3 and ε4 variants with MI. In these studies researchers found a significant relationship between ε4 and MI. Batalla *et al*. showed that, ε4 allele carriers were found significantly high in patients than controls[18]. Lambert *et al*. demonstrated that ε4 variant was associated with formation of MI[16]. Wang *et al*. observed that while ε2 allele had a significantly protective role against MI, ε4 variant increases the risk of MI[19]. Lahoz *et al*. showed that there is a relationship between ε2, ε3 and ε4 variants with MI[20]. In some studies, ε4 variant was found high in early-onset MI patients[18]. Schachter *et al*. demonstrated that ε2 was more frequently found in older patients than younger patients whereas ε4 was more frequently found in younger group[21]. Biggart *et al*. and Sandkamp *et al.* showed that while ε2 may play a protective role for early-onset MI, ε4 may associated with formation of early-onset MI[22,23].

Table 2 — Distribution of *ApoE* variants between groups

Apo E variants	Control group (n=30)	Patient group (n=30)	*P* values
ε2	8* (26.7%)	2(6.7%)	0.04*
ε3	20 (66.7%)	21 (70%)	1.00
ε4	2 (6.7%)	7 (23.3%)	0.145

*P<0.05

Table 3 — Distribution of *CYP2C19* variations among groups

CYP2C19 variants	Control group (n=30)	Patient group (n=30)	*P* values
*CYP2C19*2*	5 (16.7%)	15*(50%)	0.013*
*CYP2C19*3*	0 (0%)	0 (0%)	n.e.

*P<0.05, n.e. unevaluated

Table 4 — Statistically Significant Relations Between Alleles and Risk Factors

Alleles	Risk factors	Variation absent	Variation present	*P* values
ApoE-ε2	Hypertension	22	0	0.01*
	LDL (mg/dL)	107.40±38.99	81.3±19.56	0.041*
	HDL[#] (mg/dL)	49.8±15.85	70.9±26.82	0.02*
	Fasting blood glucose (mg/dL)	105.94±46.85	81.2±5.20	0.039*
ApoE-ε4	Total cholesterol (mg/dL)	173.65±33.38	235±72.46	0.004*
	LDL (mg/dL)	96.33±31.04	141.11±50.12	0.004*
	HDL[#] (mg/dL)	55.21±19.41	42.56±17.46	0.02*
	Triglyceride (mg/dL)	106.12±69.79	307.33±134.82	0.011*
*CYP2C19**2	Hypertension	9 (% 22,5)	13(% 65)	0.002*
	Fasting blood glucose (mg/dL)	91.53±30.53	122.4±57.97	0.002*
	Triglyceride (mg/dL)	103.7±72.73	201.5±101.92	0.032*
	BMI[†]	24.16±3.6	26.72±4.02	0.012*

*P<0.05, LDL: Low density lipoprotein, [#]High density lipoprotein, [†]Body mass index

Contrary to these findings Mohammad *et al*. did not found any association between *ApoE* variants with early-onset MI[24]. Our results are also consistent with these studies. In our study, ε2 variant of *ApoE* was found significantly high in control group therefore it may have a protective role in early-onset MI. Additionally ε4 variant of *ApoE* was found high in patient group however it was not found statistically significant. Thus ε4 variant may be associated with the occurrence of the disease, since the difference between the two groups was not statistically significant, it was concluded that other studies which are conducted by increasing the number of patients would be useful to investigate the relationship between this variant with early-onset MI.

The *CYP2C19* gene is a member of the cytochrome P450 gene family. Approximately 25 genetic variants in the exonic region of *CYP2C19* gene have been identified and most common of them is *CYP2C19*2*[25]. Bai *et al*. showed that *CYP2C19* polymorphism effect the onset-ischemic stroke[26]. Yi X. *et al*. studied 375 patients who have ischemic stroke stories and observed that there is a significant relationship between *CYP2C19*2* (rs4244285) AA/AG genotypes and formation of acute ischemic stroke[27]. When Mega *et al*. compared *CYP2C19* polymorphism (*CYP2C19*2* and *CYP2C19*3*) carriers with the *CYP2C19* non-carriers, they detected that *CYP2C19* variations increase the risk of cardiovascular death, myocardial infarction, or stroke in 26.3% of the overall study population[28]. Kirac *et al*. found that CYP2C19*2 variation is related to stent thrombosis in coronary artery disease[29]. Xie-X *et al*. divided the participants into 3 groups as extensive metabolizers (EMs) (*CYP2C19*1/*1* genotype), intermediate metabolizers (IMs) (*CYP2C19*1/*2* or **1/*3* genotype), and poor metabolizers (PMs) (*CYP2C19*2/*2*, **2/*3*, or **3/*3* genotype) and examined *CYP2C19* polymorphisms (*CYP2C19**2 and *CYP2C19*3*) in the study. They observed that PMs had a higher incidence of MI compared to EMs[30]. Although there are studies in the literature that shows the relationship of *CYP2C19* polymorphisms with MI, iskemic stroke and drug resistance, no study has been found on early-onset MI and its relationship with *CYP2C19* polymorphisms. In our study, *CYP2C19*2* variation was statistically high in patient group (P<0.05). It was considered that *CYP2C19*2* variation may be associated with early-onset MI. *CYP2C19*3* variation was not detected in both of the groups, therefore it could not be evaluated.

High total cholesterol and LDL levels are the risk factors for coronary artery disease[31]. In various studies, it has been found that *ApoE* variants affect the lipid profile, that the ε2 variant is associated with low total cholesterol and LDL levels, and the ε4 variant is associated with high total cholesterol and LDL levels thus cause coronary artery disease and MI[32-34]. Batalla *et al*. found that increased risk for early-onset MI was associated with high cholesterol concentration among ε4 carriers[18]. It has been reported that the ε2 and ε4 alleles are also associated with triglyceride levels. In addition, related mutations are known to affect the plasma concentration of *ApoE*[32,35]. Larifla *et al*. found that total cholesterol/HDL and LDL/HDL ratios did not differ significantly among the 3 allelic groups of *ApoE* (ε2, ε3, ε4)[36]. However, Lumsden *et al*. showed that the ε2 allele had an effect on lowering LDL and HDL levels. But *ApoE*-ε4 allele has an opposite effect from ε2 allele, it increases LDL and HDL levels[37]. In our study, LDL level were found significantly low and HDL level was found statistically high in individuals who have ε2 variant. Additionally total cholesterol, LDL and triglyceride levels were significantly high, and HDL levels were statistically low in individuals who have ε4 variant.

Shi *et al*. showed that the *ApoE*-ε2 allele may have a protective effect on hypertension. On the contrary, Weize *et al*. found that the ε2 allele causes the significant 2.81-fold increased hypertension risk in a Han ethnic group[38,39]. Ban *et al*. found that there were no statistically significant differences for plasma glucose in their study on ε2 carriers[40]. In our study, hypertension was mostly detected in individuals who have not got ε2 variant and fasting glucose levels were significantly low in individuals who have ε2 variant.

In some studies also relations were detected between *CYP2C19* mutations with hypertension and lipid profile. Ma *et al*. found that patients who carry *CYP2C19* rs10509676 AA genotype are have genetic risk factor for hypertension[41]. Bai *et al*. showed that *CYP2C19* gene polymorphisms are related to lipid metabolism, triglyceride and total cholesterol[26]. In our study, hypertension, BMI, fasting blood glucose and triglyceride levels were statistically high in individuals who have *CYP2C19*2* variant. Since significant risk factors may be associated with early-onset MI, it is concluded that it would be appropriate to investigate the genotype-phenotype relationship with more comprehensive studies. Additionally since

there were a small number of individuals in the groups, genotype distributions by gender were not examined. It would be appropriate to expand our research with studies involving large cohorts.

Conclusion

CYP2C19*2 variant has a strong association with early-onset MI and the ε2 variant of ApoE may have a protective role. In addition, low LDL and high HDL levels in patients carrying the ε2 variant; high total cholesterol, LDL, triglyceride levels and low HDL levels in patients carrying the ε4 variant indicate that ε2 variant has a protective effect in regulating cholesterol levels, whereas ε4 variant has an opposite effect. The presence of hypertension in individuals who do not carry the ε2 variant and have the CYP2C19*2 variation; the high BMI, triglyceride, blood glucose levels in patients who carry the CYP2C19*2 variation also support the effect of these factors to early-onset MI. In conclusion, it was considered that genetic screening of individuals for *ApoE* and *CYP2C19* gene variations and evaluation of the risk factors may provide information about early-onset MI.

Conflict of Interest

The authors declare no conflict of interest.

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