Correlation between plasma homocysteine and first myocardial infarction in young patients: Case-control study in Constanta County, Romania

CRISTINA NEDELCU[1], MIHAELA IONESCU[2], ANCA PANTEA-STOIAN[3], DANIEL NIŢĂ[4*], LUCIAN PETCU[5], LAURA MAZILU[2*], ANDRA-IULIA SUCEVEANU[2], LILIANA-ANA TUŢĂ[2*] and IRINEL-RALUCA PAREPA[2]

[1]Cardiology Department, Constanta County Army Hospital; [2]Department of Clinical Medical Sciences, Faculty of General Medicine, 'Ovidius' University of Constanţa, 900527 Constanţa; [3]Department of Metabolic Diseases of The Clinical Emergency Hospital, 'Carol Davila' University of Medicine and Pharmacy Bucharest, 050474 Bucharest; [4]Department of Interventional Cardiology, Army's Center for Cardiovascular Diseases, 010825 Bucharest; [5]Department of Biophysics, Faculty of General Medicine, 'Ovidius' University of Constanţa, 900527 Constanţa, Romania

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Abstract. An elevated level of total plasma homocysteine has been associated with a higher risk of atherosclerosis and coronary heart disease. The aim of our research was to study the relation between homocysteine and myocardial infarction (MI) in young patients. We conducted a case-control study in Constanţa County, Romania including 61 patients, divided in two groups. The first group, the MI group, consisted of 28 patients, male (67.9%) and female (32.1%) aged less than 45 years who were consecutively admitted to the Intensive Coronary Care Unit of the Emergency County Hospital of Constanţa from September 1, 2017 to August 31, 2018 (12 months), with an established diagnosis of first acute MI. The second group, the control group, included 33 patients, male (75.8%) and female (24.2%) aged less than 45 years, with cardiovascular risk factors and/or stable angina pectoris that were consecutively addressed for ambulatory cardiac evaluation at the Outpatient Clinic of Emergency County Hospital of Constanţa during the same period. Fasting plasma homocysteine was determined in both groups, within 24 h after MI onset, respectively after first cardiac exam in the controls. High homocysteine was statistically confirmed to be a risk factor in the study group, especially in association with smoking, chronic kidney disease (CKD), and to a lesser extent with diabetes mellitus (DM) and hypertension. Data analysis was performed using IBM SPSS Statistics 23. The procedures used included descriptive statistics, parametric statistical tests (Independent sample t-test), non-parametric statistical tests [Chi-square test of the association, with the evaluation of odds ratio (OR)]; the significance level used in the analysis (P-value) was 0.05. After adjusting for variables, our study results pointed out a strong association between plasma homocysteine and first acute MI among young patients, emphasising plasma homocysteine as a possible risk factor for myocardial infarction.

Correspondence to: Professor Irinel-Raluca Parepa or Dr Mihaela Ionescu, Department of Clinical Medical Sciences, Faculty of General Medicine, 'Ovidius' University of Constanţa, 124 Bd. Mamaia, 900527 Constanţa, Romania
E-mail: irinel_parepa@yahoo.com
E-mail: ciucea_mihaela@yahoo.com

*Contributed equally

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Introduction

An elevated level of total homocysteine is known to be associated with a higher risk for cardiovascular disease (1). McCully was the first one to report an association between elevated levels of homocysteine and arterial damages (2). He reported two cases of premature atherosclerosis and arterial thrombosis in children with elevated levels of homocysteinemia and homocysteinuria. He concluded that increased concentrations of homocysteine could be responsible for premature atherosclerotic vascular disease. These children were found to have an inborn error in homocysteine metabolism and had extremely high levels of plasma homocysteine. In other studies, the methylene tetrahydrofolate reductase (MTHFR) 677T polymorphism was demonstrated to cause the strongest modulation of total homocysteinemia of all genes associated with homocysteine and folate metabolism (3-5). The aim of the present study was to investigate whether the risk for myocardial infarction (MI) is increased by elevated levels of plasma homocysteine in patients aged less than 45 years.

Patients and methods

Our study included 28 patients ≤45 years of age who suffered a first MI (MI group) and 33 patients matched in regards to

age, sex, and risk factors (control group). All subjects were Romanians. Exposure items were assessed, including lifestyle [smoking status, obesity (calculation of body mass index (BMI) and physical activity (MET levels), medical history [diabetes mellitus (DM), hypertension, previous cardiovascular disease (CV) and chronic kidney disease (CKD)] and laboratory tests (serum LDL-cholesterol). We determined the plasma levels of homocysteine by enzymatic method, within 24 h after MI onset, respectively within 24 h after first cardiac exam in the controls (cut-off value 15 μmol/l).

Statistical analysis. Data analysis was performed using IBM SPSS Statistics version 23 (IBM Corp.). The procedures used included descriptive statistics, parametric statistical tests (independent sample t-test), non-parametric statistical tests [Chi-square test of the association, with the evaluation of odds ratio (OR)], adjustments for accounted variables. The significance level used in the analysis (P-value) was 0.05.

Results

Patient frequency is depicted in Table I. Both study groups were statistically balanced [P=0.522 >α=0.05 (one sample Chi-square test)].

Ages (mean, minimum and maximum) across the study groups are documented in Table II. There were no mean age differences between the two studied groups [P=0.699 >α=0.05 (one sample Chi-square test)].

There was no significant statistical difference between sex distributions between the study groups [P=0.625 >α=0.05 (one sample Chi-square test)] (Table III).

We found a higher prevalence of smoking status in the MI group [OR, 4.4; 95% confidence interval (CI)=1.417-13.666; χ^2=6.961, P=0.008) as shown in Table IV. Hypertensive subjects were 64.3% in the MI group vs. 36.4% in the control group (Table IV), being slight significantly more numerous (χ^2=4.725, P=0.030) in the MI group (OR, 3.15; 95% CI=1.103-8.993).

Obesity had a similar frequency (χ^2=0.286, P=0.593) in both study lots (OR, 0.754; 95% CI=0.267-2.125). In addition, we found no significant differences for LDL-cholesterol serum levels (χ^2=2.382, P=0.123) (OR, 0.427; 95% CI=0.143-1.272). Physical activity level was sensitively equal (χ^2=1.125, P=0.289) across both groups (OR, 1.759; 95% CI=0.617-5.018) (Table V).

We also studied the prevalence of high cardiovascular risk conditions such as DM, CKD and pre-existent CV disease in both groups. There was a significantly higher prevalence of pre-existent cardiovascular (CV) disease in the control group vs. the MI group (33.3 vs. 10.7%) showing a negative correlation with the index event in the MI group (Table VI). DM (χ^2=4.560, P=0.033, OR, 3.624; 95% CI=1.073-12.235) and CKD (χ^2=6.879, P=0.009, OR, 4.286; 95% CI=1.402-13.098) were more prevalent among subjects from the MI group (Table VI).

Finally, we found a significantly higher prevalence for increased homocysteinemia (cut-off value 15 μmol/l) among patients from the MI group (χ^2=17.632, P<0.001), showing a strong correlation between hyperhomocysteinemia and index event in the MI group (OR, 11.822; 95% CI=3.425-40.802) (Table VII).

Table I. Frequencies in the study groups.

Study group	Frequency	Percent	Valid percent
MI group	28	45.9	45.9
Controls	33	54.1	54.1

MI, myocardial infarction.

Table II. Mean, maximum and minimum age (years) across the study groups.

	Age (years)			
Study group	Minimum	Maximum	Mean	SD
MI group	29.00	45.00	40.0714	5.08395
Controls	31.00	45.00	40.5152	3.54543

MI, myocardial infarction; SD, standard deviation.

Table III. Sex distribution of the two studied groups.

	Sex	
Study group	Male	Female
MI group		
Count	19	9
% within lot	67.9%	32.1%
% of total	31.1%	14.8%
Controls		
Count	25	8
% within lot	75.8%	24.2%
% of total	41.0%	13.1%

MI, myocardial infarction.

Discussion

In young patients with myocardial infarction (MI), the evidence of atherosclerotic coronary disease is not always discernible, which highlights a potential importance of prothrombotic risk factors (6,7). World-wide research regarding the role of homocysteine in favoring ischemic heart disease (IHD) has provided controversial results. Some studies have suggested that hyperhomocysteinemia is an independent risk factor for IHD, especially acute ST elevation MI (8-12), while others revealed no association between hyperhomocysteinemia and acute MI (13-15).

In our case-control study, we evaluated the association between an increased level of homocysteinemia and first MI in patients aged less than 45 years. Our results showed a significant (P<0.001) risk for MI in patients with a high fasting plasma homocysteine levels (OR, 11.822; 95% CI=3.425-40.802). It was

Table IV. Smoking and hypertension status across the study groups.

	Smoking		Hypertension		
Study group	Yes	No	Yes	No	Total
MI group					
Count	22	6	18	10	28
% within lot	78.6%	21.4%	64.3%	35.7%	100.0%
% of total	36.1%	9.8%	29.5%	16.4%	45.9%
Controls					
Count	15	18	12	21	33
% within lot	45.5%	54.5%	36.4%	63.6%	100.0%
% of total	24.6%	29.5%	19.7%	34.4%	54.1%

MI, myocardial infarction.

Table V. Obesity, serum LDL-cholesterol levels (cut-off value 100 mg/dl) and physical activity across study groups.

	Obesity		LDL-cholesterol		Physical activity		
Study group	Yes	No	Yes	No	Yes	No	Total
MI group							
Count	10	18	16	12	19	9	28
% within lot	35.7%	64.3%	57.1%	42.9%	67.9%	32.1%	100.0%
% of total	16.4%	29.5%	26.2%	19.7%	31.1%	14.8%	45.9%
Control group							
Count	14	19	25	8	18	15	33
% within lot	42.4%	57.6%	75.8%	24.2%	54.5%	45.5%	100.0%
% of total	23.0%	31.1%	41.0%	13.1%	29.5%	24.6%	54.1%

MI, myocardial infarction.

Table VI. Pre-existent CV disease, DM and CKD across the study groups.

	Pre-existent CV disease		DM		CKD		
Study group	Yes	No	Yes	No	Yes	No	Total
MI group							
Count	3	25	11	17	15	13	28
% within lot	10.7%	89.3%	39.3%	60.7%	53.6%	46.4%	100.0%
% of total	4.9%	41.0%	18.0%	27.9%	24.6%	21.3%	45.9%
Control group							
Count	11	22	5	28	7	26	33
% within lot	33.3%	66.7%	15.2%	84.8%	21.2%	78.8%	100.0%
% of total	18.0%	36.1%	8.2%	45.9%	11.5%	42.6%	54.1%

MI, myocardial infarction; CV, previous cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus.

the strongest risk factor in our MI case study group, followed by smoking (OR, 4.4; 95% CI=1.417-13.666), chronic kidney disease (CKD) (OR, 4.286; 95% CI=1.402-13.098), diabetes mellitus (DM) (OR, 3.624; 95% CI=1.073-12.235) and hypertension (OR, 3.15; 95% CI=1.103-8.993). Other traditional cardiovascular risk factors (obesity, high LDL-cholesterol

Table VII. Homocysteine cut-off distribution across the studied groups.

	Homocysteine		
Study group	Yes	No	Total
MI group			
Count	19	9	28
% within lot	67.9%	32.1%	100.0%
% of total	31.1%	14.8%	45.9%
Control group			
Count	5	28	33
% within lot	15.2%	84.8%	100.0%
% of total	8.2%	45.9%	54.1%

MI, myocardial infarction.

levels and sedentary lifestyle) were equal across the MI and control groups.

Pathophysiological background of these findings is supported by the 'arteriosclerosis' theory, previously expressed by McCully (2). Significant stiffness and damage but without lipid storages, atherosclerotic plaque and fibrosis (similar to common atherosclerosis in older adulthood) were the modifications in the arterial walls observed in children with homocystinuria (16). Thus, elevated total plasma homocysteine may lead to vascular occlusion, either by thromboembolic events, or by arterial damage due to endothelial dysfunction (17).

High homocysteine plasma concentration is particularly associated with renal function impairment (18,19), and this rationally explains the association between these two risk factors that we found in our study. Another factor for hyperhomocysteinemia is a common polymorphism (C677T) in methylenetetrahydrofolate reductase (MTHFR), which induces high thermolability of the enzyme and high susceptibility to insufficient folate levels; ~12% of the white population is homozygous (*TT* genotype) (15), and this status may be associated with hyperhomocysteinemia especially when combined with poor folate (and vitamin B12) intake (15,20). Yet, reports concerning either homozygous or heterozygous subjects did not show any association of high homocysteine plasma levels and IHD (15,21-23).

It was demonstrated that homocysteine enhances oxidative stress (24), and consecutively promotes endothelial dysfunction, with altered NO-dependent vasodilatation (25,26). These findings may explain the association between hyperhomocysteinemia and hypertension as risk factors in our MI case group. Regarding coronary flow, an inverse relationship has also been demonstrated between homocysteinemia and endothelium-dependent blood flow, especially in young patients (27), results that corroborate our findings and may rationally explain it. On the other hand, the relationship between mild hyperhomocysteinemia and IHD may be inverse as atherosclerosis (especially in the setting of hypertension and DM) accelerates the fall in renal function, thus increasing plasma levels of homocysteine (28). Even if reducing very high plasma homocysteine concentrations in patients decreases cardiovascular risk (29), this may be due to folate replacement, and not to the correction of hyperhomocysteinemia itself (30,31).

In conclusion, our findings support a strong association between elevated homocysteine plasma levels and first MI in young patients, mainly with no previously diagnosed cardiovascular disease, but with other significantly prevalent cardiovascular risk factors such as smoking, CKD, hypertension, and DM.

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Availability of data and materials

Data used in the current original study were obtained from patient archive files, Constanţa County Emergency Hospital, Romania. Any further information regarding the present study is available from the corresponding author upon reasonable request.

Authors' contributions

CN, AIS and LM designed the study and collected data from recruited cases. DN performed the arteriographies and angioplasties. LP, APS and LAT analyzed data and performed the statistics. MI and IRP analysed and wrote the Results and Discussion section including the literature review, prepared the manuscript, translated it and managed all the correspondence for publishing. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This non-interventional study was approved by the local Ethics Commission of Constanța County Emergency Hospital, Romania (no. 29/24.08.2017).

Patient consent for publication

Not applicable.

Competing interests

There are no competing interests regarding the authors of this research.

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