Genetic variability and the risk of myocardial infarction in Poles under 45 years of age

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Abstracts

Introduction: Myocardial infarction is caused by the obstruction of an artery in places of atherosclerosis plaque rupture. Endothelial cells during their activation express chemoattractant and adhesion molecules whereas infiltrating inflammatory cells produce enzymes, predisposing a lesion to rupture.
Material and methods: We investigated the correlation between polymorphisms in the human genes E-selectin (Ser128Arg), ICAM1 (K469E), OLR1 (K167N), MMP1 (1G/2G) and MMP3 (-1612 5A/6A) and the risk of MI in young Poles under 45 years. There was no significant difference in the frequency of single nucleotide polymorphism (SNP) of the studied genes E-selectin (Ser128Arg), ICAM1 (K469E), OLR1 (K167N) and MMP3 (–1612 5A/6A) between patients with MI and controls.
Results: The analysis of the association of the 1G2G polymorphism with the risk of myocardial infarction indicated an odds ratio (OR) of 5.68 (95% confidence interval [95% CI] 2.60 to 12.36). Other factors associated with myocardial infarction were: smoking (OR 4.12; 95% CI 1.63-10.44), male sex (OR 16.02; 95% CI 5.90-43.46), hypercholesterolaemia (OR 2.74; 95% CI 1.29-5.83) and arterial hypertension (OR 4.56; 95% CI 1.66-14.47).
Conclusions: We found that only MMP1 1G/2G polymorphism is associated with myocardial infarction in the Polish population of individuals younger than 45 years. Clinical factors seemed to play a greater role in the analysed group.

Key words: gene polymorphism, coronary artery disease, atherosclerosis.

Introduction

Myocardial infarction (MI) is the main cause of death in Poland, estimated at about 40% of all deaths [1]. Data from CDC (Centers for Disease Control and Prevention) have shown that men have a significantly higher prevalence of MI history than women (5.5 vs. 2.9%) [2].

The most important clinical risk factors for CAD (coronary artery disease) are: arterial hypertension, smoking, hypercholesterolaemia, diabetes mellitus and age [3-6]. Data have indicated that patients under 45 years of age constitute approximately 10% of the whole population of subjects with myocardial infarction [2, 7]. Furthermore, studies conducted on monozygotic twins have shown the role of genetic factors in mortality due to coronary heart disease at different ages, among both women and men [8-10].

Approximately 90% of all cases of myocardial infarction are the result of acute thrombus causing obstruction of an artery in places of atherosclerosis plaque rupture [1, 11-13].

Arteriogenesis requires an inflammatory process which is started by endothelial dysfunction and its activation [14]. This activation is related to increased expression of chemoattractant cytokines and adhesion molecules (E-selectin, ICAM1, VCAM). E-selectin and ICAM1 play an important role in the rolling of leukocytes on activated endothelial cells and may also participate in the transition to stable adhesion that precedes transmigration [15, 16]. Amino acid change from serine (S) to arginine (R) in codon 128 (S128R) in the EGF (amino-terminal lectin-like) domain of the E-selectin gene changes the protein structure, as well as its function [17]. Yoshida *et al.* found that Ser128Arg mutation of E-selectin significantly enhanced its adhesion to leukocytes under physiological flow conditions, which may play a role in the development of atherosclerosis [15].

Intercellular adhesion molecule-1 (ICAM1) is related to the adhesion of circulating leukocytes to the activated endothelium. The K469E polymorphism represents a change of amino acid, which occurs in Ig domain 5. E469 increases the adhesion of circulating leukocytes to the activated endothelium, which is related to the development of atherosclerosis [16].

The production of leukocyte binding molecules (E-selectin, ICAM1) is induced by oxidized LDL bound with their receptor ORL-1 on the surface of the endothelium [18]. The G501C genotype of the OLR1 gene which resulted in the missense mutation of K167N in the extracellular ligand-binding domain of the LOX-1 protein may affect the binding affinity between Ox-LDL and LOX-1. Tatsuguchi *et al.* and Hattori *et al.* found that carriers of the C allele have higher risk of MI or CAD than GG homozygotes [18, 19].

The mechanism leads to the recruitment and adhesion of inflammatory cells to the endothelium. Migration of the monocytes and their transformation into macrophages leads to the increased expression of scavenger receptors on their surface. Macrophages use them to bind modified LDL and transform themselves into foam cells, which are the main component of an atherosclerotic lesion. Apart from foam cells, the lesions contain numerous other inflammatory cells, smooth muscle cells and the extracellular matrix (collagen, elastin and proteoglycans). Macrophages and smooth muscle cells produce the metalloproteinases (MMPs). MMPs, particularly MMP1, MMP2, MMP3 and MMP9, are involved in the degradation of extracellular matrix, resulting in weakening of the fibrous cap and the subsequent destabilization of atherosclerotic lesions [20-22]. MMP1 can degrade collagens type I and III and its expression significantly increases in atherosclerotic plaque characterized by having a thin fibrous cap [23]. The MMP1 GG/GG polymorphism is associated with enhanced translation into functional MMP1 [24], so we postulated that this polymorphism can promote atherosclerotic plaque rupture.

MMP3 has a broad substrate spectrum, which includes most major constituents of the arterial wall, such as fibronectin, type IV, V, IX, and X collagens, gelatin, laminins, elastin, and proteoglycan proteins [21]. The 5A/6A polymorphism in the promoter has been shown to have an effect on MMP3 expression. The 5A allele is related to higher transcriptional activity than 6A [25]. Some studies have found that 5A/5A homozygotes have significantly higher risk of MI than non-carriers [26, 27].

Recently, we have examined the relation between the polymorphism of human genes E-selectin (Ser128Arg), ICAM1 (K469E), OLR1 (K167N), MMP1 (1G/2G) and MMP3 (-1612 5A/6A) and the risk of MI in young Poles aged 45 years or less.

Material and method

Study population

Blood samples were collected from 163 unrelated patients with myocardial infarction in whom the first incident of MI occurred before 45 years of age. All subjects were white Caucasians and showed no typical symptoms of CAD before the first incident of MI. Myocardial infarction was confirmed by chest pain associated with specific ischaemic ECG changes, high serum troponin (T or I) and increased CKMB activity. All participants reported having undergone coronary angiography during their first hospitalization to determine the level of atherosclerotic lesion progression. The coronary segments (right coronary artery: proximal, middle, distal; left main coronary artery; left anterior descending artery; two segments of diagonal branches, left circumflex artery and marginal branches), identified visually as abnormal, were measured quantitatively.

The control group consisted of 140 unrelated, asymptomatic, apparently healthy subjects. The inclusion criteria for the control group were set as follows: age > 45 years, no symptoms of CAD and a SCORE index below 4%. The SCORE (Systematic Coronary Risk Evaluation) and the SCORECARD allow the estimation of fatal coronary risk in asymptomatic, apparently healthy subjects. Those who are at 4% and lower have low risk of developing fatal cardiovascular events [28]. Arterial hypertension according to WHO/ISH criteria [29], hypercholesterolaemia (elevated total serum cholesterol levels > 200 mg/dl) and the habit of smoking were not exclusion criteria.

All controls without symptoms of CAD were recruited from the same geographical region as the patients.

Patients and controls with diabetes mellitus were not enrolled in the study. We also collected information about positive MI or CAD family history of the first degree, smoking habit and blood pressure

(with respect to patients all information was related to the period before the first CAD incidence).

The Institutional Ethics Committee has approved of the study protocol and the size of samples. All participants were obliged to sign an informed consent form prior to enrolment in the study.

Genotype determination

Venous blood from all individuals in the study was collected into vials containing 3.2% sodium citrate. The samples were stored frozen at –20°C until the extraction of DNA. Genomic DNA was extracted from blood leukocytes using standard methods (phenol/chloroform).

The samples of 100 ng genomic DNA template and 50 pM of each primer were used in the polymerase chain reaction (PCR). Denaturation was performed at 94°C for 60 s and annealing at 55-60°C for 60 s, with extension at 72°C for 45 s with a 30-cycle amplification. DNA amplification was followed by restriction enzymes digestion and agarose gel electrophoresis (restriction fragment length polymorphism – RFLP). Primers for all examined polymorphic sites are presented in Table I.

Statistical analysis

Age was expressed as median and interquartile range (IQR) due to non-normal distribution. Nominal data were expressed as percentages or fractions. Frequency of alleles was tested against the Hardy-Weinberg equilibrium. The Pearson χ^2, Yates corrected χ^2 or Fisher exact test was used for data comparisons depending on the number of cases. Logistic regression analysis was performed to determine the association of particular factors with the incidence of a myocardial infarct prior to 45 years of age. Univariate comparisons were performed for all analysed factors, and the factors with p values < 0.15 were entered into a multivariate backward, stepwise model. A p value of < 0.05 was deemed as statistically significant in multivariate analysis. Statistica 7.0 and MedCalc 8.0 statistical packages were used for all computations.

Results

During the study period, a group of 163 eligible patients and 140 controls were enrolled. The analysed clinical factors such as hypertension, hypercholesterolaemia and smoking (past or active) were more frequent in the study group than in the controls. In our research we had individuals with a past or active smoking habit. However, in the control group only 2 out of 82 smokers were past smokers. The study group consisted of 142 past or active smokers, 75 of whom were past smokers but they stopped smoking only after the first incident of myocardial infarction. Due to this fact we did not separate smokers into two groups of past and active ones. The patients in the study group were younger than the controls and in the MI group there were more males compared with healthy participants (83.4 vs. 47.1%). Detailed characteristics of the studied groups are presented in Table II.

Table I. Primers and restriction enzymes used for the detection of the sequence variants

Gene	SNP	Primers	Restriction enzyme	Reference
E-selectin	Ser128Arg	For 5'-ATGGCACTCTGTAGGACTGCT-3' Rev 5'-GTCTCAGCTCACGATCACCAT-3'	PstI	Ye *et al.* (1999) [30]
ICAM1	K469E	For 5' AGGATGGCACTTTCCCACT- 3' Rev 5' GGCTCACTCACAGAGCACAT- 3'	BstUI	Yokoyama *et al.* (2005) [14]
OLR1	K167N	For 5'-GGCTCATTTAACTGGGAAAG-3' Rev 5'-CCGTCCAAGGTCATACACAA-3'	NlaIV	Trabetti *et al.* (2006) [31]
MMP1	–1607 1G/2G	For 5'-TCGTGAGAATGTCTTCCCATT-3' Rev 5'-TCTTGGATTGATTTGAGATAAGT GAAATC-3'	XmnI	Dunleavey *et al.* (2000) [32]
MMP3	–1612 5A/6A	For 5'- CTTCCTGGAATTCACATCACT GCCACCACT -3' Rev 5'-GGTTCTCCATTCCTTTGATGG GGGGAAAGA – 5'	Tth11I	Agostino *et al.* (2000) [33]

Table II. Detailed characteristics of the studied population

Characteristic	Study group	Control group	Value of p
Age	41 ±4.9	54 ±8.6	< 0.0001
Male sex (fraction and %)	136/163 (83.4%)	66/140 (47.1%)	< 0.001
Smokers (fraction and %)	142/163 (87.1%)	82/140 (58.6%)	< 0.001
Arterial hypertension (fraction and %)	62/163 (38%)	21/140 (15.0%)	< 0.001
Hypercholesterolaemia (fraction and %)	93/151 (57.1%)	44/140 (31.4%)	< 0.001

Full genetic screening of E-selectin, ICAM1, OLR1, MMP1 and MMP3 genes was performed in 276, 291, 280, 216 and 235 participants (study and control) respectively. The discrepancy between the results of genetic screening for both groups results from the impossibility of obtaining satisfactory quality findings of some samples. The frequency of E-selectin, ICAM1, OLR1, MMP1 and MMP3 alleles and genotypes is given in Table III.

The genotypes represent homozygotes of the more frequent allele (A/A), heterozygotes (A/a) and minor allele homozygotes (a/a). All values are given as Ns. (H-W E – Hardy-Weinberg equilibrium, a $p < 0.05$ suggests non-random distribution of alleles in the group.)

No statistically significant difference was observed in genotype frequencies for E-selectin, ICAM1, OLR1 and MMP3 polymorphisms in the study and the control group. The genotype distribution of the E-selectin (A561C → Ser128Arg) polymorphism was: AC + CC 28.3% for the study group vs. 25% for the controls. For ICAM1 (K468E) the percentage of patients who had either KE or EE genotypes was 66.3 vs. 63.4% for the controls. For OLR1 (K167N) the distribution of genotypes was as follows: KN + NN 14.3% for the study group vs. 16.5% for the controls. For MMP3 (–1612 5A/6A) it was 5A/6A + 6A/6A 37.1% for the MI group vs. 35.3% for the controls. Comparisons of minor allele carriage frequencies are presented in Table IV.

The frequency of MMP1 alleles deviated significantly from values expected from the Hardy-Weinberg equilibrium. Only the MMP1 GG allele carriage differed in frequency between the compared groups. The results for univariate and multivariate analysis of the GG allele in MMP1 were OR 3.6995, 95% CI 2.1026-6.5062, $p = 0.001$ and OR 5.6751, 95% CI 2.6035-12.3609, $p = 0.0001$, respectively. Tables V and VI show the results of univariate and multivariate logistic regression analyses. The carriage of the GG allele in MMP1 was the only evaluated genetic factor associated with the incidence of myocardial infarct, and showed significantly increased risk of MI. We did not consider age in the univariate and multivariate logistic regression because in our study age is not a risk factor of MI but it is a criterion of group selection.

The following analysed clinical factors increased the risk of early myocardial infarction: male sex (OR 16.02; 95% CI 5.90-43.46), smoking habit (OR 4.12; 95% CI 1.63-10.44), arterial hypertension (OR 4.56; 95% CI 1.66-14.47) and hypercholesterolaemia (OR 2.74; 95% CI 1.29-5.83).

Discussion

The aim of this study was to investigate functional polymorphisms in the genes related to atherosclerosis to elucidate their impact on myocardial infarction in young Poles under 45 years of age. The polymorphism association study was related to 5 different genes: E-selectin (Ser128Arg), ICAM1 (K469E), OLR1 (K167N), MMP1 (–1607 1G/2G) and MMP3 (–1612 5A/6A). Previous studies have shown that these polymorphisms are implicated in

Table III. Frequencies of particular alleles and genotypes in the control group

Gene	Minor allele frequency	A/A	A/a	a/a	*P* value of H-W E testing
E-selectin (Ser128Arg)	14.3% 128Arg	102 (Ser/Ser)	29 (Ser/Arg)	5 (Arg/Arg)	0.12
ICAM1 (K469E)	37.0% 469E	48 (K/K)	69 (K/E)	14 (E/E)	0.14
OLR1 (K167N)	8.9% 167N	106 (K/K)	20 K/N	1 (N/N)	0.97
MMP1 (–16071G/2G)	35.2% (–1607 1G)	41 (2G/2G)	61 (1G/2G)	6 (1G/1G)	0.001
MMP3 (–1612 5A/6A)	19.3% (–1612 5A)	77 (6A/6A)	38 (5A/6A)	4 (5A/5A)	0.79

Table IV. Minor allele carriage frequencies in cases and controls

Gene	Study group	Control group	Value of *p*
E-selectin	46/162 (28.3%)	34/136 (25%)	0.59
ICAM1	106/160 (66.3%)	83/131 (63.4%)	0.63
OLR1	22/153 (14.3%)	21/127 (16.5%)	0.62
MMP1	33/98 (33.7%)	77/118 (65.3%)	< 0.001
MMP3	43/116 (37.1%)	42/119 (35.3%)	0.78

Table V. Univariate logistic regression results of factors tested for association with myocardial infarction under 45 years of age (95%CI – 95% confidence interval)

Variable	Odds ratio	95% CI	Value of *p*
Scavenger receptor N allele carrier	0.8477	0.4423-1.6246	0.61
E-selectin C allele carrier	1.1897	0.7094-1.9950	0.51
MMP1 GG carrier	3.6995	2.1026-6.5062	0.001
MMP3 5A allele carrier	1.0799	0.6342-1.8389	0.78
ICAM1 E allele carrier	1.1352	0.7000-1.8409	0.61
Arterial hypertension	3.4785	1.9841-6.0986	0.0001
Male sex	4.9853	2.9893-8.3142	0.0001
Smoking habit	4.3669	2.5089-7.6010	0.0001
Cholesterol > 200 mg/dl	3.4984	2.1548-5.6800	0.0001

Table VI. Multivariate logistic regression results of factors tested for association with myocardial infarct under 45 years of age (95% CI – 95% confidence interval)

Variable	Odds ratio	95% CI	Value of *p*
Smoking habit	4.1252	1.6306-10.4367	0.003
Gender	16.0168	5.9029-43.4598	0.0001
Hypertension	4.5557	1.6643-12.4705	0.003
Cholesterol > 200	2.7413	1.2891-5.8298	0.009
MMP1 GG carrier	5.6754	2.6035-12.3609	0.0001

the invasion of the vascular wall by inflammatory cells and in atherosclerotic plaque formation and rupture [14, 30, 34]. Furthermore, some groups of researchers have found a relation between these polymorphisms and increased risk of CAD or MI [16, 18, 30]. For these reasons, we wanted to check whether these polymorphisms may have an impact on myocardial infarction in the Polish population.

E-selectin (CD62E) is strongly expressed on the endothelial cell after its activation. It mediates the rolling of leukocytes on endothelial cells [35, 36]. This process contributes to vascular disease such as acute or chronic inflammation and atherosclerosis [35]. Four domains have been identified in the selectin family: amino-terminal lectin-like domain, epidermal growth factor (EGF)-like domain, transmembrane domain and a short cytoplasmic domain [35]. The common Ser128Arg polymorphism has been reported in the EGF domain of the E-selectin gene [35, 36]. It alters the binding specificity of E-selectin and enhances the interaction between inflammatory cells and endothelium. A recent study demonstrated that this polymorphism can influence the regulation of plasma levels of sE-selectin [36].

Ye *et al*. showed a relation between Ser128Arg polymorphism and CAD in the Caucasian population [30]. According to Li Yan *et al*., the frequency of the 128Arg allele was higher among CAD patients compared to the controls (6.7 vs. 3.1%) [37]. Moreover, another group of researchers has reported an association of this polymorphism with myocardial infarction in Japanese patients [35]. We did not confirm the latter relation, probably due to different ethnic and genetic backgrounds of studied subjects.

Many studies have shown an association between K469E polymorphism of the ICAM1 (CD54) gene and CAD or atherosclerosis [16, 38, 39]. This molecule is engaged in binding and interacting with leukocyte integrin receptors and thus leads to the attachment of leukocytes to endothelial cells. This process is required for the transendothelial migration of leukocytes into the vascular wall [16]. ICAM1 has been found on macrophages, fibroblasts, circulating leukocytes and on the surface of endothelial cells or smooth muscle cells in atherosclerotic plaques [14, 16]. A single nucleotide polymorphism C/T of the gene ICAM1 that results in substitution of lysine (K) by glutamic acid (E) in the ICAM1 protein alters the normal structure of ICAM1 protein and thus leads to different interactions of ICAM1 with its ligands [16]. In their study, Jiang and associates reported that the allele distribution of the ICAM1 K 469 allele was significantly increased in German patients with CAD and MI [16]. A high correlation between K469 genotype and plasma fibrinogen or early atherosclerotic change was found by Yokoyama *et al*. [14]. The ICAM1 K469E polymorphism is related to stroke [40] and Graves disease [41]. In contrast to previously described studies, we found no

correlation between MI and ICAM1 K469E polymorphism and our results are in agreement with the study of Sarecka-Hujar *et al.* [42]. According to Sarecka-Hujar *et al*., Polish carriers of one ICAM1 K469E polymorphism have no higher risk of MI but triple combinations among C677T MTHFR, K469E ICAM1 and G174C IL-6 polymorphisms increased the risk of CAD [42].

In the pathogenesis of cardiovascular disease and atherosclerosis, the main role is played by oxyLDL and their accumulation within blood vessel walls [43]. Many studies have indicated that oxyLDL induces endothelial dysfunction and leads to its activation [18, 44, 45]. This activation is related to expression of the scavenger receptor LOX1 (or OLR1) on endothelial cells. OxyLDL binding to the receptor stimulates endothelial cells to produce leukocyte adhesion molecules, chemokines, endothelin-1 and the superoxide anion [18, 43]. OLR1 can also bind red blood cells, apoptotic cells and activated platelets [18, 46]. OLR1 has not only been found on endothelial cells but is also expressed in macrophages, vascular smooth muscle cells (SMC), monocytes, cultured rat and human chondrocytes, and human INT-407 intestinal cells [18, 44]. Macrophages use the scavenger receptor to bind modified LDL and to transform themselves into foam cells, which form the main component of the atherosclerotic lesion [44]. In the OLR1 gene a G501C single nucleotide polymorphism was found by Tatsuguchi *et al.* [5, 18]. This polymorphism leads to the missense mutation of K167N, which is located at the C-type lectin-like domain in the extracellular portion of OLR1. This polymorphism may affect the affinity of interaction between Ox-LDL and OLR1 [19]. Some studies have pointed to a significant association of the 501C genotype of OLR1 with the risk of coronary artery disease or MI [5, 18, 19, 44, 47]. According to Tatsuguchi *et a*l., carriers of the C501 allele have significantly higher predisposition to MI 2.89 (95%CI 1.51-5.53) than GG homozygotes [18]. But Ohomori *et al.* and Trabetti *et al.* failed to show any relation between G501C genotype and acute myocardial infarction [48, 49]. Their observations were confirmed in the present study. This discrepancy may be related to a different genetic background in the population studied, or to the different selection of patients and healthy controls.

Our results show a relation between matrix metalloproteinase-1 promoter polymorphism and higher risk of MI in young Poles. This study showed that carriers of the GG (2G) allele have higher risk of MI than 1G homozygotes. We believe that a higher level of MMP1 can contribute to plaque instability. Nikkari *et al*. found that in human carotid arteries, MMP1 is expressed in advanced atherosclerotic plaques and this enzyme contributes to plaque expansion, disruption and thrombosis [22]. MMP1 is the major collagenase that can cleave native collagen types I and III, components of the fibrous plaque cap [50]. MMP1 expression is significantly increased in atherosclerotic plaque which is characterized by a thin fibrous cap and a large lipid core. Studies have shown that carriers of –1607 insertion of G nucleotide (2G homozygotes) have over 20-fold higher transcriptional activity of MMP1 compared with 1G homozygotes. Rutter *et al.* have reported that 1G/2G polymorphism has an influence on binding of an Ets1 transcription factor by the creation of a core binding site for this factor [51].

Many researchers have suggested a positive correlation between increased MMP1 expression and atherosclerotic plaque rupture, which is the main cause of myocardial infarction [23, 25, 52]. Martin *et al*. reported a statistically significant association between carriers of the 2G polymorphism and increased risk of remodelling after MI [24].

The genetic data indicated that the MMP1 gene 1G/2G variations are strong candidates for coronary artery disease [50, 53]. Furthermore, Noijri *et al*. have found that 1G/2G MMP1 and 5A/6A MMP3 polymorphisms are in strong linkage disequilibrium and that the 5A-1G haplotype is associated with MI in Japanese [52].

MMP3 metalloproteinase possesses proteolytic activity on II, IV, and IX collagen, proteoglycans, laminin, fibronectin, gelatins and elastin [25]. The –1612 5A/6A polymorphism has an effect on MMP3 expression. Individuals with the 5A allele have higher gene expression than those with the 6A allele. This difference is related to different affinity for transcriptional repressor p50/p50. The higher promoter activity is the result of reduced binding of the transcriptional repressor [25, 54]. Thus the 6A allele is related to increased matrix protein deposition around an atherosclerotic lesion, whereas the 5A allele is associated with increased matrix degradation [11, 52]. Many studies have reported that 5A/5A homozygotes have higher predisposition to myocardial infarction [27, 52, 54]. According to Beyzade *et al*. and Terashima *et al*., carriers of the 5A allele have 1.5-2.0-fold higher risk of MI than non-carriers [27, 54]. However, our observations did not confirm this relation. The discrepancy could be due to the differences between the population groups and the environmental exposures.

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