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INCIDENCE OF HYPERHOMOCYSTEINEMIA AMONG PATIENTS WITH ACUTE MYOCARDIAL INFARCTION YOUNGER THAN 45 YEARS

INCIDENCA HIPERHOMOCISTEINEMIJE KOD BOLESNIKA S AKUTNIM INFARKTOM MIOKARDA MLAĐIH OD 45 GODINA

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Summary: Hyperhomocysteinemia (HHcy) is considered one of the factors related to premature atherothrombosis. Study compares incidences of HHcy, defined as homocysteinemia above 12 μmol/L, and medians of homocysteinemia between the groups of 212 patients with acute myocardial infarction (AMI) younger than 45 years of age and 45 age-matched healthy persons. Homocysteine was determined by a HPLC method with fluorescent detection. Results were compared by chi-square, Mann-Whitney U and Kruskal-Wallis tests. Significant difference (p=0.001) was observed between incidence of HHcy in patients (44.8%) and incidence in controls (17.8%). Medians of homocysteinemia levels in patients (11.4 μmol/L) and controls (9.7 μmol/L) were significantly different (p=0.001). Gender-specific differences in incidence of HHcy and in median homocysteinemia value in patients were not significant. Incidences of HHcy in female patients (47.1%) and in healthy women (4.8%) were significantly different (p=0.001). Comparison of median homocysteinemia levels in women with AMI (10.9 μmol/L) and in female controls (9.0 μmol/L) revealed significant difference (p=0.025). Such differences were not observed in male subjects of our study. No significant difference was found when incidences of HHcy and medians of homocysteinemia were compared between defined age groups of patients. We conclude that young patients with AMI have higher incidence of hyperhomocysteinemia and higher level of homocysteinemia than healthy persons. Young women with AMI have higher incidence of hyperhomocysteinemia and higher level of homocysteine than healthy young women.

Keywords: hyperhomocysteinemia, acute myocardial infarction, young adults

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Kratak sadržaj: Hiperhomocisteinemija (HHcy) se smatra jednim od faktora povezanih sa preuranjenom aterotrombozom. Studija upoređuje incidence HHcy, definisane kao homocisteinemija iznad 12 μmol/L, i medijane homocisteinemija između 212 bolesnika sa akutnim infarktom miokarda (AIM) mlađih od 45 godina i 45 zdravih osoba odgovarajuće starosti. Koncentracija homocisteina određivana je HPLC metodom sa fluorescentnom detekcijom. Rezultati su statistički obrađeni pomoću χ^2, Mann Whitney U i Kruskal Wallis testa. Značajna razlika (p=0,001) uočena je između incidence HHcy kod bolesnika (44,8%) i u kontrolnoj grupi (17,8%). Medijane homocisteinemija bolesnika (11,4 μmol/L) i kontrolne grupe (9,7 μmol/L) bile su statistički značajno različite (p=0,001). Polne razlike u incidenci HHcy i medijani homocisteinemije kod bolesnika nisu bili značajni. Incidence HHcy kod ženskih bolesnika (47,1%) i kod zdravih žena (4,8%) bile su značajno različite (p=0,001). Značajna razlika (p=0,025) otkrivena je upoređivanjem medijana vrednosti homocisteina između žena sa AIM (10,9 μmol/L) i zdravih žena (9,0 μmol/L). Kod muškaraca uključenih u studiju ovakve razlike nisu uočene. Upoređivanjem incidenci HHcy i medijana homocisteinemije između definisanih starosnih grupa pacijenata nije nađena značajna razlika. Zaključujemo da je hiperhomocisteinemija češća i koncentracija homocisteina viša kod bolesnika sa AIM mlađih od 45 godina nego kod zdravih osoba iste dobi. Mlađe bolesnice sa AIM imaju veću incidencu HHcy i višu homocisteinemiju nego zdrave žene iste starosti.

Ključne reči: hiperhomocisteinemija, akutni infarkt miokarda, mladi pacijenti

Introduction

Homocysteine (Hcy) is a non-proteinogenic, sulfur-containing amino acid, incorporated into methionine metabolism. The term »total homocysteine« comprises protein-bound Hcy (70–80%), disulfide forms of Hcy and free Hcy (1–2%) (1).

Hyperhomocysteinemia (HHcy) is nowadays established as an independent risk factor for cardiovascular disease, which is held responsible for 10% of the total risk (2). Recent prospective and retrospective studies (3–9) demonstrated the association of HHcy with increased risk for coronary artery disease. There is evidence (10–12) to consider hyperhomocysteinemia as one of the factors related to premature atherothrombosis.

The aim of the study was to compare incidences of HHcy and homocysteinemia levels between a group of patients with acute myocardial infarction (AMI) younger than 45 years, and an equivalent control group. Also, the influence of gender and patients' age on the incidence of HHcy and homocysteinemia level was examined.

Materials and Methods

Study enrolled 212 patients (178 men and 34 women) with AMI younger than 45 years of age whose mean age was 39.7 ± 5.4 years. Patients were divided into three age groups: younger than 30 years (12 male patients, mean age 24.4 ± 3.5 years), 30 to 39 years (62 patients, 54 men and 8 women, mean age 35.7 ± 2.7 years) and 40 to 45 years (138 patients, 112 men and 26 women, mean age 42.7 ± 1.8 years). No comorbidities which could influence the homocysteine concentration (e.g. renal insufficiency, diabetes mellitus, malignancies) were present in the patients. The control group comprised 45 healthy persons (24 men and 21 women) with no history of coronary heart disease, diabetes mellitus and cerebrovascular diseases. Their mean age was 33.7 ± 5.8 years. Subjects from both groups received no dietary supplementation with vitamin B_{12}, B_6 and folate before the collection of blood for Hcy determination.

Blood samples were obtained from patients during the 48 hours after admission, and after 12 hours of overnight fasting from the controls. Total Hcy concentration was determined in serum by an optimised high performance liquid chromatography (HPLC) method with fluorescent detection (13). Hcy concentrations above 12 μmol/L were considered as hyperhomocysteinemia.

The significance of differences in HHcy incidence was tested by the chi-square test. The distribution of Hcy concentrations in our study population was non-normal, so the results were expressed as medians (Me) and compared by non-parametric tests (Mann Whitney U-test for comparing medians of patients and controls, and gender subgroups of patients and controls; Kruskal Wallis test when comparing defined age groups of patients). A p-value of less than 0.05 was defined as significant. Statistical analyses were performed using the Statgraphics version 4.2 programme.

Results

HHcy was present in 44.8 % of patients with AMI, which was significantly higher (p=0.001) compared to the incidence observed in controls (17.8%), as illustrated in *Figure 1*. The medians of homocysteinemia values in patients (11.4 μmol/L) and controls (9.7 μmol/L) were significantly different (p=0.001).

HHcy was present with significantly higher (p=0.033) incidence in healthy men (29.2%) than in healthy women (4.8%). Difference in the incidence of HHcy between male (44.4%) and female (47.1%) patients was not significant. *Figure 2* illustrates the diffe-

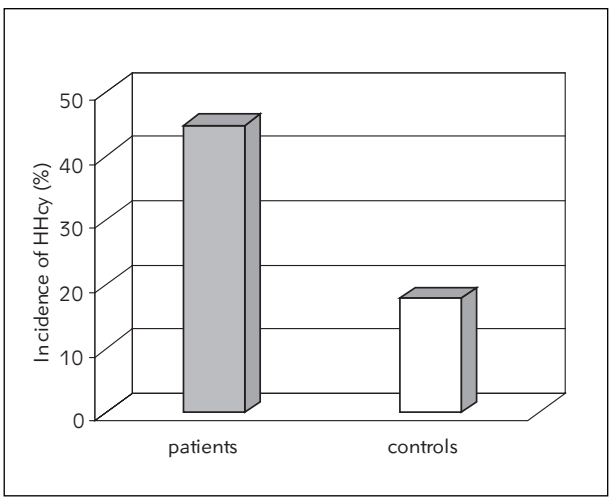

Figure 1 Comparison of incidence of HHcy among patients and controls (statistically significant difference; p=0.001).

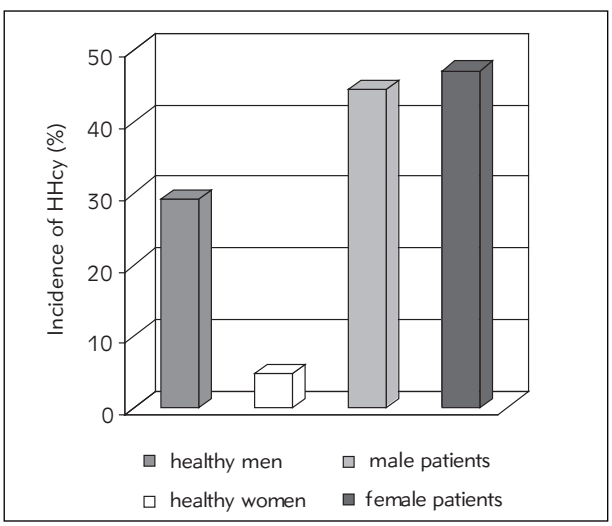

Figure 2 Difference in incidences of HHcy in patients and controls according to gender. Difference is statistically significant between healthy men and healthy women (p=0.001), while no significance is observed when comparing male and female patients (p>0.05).

rence in incidences of HHcy in patients and controls according to gender. The difference between median homocysteinemia values in healthy men (10.5 μmol/L) and in healthy women (8.6 μmol/L) was significant (p=0.004), while no significant difference was observed between medians of homocysteinemia levels in male (11.4 μmol/L) and female (10.9 μmol/L) patients.

Comparison of the incidence of HHcy in women with AMI (47.1%) and in healthy women (4.8%) revealed significant difference (p=0.001). Accordingly, the difference between medians of homocysteinemia in healthy women (9.0 μmol/L) and in female patients (10.9 μmol/L) was found to be significant. No significant differences were observed when incidences of HHcy and medians of homocysteinemia levels were compared between male patients and healthy young men.

Patients younger than 30 years had an incidence of HHcy of 41.7% and median homocysteine level 10.5 μmol/L. HHcy was present in 40.3% of patients whose age was between 30 and 39 years, while their median homocysteine concentration was 10.7 μmol/L. In the group of our patients older than 40 years median homocysteinemia was 11.5 μmol/L and HHcy was present with an incidence of 47.1%. No significant differences were found when incidences of HHcy and medians of homocysteine concentration were compared between the defined age groups of patients.

Discussion

First studies indicating the relationship between HHcy and thrombo-occlusive vascular changes were conducted on groups of young adults (1). The investigation of etiopathogenesis for AIM in young adults is a relatively challenging task because traditional risk factors (e. g. diabetes mellitus, hypertension, hyperlipoproteinemia) have a considerably lower incidence in their population than in older persons. According to the results of some studies (10–12), one of the new factors responsible for premature atherothrombosis might be hyperhomocysteinemia.

Cut-off value for hyperhomocysteinemia was set at 12 μmol/L, according to recent suggestions that the previous upper reference limit of 15 μmol/L might be unappropriately high (2). For most European populations, it is recommended to maintain a homocysteinemia value of less than 10 μmol/L. Homocysteine concentrations between 10 and 12 μmol/L are considered tolerable, while homocysteinemia in range from 12 to 15 μmol/L represents a borderline for hyperhomocysteinemia (2). Results of the Framingham study (2) revealed an onset of increase in cardiovascular risk in subjects with homocysteinemia of 11.4 μmol/L, and some authors (14) reported a double increase of risk for vascular damage associated with a homocysteinemia value of 10.2 μmol/L.

Results of this study point to a significantly higher incidence of HHcy in patients with acute myocardial infarction younger than 45 years than in persons from the equivalent control group. Some studies (2) previously reported significant prevalence of HHcy (20–40%) in patients with coronary disease. The presence of HHcy is associated with faster progression of coronary plaque (16) and higher probability for recurrent cardiovascular events (6, 9). In myocardial infarction, HHcy is considered a predictive factor of mortality, independent of other predictive factors (4, 17, 18).

According to the results of our study, it can be stated that young patients with AMI have significantly higher levels of homocysteinemia when compared to healthy persons. Results of a large cohort study, conducted in Norway (19), demonstrated that an elevation in homocysteinemia value of 4 μmol/L increases by 1.4 times the relative risk for coronary heart disease. Our results, evaluated in sense of such findings, strengthen the hypothesis that hyperhomocysteinemia has a very significant role in the development of AMI in young adults.

In the control group, men had a higher incidence of HHcy and higher homocysteine values than women, while gender had no influence on the incidence of HHcy and homocysteinemia values in the group of patients. Literature data state that men have 21–25% higher Hcy concentrations than women (1, 9), what is in accordance with the finding in our control group that healthy men had 18.1% higher homocysteine concentrations than healthy women. Possible explanation for the absence of difference in homocysteine levels between male and female patients is that female patients also have high levels of homocysteinemia because hyperhomocysteinemia has a significant role in the etiopathogenesis of AMI in both genders.

There is a significant difference in homocysteinemia between healthy women and women with AIM, which cannot be observed if we compare homocysteine concentrations between healthy men and men with AIM. The difference between healthy women and women with AIM reached the level of statistical significance, because the median of homocysteinemia is significantly lower in healthy women than in healthy men, while in male subjects such difference can be described as a trend without statistical significance.

Our study offers the finding that age has no influence on the incidence of HHcy and the homocysteinemia level in young patients with AMI. Literature data (1) suggest that homocysteine concentration increases with age. Our finding may be explained by two facts. The generally mentioned age at which Hcy concentration starts to increase is 50 years (1), and all our subjects are younger. Also, we should consider that our age subgroups have a relatively small span to observe age-induced differences.

According to the mentioned results, we can conclude that hyperhomocysteinemia could be a very important risk factor in the etiopathogenesis of acute myocardial infarction in young adults. Our conclusion, together with the controversial results in lowering cardiovascular risk in patients with hyperhomocysteinemia by supplementation with vitamins B_{12}, B_6, and folate, focuses the clinical follow-up of young adults with hyperhomocysteinemia on the early detection of signs of premature atherosclerosis and eliminating other risk factors that can protrude deleterious effects of hyperhomocysteinemia.

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