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Professional paper

THE ROLE OF HOMOCYSTEIN IN THE DEVELOPMENT OF CARDIOVASCULAR DISEASE

Art ZYLBEARI[1,2], Nadir AJRULI[1], Koço ÇAKALAROVSKI[3], Gazmend ZYLBEARI[1,2], Elita MASHA[2], Milka ZDRAVKOVSKA[2]

1. Faculty of Medical Sciences UT, Tetovo, Republic of North Macedonia
2. Faculty of Medical Sciences, Goce Delcev University in Shtip, North Macedonia
3. Faculty of Medical Sciences, University, "St. Cyril and Methodius" in Skopje, Republic of North Macedonia

Abstract

Cardiovascular diseases (CVD) are the leading cause of excess death worldwide, but to this day it is not clear how their multifactorial pathology develops. In recent years, a large number of studies have proven that the incidence of cardiovascular morbidity and mortality from CVD varies from both genetic predisposition and metabolic disorders of the methionine cycle of homocysteine (Hcy) metabolism, which leads to hyperhomocysteinemia (HHCy) and the occurrence of premature and accelerated cardiac atherosclerosis (Ath) and premature death. The impact of HHcy on the occurrence of CVD remains unclear, but it is assumed to be related to the role of H_2S by increasing H_2S production, which reduces the expression of adenosine A_2A receptors on the surface of cardiovascular cells, activates Nuclear Factor-kappa B (NF-κB),conversion to Hcy-thiolactone and induction of autoimmune response and thrombo-genesis.Increase in proinflammatory cytokines to cause inflammation, premature atherosclerosis, myoca-rdial infarction, cerebrovascular disease, peripheral arterial disease and coronary ischemia. HHCy acts on endothelial cell permeability by inhibiting endothelial nitric oxide synthase,which produces nitric oxide (NO) leading to coronary ischemia.HHCy is a condition in which the plasma HCy concentration is elevated ≥15 μmol/L (refer.value 5-15 μmol/L), which occurs as a result of an imbalance between its biosynthesis and catabolism. Supplementation with vitamins B6,B12 and folic acid has been shown to have very positive effects on reducing homocysteine as well as on reducing vascular premature Ath changes in the coronary, cerebral and peripheral blood vessels. Previous research proposed a positive role of H_2S in the cardiovascular system, and we discuss some recent data suggesting that HHcy worsens CVD by increasing the production of H_2S, which decreases the expression of adenosine A_{2A} receptors on the surface of immune and cardiovascular cells to cause inflammation and ischemia, respectively[1].

Keywords: cardiovascular disease (CVD), Homocystein (Hcy), Hyperhomocysteinemia (HHcy).

1. Introduction

CVD continues to be a major cause of disability and mortality in both developed and developing countries. Elevated Hcy (HHcy) concentrations are considered a risk factor for the occurrence of premature atherosclerotic processes and atherosclerotic changes in coronary, cerebral and peripheral blood vessels. HHcy increases the risk of CVD through several mechanisms: damage to endothelial cells, reduced production of nitric oxide (NO) which affects blood vessels, with vasoconstriction and formation of atherosclerotic plaques, increased oxidative stress, increased free radicals[1,2,3].HHcy affects the activation of the renin-angiotensin-aldosterone system (RAAS) by increasing vasoconstriction, sodium and water retention, which affects the increase in arterial pressure. Although the increase in Hcy levels in patients with CVD has not been definitively established, it is assumed that HHcy occurs as a result of an increase in the rate of Hcy production (i.e., transmethylation, transsulfuration), decreased excretion due to reduced renal metabolic clearance, decreased peritubular excretion, or as a result of any genetic defect in Hcy metabolism (which contributes to the increase in Hcy levels) [4,5,6,7]. Patients with very high levels of total Hcy (>100 μmol/L) due to inborn metabolic defects affecting cystathionine-β-synthase are potential candidates for the development of premature atherosclerotic processes and thrombolytic disorders. Homocysteine (Hcy) is a nonessential

sulfur-containing amino acid and plays an important role in the Hcy-methionine cycle through its interaction with folic acid and vitamin B12. Disruption of this metabolic process can result in the accumulation of Hcy, which affects vascular tissue damage, damage to the coronary, cerebral and peripheral arteries. In recent years, many studies have been conducted on the effect of HHcy and its influence on the occurrence of premature atherosclerotic changes, and all have proven that HHcy is an important parameter for the early occurrence of atherosclerotic processes in the coronary arteries and cardiovascular diseases [8-11].Treatment of HHcy may affect the prevention of occlusive vascular damage. The harmful effects of HHcy are due to the production of oxidants (reactive oxygen species) generated during the oxidation of Hcy and disulfides in the blood. Numerous studies have shown that the level of total Hcy increases as a result of folic acid, cyanocobalamin, pyridoxine deficiency, smoking, and aging. Numerous studies have confirmed that there is a high positive correlation between HHcy, arterial hypertension, and hypertriglyceridemia, while there is a high negative correlation between HHcy and glomerular filtration rate (an increase in Hcy is accompanied by a decrease in glomerular filtration rate[12,13,14].

2. Purpose of the paper

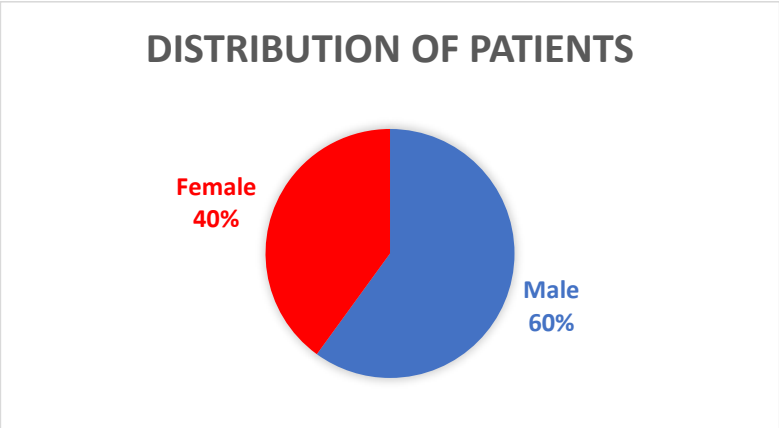
Was to emphasize the importance of monitoring homocysteine as a potential biomarker in the prevention and management of cardiovascular diseases (CVD).

3. Material and methods

The study included 100 patients with cardiovascular diseases (of which 60 were men and 40 women with an average age of 54.30±8.00 years, and 70 healthy subjects (40 men and 30 women with an identical age of 52.00±5.00 years) voluntary blood donors who served to compare the results obtained between patients with CVD and the control group. In both patients and the control group, the Hcy values were measured every 6 months for a period of 24 months.

Table 1: distribution of patients and the control group according to gender and average age

Number of patients=100	**Average age ±SD**	**Control group=70**	**Average age ±SD**
Female=40	**54.30±8.00 years**	**30**	**52.00±8.00 years**
Male=60	**54.30±8.00 years**	**40**	**52.00±8.00 years**



4. Statistical processing of the results

The results obtained from the patients examined with IRK, IRKT and the control group were statistically processed with arithmetic mean value, standard deviation X ± SD, with the student's "t" test, Mann-Whitney and Wilcoxon test.The results were processed with the SPSS V26 program.

5. Results:

The results obtained present the average values, obtained within 24 months. The difference in parameters between patients and the control group was significant for p<0.001.In all patients at the beginning of the study, the Hcy values were =19.00±2.00 μmol/L, while at the end of the study (after 24 months) the average values were increased to=28.60±4.00μmol/L,indicating a progressive deterio-ration of this biochemical indicator, which is closely related to the risk of cardiovascular diseases. In healthy subjects, Hcy values were=8.50±3.20 μmol/L.The difference between Hcy values in patients with CVD and the control group of healthy subjects was significant at p<0.001.It is worth noting that men had significantly higher Hcy levels compared to women, both at the beginning of the study and after the end of the follow-up period.These data indicate that increased Hcy may have a direct or indirect impact on the progression of cardiovascular pathologies,especially in groups with a higher predisposition.

Table 2: Presentation of patients according to CVD

Number of patients =100	**Female40, Male=60**
With a history of CVD	**40**
Angina pectoris non stabilis	**35**
Status post Infarctum myocardi	**45**
Diabetes mellitus	**40**
Adipose with BMIx>25-30 kg/m^2	**20**
Hypertension	**40**

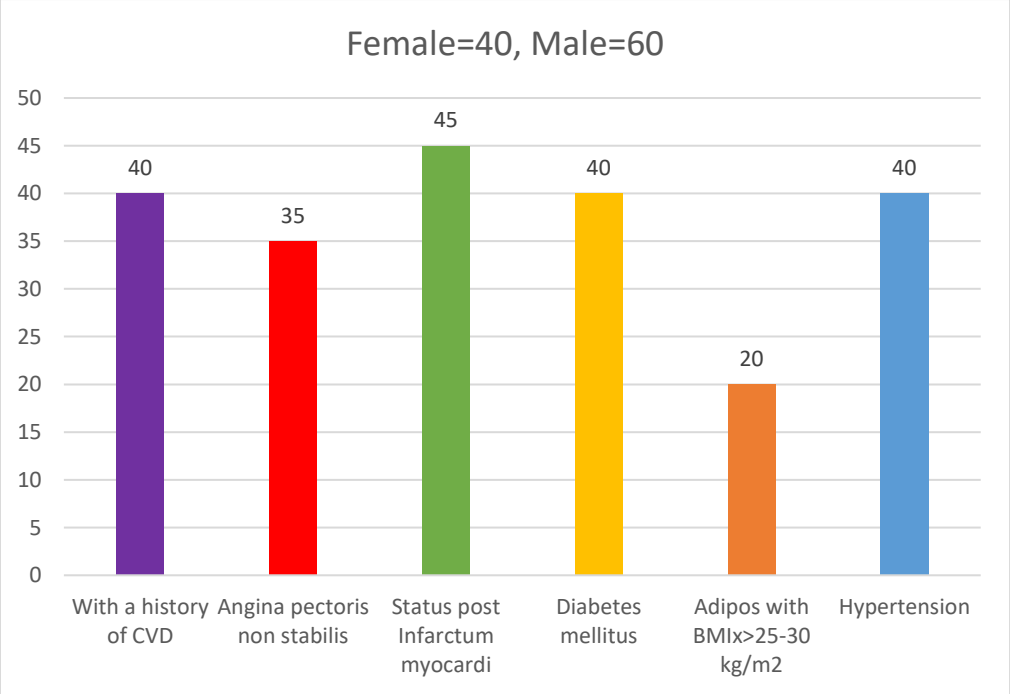


Table 3: Obtained results from the patients and the control group

Patients with CVD	TG mmol/l	HDL-ch mmol/l	LDL-ch mmol/l	tHcy µmol/L
100	3.40±0.50↑	0.96±0.20↓	4.50±0.60↑	28.60±4.00↑
Contr. Group=70	1.45±0.40	2.48±0.45	3.40±0.30	8.60±0.3.20
p	0.001	0.001	0.001	0.001

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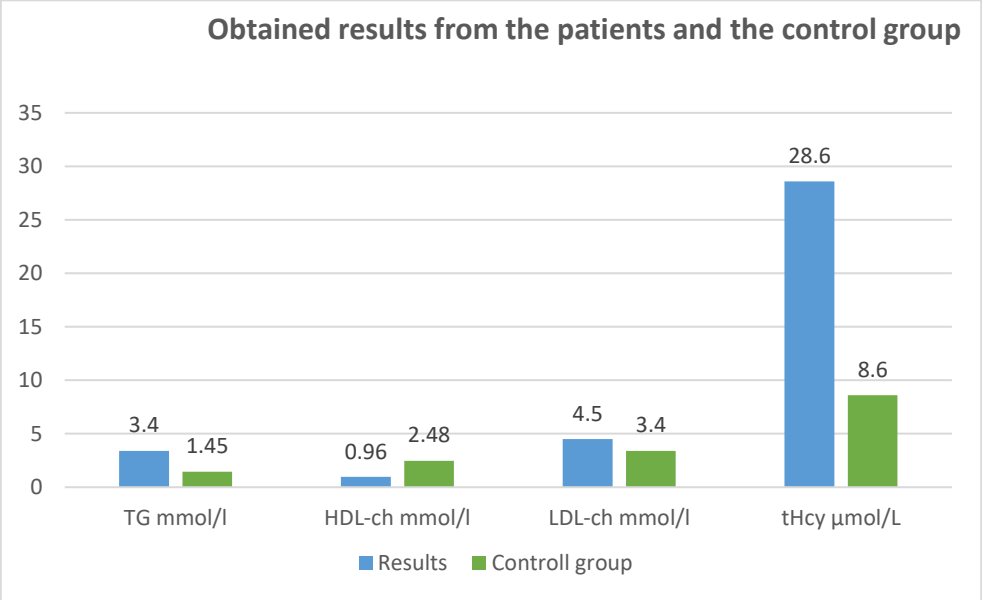

6. Discussion

CVD is a leading cause of death, but how the multifactorial pathology develops is unclear. The incidence of cardiovascular morbidity-mortality from CVD varies depending on conventional risk factors [15,16].Factors that influence the risk of developing CVD include genetic history (gender, family or ethnicity) or poor lifestyle (smoking, alcohol use, lack of activity or unhealthy diet). Hypertension is the most common modifiable risk factor for CVD [17,18].CVD are the main cause of death in 44-75% of victims with CKD, Life expectancy of individuals with CKD is significantly lower than those with normal kidney function, estimated to be less than 50% compared to the general population. Of which only 22% from acute coronary syndrome. Hcy is a sulfur-containing non-essential amino acid that plays a role in the Hcy-methionine cycle through its interaction with folic acid and vitamin B12. Hcy is considered an unconventional prognostic biomarker for CVD both in the general population. It has been verified that reducing Hcy concentrations in serum reduces the risk of premature atherosclerosis and CVD. The decrease in NO synthesis has a key role in the development of the atherosclerosis process. The definition of HHCy is controversial, but it is generally defined as plasma HCy ≥ 10 µmol/L. However, a slight increase (10–15 µmol/L) in plasma HCy level is associated with morbi-mortality and a higher cut-off (≥15 µmol/L) was also considered to designate HHCy [19,20]. In conclusion, HHCy is categorized into three classes as mild, moderate and severe HHCy with plasma HCy levels ranging from 15 to 30 µmol/L, 31 to 100 µmol/L and > 100 µmol/L, respectively [21].HHcy contributes to the development of CVD through several mechanisms, including the negative effects of Hcy on vascular endothelium and smooth muscle cells, which lead to changes in arterial structure and function. Hcy is an independent risk factor

for the development of premature atherosclerosis leading to CVD [22,23].And HHcy is highly correlated with plasma HCy levels and the severity of atherosclerosis. HHCy is associated with the etiology of myocardial infarction and cerebral stroke,but the mechanisms of HCy-induced CVD are unclear [24,25]. HHCy activates Nuclear Factor-kappa B (NF-κB), which regulates the transcription of genes involved in inflammatory and immune responses to increase pro-inflammatory cytokines and decrease anti-inflammatory cytokines and also causes endothelial cell dysfunction by decreasing endothelial antioxidant defenses to cause oxidative stress and an increase in intracellular concentration of reactive oxygen species (ROS)[26,27].ROS affect lipoprotein metabolism, and contribute to the growth of atherosclerotic vascular lesions. The effects of HHCy on CVD may also be due to increased production of hydrogen sulfide (H_2S].HCy acts on blood vessels by controlling vascular smooth muscle cell contractility and endothelial cell permeability through inhibition of endothelial nitric oxide synthase, which produces nitric oxide (NO) [28,29,30].To alleviate intracellular accumulation of HCy when the remethylation pathway is impaired, endothelial cells export HCy into the circulation. The mechanism of HCy transport in the vascular endothelium is not well defined, but human aortic endothelial cells bind and import HCy via at least four known sodium-dependent cysteine transport systems.

7. Conclusions

In conclusion, we recommend that Hcy testing be introduced in patients with a predisposition to CVD in examinations in order to prevent frequent cardiovascular, cerebral and peripheral disorders. In this context, regular monitoring of Hcy and consideration of interventions aimed at its reduction (such as folic acid and vitamin B supplementation) may be important steps in the prevention and long-term management of cardiovascular risk.

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