Risk Factors for Atherosclerosis in Survivors of Myocardial Infarction and Their Spouses: Comparison to Controls Without Personal and Family History of Atherosclerosis

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To explore the hypothesis that an interplay between genetic and environmental factors contributes to the development of coronary atherosclerosis, we compared the prevalence of risk factors for atherosclerosis among survivors of myocardial infarction (MI) and their spouses and apparently healthy men and women (spousal pairs) with no personal and family history of atherosclerosis in three generations. There were no significant differences in life-style and dietary habits between the groups. The daily vegetable and/or fruit intake was generally low and did not differ between the groups. Thirty percent and 25% of men and women did not consume any vegetables or fruits, respectively. All differences found in the male MI survivors and control men were also found between the female groups: MI survivors and their spouses were significantly more obese and had higher systolic and diastolic blood pressure and more pathologic plasma lipid levels compared with control males and females, respectively. Compared with the control men and women, MI survivors and spouses had higher plasma homocysteine (Hcy) levels (15.3 ± 10.5, 11.9 ± 4.0, 16.9 ± 5.5, and 14.3 ± 4.0, μmol/L, respectively, $P = .01$). The frequency of the homozygous C677T 5,10-methylenetetrahydrofolate reductase (MTHFR) polymorphism in MI survivors was twice that observed in their spouses and controls (12.1%, 4.8%, and 5.8%, respectively), but this difference did not reach statistical significance. A statistically significant association of the MTHFR genotype and Hcy concentration (multiple ANOVA) was shown. Neither the frequencies of apolipoprotein E (apoE) alleles nor Asp9Asn mutation of exon 2, Asn291Ser mutation of exon 6, and Ser447Ter of exon 9 of the lipoprotein lipase (LPL) gene varied significantly among the groups. A possible explanation for our findings is that individuals with a genetic predisposition for atherosclerosis and their spouses share a life-style that results in a higher body mass index (BMI) and waist to hip ratio (WHR). On the other hand, individuals with no family history of atherosclerosis, despite an unhealthy life-style similar to that in the affected families (diet and physical activity), had a lower BMI and WHR and more favorable metabolic parameters, including plasma Hcy. In conclusion, we have shown that a personal and/or family history of atherosclerosis corresponds to the prevalence and level of risk factors for atherosclerosis. A combination of life-style factors and inherited metabolic abnormalities, including high plasma Hcy, are the more likely explanation for our findings.

WORLD HEALTH ORGANIZATION (WHO) data show that the age-standardized mortality from cardiovascular disease (men aged 0 to 64 years) in the former Czechoslovakia is more than 2 times higher compared with neighboring Austria.[1] These findings may be partly explained by the WHO multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) Project that provided information on both cardiovascular mortality and the prevalence of risk factors in Western and Eastern European countries. While the MONICA survey showed a higher prevalence of hypertension and smoking in the male population of postcommunist countries compared with Western Europe,[2] the overall differences could not fully account for the higher cardiovascular mortality. Furthermore, the prevalence of hypercholesterolemia in these populations was lower than that of Western Europe.[3] Thus, the high cardiovascular mortality in Eastern European countries cannot be fully attributed to "traditional" risk factors.

The development of atherosclerosis is affected by both genetic and environmental factors. Thus, for example, many epidemiologic and case-control studies have shown a strong impact of apolipoprotein E (apoE) gene polymorphisms on plasma total and low-density lipoprotein cholesterol (LDL-C), explaining about 10% of their interindividual variation in the population.[4,5] Recently, certain mutations in the lipoprotein lipase (LPL) gene have been linked to an increased risk for coronary artery disease (CAD), presumably by influencing the metabolism of triglyceride-rich lipoproteins and/or reverse cholesterol transport.[6-11] Similarly, factors that contribute to elevated plasma total homocysteine (Hcy) have attracted great interest. Because the major role of Hcy in the pathogenesis of atherosclerosis is its effect of increasing the oxidative stress, differences in Hcy levels between populations may partly explain differences in cardiovascular mortality.[12-15] Decreased activity of 5,10-methylenetetrahydrofolate reductase (MTHFR) is one of the most frequent causes of increased plasma levels of Hcy.[16,17] A polymorphism (nucleotide C677T) that is inherited as an autosomal codominant trait results in the production of a thermolabile variant of MTHFR enzyme with a specific activity less than 50% of the level in normal controls.[17] The frequency of this polymorphism varies among different populations.[18,19]

Case-control studies of different populations and ethnic groups represent important tools for a better understanding of the role of genetic and environmental factors in the susceptibility to atherosclerosis. To explore the hypothesis that an

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interplay between genetic and environmental factors contributes to the development of coronary atherosclerosis, we compared the prevalence of the major "traditional" risk factors (cholesterol, triglycerides, high-density lipoprotein cholesterol [HDL-C], family history, hypertension, etc.) and the new risk factors (hyperhomocysteinemia and the frequency of apoE, LPL, and MTHFR gene polymorphisms) in 3 different groups: (1) middle-aged survivors of myocardial infarction (MI), (2) their spouses, and (3) apparently healthy age-matched controls (spouse pairs) with no family history of premature atherosclerosis in the parents, siblings, and offspring.

SUBJECTS AND METHODS

Subjects

Seventy-one middle-aged (51.2 ± 7.7 years) men who survived a MI by the age of 50 were examined. MI survivors were recruited from the patients of various Bratislava cardiologic outpatient clinics. The diagnosis of MI was based on typical clinical symptoms, electrocardiogram (ECG) changes, and enzyme elevations. The subjects were examined at least 6 months after surviving a coronary event. All MI survivors used aspirin and most of them also used nitrates; where indicated, they were also treated with β-blockers and/or angiotensin-converting enzyme inhibitors. Their characteristics are shown in Table 1.

Fifty-four spouses of MI survivors (aged 46.9 ± 7.1 years) who shared the same family environment as the MI survivors and were apparently healthy were examined. Seventeen spouses refused to participate in the study. Seventy-one control subjects, most of them spousal pairs, had a negative personal and family history of premature atherosclerosis (MI, stroke, or peripheral vascular disease by the age of 60) in three generations (parents, sibs, and offspring; 33 men and 38 women with mean age 46.8 ± 6.2 and 45.2 ± 5.5 years, respectively) and were apparently healthy (control men and women).

Informed consent was obtained from all subjects, and the study was approved by the Ethics Committee of the Institute of Preventive and Clinical Medicine, Bratislava.

Clinical Examination

The personal and family history and the assessment of risk factors were obtained from the subjects by administering a questionnaire supervised by a physician. A physical examination and body weight and height, ECG, and blood pressure measurement (in the sitting position after 10 minutes of rest, with mercury sphygmomanometry) were performed at the same time. The body mass index (BMI) was calculated as body weight divided by height squared, and the waist to hip ratio (WHR) was calculated as the circumference of the waist (centimeters) divided by the circumference of hips (centimeters).

Life-Style Assessment

Diet, physical activity, smoking, and alcohol consumption were evaluated using a standard questionnaire that was completed by the patient and reviewed by a physician. The physical activity at work was classified in 4 categories: (1) sedentary, (2) proportionally sedentary and walking, (3) light physical work, and (4) hard physical work. Home physical activity and its frequency per week was classified as (1) sedentary, (2) recreational (gardening, cycling, or walking at least 4 hours per week), (3) regular sport without competition, and (4) regular sport as competition. The frequency of intensive physical activity taking at least 30 minutes and resulting in sweating was evaluated. The subjective assessment of the physical condition was also examined. Diet was assessed by a food-frequency questionnaire with regard to the portions of meat (beef, pork, lamb, and mutton), meat products, poultry, fish, dairy products, sweets, chips, fruits, and vegetables per week; however, the portion sizes were not examined. The quantitative intake of sugar, coffee, tea, fat, milk according to fat content, bread, and eggs was also assessed. Smoking status was determined as "former" and "current" and the number of pack/years was determined. Alcohol (beer, wine, and distillates) intake was assessed as volume consumption and calculated in grams of pure alcohol per week.

Laboratory Measurements

Blood samples were obtained in EDTA vacutainers after a 12- to 14-hour overnight fast. The blood cell count, sedimentation, and urinalysis were determined on all subjects in a clinical laboratory by standard methods.

Lipid and Apolipoprotein Measurements

Plasma total cholesterol and triglycerides were determined enzymatically. ApoB and apoAI levels were measured by an immunoturbidimetric method using chemicals from Boehringer (Mannheim, Germany) and a Hitachi 911 autoanalyzer (Tokyo, Japan). The HDL-C level was measured by dextran sulfate precipitation, followed by enzymatic determination of cholesterol.[20] LDL-C was calculated using the Friedewald formula (triglyceride levels in all patients were < 4.6 mmol/L).[21] The risk index (RI) was calculated as the ratio of LDL-C to HDL-C.

Table 1. Risk Factors in MI Survivors, Spouses, and Controls

Risk Factor	MI Survivors (n = 71)	Control Males (n = 33)	Spouses (n = 54)	Control Females (n = 38)
Hypertension (n)	25 (35%)	7 (21%)	12 (22%)	3 (8%)
Diabetes mellitus (n)	6 (8%)	1 (3%)	4 (7%)	0
Smokers	10 (14%)	10 (30%)*	18 (33%)	8 (21%)
Alcohol consumption (g/100 mL/wk)	57 ± 47	99 ± 76‡	16 ± 19	33 ± 34*
Family history of premature atherosclerosis (%)	51	0	27	0
WHR	0.95 ± 0.05	0.91 ± 0.04†	0.84 ± 0.09	0.76 ± 0.05†
BMI (kg/m^2)	28.7 ± 4.03	26.5 ± 3.31†	27.2 ± 4.95	25.1 ± 4.6*
Blood pressure (mm Hg)				
Systolic	136.2 ± 19.5	122.8 ± 12.6‡	133.2 ± 20.4	122.8 ± 17†
Diastolic	88.95 ± 11.3	81.21 ± 9.5†	84.63 ± 11.5	77.5 ± 12.6†

NOTE. Values are the mean ± SD unless otherwise indicated.

*$P < .05$.

†$P < .01$.

‡$P < .01$.

Homocyst(e)ine Assay

Blood was collected in EDTA tubes and centrifuged within 1 hour for 15 minutes at 4°C. The plasma was stored at −70°C until analysis. Hcy plasma levels were quantified by high-performance liquid chromatography using a reverse-phase C-18 column and fluorescence detection (Beckman System Gold; Beckman, Fullerton, CA) at the Vancouver General Hospital.[22] The interassay coefficient of variation of the method was 5%. Hcy levels were determined in 58 MI survivors, 32 control males, 42 spouses, and 37 control females.

Genotyping

DNA was isolated from peripheral blood leukocytes by the phenol extraction method. Genotypes for apoE were determined by polymerase chain reaction (PCR) gene amplification and cleavage with *Hha*I.[23]

The C677T polymorphism of MTHFR was analyzed by PCR using forward primer 5′-TGAAGGAGAAGGTGTCTGCGGGA and reverse primer 5′-AGGACGGTGCGGTGAGGAGGTG. Amplified DNA was digested by *Hin*fI at 37°C for 1 hour. Restriction fragments were electrophoresed in Visigel (Stratagene, La Jolla, CA).[17] The Asp9Asn mutation of exon 2 of the LPL gene was analyzed by PCR[7] using normal primer 5′-CTCTTCCCCAAAGAGCCTCC-3′ and mismatch primer 5′-CTCATATCCAATTTTTCCTTTCCAGAAAGAAGAGATTTGATC-3′. Amplified DNA was digested with *Bcl*I at 37°C for 1 hour. Restriction fragments were separated on agarose gel. The Asn291Ser mutation of exon 6 of the LPL gene was analyzed by PCR[9] using normal primer 5′-GCCGAGATACAATCTTGGTG-3′ and mismatch primer 5′-GAGAACGAGTCTTCAGGTGCATTTTGCTGCTTCTTTTGGCTCTGACTGTA-3′. Amplified DNA was digested with *Rsa*I at 37°C for 2 hours. Restriction fragments were separated on agarose gel. The Ser447Ter of exon 9 of the LPL gene was analyzed by PCR[10] using forward primer 5′-TACACTAGCAATTGTCTAGGTGA-3′ and reverse primer 5′-TCAGCTTTAGCCCAGAATGC-3′. Amplified DNA was digested with *Mnl*I at 37°C overnight (or for a minimum of 4 hours). Restriction fragments were separated on agarose gel.

Statistical Analyses

The data were stored on Metabolic Data Base Software (J. Kudlac, Slovak Republic, Bratislava). The normal distribution of the examined parameters was tested by the Kolmogorov-Smirnoff test. Differences between the quantitative parameters were compared by the Student *t* test or by *U* test for parameters that showed skewed distribution (triglycerides and Hcy). Because of the skewed distribution of Hcy concentrations, the values were logarithmically transformed for ANOVA and all multivariate analyses. Allele frequencies were calculated using Hardy-Weinberg equilibrium. The allele and genotype frequencies were compared by χ^2 or Z-criterium test.

The subjects were defined as MI survivors, spouses, and controls with respect to their history of CAD; for statistical analysis, we used the term status. The relationships between genotype, status, sex, and quantitative parameters were assessed using multifactor ANOVA. Because of the low number of apoE 2/2 and 4/4 genotypes, these were evaluated together with apoE 3/2 and 3/4, respectively.

Statistical analyses were performed using SAS statistical software (SAS Institute, Cary, NC) and Statgraphics. All statistical tests used an α level of .05 as the level of significance.

RESULTS

Risk Factors for Atherosclerosis and Plasma Lipid and Homocyst(e)ine Levels

Table 1 summarizes the characteristics of the subjects and their major risk factors for CAD. The frequency of hypertension and diabetes, while highest in MI survivors, was not statistically different versus the other groups. In the control men, the frequency of smokers was significantly higher ($P < .05$) compared with MI survivors; however, 64% of MI survivors were former smokers. There were no significant differences in dietary habits based on the food-frequency questionnaire between MI survivors and control men and between spouses and control women. The daily vegetable and/or fruit intake was generally low and did not differ between the groups (Table 2). Thirty percent and 25% of the men and women did not consume any vegetables or fruits, respectively.

The evaluation of physical activity at work did not show any differences between MI survivors and control men. However, control women had significantly higher sedentary work and less light physical work than spouses (81% and 6% *v* 47% and 22%, respectively, $P = .01$). This was also expressed in significantly higher daily physical activity resulting in sweating in spouses (21% *v* 3%, respectively, $P = .05$). We did not find significant differences in home physical activity between the groups. A sedentary life-style was reported by 31% of MI survivors, 42% of control men, and 46% and 47% of spouses and control women, respectively. Light home physical activity, mainly gardening, characterized 49% to 61% of subjects. However, the frequency of this home physical activity was higher in MI survivors and their spouses than in the control men and women (4 ± 1.7- and 4.2 ± 1.5-fold per week *v* 2.1 ± 1- and 2.7 ± 1.2-fold per week, respectively, $P = .003$).

MI survivors and their spouses were significantly more obese and had higher systolic and diastolic blood pressure compared with control men and control women, respectively. Table 3 shows the lipid, lipoprotein, apolipoprotein, and Hcy concentrations. No differences were found between MI survivors and control men in any of the lipid parameters except for the LDL-C:HDL-C ratio, which was significantly higher in MI survivors. Hcy concentrations were significantly higher in MI survivors. Somewhat surprisingly, we found many differences

Table 2. Frequency of Consumption of Meals, Fruits, and Vegetables

Item	MI Suvivors (n = 71)	Control Males (n = 33)	Spouses	Control Females
Bread (pieces per day)	3.1 ± 1.7	3.4 ± 1.5	2.2 ± 1	2.4 ± 1.1
Eggs (per week)	2.5 ± 1.3	2.6 ± 2.2	2.6 ± 1.8	2.6 ± 1.7
Meat (portions per week)	4.3 ± 3.9	3.7 ± 3.5	3.4 ± 3.5	2.8 ± 2.5
Fish (portions per week)	0.7 ± 0.5	0.7 ± 0.7	0.6 ± 0.6	0.7 ± 0.8
Cheese and dairy products (portions per week)	2.3 ± 2.5	3.2 ± 3.7	3.1 ± 2.6	4.3 ± 3.9
Cakes (portions per week)	0.7 ± 1.4	1.3 ± 1.8	1.1 ± 1.8	1.4 ± 1.5
Chips (portions per week)	0.2 ± 0.4	0.4 ± 0.7	0.4 ± 0.6	0.2 ± 0.4
Vegetables (portions per week)	2.7 ± 2.6	2.4 ± 3.9	2.8 ± 2.6	3.3 ± 2.5
Fruits (pieces per week)	3 ± 2.9	3.3 ± 2.6	3.8 ± 3.2	4.3 ± 3.2

NOTE. Values are the mean ± SD

Table 3. Plasma Lipid, Lipoprotein, Apolipoprotein, and Hcy Concentrations in MI Survivors, Spouses, and Controls

	Cholesterol (mmol/L)	Triglyceride (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	ApoA1 (g/l)	AopB (g/l)	RI	Hcy
MI survivors	6.02 ± 0.99	2.54 ± 1.9	1.13 ± 0.39	3.86 ± 0.91	1.24 ± 0.25	1.03 ± 0.26	3.6 ± 1.31	16.9 ± 5.5
Control males	5.60 ± 0.89	2.24 ± 1.55	1.22 ± 0.28	3.35 ± 0.9	1.3 ± 0.8	0.99 ± 0.22	3.01 ± 0.79*	15.3 ± 10.0‡
Spouses	5.75 ± 1.3	1.99 ± 1.7	1.29 ± 0.3	3.59 ± 0.9	1.44 ± 0.2	0.99 ± 0.2	2.93 ± 1.0	14.3 ± 4.0
Control females	5.25 ± 0.7*	1.22 ± 0.5†	1.48 ± 0.3†	3.2 ± 0.7*	1.47 ± 0.2	0.83 ± 0.2	2.37 ± 1.0*	11.9 ± 4.0†

NOTE. Values are the mean ± SD

*$P < .05$.

†$P < .01$.

‡$P < .005$.

between the female groups. They differed in all of the examined parameters except the apoAI concentration.

There were no differences between MI survivors, spouses, and controls in the frequency of apoE genotypes and alleles (Table 4). To examine the impact of apoE genotypes and status (MI survivors, spouses, and controls) on cholesterol, LDL-C, and apoB concentrations in men and women, we analyzed the data by multiple ANOVA. In men (MI survivors and controls), we did not find any effect of apoE genotype and status. In women (spouses and controls), there was no significant effect of apoE genotype on lipid levels. However, a statistically significant effect of status was confirmed.

The frequencies of MTHFR genotypes and alleles are shown in Table 5. The differences between MI survivors, spouses, and controls in the frequency of homozygosity for C677T MTHFR polymorphism (T/T) were not statistically significant. The association of the MTHFR genotype and Hcy concentration (analyzed by multiple ANOVA) showed a statistically significant effect of the genotype on Hcy levels. This effect persisted even after controlling for sex and status (MTHFR, $F = 5.906$, $P < .005$; Status, $F = 6.495$, $P < .005$; sex, $F = 5.649$; $P < .05$; Fig 1). There was no influence of age on Hcy levels.

We did not find any homozygotes for mutations of Asp9Asn of exon 2 of the LPL gene. The frequency of heterozygotes of the Asp9Asn LPL mutation did not differ between the groups (1.7%, 1.5%, and 2.8%, respectively). The examination of the Asn291Ser mutation of exon 6 showed no case of homozygosity and a 6.9%, 2.85%, and 2.7% frequency of heterozygotes in MI survivors, spouses, and controls, respectively. The distribution of the heterozygote genotype of the Ser447Ter mutation was 12.7%, 6%, and 18.8% in MI survivors, spouses, and controls, respectively. However, none of these differences reached statistical significance.

DISCUSSION

We compared the prevalence of risk factors for atherosclerosis among survivors of MI, their spouses, and apparently healthy men and women (92% spousal pairs) with no personal and family history of premature atherosclerosis in three generations (parents, sibs, and offspring). The design of the study using spousal pairs has the advantage of sharing the same environment, and thus the genetic component effects are accentuated. By choosing apparently healthy individuals with no premature atherosclerosis in three generations as control groups of men and women, we selected individuals less likely to carry genes that predispose to symptomatic CAD. Thus, the contrast in phenotypes between MI survivors, their spouses (who represent a sample of the general population), and controls would be more significant.

Studies from Europe,[5,11] Canada,[6] and elsewhere[24,25] have attempted to quantify the extent of genetic and environmental effects on the phenotype. However, none of the previous studies compared subject groups based on both the personal and family history of CAD. While it is likely that the risk profile of the MI survivors improved after the event, the point remains that compared with the control men, MI survivors had a higher

Table 4. Distribution of ApoE Alleles and Genotypes in MI Survivors, Spouses, and Controls

Group	ε2	ε3	ε4	E22	E23	E33	E43	E44	E43
MI survivors									
No.	13	111	14	2	8	46	11	1	1
%	9.4	80.4	10.1	2.9	11.6	66.7	15.9	1.45	1.45
Spouses									
No.	9	88	11	0	8	35	10	0	1
%	8.3	81.5	10.2		14.8	64.8	18.5		1.8
Controls									
No.	7	114	17	1	5	47	15	1	0
%	5.07	82.6	12.3	1.45	7.25	68.1	21.7	1.45	

NOTE. No. is the number of subjects with the genotype or the number of chromosomes used to estimate ε-allele frequencies.

Table 5. Distribution of C677T Alleles and Genotypes of MTHFR in MI Survivors, Spouses, and Controls and Hcy Levels in Genotypes

	MTHFR				
Group	T	C	C/C	C/T	T/T
MI survivors					
No.	43	73	22	29	7
%	37	63	37.9	50.0	12.1
Spouses					
No.	21	63	23	17	2
%	25	75	54.8	40.5	4.8
Controls					
No.	37	101	36	29	4
%	27	73	52.5	42.0	5.8

NOTE. No. is the number of subjects with the genotype or the number of chromosomes used to estimate C and T allele frequencies.

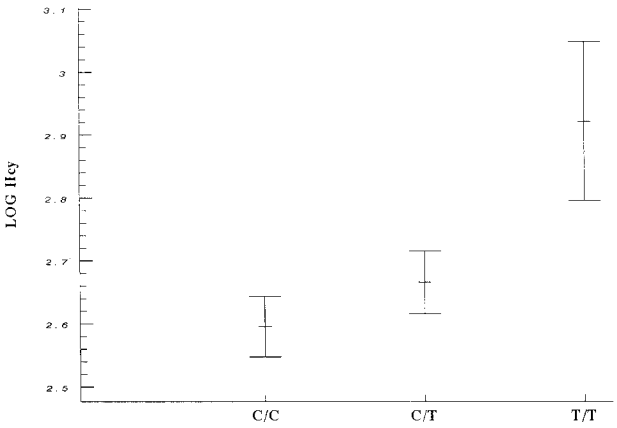

Fig 1. Association of MTHFR genotype and Hcy level (95% least-significant difference intervals for factor means).

BMI and WHR, systolic and diastolic blood pressure, and plasma LDL-C:HDL-C ratio. Of greater interest is the fact that all of the differences found in the MI survivors and control men were also found between the female groups: spouses of MI survivors also had significantly higher blood pressure, BMI, WHR, plasma triglycerides, apoB, and LDL-C and lower HDL-C than the control women. When the subgroup of spouses of MI survivors were analyzed with respect to positive or negative family history of CAD (27% and 63%, respectively), there were significantly higher values for the BMI, cholesterol, LDL-C, triglycerides, apoB, and LDL-C:HDL-C ratio in those with a positive family history of premature CAD, suggesting a strong genetic influence on these parameters. Similar findings of a clustering of lipid abnormalities with other major CAD risk factors in high-risk subjects were reported by Williams et al.[26,27] In a population study of Utah adolescents with a positive family history of CAD, they demonstrated a prevalence of inherited lipid abnormalities in 85% of young subjects. They suggested that inherited metabolic abnormalities may explain some coaggregation of hyperinsulinemia, obesity, and hypertension,[27] which resembles our finding of a clustering of similar risk factors in subjects with a positive history of atherosclerosis. Not only the lipid factors but also plasma Hcy levels were higher in MI survivors and their spouses. The frequency of the homozygous C677T MTHFR polymorphism in MI survivors was twice that observed in their spouses and controls (this difference did not reach statistical significance). Similar to previous findings,[25,28,29] a multivariate analysis showed a significant association between Hcy concentrations, MTHFR genotype, and history of CAD. While we did not measure the serum level of folate, it is unlikely that high folate levels would mask the effect of the T/T polymorphism, as the dietary intake of folate was low in all groups and none of the subjects used vitamin supplements. This may also account for the fact that the mean Hcy levels in this population were higher than reported in some populations[29] but similar to others.[15] There were no major differences in life-style and dietary habits between the subjects. While the MI survivors and their spouses reported lower alcohol consumption than the controls, these data must be carefully accepted because patients typically pretend to have a much lower alcohol consumption due to frequent health recommendations. MI survivors and their spouses had slightly higher physical activity compared with the controls, but it was not reflected in a lower BMI; the opposite was true. This finding again supports the hypothesis that inherited metabolic abnormalities are related to the risk factor prevalence, including a high BMI. However, more subtle differences in the subjects' diet that were not revealed by the questionnaire or a real consumption of more fat and calories than admitted by MI survivors also may be responsible for the higher BMI and other metabolic abnormalities.

The daily vegetable and fruit consumption was generally low and did not differ between the groups. Thirty percent of men and 25% of women did not consume any vegetables or fruits. It has been shown that such a diet greatly increases Hcy levels in subjects with the T allele in comparison to those with normal C/C genotypes.[14] A comparison of traditional and new risk factors for CAD in random samples of men from countries with high, medium, and low cardiovascular mortality (Czech, German, and Israeli, respectively) showed striking differences for plasma Hcy and carotenoids. Thus, the results of Bobak et al[15] and our findings seem to reflect a low dietary intake of fruits and vegetables. However, it is possible that the estimations of diet and physical activity habits, which were "one point in time" assessments, may not reflect the lifelong situation, eg, the life-style before the acute MI.

Neither the frequency of apoE nor LPL polymorphisms varied significantly among the groups. This is not surprising in view of the small number of subjects—a fact that precludes any definitive conclusions. The finding of no differences in apoE4 genotypes between the MI survivors and control males may be responsible, at least in part, for the lack of differences in cholesterol and LDL-C between these groups. However, despite the small set of data, it appears that the allele frequencies for these genotypes are similar in the Slovak and other European populations studied.[30]

A possible explanation for the findings of our study is that men with a genetic predisposition for CAD (defined by personal and/or family history of myocardial infarction) share a life-style that results in an increased prevalence of a cluster of major risk factors (unfavorable BMI, WHR, blood pressure, and lipid profile) in both the patient and his spouse. On the other hand, individuals with no family history of CAD, despite a life-style similar to that in the affected families (diet and physical activity), had a lower BMI and more favorable metabolic parameters, including plasma Hcy. Another less likely but possible scenario is that people with either healthy or unhealthy life-styles attract each other. However, our data on diet and physical activity do not support this view.

There are several limitations to our study. As mentioned before, the number of subjects was relatively small mainly because of the difficulty in meeting the criteria for control group spousal pairs. As discussed previously, the questionnaire method may not have revealed some important differences in the diet and other aspects of the life-style.

In conclusion, we have shown that a personal and family

history of atherosclerosis corresponds to the prevalence and level of risk factors for atherosclerosis. A combination of life-style factors and inherited metabolic abnormalities, including high plasma Hcy concentrations, are the more likely explanation for our findings.

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