Homocysteine in Angiographically Proven Coronary Disease

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SUMMARY

The research included 200 subjects, of which 150 had angiographically proven coronary disease with the coronary artery stenosis of 50% or more, and 50 subjects who did not have angiographically proven coronary disease. Patients were chosen randomly out of approximately 1000 patients who underwent angiography. All the subjects were treated at the Clinical Center of University of Tuzla – at the Clinic for Cardiovascular Diseases. The average value of homocysteine concentration in plasma of patients with angiographically proven coronary disease was 13.86 μmol/L, and 10.65 μmol/L in the controls, which is statistically significant difference (P<0.0001). Lowered values of ejective fraction of the left ventricle of 50% and over was found in 25 patients (or 16.66%) with angiographically proven coronary disease, while the control group had only 4 subjects (or 8%). Student’s t-test have proven that the average values of ejective fraction of the left ventricle of subject with angiographically proven coronary disease were statistically significantly different in comparison with the values of ejective fraction of the subjects in the control group (t=5.87, df=197, P<0.0001). In all the groups the negative values of coefficients of correlation (R) shows that with the increase of plasma homocysteine concentrations the ejective fractions of the left ventricle dropped. Using logistical regressive analysis it was established that the following factors contribute the most to the development of coronary disease: increased concentration of plasma LDL-cholesterol, increased concentration of plasma homocysteine, diabetes mellitus and hereditary factors. In all the different forms of angiographically proven coronary disease (coronary disease in a one-vessel or in multiple-vessels), the increased concentration of plasma homocysteine was the significant risk factor for the development of coronary disease.

Keywords: coronary artery disease, homocysteine, ejective fraction

1. INTRODUCTION

Coronary (ischemic) heart disease is a clinical syndrome caused by a narrowing or blockage of coronary arteries, resulting in imbalance between supply of heart muscle with blood and its needs. Forms of coronary heart disease are: stable angina pectoris, acute coronary syndrome (unstable angina pectoris, myocardial infarction, and sudden cardiac death), heart rhythm disturbances, heart failure and asymptomatic coronary artery disease (heart ischemia without symptoms).

Atherosclerosis is the most common cause of coronary heart disease. In rare cases it can be caused by rheumatoid arthritis, polyarthritis, embolism, congenital anomalies of coronary arteries or functional changes in the partially altered coronary blood vessels (vasospasm). Display of coronary artery disease is made on Figures 1 (a, b, c).

Today, as a risk factor for the occurrence of coronary heart disease among others is considered homocysteine (HCY), which multiple and very complex activity accelerates the creation and development of atherosclerosis and the occurrence of coronary heart disease, cerebrovascular and peripheral vascular disease. It is first discovered in 1932 trough work of de Vigneaud as a catabolism product of essential amino acid methionine. It is metabolized by the processes of transulfuration and remetilation (1). Causes of hyperhomocysteinemia can be congenital and acquired.

Congenital causes of hyperhomocysteinemia include: transulfuration disorders, lack of cistation-β-synthase, remetilation disorders, reduced coenzyme synthesis, transport of vitamin B12 disorders, disturbance of the synthesis of methionine. Acquired hyperhomocysteinemia causes include: chronic kidney disease, acute leukemia lymphoblast, psoriasis, and some medications (metotrexat, phenytoin, carbamazepine, theophylline).

The concentration of homocysteine in plasma is under influence of diet, physical activity and socio-economic factors. A large number of scientific papers indicate the impact of folic acid, vitamins B6 and B12 on the homocysteine concentration in plasma (2). HCY adverse effect takes place under the influence of free radicals such as superoxide anions, hydrogen peroxide, which occur during auto oxidation of HCY.

Hyperhomocysteinemia reduces the concentration of nitrous oxide and thereby affect vascular reactivity. Increased concentrations of homocysteine inhibit the enzyme lizil-oxidase (LOX) and reduce its expression in en-

Figure 1A. One vessel coronary disease; 1B. Two vessels coronary disease; 1C. Three vessels coronary disease
Homocysteine induces production of interleukin-8, and is associated with proinflammatory states. Many clinical studies indicate the importance of homocysteine in the development of coronary disease. They confirm that hyperhomocysteinemia is the risk of cardiovascular disease and has a significant share of the population mortality (3).

Contemporary studies in the field of interventional cardiology highlight the importance of the hyperhomocysteinemia in development of coronary disease. Found are significantly higher concentrations of homocysteine in plasma of people with coronary disease compared to those of control groups which suggest a role of hyperhomocysteinemia in process of atherothrombogenesis (4). Pointed is also the correlation between the concentrations of homocysteine in plasma of people with coronary disease and the degree of stenosis of the coronary blood vessels, as well as the degree of left ventricular dysfunction (5,6).

Although homocysteine is considered to be a risk factor for the occurrence of coronary heart disease still is not yet been sufficiently clarified how homocysteine alone and how combined with other known risk factors contributing to the development of coronary disease. In Bosnia and Herzegovina there was no previous clinical study on homocysteine and coronary disease, which is proved by angiogram.

2. RESEARCH GOALS

In patients with angiographically proven coronary disease to determine the value of homocysteine in plasma,

Determine the value of homocysteine in plasma of subjects in which is no angiographically proven coronary disease,

Determine the correlation between homocysteine concentration with the values of total cholesterol, HDL and LDL cholesterol, as well as other risk factors for the occurrence of coronary disease (arterial hypertension, cigarette smoking, obesity, diabetes mellitus, genetic factors)

In patients with angiographically proven coronary disease determine correlation between homocysteine concentrations in plasma and left ventricular ejection fraction.

3. MATERIAL AND METHODS

The study involved 150 patients suffering from angiographically proven coronary artery disease and 50 randomly selected control subjects.

Data about patients were taken from the history of the disease. The study did not include people affected by chronic kidney disease, acute lymphoblast leukemia, psoriasis, and subjects which used methotrexat, carbamazepine, phenytoin, and theophylline.

4. RESEARCH RESULTS

Patients with coronary disease and coronary artery stenosis of 50% or more were 150, of which 112 were men and 38 women. The control group consists of 50 respondents, including 29 men and 21 women. Out of the total number of patients, one vessel coronary disease had 63 or 42%, two vessel 46 or 30.66% and three vessels 41 or 27.33% of the patients (Figure 2).

Increased concentrations of homocysteine in plasma of people with angiographically proven coronary artery disease had 28 respondents or 18.66%, of which 5% are women, or 13:16, or 20:54, and 23% men.

Increased concentrations of homocysteine in plasma at the control group had 1 subject or 4.76% of women and 2 or 6.9% men (Figure 3).

Chi-square test showed that the frequency of increased concentrations of homocysteine in plasma of 2.77 times higher is in the group suffering from angiographically proven coronary artery disease compared to the control group of respondents (95% CI: 0.78-15.11). Average value of the concentration of homocysteine in plasma for control group was 10.65 μmol/L, in men 10.55, and women 10.81 μmol/L. Student’s t-test show that the mean concentrations of
Homocysteine in plasma of people with angiographically proven coronary artery disease and control group are significantly different ($t = 4.62$, $df=197$, $P<0.0001$).

Mean value of plasma homocysteine concentration in the group suffering from single vessel coronary disease was 13.29, two vessels coronary disease 13.89 and three vessels coronary disease 13.05 μmol/L, while the mean plasma homocysteine concentration of the control group was 10.66 μmol/L (Figure 4).

Analysis of variance (ANOVA) tested whether there was a statistically significant difference between mean concentrations of homocysteine in plasma of people with single vessel, two vessels and three vessels coronary disease and control group. Concentrations of homocysteine in plasma of people with angiographically proven coronary artery disease is significantly different from the concentrations of homocysteine in plasma of control group ($F=7.22$, $P<0.0001$). This is proved using Scheffe test.

In the group of subjects suffering from angiographically proven coronary artery disease reduced left ventricular ejection fraction for 50% or more had 25 or 16.66% patients, of which 7 or 11.1% with single vessel, 8 or 17.4% with two vessels and 10 or 24.4% with three vessels coronary disease. In the control group subjects left ventricular ejection fraction of less than 50% had 4 or 8% of respondents. Average value of ejection fraction of the left ventricle in patients with angiographically proven coronary artery disease had 51.21%, 51.53 men and 50.27% of women. Average value of ejection fraction of the left ventricle of the respondents in the control group was 59.96%, 59.34 for men and for women 60.81% (Figure 5).

Student’s t-test proved that the mean left ventricular ejection fraction in patients suffering from angiographically proven coronary artery disease and control groups of respondents differ significantly ($t=5.87$, $df=197$, $P<0.0001$). In patients with angiographically proven coronary disease found are increased concentrations of total cholesterol in 95 or 63.3% of cases, low HDL-cholesterol values in 60 or 40%, increased concentrations of LDL-cholesterol in 72 or 48%, and increased concentrations of triglycerides in 42 or 28% of patients. In the control group increased concentrations of total cholesterol were found in 21 or 42% of cases, reduced the value of HDL-cholesterol concentrations in 10 or 20%, increased concentrations of LDL-cholesterol in 6 or 12%, and increased concentrations of triglycerides in 13 or 26% respondents (Figure 6).

In the control group mean concentrations of total cholesterol in plasma was 5.54, HDL-cholesterol 1.05, LDL-cholesterol and triglycerides 1.84 mmol/L. Student’s t-test found that there is a statistically significant difference between high concentrations of total cholesterol, HDL-cholesterol and LDL-cholesterol in the group suffering from angiographically proven coronary disease and control group. Increased concentrations of homocysteine in plasma will increase the chances of occurrence of coronary heart disease by 4.92, with minimum of 1.13 times.

In all cases, when the analysis included all forms of coronary disease, single vessel, two vessels or three vessels coronary disease, increased concentrations of homocysteine in plasma is a significant risk factor for the occurrence of coronary disease.

5. DISCUSSION

Coronary artery disease is manifested in four clinical forms: angina pectoris (stable and unstable), myocardial infarction, sudden cardiac death
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and ischemic miocardiopathy. It represents the most significant factor in morbidity and mortality in developing countries and industrialized countries. Usually present in middle age groups, often affected are people at working age, and this is why the issue of primary, secondary and tertiary prevention of coronary heart disease is of primary importance.

In the emergence of coronary artery atherosclerosis, as well as atherothrombosis development and creation of stable or unstable atherosclerotic pressure homocysteine has a significant role. Numerous studies highlight the importance of homocysteine in the development of coronary disease. Hyperhomocysteinemia confirm that the risk of cardiovascular disease and development, and that has a significant share of the population mortality (7).

Also mentioned is the correlation between the concentrations of homocysteine in plasma of patients with coronary disease and the degree of stenosis of the coronary blood vessels, as well as the degree of left ventricular dysfunction (5,6). In our group of patients suffering from angiographically proven coronary artery disease hyperhomocysteinemia was significantly more present in relation to its presence among respondents of control group. In patients with angiographically proven coronary disease hyperhomocysteinemia was found in 28 or 18.66% of cases, 5 or 13.16% of women and 23 or 20.54% of men. Similar results found Faria-Neto, et all. (8).

Stanger et all. (9) state representation of hyperhomocysteinemia in 5-10% of the total population and 40% of patients with vascular disease. Indicate that the homocysteine concentration greater than 10 μmol/L is a risk factor for coronary heart disease, and represent 10% of the total risk of coronary heart disease. In a group of patients with angiographically proven coronary artery disease mean concentrations of homocysteine in plasma was 13.86 μmol/L, in men 13.63, and women in 14.54 μmol/L. In the control group mean plasma homocysteine concentration was 10.65 μmol/L, with mean value of 10.55 in men, and 10.81 μmol/L in women (t = 4.62, df=1.97, P <0.0001). Similar results in patients with angiographically proven coronary disease and control groups were found other authors (10). Many clinical studies in interventional cardiology highlight the importance of homocysteine in the development of coronary artery disease. Found are significantly higher concentrations of homocysteine in plasma in patients with angiographically proven coronary disease compared to those of the control group (11, 12).

Mean concentrations of homocysteine in plasma of people with single and multiple vessels coronary disease is significantly different from the mean concentrations of homocysteine in plasma of subjects in control group. It has been proved analysis by of variance using ANOVA and Sheffe test (F=7:22, P<0.0001).

Proven is the correlation between left ventricular ejection fractions and concentrations of homocysteine in plasma in patients with angiographically proven coronary disease and control group. This is confirmed by the work of Strauss et all. (13). A negative correlation coefficient (R) in all analyzed groups of respondents shows that increasing concentrations of homocysteine in plasma decrease ejection fraction of the left ventricle. Student's t-test prove statistically significant difference in homocysteine concentrations of people with angiographically proven coronary artery disease and those in the control group ejection fraction of the left ventricle of 60% greater (P=0,001), as well as the value of ejection fraction of the left ventricle 50-60% (P = 0.002). Similar results found May et all. (14), which quote increased concentrations of homocysteine in plasma in patients with angiographically proven coronary disease correlate with reduced left ventricular ejection fraction and the occurrence of cardiac weakness.

This is confirmed by the work of Gueant-Rodriguez et all. (15), which indicate that significantly increased concentrations of homocysteine in patients with angiographically proven coronary disease followed with left ventricular systolic dysfunction. Cesari et all. (16) state that the hyperhomocysteinemia is independent risk factor, and associated with other known risk factors for the occurrence of coronary disease amplifies development of atherosclerosis and coronary artery thrombosis. Kobori et all. (10) through multivariate analysis cited as important risk factors for the occurrence of coronary disease diabettes mellitus, arterial hypertension and increased concentrations of homocysteine in plasma.

From logistic regression analysis examining risk factors for the occurrence of coronary disease in our subjects is shown that to have increased concentrations of homocysteine in plasma is a significant risk factor for the occurrence of coronary disease. This is confirmed by the works of Souissi et all. (17) and Troughton et all. (3), which state that the hyperhomocysteinemia is a significant risk factor for the occurrence of coronary disease and a predictor of mortality in patients with ischemic heart disease.

Lee et all. (18) have investigated multiple biomarkers as risk factors for coronary disease: homocysteine, interleukin-6, C-reactive protein and serum amyloid A protein (SAA). They stressed the special importance of homocysteine and interleukin 6 as a biomarker for coronary disease, which require further scientific studies about the importance of homocysteine as a risk factor for coronary disease, its relationship and interaction with other conventional factors for the occurrence of coronary disease, particularly lipoproteins, endothelin, endoperoxides (NO) and prostaglandins.

Special significance have the toxic effects of homocysteine on intra cellular structure of blood vessels and their relation to coagulation factors, platelets and blood fibrinolitic system.

6. CONCLUSIONS

In patients with angiographically proven coronary disease were significantly higher concentrations of homocysteine in plasma in relation to the concentration of homocysteine in plasma of respondents from control group.

The concentration of homocysteine in plasma of respondents in the control group without angiographically proven coronary artery disease was significantly lower in comparison to patients suffering from angiographically proven coronary artery disease.

From correlation of homocysteine concentrations in plasma with concentrations of total cholesterol, HDL, LDL, cholesterol and other risk factors for the occurrence of coronary disease (arterial hypertension, cigarette smoking, obesity, diabetes mellitus, inheritance) lo-
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gistic regression analysis determined that the for the occurrence of coronary disease the most important are: the increased concentration of LDL-cholesterol in plasma, genetic factors, diabetes mellitus, and increased concentrations of homocysteine in plasma.

Levels of homocysteine in plasma at low values of ejection fraction of the left ventricle were significantly higher in relation to concentrations of homocysteine in plasma of respondents from the control group.

Increased concentrations of homocysteine in plasma are a significant risk factor in all forms of angiographically proven coronary artery disease (single or multiple vessels).

Combined activity of increased plasma concentrations of homocysteine with other risk factors significantly amplifies formation and development of coronary disease.

REFERENCES


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