Smyrna Tıp Dergisi ***Araştırma Makalesi***

Gene Mutations Associated with Hypercoagulopathy and Atherosclerosis in Young Adult Patients Presenting with Acute Coronary Syndromes
Akut Koroner Sendrom ile Başvuran Genç Erişkin Hastalarda Hiperkoagülopati ve Ateroskleroz ile İlişkili Gen Mutasyonları

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Summary
Objective: Acute coronary syndromes are usually the disease of people over 45 years old; however, a number of younger patients are also diagnosed with acute coronary syndrome. In this study, it was aimed to elucidate the relationship between genetic hypercoagulable and atherosclerotic states and acute coronary syndromes in the young adults.
Material and Methods: Between January 2008 and June 2010, 68 young adult patients with acute coronary syndrome (62 men, mean age: 36.8±6.4) and 69 healthy individuals (56 men, mean age: 35.1±5.9) were recruited in this cross-sectional study. The diagnosis of acute coronary syndrome was based on the criteria of the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/Word Heart Federation Task Force the definition of MI definition. Blood samples were obtained during the first hour after admission to the Coronary Care Unit. Plasma samples were stored at -80°C until used. Polymerase chain reaction was used for the genotype analysis.
Results: Statistically significant difference was found between groups for factor V Leiden and methylenetetrahydrofolate reductase gene mutation (for both mutation p:0.006); whereas there was no statistically significant difference for prothrombin gene mutation, plasminogen activator inhibitor-1 4G/5G polymorphism and angiotensin converting enzyme I/D polymorphism (p:0.551, p:0.291 and p:0.469, respectively). The study group had significantly higher homocysteine levels than control group (14.45±5.50 µmol/L versus 11.17±3.79 µmol/L, p<0.001).
Conclusion: Factor V Leiden and methylenetetrahydrofolate reductase gene mutations might play a part in the pathophysiology of acute coronary syndromes in the young adult patients. Also, it was found that Turkey looks like a factor V Leiden mutation region as opposite to known current literature in this study.
Key words: Acute coronary syndrome, angiotensin converting enzyme, factor V leiden, methylenetetrahydrofolate reductase, plasminogen activator inhibitor-1, prothrombin

Özet
Amaç: Akut koroner sendromlar genellikle 45 yaş üzeri görülen hastalıklardır fakat bazı genç hastalar da akut koroner sendrom tanısı alır. Bu çalışmada, genetik hiperkoagülopati ve aterosklerotik durumlar ve genç yaş akut koroner sendromlar arasındaki ilişkinin aydınlatılması amaçlandı.
Gereç ve Yöntem: Ocak 2008 ve Haziran 2010 arasında, 68 genç akut koroner sendrom hastası (62 erkek, ortalama yaş: 36.8±6.4) ve 69 sağlıklı birey (56 erkek, ortalama yaş: 35.1±5.9) bu kesitsel çalışmaya alındı. Akut koroner sendrom tanısında Avrupa Kardiyoloji Derneği/Amerikan Kardiyoloji Cemiyeti/Amerikan Kalp Derneği/Dünya Kalp Federasyonu kriterleri kullanıldı. Kan örnekleri, yoğun bakım ünitesine kabulden sonraki 1 saat içerisinde elde edildi. Plazma örnekleri kullanılıncaya kadar -80°C'de bekletildi. Genotip analizleri için polimeraz zincir reaksiyonları kullanıldı.
Bulgular: Gruplar arasında protrombin gen mutasyonu, plazminojen aktivatör inhibitör-1 4G/5G polimorfizmi ve anjiyotensin dönüştürücü enzim I/D polimorfizmi için istatistiksel anlamlı bir fark yokken; polymorphism (sırasıyla p:0.551, p:0.291 ve p:0.469), faktör V leiden ve metiltetrahidrofolat redüktaz gen mutasyonları arasında istatistiksel anlamlı fark bulundu. (ikisi için de p:0.006). Çalışma grubunda kontrol grubuna kıyasla

anlamlı olarak daha yüksek homosistein seviyeleri tespit edildi (14.45±5.50 µmol/L karşın 11.17±3.79 µmol/L, p<0.001).
Sonuç: Faktör V leiden ve metiltetrahidrofolat redüktaz gen mutasyonları genç erişkin hastalarda akut koroner sendromların patofizyolojisinde rol oynayabilir. Ayrıca, çalışmada bilinen güncel litaratürün aksine Türkiye'nin bir Faktör V leiden mutasyon bölgesi gibi göründüğü bulundu.
Anahtar Kelimeler: Akut koroner sendrom, anjiyotensin dönüştürücü enzim, faktör V leiden, metiltetrahidrofolat redüktaz, plazminojen aktivatör inhibitör, protrombin

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Introduction

Myocardial infarction (MI) is a major cause of morbidity and mortality in all over the world (1). The underlying pathophysiology of MI in around 70% of fatal events is partial or complete epicardial coronary artery occlusion from atherosclerotic plaques which is vulnerable to rupture or erosion (2). Although MI is usually the disease of people over 45 years old, a number of younger patients can also suffer from MI. 0,5% of men and 0,18% of women between 35 and 44 years were diagnosed with acute coronary syndromes (ACS); whereas the disease was found to be 20,5% of men, and 17,1% of women over the age of 60 years (3). In addition to atherosclerosis, non atherosclerotic coronary artery diseases or hypercoagulable states should also be considered in these patients (4).

In this study, it was aimed to elucidate the relationship between gene mutations including prothrombin gene mutation (P G20210A), factor V Leiden (FVL), methylenetetrahydrofolate reductase (MTHFR) gene mutation, plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphism and angiotensin converting enzyme (ACE) I/D polymorphism and the ACS in young adults.

Material and Methods

Patient enrollment and data collections were performed prospectively. Between January 2008 and June 2010, a total number of 392 patients with ACS were admitted to coronary care unit. Of 68 patients with <45 years old (62 men, mean age:36.8±6.4) and 69 healthy controls (56 men, mean age:35.1±5.9) were included in this cross-sectional study. ACS defined as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). The diagnosis of ACS was based on the criteria of the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/Word Heart Federation (ESC/ACC/AHA/WHF) Task Force the universal definition of MI definition (5). The cut off age of 45 has been used in the study for selection of young group as it has been used in most studies to define young patients with ACS.

Patients who refused to participate (4 patients), who had clinical evidence of cancer, bleeding diathesis, active infection, active or chronic inflammatory or autoimmune diseases, or pregnancy, who was older than 45 years old or younger than 18 years old were excluded from the study.

Blood samples were obtained during the first hour after admission to the Coronary Care Unit (CCU). Plasma samples were stored at -80°C until used. The study was approved by the Institutional Ethics Committee and informed consent was obtained from all subjects.

Genetic analysis for FVL (G1691A) and P G20210A

Genomic deoxyribonucleic acid (DNA) recovered from the peripheral blood leukocytes of patients with DNA extraction kit (Nucleospin Blood, Macherey-Nagel/Germany) according to the manufacturer's protocol. Polymerase chain reaction–based restriction fragment length polymorphism (PCR–RFLP) was used for the genotype analysis of FVL (G1691A) and P G20210A mutations according to previously reported study (6). PCR reaction was performed in a total volume of 25 µl containing approximately 100 ng DNA, 5 µl of 10× buffer, 2.0 mM MgCl2, 0.4 mM dNTPs, 2.0 pmol of each FVL primer, 0.4 pmol of each prothrombin primer, and 0.5 U of Taq polymerase. PCR conditions consisted of an initial denaturation at 95 °C for 5 minutes (min), plus 40 cycles at of 95 °C for 30 seconds (s), 57 °C for 30 s, and 72

°C for 60 s, followed by final extension at 72 °C for 10 min. Amplified PCR products were then digested with Hind III restriction enzyme for genotypic analysis. Digested products were electrophoresed on 3% standard agarose gel and visualized by ethidium bromide under ultraviolet (UV) transilluminator (figure 1a).

Genetic analysis for MTHFR C677T

PCR–RFLP was used for the genotype analysis of MTHFR C677T mutation according to previously reported study (7). PCR reaction was performed in a total volume of 25 µl containing approximately 100 ng DNA, 5 µl of 10× buffer, 2.0 mM MgCl2, 0.4 mM dNTPs, 2.0 pmol of each MTHFR primer, 0.4 pmol of each MTHFR primer, and 0.5 U of Taq polymerase. PCR conditions consisted of an initial denaturation at 94 °C for 5 min, plus 40 cycles at of 94 °C for 30 s, 57 °C for 30 s, and 72 °C for 1.5 min, followed by final extension at 72 °C for 12 min. Amplified PCR products were then digested with HinfI restriction enzyme for genotypic analysis. Digested products were electrophoresed on 3% standard agarose gel and visualized by ethidium bromide under UV transilluminator (figure 1b).

Genetic analysis for ACE I/D and PAI 4G/5G polymorphisms

ACE I/D and PAI 4G/5G polymorphisms were determined by PCR and allele-specific PCR according to previously reported studies, respectively (8,9). PCR reaction was performed in a total volume of 25 µl containing approximately 100 ng DNA, 5 µl of 10× buffer, 2.5 mM MgCl2, 0.2 mM dNTPs, 0.4 pmol of each ACE primer, 0.75 pmol of each PAI primer, and 0.5 U of Taq polymerase. PCR conditions for the ACE I/D consisted of an initial denaturation at 95 °C for 5 min, plus 40 cycles at of 95 °C for 30 s, 58 °C for 30 s, and 72 °C for 60 s, followed by final extension at 72 °C for 10 min. PCR conditions for the PAI 4G/5G consisted of an initial denaturation at 95 °C for 5 min, plus 40 cycles at of 95 °C for 30 s, 61 °C for 30 s, and 72 °C for 45 s, followed by final extension at 72 °C for 10 min. PCR products for ACE I/D (figure 2a) and PAI 4G/5G polymorphisms (figure 2b) were electrophoresed on 3% standard agarose gel and visualized by ethidium bromide under UV transilluminator.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 15 (SPSS Inc., Chicago, Illinois, USA). The continuous variables were investigated using visual (histograms, probability plots), and analytic methods (Kolmogorow-Simirnow's test) to determine whether or not they are normally distributed. These variables were presented as means ± standard deviation (SD) if normally distributed or as medians and interquartile range (IQR) if non-normally distributed. Student's t-test was used to compare the normally distributed parameters among the study groups. Since triglyceride measurements were not normally distributed, the Mann-Whitney U test was used to compare the triglyceride levels between the patient and healthy groups. The categorical variables were presented as frequencies and percentages. Comparison for categorical variables was made with chi-square or Fisher exact tests. An overall p-value of less than 0.05 was considered to show a statistically result for all variables.

Results

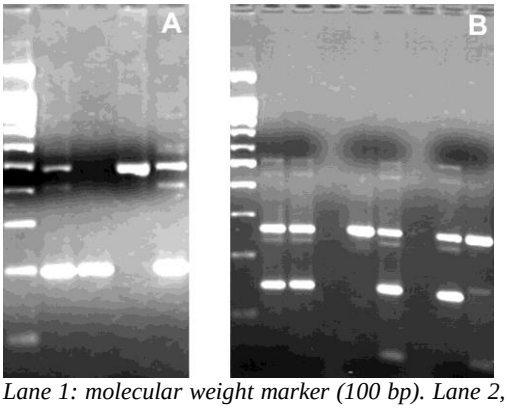
The basal characteristics of the study population are shown in table 1. This study consisted of 137 individuals, 68 patients (62 men, 91.2%, mean age:36.8±6.4) with ACS and 69 healthy individuals (56 men, 81.2%, mean age:35.1±5.9). Pulse rate was higher in the patient group than in the control group at statistically significant level (79.04±14.92 vs 73.42±8.76, p:0.008). History of hypertension was also more common in the patient group than the control group (17.6% vs. 4.3%, P:0.013). In addition, we found that homocysteine and triglyceride levels were higher (14.45±5.50 µmol/L vs 11.17±3.79 µmol/L, p<0.001 and 157 [117.50-224.50] vs 136 [85.50-187.50], p:0.029, respectively) whereas HDL-C level was lower (37.24±8.60 mg/dl vs 43.13±10.06 mg/dl, p<0.001) in the patient group than the control group. Clinical and angiographic charachteristics of the patients are shown in table 2. Of 2 patients had normal coronary anatomy, 9 had mild coronary artery disease (CAD) and rest of them had severe CAD with regard to Gensini score (table 2). Most of the patients (58.9%) were admitted to the coronary care unit with STEMI and half of them had single vessel disease (50%). P G20210A, FVL, MTHFR, ACE ve PAI-1 gene

mutations are summarized in table 3. The frequency of The FVL mutation was found statistically higher among patients with ACS than among healthy controls (22.1% versus 5.8%, p:0.006). The P G20210A mutation was detected in 2 (2.9%) of the 68 patients and in 1 (1.4%) of the 69 healthy individuals, but the difference was not statistically significant (p:0.551) (figure 3).

The homozygous mutations for both the FVL mutation and the P G20210A mutation were found to be absent in this study. In addition, frequency of the MTHFR C677T polymorphism was found statistically higher among patients with ACS than among healthy controls (61.8% versus 39.1%, p:0.006). Homozygous C677T mutation was observed in 11.8% of patients when compared to 1.4% in healthy individuals (p:0.004) (figure 4).

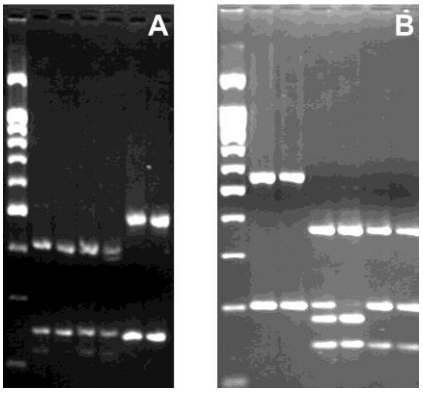
Plasma homocysteine level was strongly correlated proportionally with mutation severity among the study population (table 4). Frequencies of PAI-1 4G/4G and 5G/5G homozygous were 30.9% and 13.2% in the patient group and were 30.4% and 23.2% in the control group respectively. The difference in the frequency of alleles was not statistically significant between patient and control groups (p:0.291). Furthermore, frequencies of ACE I/I and D/D homozygous were 20.6% and 27.9% in the patient group and were 13% and 33.3% in the control group respectively. There was also no statistical difference between young ACS group and healthy controls with regard to mutation genotypes (p:0.469).

Figure 1a-1b. *Analysis of FVL (G1691A) and P G20210A mutations with agarose gel electrophoresis.*



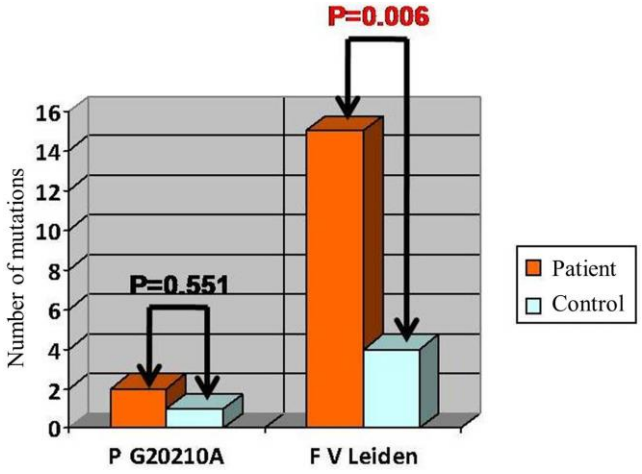
Lane 1: molecular weight marker (100 bp). Lane 2, 4: Heterozygote for FVL and wild type (normal allele) for P G20210A. Lane 3: Wild type (normal allele) for FVL and P G20210A mutations. Lane 5: Heterozygote for FVL and P G20210A mutations. Lane 6,7: PCR products before Hind III restriction enzyme digestion (a). Analysis of Factor MTHFR C677T mutation with agarose gel electrophoresis. Lane 1: molecular weight marker (100 bp). Lane 2,3: PCR products before Hin f1 restriction enzyme digestion. Lane 4: Heterozygote for MTHFR C677T mutation. Lane 5: Homozygote for MTHFR C677T mutation. Lane 6, 7: Wild type (normal allele) (b).FVL; Factor V Leiden, MTHFR; Methylenetetrahydrofolate Reductase, PCR; Polymerase Chain Reaction, P G20210A; Prothrombin Gene.

Figure 2a-2b. *ACE I/D genotype determination with agarose gel electrophoresis.*



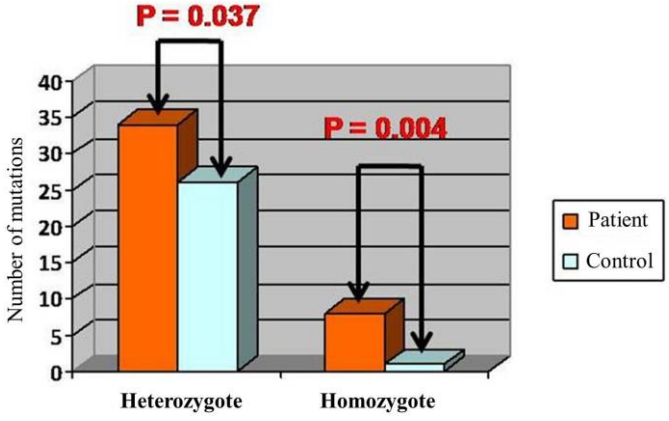
Lane 1: molecular weight marker (100 bp). Lane 2, 5: ACE I/D genotype. Lane 3: ACE D/D geneotype. Lane 4: ACE I/I genotype (a). Analysis of PAI 4G/5G polymorphisms with agarose gel electrophoresis. Lane 1: molecular weight marker (100 bp). Lane 2, 3: PAI-1 4G/5G genotype. Lane 5, 6: PAI-1 5G genotype. Lane 8, 9: PAI-1 4G genotype (b). ACE; Angiotensin Converting Enzyme, PAI; Plasminogen Activator Inhibitor.

Figure 3. *Comparison of P G20210A and FVL among study groups.*



FVL: Factor V Leiden, P G20210A: Prothrombin Gene.

Figure 4. *Comparison of MTHFR C677T mutation among study groups.*



MTHFR: Methylenetetrahydrofolate Reductase

Discussion

Statistically significant difference between groups was detected for FVL and MTHFR gene mutation; whereas there was no statistically significant difference for P G20210A mutation, PAI-1 4G/5G polymorphism and ACE I/D polymorphism (table 3).

Acute MI generally develops following a critical narrowing of the coronary artery or a narrowing or complete occlusion of the coronary vessel by an acute plaque rupture. Coronary artery anatomy is mostly found to be normal angiographically in young adults presenting with ACS (4,10). MI in young adults may be categorized into two groups as normal coronary artery anatomy and CAD accompanied by various etiologies, and conditions associated with hypercoagulopathy play important role in the pathophysiology of both groups (4,11,12).

Two most common reasons of familial thrombophilia are P G20210A and FVL. P G20210A is frequently seen in Southern European countries and most notably in countries that have coast to the Mediterranean (13). Despite conflicting results, some studies have shown that the combination of known risk factors and P G20210A is a risk factor for the development of arterial thrombus and ACS. Presence of metabolic risk factors and particularly smoking appear to be necessary for the development of infarction (14). A meta-analyses by Burzotta et al. (15) report that P G20210A may increase the development of MI in the presence of mild atherosclerosis but is not a risk factor for the development of atherosclerosis. A large population based meta-analysis

Table 1. *Basal characteristics of the study groups*

	Patient (n=68)	**Control (n=69)**	**P-Value**
Age,years	36.8±6.4	35.1±5.9	0.101
Sex, Men, n	62 (91.2%)	56 (81.2%)	0.090
Pulse, BPM	79.04±14.92	73.42±8.76	**0.008**
Systolic Blood Pressure, mmHg	127.18±19.10	127.49±9.70	0.903
Diastolic Blood Pressure, mmHg	77.51±13.32	78.87±6.22	0.446
BMI, kg/m^2	27.59±2.56	26.74±3.04	0.082
Risk Factors			
Hypertension, n	12 (17.6%)	3 (4.3%)	**0.013**
Diabetes Mellitus, n	4 (5.9%)	1 (1.4%)	0.167
Smoking, n	35 (51.5%)	33 (47.8%)	0.670
Family History, n	21 (30.9%)	18 (26.1%)	0.534
Laboratory Findings			
Homocysteine, µmol/L	14.45± 5.50	11.17±3.79	**<0.001**
Total Colesterol, mg/dl	192.03±45.74	191.52±30.92	0.939
LDL-C, mg/dl	120.50±36.57	119.57±28.03	0.867
HDL-C, mg/dl	37.24±8.60	43.13±10.06	**<0.001**
Triglyceride, mg/dl*	157 (117.50-224.50)	136 (85.50-187.50)	**0.029**

*Data are given mean±SD, n(%) and *median with interquartile range (25%-75%). BPM; Beats Per Minute, HDL-C; High Density Lipoprotein-Colesterol, LDL-C; Low Density Lipoprotein-Colesterol, SD; Standard Deviation.*

Table 2. *Clinical and angiographic charachteristics of the patient group*

Clinical characteristics	**Patient (n:68)**
Preinfarct Angina	20 (29.4%)
Previous MI history	8 (11.8%)
Single Vessel Disease	34 (50%)
Multiple Vessel Disease	34 (50%)
STEMI	38 (55.9%)
NSTE-ACS	30 (44.1%)
Angiographic charachteristics (Gensini Score)	
Normal (0)	2 (2.94%)
Mild CAD (1-20)	9 (13.24%)
Severe CAD (>20)	57 (83.82%)

Data are given n (%). CAD; Coronary Artery Disease, MI; Myocardial Infarction, NSTE-ACS; Non ST-segment Elevation Acute Coronary Syndrome, STEMI; ST-segment Elevation Myocardial Infarction.

Table 3. *Gene mutations*

	Patient (n=68)	**Control (n=69)**	**P-Value**	**Total**
P G20210A				
Normal	66 (97.1%)	68 (98.6%)	0.551	134 (97.8%)
Heterozygote	2 (2.9%)	1 (1.4%)		3 (2.2%)
FVL				
Normal	53 (77.9%)	65 (94.2%)	**0.006**	118 (86.1%)
Heterozygote	15 (22.1%)	4 (5.8%)		19 (13.9%)
MTHFR				
Normal	26 (38.2%)	42 (60.9%)	**0.006**	68 (49.6%)
Heterozygote	34 (50.0%)	26 (37.7%)		60 (43.8%)
Homozygote	8 (11.8%)	1 (1.4%)		9 (6.6%)
ACE				
I/D	35 (51.5%)	37 (53.6%)	0.469	72 (52.6%)
I/I	14 (20.6%)	9 (13.0%)		23 (16.8%)
D/D	19 (27.9%)	23 (33.3%)		42 (30.7%)
PAI-1				
4G/5G	38 (55.9%)	32 (46.4%)	0.291	70 (51.1%)
4G Homozygote	21 (30.9%)	21 (30.4%)		42 (30.7%)
5G Homozygote	9 (13.2%)	16 (23.2%)		25 (18.2%)

Data are given n (%). ACE; Angiotensin Converting Enzyme, FVL; Factor V Leiden, MTHFR; Methylenetetrahydrofolate Reductase, PAI-1; Plasminogen Activator Inhibitor -1, P G20210A; Prothrombin G20210A.

Table 4. *Plasma homocysteine level*

	Normal	**Hererozygote**	**Homozygote**
Patient	10.59 µmol/L	14.15 µmol/L	20.56 µmol/L
Control	10.36 µmol/L	12.07 µmol/L	22.50 µmol/L

reported the association between P G20210A polymorphism and CAD risk (16). After adjusting the data by ethnicity, P G20210A polymorphism was found to be statistically significant among Europeans, whereas there was no statistical difference among Americans and Asians. Therefore, they concluded that P G20210A is a low-penetrant risk factor among Europeans (16).

In the study, there was no statistically significant difference between the patient and control groups (2.9% vs. 1.4%, p:0.551). P G20210A was found to be heterozygotic in 3 (2.2%) among a total of 137 cases. In the study by Akar et al. (17), P G20210A prevalence was reported as 6.2% for Turkey which is similar to the rate in Mediterranean countries; however, this finding is contradictory to the study. Despite being a Mediterranean country; Turkey is located right in the middle of 3 continents and has a distinctive geography. Therefore, the prevalence of FVL mutation rather than P G20210A may be more frequent particularly in Central Anatolian, Eastern Anatolian and Black Sea Regions similar to the Northern European countries. The data are conflicting with regard to the relation of FVL mutation with the development of CAD and ACS. A study investigating ACS patients of all age groups did not demonstrate a statistically significant difference (18). However, large studies investigating young ACS patients have reported that FVL mutation was found to be statistically significant (19). Furthermore, young patients with ACS related with FVL mutation has also been reported (20,21). Similarly, in the study it was found that FVL mutation was statistically significant in the patient group compared to the control group (22.1% vs. 5.8%, p:0.006).

Many studies and meta-analyses have confirmed that hyperhomocysteinemia is associated with increased vascular disease risk. It is also known that hyperhomocysteinemia is an independent risk factor and combined with other risk factors, it may result in a synergistic effect (22). Kang et al. (23) reported MTHFR gene mutation as the most frequent genetic disorder among individuals suffering from cardiovascular disease. Some studies have demonstrated that the presence of a mutation and increased homocystein levels are paralleled to increase the risk of cardiovascular disease (22). Wald et al. (24) reported in their meta-analysis that specifically an increase of 5μmol/L is associated with ischemic heart disease and stroke. Contrary to these reports, some meta-analyses show that, in the presence of a mutation, cardiovascular risk does not increase despite increased homocystein levels (22). On the other hand; a recent study reported that diabetes mellitus patients with severe cardiovascular disease had no significant relationship with MTHFR mutation (25). In the study, we found a statistically significant difference predominantly in the homozygous group when heterozygous (56.7% vs. 38.2%, p:0.037) and homozygous (23.5% vs. 2.3%, p:0.004) mutations of the MTHFR gene are examined separately (figure 4). Plasma homocystein levels were also statistically higher in the patient group (14.45±5.50 μmol/L vs. 11.17±3.79 μmol/L, p<0.001). In addition, the increase in plasma homocystein levels was directly proportional with the degree of mutation in both groups (table 4).

The most recent pilot study to investigate the role of hemostatic gene polymorphisms including, FVL, P G20210A and MTHFR gene mutations in young Egyptian patients with acute MI was performed by Alkhiary et al (26). They found an increased risk of acute MI with FVL and P G20210A. But there was no statistically significant difference for MTHFR gene mutations between patients and controls. It was also found that FVL mutation was associated with acute MI. However, MTHFR gene mutation was statistically significant in the patient group compared to the control group and there was no statistically significant difference for P G20210A as opposed to that study (26).

In addition, another important point in the study is that there was no difference among groups related with family history. However, studies have shown that the combination of known risk factors and familial thrombophilia including P G20210A FVL and MTHFR is a risk factor for the development of arterial thrombus and ACS. The known risk factors for ACS including history of hypertension, increased triglyceride and homocysteine levels and decreased HDL-C level are more common in the patient group than the control group. It is because of that family history was not found statistically significant among the study groups.

Increased PAI-1 activity is associated with increased ischemic cardiovascular events and tissue fibrosis (27). It has been demonstrated in the meta-analysis of 9 studies that the risk of MI is increased by 20% in 4G homozygous mutation group (28). Another meta-analysis comprising 37 studies, however, reported a very poor relation (29). PAI-1 is synthesized by many tissues and cells and have been shown to accompany increased activity of 4G homozygous mutation and to have many systemic effects (27). In the study, we did not find a statistical difference when either groups were compared for PAI-1 mutation (p:0.291). It was observed that the rate of 4G polymorphism that is supposed to significantly increase the risk of cardiovascular events was equal between the patient (21, 30.9%) and control (21, 30.4%) groups.

In ACE gene, homozygous mutations of the D allele are associated with highest ACE enzyme levels (30). There are many studies that have investigated the relation between ACE polymorphism and atherosclerosis by measuring carotid intima-media thickness (IMT). A positive relation has been detected with the D allele in a meta-analysis of these studies, and it has also been found that the individuals with higher risk in particular contributed to the significant difference (31). Some studies have reported that ACE gene polymorphism in the presence of the D allele has affect on the mechanisms of blood pressure (32,33). Autopsies and coronary artery calcification measurements have also been used to reflect the relation of ACE polymorphism and atherosclerosis. These studies, however, did not reveal any positive correlation (34). For the first time in 1992, Cambien et al. (35) reported a positive relation between the D allele and MI. In our study, we did not find a statistical difference between young ACS group and healthy controls with regard to mutation genotypes (p:0.469). Consistent with our findings; Agerholm-Larsen et al. (36) also could not find a significant difference between MI and mutation genotypes in their large study.

This study has three main limitations. The first, this is a single center study from a relatively small group of patients. The second, study population is selected according to younger age (aged less than 45 years), so the results are only applicable to that population profile; and the third, although increased PAI-1 and ACE activities were mainly related with atherosclerosis we did not measure their activities in the present study. Also, there are lots of other risk factors (including protein C deficiency, Protein S deficiency, anticardiolipin antibodies, fibrinogen and lipoprotein (a) etc.) which may cause ACS. Therefore, further prospective controlled studies in larger patient populations with careful analysis of other risk factors and mutations related to atherosclerosis are needed to understand the pathophysiological process of the ACS.

In conclusion, data suggest that patients with ACS carrying the FVL mutation and the MTHFR C677T polymorphism might have a role on the pathophysiology of developing ACS. Therefore clinicians should keep in mind that these mutations are important risk factors for screening and thromboprophylaxis in young adult patients presenting with ACS. On the other hand; Turkey is a FVL mutation region rather than P G20210A mutation region similar to the Northern European countries as opposed to known current literature.

References

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