HYPERHOMOCYSTEINEMIA AND LIPIDS ON THE ONSET ESSENTIAL ARTERIAL HYPERTENSION AND CORONARY DISEASE

1. Doc.Dr.Sc. Med. Lutfi Zulbeari, MD,PhD1,2, 2. Prof. Dr. Nasir Behxheti3, 3. Dr. Zamira Bexheti 1, 4. Dr. Gazmend Zylbeari 5. Mr. Phar.Mirilind Behxheti

1. State University of Tetova, Faculty of Medical Sciences, Tetova,Macedonia
2. Private Special Hospital for Nephrology and Hemodialysis ‘Vita Medical Group’- Tetova, Macedonia

Abstract

Summary: Cardiovascular diseases(CVD) still remain as main factor of invalidity, morbidity and mortality in developed and developing countries. Despite known factors (genetic predisposition, gender, age, arterial hypertension, smoking, obesity, diabetes, dyslipidemia, C reactive protein) recently in the ethiology of CVD raised total Homocysteine (Hcyt) is considered also. Correlation between raised Hcyt and CVD was dissscovered 25 years ago by Carson and Neil, who saw a defect of Hcyt metabolism in a patient with raised Hcyt. In this cases is verified lack several enzymes which enable normal metabolism of Hcyt. Therefore as result of these metabolic disorders of Hcyt, clinical picture of raised Hcyt and its accumulation in blood-hyperhomocysteinemia appears. Several studies have verified that 15-30% of cases with CVD are result of hyperhomocysteinemia (1). Aim of this paper: Aim of this paper is to examine concentrations of Hcyt and lipid profile in patients with essential arterial hypertension and positive personal history for CVD, comparing them with the control group composed from healthy individuals. Our study aimed to verify the role of Homocysteine as new independent risk factor on the onset of early atherosclerosis (arteriosclerosis prematura) and atheromateous processes in coronary arteries in patients with CVD and the impact of raised Hcyt in evaluating arterial hypertension. This paper aimed to propose medical measures to correct and treat hyperhomocysteinemia, which obviously would decrease the consequences of Hcyt on CVD and arterial hypertension.

Material and methods: As working material was used blood from 360 patients with positive personal anamnesis for CVD and essential arterial hypertension (HTA ess). Our study aimed to verify the role of Homocysteine as new independent risk factor on the onset of early atherosclerosis (arteriosclerosis prematura) and atheromateous processes in coronary arteries in patients with CVD and the impact of raised Hcyt in evaluating arterial hypertension. This paper aimed to propose medical measures to correct and treat hyperhomocysteinemia, which obviously would decrease the consequences of Hcyt on CVD and arterial hypertension.

Material and methods: As working material was used blood from 360 patients with positive personal anamnesis for CVD and essential arterial hypertension (HTA ess). Our study aimed to verify the role of Homocysteine as new independent risk factor on the onset of early atherosclerosis (arteriosclerosis prematura) and atheromateous processes in coronary arteries in patients with CVD and the impact of raised Hcyt in evaluating arterial hypertension. This paper aimed to propose medical measures to correct and treat hyperhomocysteinemia, which obviously would decrease the consequences of Hcyt on CVD and arterial hypertension.

Material and methods: As working material was used blood from 360 patients with positive personal anamnesis for CVD and essential arterial hypertension (HTA ess). Our study aimed to verify the role of Homocysteine as new independent risk factor on the onset of early atherosclerosis (arteriosclerosis prematura) and atheromateous processes in coronary arteries in patients with CVD and the impact of raised Hcyt in evaluating arterial hypertension. This paper aimed to propose medical measures to correct and treat hyperhomocysteinemia, which obviously would decrease the consequences of Hcyt on CVD and arterial hypertension.

Concentration of homocysteine and lipids in patients with CVD compared to the control group showed statistically significant difference in Hcyt (24.50 ± 5.20 µmol/L) with p<0.0001 except for ChT where no significance between two groups was found (in patients with CVD ChT= 5.20 ± 1.20 mmol/l while in control group=4.90±1.60 mmol/l with p=0.7400). Concentrations of homocysteine and lipids in patients with CVD compared to the control group showed statistically significant difference especially for homocystine =18.20 ± 6.40 (which was object of our study) with p=0.0001, but levels of Hcyt in this group were lower than Hcyt in patients with CVD=24.50 ± 5.20 µmol/L. These facts show that raised Hcyt have more impact on the onset of CVD and less impact on the onset of arterial hypertension.When Hcyt levels are raised in blood, the activity of cystathionine—synthetase enzyme is raised. It is believed that this enzyme plays vital role on the metabolism of Hcyt. Hyperhomonocysteinemia and its impact on the onset of coronary and cerebral atherosclerosis and all have verified that hyperhomocysteinemia is a significant parameter for the onset of early atherosclerosis of coronary and cerebral arteries (5). When homocysteinaemia is correlated with lipid disorder (dyslipidemia, hypertygliceridemia, hypercholesterolemia) effects on cardiovascular system and CVD prevalence is higher. For this reason we decided in our study to include lipid panel also in patients with CVD and HTA ess. Conclusion: In the end we can conclude that also in our study high levels of Hcyt in patients with CVD and HTA ess were found, which are in line with many multicentric studies on the role of Hcyt as new independent risk factor for early coronary arteriosclerosis and its moderate effect on the onset of HTA ess.In above mentioned cases it is recommended substitutive therapy with folic acid, pyridoxine, cyanocobalamine, tocopherol and other antioxidants which is found that have effect on prevention of premature arteriosclerosis in patients with CVD and raised Hcyt: PTCA, CARB, acute myocardial infarction, angiina pectoris, Stenting and prevention of stroke.

Term Index: Total Homocysteine (Hcyt), lipid profile, Cardiovascular diseases (CVD), essential arterial hypertension (HTA ess).

1 Introduction
CVD and their high mortality still remain as big problem and with high prevalence in general population. High concentrations of Hcy in serum are considered as risk factor for CVD and can be associated with hypertension. Although between hyperhomocysteinemia and CVD is found a significant correlation, still the role of homocysteine on cardiovascular manifestations remain unclear. It is verified that concentrations of homocysteine increases with smoking, aging and some diets with low folates, cyanocobalamin and pyridoxine. Many studies have verified a significant relationship between raised Hcy and arterial hypertension and lipid disorders, compared with normotensive individuals. Lowering Hcy concentrations can have some benefits in decreasing the risk of CVD in old age. Correlation between high levels of homocysteine and coronary artery diseases is discovered 25 years ago, when for first time was verified that patients with hyperhomocysteinuria are potential candidates for developing early atherosclerosis in puberty and before 20 years of age. In these cases is verified the lack of some enzymes responsible for metabolism of Hcy, as result hyperhomocysteinemia occurs. Increased C reactive protein, positive history for any CVD disease, hypercreatinemia, hyperuricemia, hyperuremia, von Willebrand factor, old age, smoking, genetic predisposition and adiposity are important factors for developing CVD and HTAs. Homocysteine was discovered in 1932, and chemical analysis showed similarity with cysteine. For this discovery, Vincent du Vigneaud in 1955 was awarded Nobel Prize in Chemistry for his work on sulfur components, especially for synthesis of polypeptide hormone (3). Homocysteine is sulfenic acid of methionine and cysteine (4).

**Doc. Dr. Sci. Med. Lutfi Zulbeari, MD, PhD**

1- State University of Tetova, Faculty of Medical Sciences, Tetova, Macedonia.

Private Special Hospital for Nephrology and Hemodialysis ‘Vita Medical Group’ - Tetova, Macedonia.

Prof. Dr. Nasir Behxheti 1 - State University of Tetova, Faculty of Medical Sciences, Tetova, Macedonia.

Dr. Zamira Bexheti 1 - State University of Tetova, Faculty of Medical Sciences, Tetova, Macedonia.

Private Special Hospital for Nephrology and Hemodialysis ‘Vita Medical Group’ - Tetova, Macedonia.

4. Dr. Gazmend Zylbeari 2 – Private Special Hospital for Nephrology and Hemodialysis ‘Vita Medical Group’ - Tetova, Macedonia.

Mr. Phar. Mirlind Behxheti 2 - State University of Tetova, Faculty of Medical Sciences, Tetova, Macedonia.

Hcy in serum is found in three forms: 1% is in free form, 70-80% as residual sulfides and 20-30% in combined form with other thios.

(5) Homocysteine is synthesized from essential amino acid methionine. Cystathionine-β-synthetase is an enzyme, while pyridoxine (B6) is essential cofactor which converts homocysteine in cysteine. Hyperhomocysteinemia is a condition with raised homocysteine levels in blood above 15 μmol/L (6, 7, 8). High levels of homocysteine are recorded in patients after stroke as result of neuronal damage and overstimulation of NMDA receptors (N-methyl-D-aspartate receptor). Because hypothalamus controls cardiac function by sympathetic system, in patients with stroke cardiac function is impaired also. Homocysteine is known as risk factor for CVD for its negative effects on cardiovascular endothelium. CVD have high prevalence and still remain as main reason for high mortality and morbidity in world. Ethiology of CVD is multifactorial and most often they are result of narrowed or occluded coronary arteries (9, 10). Homocysteine as risk factor for CVD, stroke, thrombotic processes, vascular hypercoagulability and atherosclerotic processes is known since early 1950. Several studies have verified a high positive correlation between coronary diseases, chronic renal injury and hyperhomocysteinemia (11). Scientists thought on homocysteine as risk factor on developing CVD still are controversial. Some scientists believe high concentrations of Hcy are not a risk factor for CVD (12), while lot of research results show high positive correlation between raised Hcy and CVD diseases. Genetic mutations of C and S homozygote can cause severe hyperhomocysteinemia where Hcy concentrations are 40 times higher than normal. This disease have incidence of 1:100.000. Another rare genetic cause of hyperhomocysteinemia is because of homozgyote mutations of MTHFR-methylene tetrahydrofolate reductase. These individuals with MTHFR defects are exposed to early CVD. Homocysteine is independent risk factor for early atherosclerosis. Atherosclerosis is progressive inflammatory injury or arterial intimal layer, with increased permeability, lipidic deposition and calcification of intima. Correlation between hyperhomocysteinemia and atherosclerosis for first time was identified by McCully in 1969. Atherosclerosis is common pathological process which leads to CVD (myocardial infarction, atheromatous processes of carotid arteries, heart failure, stroke) (13).

Some of mechanisms of these effects are: endothelial disfunction, oxidative injury, increased collagen production, damage of arterial wall and increased C reactive protein in vitro and in vivo (14).

One study has shown that in patients with CVD Hcy levels during fasting are lower, compared with the same patients after fasting, with a statistical significance of p<0.00001 (15). Many in vitro studies have verified that homocysteine
causes dilatation of blood vessels and injury of smooth muscles and plays role in increased activity of HMGCoA reductase which in turn causes increased collagen production and early manifestation of atheromatous processes on coronary and cerebral arteries. In patients with hyperhomocysteinemia changes in intima and media of carotid arteries are confirmed (16). Role of homocysteine on endothelial malfunction is believed to be intermediated by mechanisms: oxidative stress, lipid peroxidation and NF-kB factor, inflammation and and inhibition ENOSI-endothelial nitrous oxide synthet-ase. Possible mechanism of hyperhomocysteinemia on stiffness of aorta still remain unknown. But there are verified facts that hyperhomocysteinemia plays potential role on arterial wall remodeling which causes injury of blood vessels, venous thrombosis and atherosclerotic processes. Hyperhomocysteinemia plays vital role on adhesion of platelets on endothelial cells and it has role on increasing levels of prothrombotic factors such as thromboglobulin, plasminogen activation and VII factor of coagulation which causes thrombus formation. It is verified that hyperhomocysteinemia favors LDL oxidation and onset of atherosclerotic processes. Many studies have concluded that 15-30% of cases with CVD are result of high concentrations of homocysteine in blood (11). In these processes many mechanisms are believed to be involved: genetic predisposition, folate deficiency, pyridoxine and cyanocobalamin. Correlation between Hcy metabolism and atherosclerotic changes of coronary arteries for first time were described by Carson and Neill which in the blood of one patient found defect on the metabolism of Hcy and high concentration in blood. Hcy metabolism proceeds in three pathways: a) by converting Hcy in Cystathionine-Beta-synthetase enzyme is increased and plays vital role in regulating the metabolism of Hcy and its concentration in blood and urine. Recent years studies have been made on the role of raised Hcy and onset of atherosclerosis in patients with CVD and hypertension, and all have confirmed that hyperhomocysteinemia is important indicator for the onset of early atherosclerosis in coronary and cerebral arteries (18). Many authors propose that medical treatment of homocysteine should begin even when homocysteine levels in blood are >9 µmol/L. In vitro experiments in animals have verified that raised Hcy damages the vascular endothelium and as result atheromatous processes in coronary arteries occur (19) with early manifestation of CVD. Many studies have verified that by lowering high concentrations of Hcy results in decrease of atherosclerotic manifestations of coronary arteries.

Atherosclerotic effect of hyperhomocysteinemia is developed in three mechanisms: a) Hcy with its toxic effect directly damages intima and media of artery wall; b) by oxidating low density lipoproteins (LDL) and c) by interfering with factors of coagulation. It is verified that every increase of Hcy for 10% increases the risk for atherosclerosis 10% also (20). Supplementing organism with 1-2mg folic acid, 10mg pyridoxine and 400 µg cyanocobalamine can normalise high levels of homocysteine (21,22,23). In literature three forms of homocysteine disorders are known:

- mild form: 16-30 µmol/L;
- moderate form: 31-100 µmol/L;
- severe form: >100 µmol/L.

2 Material and Method

As working material was used blood taken from patients veins and control group at 8am in room temperature of 19-24 C, in lying position (to avoid all anomalies and possible variations of 9-12% if the blood could be taken in sitting or standing position) after 12 hour hunger. Homocysteine and lipid profile were analysed in 360 patients with anamnesis for CVD and HTA ess, from whom 200 were males with mean age of =62.50 8.40 while 160 were females with mean age of =59.80 15.60. Control group was composed from 260 individuals, from whom 160 were males and 100 females with identical mean age of =58.70±15.20. Obtained results represent mean values obtained once in every three months in 3 year period. 5ccm serum with some drops of heparin was sent in Clinical Laboratory of University Clinic of Skopje.

<table>
<thead>
<tr>
<th>Table 1: Number of patients and control group by mean age and gender</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total pts</strong></td>
</tr>
<tr>
<td>N=360</td>
</tr>
<tr>
<td>M=N'-200</td>
</tr>
</tbody>
</table>
Table 1: Number of patients and control group by mean age and gender

| F=N²-160 | 59.80 ± 19.60 | 59.80 ± 15.60 |

Table 2: Tabelary presentation of patients by CVD and HTAess

| With a family history for CVD | 160 (42.8 %) |
| Arterial hypertension (HTA) | 120 (38.60 %) |
| APNS | 40 (9.50 %) |
| St. Post Infarctum Myocardi | 40 (9.50 %) |
| Smoker | 290 (62.50 %) |
| Control group N²= 260 (100 %) | The average age ± SD 58.70±15.20 |

Concentrations of Hcyt were determined according to Miller’s method of American Immuno-fluorescence with Immulite DPC machine, and normal ranges are =5-13 µmol/L, while lipid profile was determined by standard routinely methods

**Statistical analysis of the examined material**

Statistical basic methods that were used are the arithmetic mean value and standard deviations X ± SD. Comparative statistics and LPL lipid parameters between the two groups was analyzed by test called STUDENTOV and for examples of dependent or independent and non-parametric tests were used the tests: Mann-Whitney and Wilcoxon's test. Statistically significant The differences between the Group of patients and control group obtained the values of lipid parameters and test LPL analyzed the so-called ,, Anova Two-Factor "with statistical accuracy for p <5%, Namely p <statistical averages and proportional / x, p /) were tested with accuracy higher than 95%, or rather, for Mr. > SEM 1.78. The results of the lipid profile and Hcys presented in the form of graphcones, 0.0005. Dependence between parameters that are examined is calculated with linear regression formula (y = Bx + A) it is also calculated the coefficient of correlation ,, r "with statistical accuracy for p 'of less than 1% Namely p <0.0001. And the frequency distribution was tested with test c² The amount of change (z) between the mean values of parameters analyzed / arithmetic averages and proportional / x, p /) were tested with accuracy higher than 95%, or rather, for Mr. > SEM 1.78. The results of the lipid profile and Hcys presented in the form of graphcones,
3 Results

Table 3: Obtained results from patients with CVD and control group for Hcyt and lipid profile

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>ChT mmol/l</th>
<th>TG mmol/l</th>
<th>HDL-ch mmol/l</th>
<th>LDL-ch mmol/l</th>
<th>tHcy µmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with CVD, St.post MI, APNS</td>
<td>240</td>
<td>5.20 ± 1.20</td>
<td>2.90 ± 0.30</td>
<td>0.90 ± 0.26</td>
<td>4.20 ± 0.80</td>
<td>24.50 ± 5.20 ↑↑</td>
</tr>
<tr>
<td>Control group</td>
<td>260</td>
<td>4.90 ± 1.60</td>
<td>1.14 ± 0.50</td>
<td>1.80 ± 0.50</td>
<td>2.80 ± 0.40</td>
<td>7.40 ± 3.0</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.7400</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 4: Obtained results from patients with HTA ess and control group for Hcyt and lipid profile

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>ChT mmol/l</th>
<th>TG mmol/l</th>
<th>HDL-ch mmol/l</th>
<th>LDL-ch mmol/l</th>
<th>tHcy µmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with HTA ess</td>
<td>160</td>
<td>5.40 ± 1.50</td>
<td>2.80 ± 0.30</td>
<td>1.02 ± 040</td>
<td>3.5 ± 1.08</td>
<td>18.20 ± 6.40 ↑</td>
</tr>
<tr>
<td>Control group</td>
<td>260</td>
<td>4.90 ± 1.60</td>
<td>1.14 ± 0.50</td>
<td>1.60 ± 0.70</td>
<td>2.80 ± 0.60</td>
<td>7.40 ± 3.0</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.7400</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 3 shows significant difference for following analysed parameters in patients with CVD for TG= 2. 90 ± 0.30, HDL-ch=0.90 ± 0.26, LDL-ch= 4.20±0.80 and Hcyt=(24.50 ± 5.20 µmol/L) with p<0.0001 except for ChT where no significant difference between two groups was found (in patients with coronary disease ChT= 5.20 ± 1.20 mmol/l while in control group=4.90±1.60 mmol/l with p=0.7400). Concentrations of homocysteine and lipids in patients with CVD compared with control group showed significant statistical difference with p=0.0001, except for total cholesterol where no significance was recorded (p=0.7400), expected results and verified by many other multicentric studies. Table 4 results from group with HTA ess for all examined parameters showed significance compared with the control group especially for homocysteine ≈18.20 ± 6.40 which was object of our study, with p=0.0001. Hcyt levels in patients with HTA ess were lower than the group with CVD (24.50 ± 5.20) which verifies that high concentrations of Hcyt have bigger impact on the onset of CVD than arterial hypertension. Therefore all facts point that hyperhomocysteinemia have impact on CVD manifestations but the effect on the onset of arterial hypertension needs more studies with longer period of time and with more patients in order to verify or dismiss its impact on arterial hypertension because nowadays thoughts are contradictory (24,25,26,27,28).
Discusion

Hyperhomocysteinemia can be caused by deficiency of folate, vitamin B6 and B12 in food. An individual with deficiency of these abovementioned vitamins can develop raised levels of Hcyt and have risk from hyperhomocysteineemia. Disorders of homocysteine metabolism and other sulfuric amino acids in patients with renal injury are described in 1980 by Willen et al. for first time, who saw that uremic patients treated with HD had raised cysteine and Hcyt (29,48). High levels of homocysteine were found in patients with chronic renal injury also, with increased uremia. This disease -homocysteinuria- because of their patients for first time was investigated 25 years by substituting B6 and B12, organism can easily correct deficiencies of folate, pyridoxine, cyanocobalamin and vitamin E deficiency. (35,36,37,48). High concentrations of Hcy can be normalized by substituting 1 or 2 from above mentioned deficient vitamins. Homocysteinuria is geneticaly transmited disorde. In a patient who inherits 2 defective alleles the risk is much higher that in patients who inherebt 1 allele. It is verified that in 100 individuals 1 person inherehts 1 defective allele. Nair et al. in a study in an Indian population verified genetic mutations of Methylen-tetra-hydrofolate-reductase, which is main cause of hyperhomocysteinemia in this population (25,26).

Many studies have found that high levels of Hcyt are risk factor for the onset of atheromatous changes in coronary, cerebral and periferical arteries. It is found that during hyperhomocysteinuria the activity of cystathionine-Beta-synthetase is enormously increased, an enzyme responsible for Hcyt metabolism. Another study has found that every increase of homocysteine for 55 µmol/L is associated with CVD consequences for 20-25%. A new multicentric study which included 80,000 female individuals, for 14 years, found that onset of CVD was lower in the group which during that time consumed suplementary therapy with vitamins or consumed with food higher concentrations of abovementioned vitamins compared with the group who havent consumed enough of them (39).

Authors Victor and Hebert in their studies concluded that low levels of folic acid are as result of decreased absorption of vitamin B12 which is tightly related with old age (42). It is verified that by lowering Hcyt in serum the risk for atherosclerosis, CVD and stroke in patients with homocysteinuria decreases also. Even after many studies regarding to hyperhomocysteinemia experts still cant conclude and verify this theory. The reason of high homocystein decreases the risk for CVD (18,39).

Regarding to this, an 4 year study in 101 patients with CVD who every day consumed folic acid, pyridoxine and cyanocobalamin found a decrease in the size of their atheromatous plaques, even better results were obtained in those patients who before the study had higher levels of Hcyt. In case of hyperhomocysteinemia in patients with chronic renal failure still is unknown, and an appropriate therapy for normalizing Hcy in these patients doesnt exist. Experts suggest that patients with CVD should analyze their Hcyt levels, and those with levels from 9-10 µmol/L should be treated at least one month with substitutive therapy, this has shown positive effects. An recent study on positive effects of folic acid and vitamin B12 (combined or separately) on hyperhomocysteinemia has verified that by substituting B6 and B12, organism can easily correct Hcyt levels. In USA, Canada and Europe an study with 60,000 individuals, still ongoing, are studying the effect of raised Hcyt and onset of myocardial infarction, cerebrovascular embolia and possible ways of decreasing it (27). Some studies have concluded that hyperhomocysteinemia is result of conversion of hydrogen peroxide in free oxygen radicals and conversion of oxidated Hcy in Homocysteine disulfide. Effect of oxidated Hcy which is increased by hydrogen peroxide explains the LDL raise. Hydrogen peroxide causes endothelial desquamation, with inhibitory effect on prostacyclines and prostaglandines who are antagonists of platelet adhesions (28,29,30,31).

Many studies have verified that patients after undergoing stenting or angioplasty with normalized Hcyt levels have lower incidence of re-occuring of atheromatous processes compared with those who have high Hcy. A recent study, which has lasted 6
months, a time which in patients vitamin B6 and B12 was given found that cardiac events and need for revascularisation was 1/3 time lower compared with patients who havent consumed abovementioned therapy (32,44). High levels of Hcyt can be as result of cyanocobalamin deficiency which occurs because of vitamin B12 malabsorption as result of gastric atrophy, which is more often seen after age of 50. B12 deficiency causes anemia. If this deficiency is let untreated it causes damage to nervous system and early atherosclerosis. Individuals above 50 years of age are advised to consume folic acid and vitamin B12 because in this age most of them have gastric atrophy. An multicentric study concluded that females during menopause have raised homocysteine and an increase of coronary diseases, compared to females before menopause (33). From all what was mentioned above, question rises: which are definitive mechanisms who can normalise Hcyt levels in organism? how can we prevent hyperhomocysteinemia? The answer for the first question is: by substituting vit. B6, B12, tocoferol and folic acid. Regarding to the second question the answer is hard, because on the onset of early atherosclerosis many unknow factors are included, which are hard to control and correct, therefore more studies need to be made, with more patients and longer timespan, with more patients.Negative effects of hyperhomocysteinemia on coronary arteries are increased even more if it is associated with hypertriglyceridemia, hypercholesterolemia (LDL-ch, LDL-ox). It is fact that hyperhomocysteinemia is in correlation with folate, pyridoxine and cyanocobalamin deficiency (33,36). Consulted literature and many studies have concluded that in the ethnology of coronary artheriosclerosis many factors are included: genetic predisposition, environment, life style, sedentary life, obesity etc. There are facts that by suplementing vitamin B12 has decreased Hcyt concentrations with 17-30%. For decreasing Hcy and correcting dyslipidemia intravenous application of acetylcysteine is required. Many studies have shown that by aplicating folic acid, vitamin B12 and B6 can reduce Hcy levels for 35% (36-42). In a larger study, it was documented that patients with coronary disease who were treated with folic acid, after 2 year follow up homocysteine decrease for 18% occurred, but mortality didnt show significant reduction (34,35,43). Documented facts exist that folic acid, cyanocobalamin and acetylcysteine have positive effects on decreasing homocysteine in one side and improving blood vessel function in other side. Nevertheless to verifi or to dismiss abovementioned facts more studies need to be made, with more patients and more countries, so the final conclusion can be taken on the effect of folic acid, cyanocobalamine and acetylcysteine on improving endothelial function of blood vessels (42-48).

5 Conclusion

We can conclude that in our paper also high levels of Hcyt were recorded in patients with CVD and HTA ess. These results are in line with many other multicentric studies, on the role of Hcyt as new independent risk factor for early atherosclerosis and moderate effect on the onset of HTA ess. In abovementioned cases it is prefered substitutive therapy with folic acid, pyridoxine, cyanocobalamin, tocoferol, acetylsalicilates and other antioxidative agents, which clearly can prevent early atherosclerosis in CVD with: PTCA, CARB, AMI, APNS, Stening and prevention of stroke.


13. Okura T, Miyoshi K, et al.. Hyperhomocysteinemia is one of the risk factors for early atherosclerosis in CVD with: PTCA, CARB, AMI, APNS, Stening and prevention of stroke.


3 38. Hackam DG and others. What level of plasma homocyst(e)ine should be treated? Effects of vitamin therapy on progression of carotid atherosclerosis in patients with homocyst(e)ine levels above and below 14 micromol/L. American Journal of Hypertension,2000;13:105-100.


40. Hyperhomocysteinemia confers an independent increased risk of atherosclerosis in end-stage renal disease and closely linked to plasma folate and pyridoxine concentrations. Circulation 2006; 94 :2742-2744.


Adress of author:

Doc. Dr.Sci Med. Prim.Mr. Lutfi Zylbeari, MD, PhD
Department of internal medicine- Clinical hospital of Tetova
Faculty of medical sciences- State University of Tetova
dr-luti@hotmail.com