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Original Study

The Association of Hereditary Prothrombotic Risk Factors with ST-Elevation Myocardial Infarction

Kalıtsal Protrombotik Risk Faktörlerinin ST Yükselmeli Miyokart Enfarktüsü ile İlişkisi

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Ethics Committee Approval: This study approved by the Duzce University Ethic Committee, 20 January 2020, 2019/290.
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ABSTRACT

Objective: *The ST- elevation myocardial infarction (STEMI), a serious health care problem, is commonly a thrombotic complication of coronary artery disease. We compare the STEMI patients and control group in terms of the possible causes of inherited thrombophilia including FactorV Cambridge G1091C, FactorV Leiden G1691A, MTHFRC677T, MTHFR A1298C, FactorII G20210A, Factor XIII (V34L), PAI-1, FGB, ITGB3, APOB, FVHR2, ACE gene variants.*
Methods: *Fifty-three patients with STEMI and 47 individuals without diagnosis of acute coronary syndrome were included in the study. Percutaneous coronary intervention was performed for patients with STEMI. Echocardiography was performed and inherited thrombophilia genes were evaluated in all subjects.*
Results: *The MTHFR A1298C, Factor XIII (V34L), ITGB, ACE and homozygous or compound heterozygous gene varations of inherited thrombophilia are significantly related with STEMI ($p<0.05$). Also significantly higher MTHFR A1298C, FactorV Leiden G1691A, PAI and ACE gene variations in MI patients who were smokers; Factor XIII (V34L), PAI and ACE gene variations in MI patients with HT; PAI and ACE gene variation in MI patients with FH and PAI gene variations in MI patients with HL were detected when compared with the control groups with all of the same risk factors ($p<0.05$).*
Conclusion: *Hereditary thrombophilia factors may show promise in the prevention and management of STEMI when supported studies with larger case series.*

Keywords: *Coronary artery disease, inherited thrombophilia, STEMI, thrombosis, hypercoagulation*

ÖZ

Amaç: *Ciddi bir sağlık sorunu olan ST yükselmeli miyokart enfarktüsü (STEMI), genellikle koroner arter hastalığının trombotik bir komplikasyonudur. STEMI hastalarını ve kontrol grubunu, FactorV Cambridge G1091C, FactorV Leiden G1691A, MTHFRC677T, MTHFR A1298C, FactorII G20210A, FaktörXIII (V34L), PAI-1, FGB, ITGB3, APOB, FVHR2 dahil olmak üzere kalıtsal trombofilinin olası nedenleri açısından karşılaştırdık.*
Yöntem: *Çalışmaya STEMI'li 53 hasta ve akut koroner sendrom tanısı olmayan 47 kişi dahil edildi. STEMI'li hastalara perkütan koroner girişim uygulandı. Tüm olgulara ekokardiyografi yapıldı ve tüm olgular kalıtsal trombofili genleri açısından değerlendirildi.*
Bulgular: *Kalıtsal trombofilinin MTHFR A1298C, FaktörXIII (V34L), ITGB, ACE ve homozigot veya bileşik heterozigot gen varyasyonu STEMI ile anlamlı olarak ilişkilidir ($p<0.05$). Ayrıca sigara içen MI hastalarında MTHFR A1298C, FactorV Leiden G1691A, PAI ve ACE gen varyasyonu, HT'li MI hastalarında Faktör XIII (V34L), PAI ve ACE gen varyasyonu, aile öyküsü olan MI hastalarında PAI ve ACE gen varyasyonu ve HL'li MI hastalarında PAI gen varyasyonu anlamlı derecede kontrol grubundan daha yüksek bulundu.*
Sonuç: *Kalıtsal trombofili faktörleri, daha büyük seri çalışmalarla desteklendiğinde STEMI'nin önlenmesi ve tedavisinde umut vaat edebilir.*

Anahtar kelimeler: *Koroner arter hastalığı, kalıtsal trombofili, STEMI, tromboz, hiperkoagülasyon*

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INTRODUCTION

According to the World Health Organization data, around 17.9 million people died from cardiovascular diseases worldwide in 2016 which corresponds to 31% of all deaths in the world. Acute myocardial infarction and stroke were responsible for 85% of these deaths[1].

ST-elevation myocardial infarction (STEMI) is a condition in which acute myocardial ischemia develops due to the development of thrombosis, usually on background of coronary artery disease. Despite advanced methods of diagnosis and treatment, since the pathophysiology of the disease cannot be clearly revealed, STEMI is still a disease with high mortality and morbidity rates worldwide. At autopsy, atherosclerotic plaques of patients who died from STEMI primarily consist of a variable degree of fibrous tissue cells and overlapping thrombus. Coronary arterial thrombus is responsible for STEMI in most cases. Thrombus consists of platelets, fibrin, erythrocytes and leukocytes, and adheres to the luminal surface of the artery[2].

Although the presence of diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), smoking and obesity are blamed for the development of the disease, it is known that some genetic risk factors have very important effects too. There are genes related with possible causes of inherited thrombophilia *[Factor V Cambridge G1091C, Factor V Leiden G1691A, MTHFRC677T, MTHFR A1298C, Factor II G20210A, FactorXIII (V34L), Plasminogen Activator Inhibitor-1 (PAI-1), FGB, ITGB3, APOB, FVHR2 and angiotensin-converting enzyme (ACE)]*[3].

To the best of our knowledge there was no study performed using broad range of the inherited thrombophilia factors including *Factor V Cambridge G1091C, Factor V Leiden G1691A, MTHFRC677T, MTHFR A1298C, Factor II G20210A, FactorXIII (V34L), PAI-1, FGB, ITGB3, APOB, FVHR2, ACE* genes in STEMI patients. Some of these genetic risk factors directly affect the formation of fibrin clots in the coagulation pathway. A demonstrative example of the mechanism of thrombus formation on the background of atherosclerosis is given under the guidance of coagulation pathway in Figure 1.

Therefore, we aimed to investigate frequencies of several inherited thrombophilia factors which may be potentially related with the coronary thrombosis and their association with clinical risk factors in patients with STEMI.

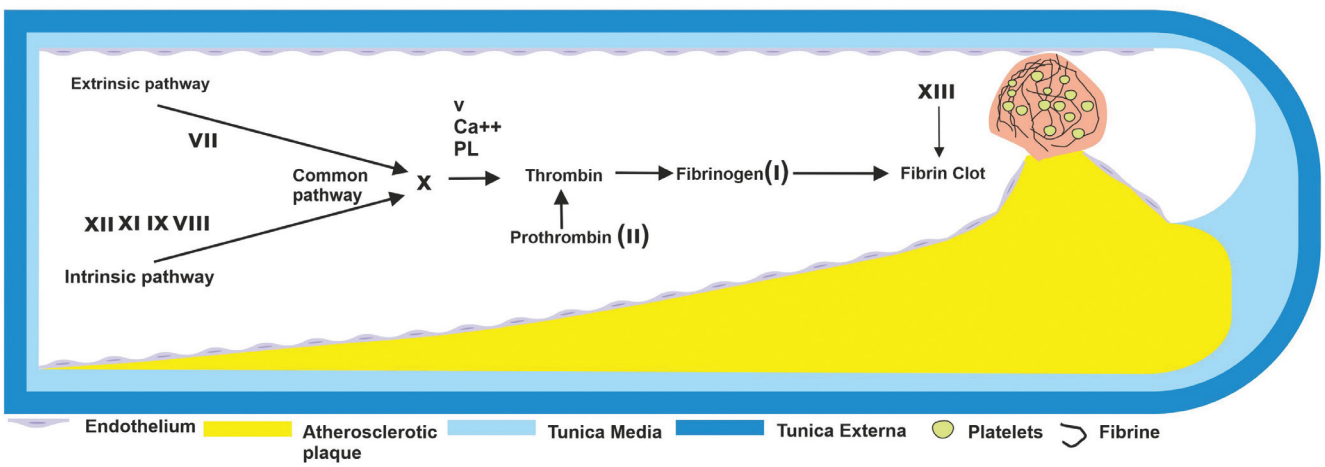

Figure 1. The mechanism of thrombosis formation on the background of atherosclerosis under the guidance of coagulation pathway.

MATERIAL and METHODS

Study design

In this study, thrombotic occlusion was evaluated by angiography in 53 patients who underwent percutaneous coronary intervention (PCI) for STEMI. Forty-seven patients without any history of acute coronary syndrome (ACS) and clinical findings suggestive of coronary artery disease were included in the control group. The diagnosis of acute myocardial infarction (AMI) was made according to the Fourth Universal Definition of Myocardial Infarction by considering clinical, electrocardiography (ECG), and cardiac enzyme findings[4]. PCI was applied to the culprit lesion in patients undergoing coronary angiography. The lesion causing more than 50% reduction in lumen diameter in other coronary arteries was accepted as coronary artery stenosis and the lesion causing less than 50% narrowing was accepted as normal or near normal coronary arteries (N/NNCAs), which was not hemodynamically significant[5]. Hypercholesterolemia was defined as serum total cholesterol: ≥5.2 mmol/L, low density lipoprotein: ≥2.6 mmol/L, triglyceride: ≥1.7 mmol/L or use of cholesterol lowering drugs[6]. Diabetes mellitus was defined based on fasting plasma glucose: >6.94 mmol/L (>125 mg/dL) levels or the use of antidiabetic therapy. Hypertension was defined as blood pressure ≥140/90 mmHg or antihypertensive drug use. Smokers were described as people who reported current smoking. Demographic features of the participants, laboratory findings (creatinine, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride, fasting blood glucose, white blood cells, hemoglobin level, platelet count, and C-reactive protein) were recorded. The study protocol was certified by the local Ethics Committee. Written informed consent was obtained from all participants. Patients with atrial fibrillation, moderate-to-severe valvular heart disease, congenital heart disease, uncontrolled hypertension, hypothyroidism, hyperthyroidism, malignancy, hepatic, renal, pulmonary and hematological disorders were excluded from the study. Total DNA was isolated using Magnesia 16 Complete Blood Genomic DNA Isolation Kit-102 in 200 ml peripheral blood samples obtained from the patients. Then Factor V Cambridge G1091C, *Factor V Leiden G1691A, MTHFRC677T, MTHFR A1298C, Factor II G20210A, FactorXIII (V34L), PAI-1, FGB, ITGB3, APOB, FVHR2, ACE* gene variants were evaluated in both STEMI and the control groups.

Electrocardiography

A resting 12-lead ECG (filter range, 0.05-150 Hz; AC filter, 60 Hz, 25 mm/s, 10 mm/mv) was recorded by available machine (NIHON KOHDEN Cardiofax ECG 1250K model) in all patients.

Echocardiography

Echocardiography was performed in all subjects included in the study using Siemens Acuson SC 2000 device. It was performed after PCI in patients with STEMI. Cardiac anatomy, valve functions, ejection fraction, and segmental wall motion abnormality were assessed using standardized projections and routine measurements were done according to the recommendations of the American Society of Echocardiography[7].

Coronary Angiography

All patients in the STEMI group included in the study underwent selective right and left coronary angiography and PCI using the standard Judkin's technique with General Electric INNOVA 2100 IQ model device. Coronary arteries were visualized in the right and left oblique positions using cranial and caudal angulation. Images were digitally recorded at 15 frames per second.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, New York, USA). Normally distributed quantitative variables were expressed as mean±standard deviation and as median (minimum-maximum) in case of non-normal distribution. Quantitative variables were expressed as

numbers and percentages. Differences between independent groups were assessed by Student t-test for normally distributed quantitative variables and Mann-Whitney U-test for variables without normal distribution and chi-square test for qualitative variables. Spearman's correlation analyses were used to assess the correlations between thrombophilia parameters and cardiovascular risk factors. All results were considered statistically significant at the level of $p<0.05$.

RESULTS

Among demographic and laboratory findings, male sex frequency (44 (83%) vs. 26 (55.3%)), body mass index (27.9±4.5 kg/m^2 (19.4 kg/m^2 -40.2 kg/m^2) vs. 25.3±4.0 kg/m^2 (17.6 kg/m^2 -36.0 kg/m^2), heart rate (71.3±13.3 (51-108) bpm vs. 74.9±8.7(49-86) bpm), diastolic blood pressure (86.0±8.6 (70-100) mmHg vs. 82.0±8.7 (60-100) mmHg), fasting blood glucose (105.1±17.1(82-140) mg/dL vs. 90.4±9.2 (78-119) mg/dL), creatinine (0.83±0.17 (0.45-1.28) mg/dL vs. 0.73±0.19 (0.26-1.15) mg/dL), total cholesterol (172.4±48.0 (94-344) mg/dL vs. 185.6±34.1 (117-270) mg/dL), low-density lipoprotein (101.0±36.1 (40-185) mg/dL vs. 114.3±26.6 (56-167) mg/dL), white blood cell count (8417±2219 (4700-17000) vs. 6876±1873 (4000-11200)) and, C-reactive protein (0.5±0.3 (0.10-1.32) mg/dL vs. 0.4±0.2 (0.10-1.07) mg/dL) were significantly higher in STEMI patients than control group (Table 1). Among the echocardiographic findings, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), septum and posterior wall thicknesses were higher and left ventricular ejection fraction (EF) was lower in STEMI patients (Table 1).

Table 1. Demographical, laboratory and echocardiographical findings of patients.

	STEMI Mean±SD (min-max)	Control Mean±SD (min-max)	Z	p
Age (years)	57.981±8.911 (35-74)	54.957±8.655 (40-71)	-1.870	0.061
Sex	M:44 (83%)/F:9 (17%)	M:26 (55.3%)/F:21 (44.7%)	-	0.03*
BMI (kg/m^2)	27.890±4.457 (19.38-40.15)	25.275±3.986 (17.58-35.94)	-3.129	0.002*
HR	71.302±13.311 (51-108)	74.936±8.736 (49-86)	-2.217	0.027*
SBP (mmHg)	133.774±20.496 (90-180)	127.234±15.245 (100-160)	-1.475	0.140
DBP (mmHg)	86.038±8.625 (70-100)	82.021±8.764 (60-100)	-1.940	0.052*
FBG (mg/dl)	105.113±17.116 (82-140)	90.362±9.242 (78-119)	-4.580	0.000*
Creatinin (mg/dL)	0.830±0.174 (0.45-1.28)	0.729±0.192 (0.26-1.15)	-2.722	0.006*
TC (mg/dL)	172.359±48.021 (94-344)	185.596±34.087 (117-270)	-1.931	0.054*
HDL (mg/dL)	40.566±8.402 (29-67)	46.894±12.541 (23-89)	-2.907	0.004*
LDL (mg/dL)	100.981±36.136 (40-185)	114.340±26.557 (56-167)	-2.280	0.023*
Triglyceride (mg/dL)	151.698±93.039 (38-597)	121.936±54.036 (37-269)	-1.578	0.115
WBC	8416.981±2219.038 (4700-17000)	6876.596±1872.944 (4000-11200)	-3.613	0.000*
Hemoglobine (g/dL)	14.145±1.473 (10.60-16.60)	13.875±1.765 (9.90-16.50)	-0.667	0.505
Platelets	257.981±62.820 (166-475)	279.447±73.967 (175-533)	-1568	0.117
CRP	0.498±0.301 (0.10-1.32)	0.351±0.244 (0.10-1.07)	-2.880	0.004*
Echocardiographical Findings				
LVEDD (cm)	4.825±0.449 (4-5.90)	4.589±0.364 (3.60-5.30)	-2.354	0.019*
LVESD (cm)	3.604±0.466 (2.80-4.80)	3.277±0.368 (2.30-4.10)	-3.716	0.000*
Septum (cm)	1.162±0.194 (0.80-1.50)	0.985±0.156 (0.7-1.5)	-4.679	0.000*
Posterior (cm)	0.951±0.151 (0.50-1.20)	0.875±0.107 (0.70-1.20)	-3.199	0.001*
EF (n %)	54.245±9.477 (30-65)	63.894±2.539 (55-65)	-6.863	0.000*

BMI: Body mass index, SBP: Systolic Blood pressure, DBP: Diastolic Blood pressure(mmHg), FBG: Fasting Blood Glucose TC: Total Cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, WBC:White Blood Cells, CRP: C-reactive protein, Min-Max: Minimum-Maximum, SD: Standard deviation, HR: Heart Rate, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left Ventricular End-Systolic Diameter, EF: Ejection Fraction

When two groups are compared in terms of cardiovascular major risk factors, the frequencies of diabetes mellitus (41.5% vs 4.3%), hypertension (69.8% vs 36.2%), hyperlipidemia (66% vs 29.8%) and problematic family history (60.4% vs 25.5%) were higher in STEMI group, while the frequency of smoking (43.4% vs 46.8%) was similar in both groups (Table 2). When the groups were evaluated in terms of hereditary thrombophilia compared to the control group, significantly higher frequencies were detected in favor of STEMI; *MTHFR A1298C* (45.3% vs. 27.7%; p=0.008), *FactorXIII* (22.6% vs. 4.3%; p=0.008), *ITGB* (17% vs. 2.1%; p=0.013), *ACE* (del/del:37.7% and ins/del:37.7% vs. del/del:27.7% and ins/del:19.1%; p=0.0110) and homozygous or compound heterozygous gene variations as the possible causes of inherited thrombophilia (x^2=26.053; p<0.001) (Table 3).

Table 2. Cardiovascular major risk factors of patients.

	STEMI (n; %)	Control Yes (n; %)	X^2	p
Diabetes mellitus	22 (41.5%)	2 (4.3%)	18.954	0.000*
Hypertension	37 (69.8%)	17 (36.2%)	11.349	0.001*
Hyperlipidemia	35 (66%)	14 (29.8%)	13.099	0.000*
Cigarette using	23 (43.4%)	22 (46.8%)	0.117	0.732
FHCD	32 (60.4%)	12 (25.5%)	12.275	0.000*

FHCD: Family History of Cardiovascular Disease

When the distribution of inherited thrombophilia risk factors according to degree of vessel diseases was considered, statistically significant differences were detected for *MTHFR A1298C* (x^2=11.032; p=0.026) and *Factor V Cambridge G1091C* (x^2=6.698; p=0.035). Additionally, hereditary thrombophilic factors were significantly higher in MI patients with cardiovascular major risk factors than the control patients with the same cardiovascular major risk factors (Table 4).

DISCUSSION

According to our results, a statistically significant difference between STEMI and control groups was detected for *MTHFR A1298C, FactorXIII, ITGB, ACE* and homozygous or compound heterozygous gene variations as the possible causes of inherited thrombophilia. Additionally, when the

Table 3. Distribution of inherited thrombophilia factors in control and STEMI group.

Genes	Groups		X^2	p
	Control (n, %)	STEMI (n, %)		
MTHFR A1298C	Het:13 (27.7%) Hom:0 (0%)	Het:24 (45.3%) Hom:5 (9.4%)	9.669	0.008*
Factor II G20210A	Het:1 (2.1%) Hom:0 (0%)	Het:3 (5.7%) Hom:0 (0%)	0.810	0.368
Factor V Leiden G1691A	Het:1 (2.1%) Hom:1 (2.1%)	Het:5 (9.4%) Hom:0 (0%)	3.416	0.181
Factor V Cambridge G1091C	Het:0 (0%) Hom:0 (0%)	Het:0 (0%) Hom:1 (1.9%)	0.896	0.344
MTHFR C677T	Het:18 (38.3%) Hom:4 (8.5%)	Het:19 (35.8%) Hom:7 (13.2%)	0.564	0.754
FactorXIII (V34L)	Het:4 (4.3%) Het:1 (2.1%)	Het:12 (22.6%) Het:9 (17%)	6.994 6.106	0.008* 0.013*
ITGB	-	-	-	-
FGB	-	-	-	-
APOB	-	-	-	-
FVHR2	4G/5G:15 (31.9%)	4G/5G:17 (32.1%)	14.643	0.001*
PAI	4G/4G:5 (10.6%)	4G/4G:22 (41.5%)		
ACE	del/del:13 (27.7%) ins/del:9 (19.1%)	del/del:20 (37.7%) ins/del:20 (37.7%)	9.120	0.010*
Hom or Compound Heterozygous	23 (48.9%)	50 (94.3%)	26.053	0.000*

**=Statistically significant, MTHFR: Methylenetetrahydrofolate reductase, ITGB: Integrin beta-1, FGB: β-fibrinogen gene, APOB: Apolipoprotein B, FVHR2: Factor V HR2, PAI:Plasminogen Activator Inhibitor-1, ACEI:Angiotensin Converting Enzyme Inhibitors*

Table 4. Relation between inherited thrombophilia and cardiovascular risk factors.

		Risk Factor							
Genes	**G**	**HT (n, %)**	**X^2 /p**	**FH (n, %)**	**X^2 /p**	**Smoking (n,%)**	**X^2 /p**	**HL (n, %)**	**X^2 /p**
MTHFR A1298C	p	-	NSA	-	NSA	Het:12 (52.2) Hom: 1 (4.3) NV:10 (43.5)	5.678 / **0.05***	-	NSA
	C	-		-		Het:5 (22.7) Hom: 0 (0) NV:17 (77.3)		-	
Factor V Leiden *G1691A*	p	-	NSA	-	NSA	Het:4 (17.4) Hom: 0 (0) NV:19 (82.6)	4.192 / **0.040***	-	NSA
	C	-		-		Het:0 (0) Hom: 0 (0) NV:22 (100)		-	
Factor XIII (V34L)	p	Het:9 (24.3) Hom: 0 (0) NV:28 (75.7)	4.962 / **0.026***	-	NSA	-		-	NSA
	C	Het:0 (0) Hom: 0 (0) NV:17 (100)		-		-		-	
PAI	p	5G/5G:8 (21.6) 4G/5G:13 (35.1) 4G/4G:16 (43.2)	8.413 / **0.015***	5G/5G:4 (12.5) 4G/5G:11 (34.4) 4G/4G:17 (53.1)	8.089 / **0.018***	5G/5G:6 (26.1) 4G/5G:3 (13) 4G/4G:14 (60.9)	13.342 / **0.001***	5G/5G:7 (20) 4G/5G:13 (37.1) 4G/4G:15 (42.9)	7.140 / **0.028***
	C	5G/5G:10 (58.8) 4G/5G: 5 (29.4) 4G/4G:2 (11.8)		5G/5G:6 (50) 4G/5G: 4 (33.3) 4G/4G:2 (16.7)		5G/5G:15 (68.2) 4G/5G: 5 (22.7) 4G/4G:2 (9.1)		5G/5G:7 (50) 4G/5G: 6 (42.9) 4G/4G:1 (7.1)	
ACE	p	del/del:15 (40.5) ins/del:14 (37.8) ins/ins:8 (21.6)	7.303 / **0.026***	del/del:15 (46.9) ins/del:11 (34.4) ins/ins:6 (18.8)	6.575 / **0.037***	del/del:5 (21.7) ins/del:12 (52.2) ins/ins:6 (26.1)	7.715 / **0.021***	-	NSA
	C	del/del:4 (23.5) ins/del:3 (17.6) ins/ins:10 (58.8)		del/del:3 (25) ins/del:2 (16.7) ins/ins:7 (58.3)		del/del:7 (31.8) ins/del:3 (13.6) ins/ins:12 (54.5)		-	
Hom or CH	p	H/CH:36 (97.3) NV:1 (2.7%)	29.368 / **0.000***	H/CH:32(100) NV:0 (0%)	15.403 / **0.000***	H/CH:23 (100) NV:0 (0%)	19.112 / **0.000***	H/CH:35 (100) NV:0 (0%)	20.417 / **0.000***
Hom or CH	C	H/CH:5 (29.4) NV:12 (70.6%)		H/CH:7 (58.3) NV:5 (41.7%)		H/CH:9 (40.9) NV:13 (59.1%)		H/CH:7 (50) NV:7 (50%)	

*G: Group, P: Patients, C: Control, HT: Hypertension, FH: Family history, HL: Hyperlipidemia, Het: Heterozygous, Hom: Homozygous, MTHFR: Methylenetetrahydrofolate reductase, CH: Coumpound Heterozygous, NV: No variation, ACE: Angiotensin Converting Enzyme, PAI: Plasminogen Activator Inhibitor-1, NSA: No Significant Association, *=Statistically significant.*

distribution of inherited thrombophilia factors according to location of culprit lesion to be taken into consideration, a statistically significant difference was detected for *PAI*.

The effects of variation in some genes on thrombosis were evaluated but their association with thrombosis is controversial. The *PAI (4G/5G polymorphism)*[8] and ACE (the D allele from the I/D polymorphism)[9] have been shown as independent risk factors for MI. *MTHFR C677T* polymorphism was shown not to be associated with STEMI[10]. *ACE*, a key enzyme in the renin-on the regulation angiotensin system, has a crucial function in blood pressure control and the development of STEMI[9]. High angiotensin II levels and low bradykinin levels may cause a chronic state of increased vascular resistance and high blood

pressure. It was reported that the insertion deletion polymorphism (rs4646994) was significantly related with MI in different ethnic populations[11-13]. Some studies have shown a significant[14-16], while others a nonsignificant association between FVL mutation and MI[17-19]. Matthijs B et al.[20] found no correlation between MI risk and *prothrombin G20201A* and FVL mutations. The *prothrombin G20201A* mutation has been related with elevated prothrombin levels. The *G20210A* polymorphism of FII gene was related with an overall nearly twofold increased risk of STEMI in young carriers while *FVL* showed no relation[21]. However, other studies reported a correlation between Prothrombin G20210A Mutation and MI[22,23].

A significant relation between increased and decreased MI risk and both homozygosity for the fibrinogen 455A allele and PAI-1 4G allele were reported, respectively[20]. A significant association between Fibrinogen β-Chain G455A polymorphism and the lower risk of MI according to recessive model but lack of any significant relation according to the dominant model was reported[23]. FXIII has a fundamental function in the thrombus formation. Significant decrease in *FXIII* antigen after MI other than different *FXIII* genotypes (L34-carriers had higher FXIII activity) was reported[24].

There are some inconsistencies in the results of studies about the relation between MI risk and genetic variations of inherited thrombophilia factors. These inconsistencies may be caused by ethnicity, design of study, sample size, inclusion or exclusion criteria in the selection of individuals etc.

Based on our results, when distribution of inherited thrombophilia factors according to the severity of vessel diseases to be considered, statistically significant differences were detected for *MTHFR A1298C and Factor V Cambridge G1091C*.

The occurrence of single vessel disease especially in the left anterior descending coronary artery is highly prevalent in patients with ACS25. Thrombosis of multiple coronary arteries seen in a patient with STEMI is an unusual angiographic finding but it can cause fatal complication[26]. Synchronous multivessel coronary thrombosis can occur secondary to different etiologies (e.g. cocaine abuse, idiopathic thrombocytopenic purpura, coronary artery spasm, increased tendency to thrombosis, anti-thrombin III deficiency, as well as thrombophilias such as antiphospholipid antibodies, *FVL* deficiency, and essential thrombocytosis)[27]. However, the underlying mechanism still remains unclear in most of these patients. A young man with coronary arterial thrombosis caused by protein C deficiency and heterozygous *FVL* was reported[28].

When the combination of inherited thrombophilia factors and other risk factors for STEMI to be considered, significantly higher *MTHFR A1298C, Factor V Leiden G1691A, PAI and ACE* gene variations were detected in smoker MI patients rather than smoker control patients ($p<0.05$). All of significantly higher *Factor XIII, PAI and ACE* gene variations were found in MI patients with HT rather than the control patients with HT ($p<0.05$). Also both *PAI and ACE* gene variations were significantly higher in MI patients with FH than the control patients with FH, too ($p<0.05$). Additionally, significantly higher *PAI* gene variation was found in MI patients with HL than the control patients with HL ($p<0.05$).

Smokers with D allele in *ACE* gene had increased risk for STEMI than nonsmokers. It was demonstrated that D allele and smoking are related with elevated levels of angiotensin II that have been shown to increase the generation of superoxide anions and degradation of nitric oxide resulting in endothelial dysfunction[9]. Also, it was shown that *FVL* carriers who smoked had increased risk for MI[20].

Similar to our study, it was reported that smoking, dyslipidemia, obesity, family history of atherothrombotic disease are the major risk factors of the STEMI[29-31]. Also smoking, dyslipidemia, obe-

sity, hypertension, and diabetes mellitus are increased risk factors for *STEMI*[9,29]. When the compound heterozygous or homozygous carriers to be considered, significantly higher compound heterozygous or homozygous carriers were detected in patients with all risk factors of DM, HT, HL, FH and smoking than the control patients with all the same risk factors ($p<0.05$). Furthermore, in the current study frequencies of diabetes mellitus, hypertension, hyperlipidemia, obesity, and family history of cardiovascular disease were significantly higher and HDL-cholesterol levels were significantly lower in STEMI group than the control group.

Study limitations

This study was done with relatively few participants selected after investigation of broad series with inherited thrombophilia. For a better understanding and management of the disease, it is important to examine wide series with hereditary thrombosis and their relationship with other risk factors that play an important roles in the development of the disease.

CONCLUSION

In addition to modifiable risk factors, hereditary thrombophilias including *MTHFR A1298C, FactorXIII, ITGB, ACE, Factor V Cambridge G1091C* and homozygous or compound heterozygous gene variations of the inherited thrombophilia should be considered in STEMI patients. Based on our screening of various gene variations, *MTHFR A1298C, Factor V Leiden G1691A, PAI* and *ACE* genes in smokers with STEMI; Factor XIII V34L, *PAI* and *ACE* genes in individuals with STEMI and HT; *PAI* and *ACE* genes in individuals with STEMI and FH; PAI gene variations in individuals with STEMI and HL could be considered as markers for STEMI risk. It can be said that hereditary thrombophilia factors show promise in the prevention and management of STEMI when supported by studies in larger case series.

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