CORELATION BETWEEN HYPERHOMOCYSTEINEMIA AND CARDIOVASCULAR DISEASES (CVD) IN PATIENTS WITH CHRONIC TERMINAL RENAL FAILURE

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Abstract: End-Stage-Renal-Disease (ESRD) is clinical condition associated with progressive and irreversible injury of renal tissue in different renal and urinary tract diseases. In ESRD we have chronic decrease of glomerular filtration (GFR) and progresive elevation of creatinine, urea, uric acid, potassium etc. ESRD can be defined as summary of common biological and clinical disorders also known as chronic uremia. The progress of ESRD is affected by other factors also: primary disease, age, gender and genetic predisposition etc. The progres of ESRD depends on primary disease which causes injury of renal tissue and nephrones. Cardiovascular diseases still remain as main cause of invalidity, morbidity and mortality in patients with ESRD treated with hemodialysis (HD) compared to the population with other diseases. Beside known factors ,genetic predisposition, age, gender, arterial hypertension, diabetes, smoking, obesity, sedentary lifestyle, stress, oxidative stress, MIA syndrome (Malnutritio-Inflamatio-Atherosclerosis) , uremic dyslipidemia, hyperfibrionogenemia, C-reactive protein, von Willebrand factor), recent years in the ethiology of cardiovascular diseases (CVD) in uremic patients as new risk factor is counted and homocysteine (tHcy) with its respective values in urine and blood (hyperhomosyteinuria and hyperhomocysteinemia). Aim of this paper:Aim of this paper was to examine Hcy concentrations and lipid profile in patients with esrd treated with HD more than 36 months and positive anamnesis for CVD compared to control group of healthy individuals and the role of Hcyt as new indipendent risk factor on the onset of early arteriosclerosis and atheromatous processes of coronary arteries in patients with CVD. This paper also aimed to propose preventive measures for corection and treatment of hyperhomocysteinemia and hyperhomocysteinuria, which would decrease effects of Hcyt in cardiovascular system in uremic patients treated with HD. Values obtained of the total homocystein and lipids (Kol.Total, TG, HDL-ch, LDL-ch) and control group are presented with mean values and standard deviation X ±SD. In the results were also calculated correlation coefficient “r "statistical value of p ,," less that 1% (p <0.0001). Statistics comparative lipid parameters between the two groups were analyzed to test the so-called Studentov ,, t "while for examples dependent or independent and non-parametric tests were used tests: Mann-Whitney-U. Because that in 95% of patients ESRD is accompanied with dyslipidemia, therefore consequences of hyperhomocysteinema toward cardiovascular system are more expressed , we decided in our paper to make a lipid profile (total cholesterol-TCh, Tryglicerides-TG, Total lipids-TL, HDL-ch and LDL-ch). Hyperhomocysteinema is indipendent risk factor for CVD in end stage renal disease with high prevalence (85-100%) (1,2,3).

Index term: ESRD(End Stage Renal Disease), Total homocysteine(tHcy) Cardiovascular Diseases (CVD), Atherosclerosis, Lipid profile.

1 INTRODUCTION

Pathophysiologicmechanisms of hyperhomocysteinema in patients with esrd testify for a decrease and reduction of metabolism of homocysteine which can occur outside or in kidneys. Patients with ESRD show a significant decrease in clearance of plasma homocysteine 12 hours after consuming Hcy. Excretion of Hcy through urinary tract is an impossible mechanism because of low renal function and decrease of GFR rate. (4,5,6).Cardiovascular diseases and high mortality still remain as problem with high prevalence in hemodialysis centers in patients with esrd (7,8). Causes of this bad prognosis in patients with esrd are complex despite that CRF is result of renal malfunctions, congenital or aquired anomalies, different metabolic disorders but as main cause remains arterial hypertension, diabetes and dyslipidemia (9). Corelation between high values of homocysteine and coronary artery diseases is discovered 25 years ago, when for first time was verified that patients with hyperho-mocysteinemia are potential candidates for early develop-pment of early atherosclerosis of coronary arteries in puberty and below 20 years of age. In these cases is verified a deficiency of several enzymes which control Hcyt metabolism, as result high concentration of Hcyt in blood and urine occur. Elevation of C-reactive protein, history of cardiovascular diseases, hypercreatinemia, hyperuricemia, urea, von Willebrand factor, late age, chronic renal injury, adiposity and presence of microalbuminuria are important

factors for the rapid progres of chronic renal injuries toward terminal stage when HD treatment is needed (10).

Nova day studies suggests that hyperhomocysteinemia in the development of arteriosclerosis of coronary arteries is with same effect even when LDL-ch levels are in normal range. Many studies have concluded that 15-30% of cases with CVD are as result of high levels of homocysteine in blood-hyperhomocysteinemia (11). In these processes is believed to be included many factors: genetic predisposition, folate pyridoxine and cyanocobalamin deficiency in blood or impaired metabolism of Hcyt. Corelation between Hcyt metabolism and aterosclerosis of coronary arteries for the first time was described by Carson and Neill, who discoverd a defect of Hcyt metabolism in the blood of one patient, and high levels in blood and urine. Normal excretion of Hcyt from organism is 3.5-10 μmol/L or 0,1% of daily production. Hcyt metabolism occurs in three pathways: 1. Conversion of Hcyt in Cystathionine and cystine with the help of pyridoxine as cofactor. 2. conversion of Hcy in methionine in direct mediation by cyanocobalamin and tetra folic acid and
(3) frombetaine, a metabolism which is strictly isolated in liver only (12). When Hcyt levels in blood are elevated, the activity of *cystathionine-Beta-synthetassae* is increased and plays important role in regulation of Hcyt metabolism and its concentration in blood and urine.

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Concentration	Mild form	Moderate form	Severe form
Hcut μmol/L	16-30	31-100	>100 μmol/L↑↑

Recent years lot of studies are made on the role of high concentrations of Hcyt and onset of arteriosclerosis of coronary arteries in uremic patients and all have concluded that high levels of Hcyt in blood are important parameter and early information for onset of early arteriosclerosis (arthe-rosclerosisprecox-prematura) in coronary and cerebrovas-cular arteries (13). All studies testify the same conclusion that high values of Hcyt are in high corelation with the onset CVD, recurrent thrombembolia, stroke and indipendend for cholesterol levels even in cases when cholesterol levels are normal. Arterioclerotic effects of Hyperhomocysteinemia are deve-loped in three ways: 1.Hcyt with its toxic effect directly injures inner cells of artery wall; 2. by interfering with coagulation factors and 3. with oxidation of low density Lipoproteins (β-LDL) because oxidated LDL is easily receptive for macrophages. It is verified that every elevation of Hcyt for 10% increases the risk for arteriosclerosis of coronary arteries for 10% also (11). Use and supplement of the organism with 1-2mg folic acid, 10mg pyridoxine and 400 μg cyanocobalamineffectivly corrects and normalizes high levels of homocysteine (14,15). Hcyt abnormalities are classified in three forms, shown in the table (1):

Many studies have concluded that with the decrease and normalisation of Hcytconcetrations, clearly are decreased consequences from arteriosclerosis of coronary arteries also. It is preferred and should be treated with drugs even when Hcyt levels are above 9 μmol/L. In vitro experiments in animals have verified that high Hcyt levels damages vascular endothelium with consequence atheromatousproceses of coronary and cerebraly arteries and early manifestation of CVD.

AIM OF THIS PAPER

Aim of this paper was to examineHcy concentrations and lipid profile in patients with IRKT treated with HD more than 36 months and positive anamnesis for CVD compared to control group of healthy individuals and the role of Hcyt as new indipendent risk factor on the onset of early arteriosclerosis and atheromatous processes of coronary arteries in patients with cardiovascular diseases. This paper also aimed to propose preventive measures for corection and treatment of hyperhomocysteinemia and hyperhomocyste-inuria, which would decrease effects of Hcyt in cardiova-scular system in uremic patients treated with HD.

2 MATHERIAL AND METODS

As working matherial was used blood taken from patients and control group veins in 8 a.m in room temperature between 19-24^{o}C, in lying position (in order to avoid all anomalies and possible variations 9-12%, if blood is taken in siting or standing postion) after 12 hour hunger. All patients were treated with bicarbonate dialysis with high flux dialyser and with HD frequence of: 3 times a week for 4.5 hour. Homocysteine and lipid profile was analysed in 80 patients, (from whom 45 were males and 35 females) with coronary artery disease, with mean age of 56.50 ± 8.40. Obtained results represent mean values obtained in one month after five consecutive measurements. Blood taken for analysis (5ccm serum mixed with some heparin drops) was send in the Institute of Clinical Biochemistry and Clinical Laboratory of University Clinic of Skopje. Control groups is

consisted of 80 healthy individuals with mean age 58.0 ± 6.30.

Table 2:Tabelary representation of patients according to coronary diseases

Total number of patients= 80(100%)	Males = 45b(55%), Females =35b(45%)
Mean age	56.50 ± 8.40
With familiar anamnesis for CVD	30 (30.8 %)
Arterial hypertension	38 (40.8 %)
APNS	30 (30.8 %)
St. Post Infarctum Myocardi	25 (31.20 %)
Smoker	50(62.50 %)
Control group = 8 0 (1 0 0 %)	*Mean age* =58.0 ± 6.30

Mean age of patients with coronary diseases was 56.50±8.40 while in control group 58.0±6.30. Data was processed with standard statistical programe Windows (Statistics for Windows software ver. 6.0 A). Hcyt levels were determined according to American Imunolumniscente method-Miller, with Immulite DPC machine, with normal values between 5-13 µmol/L. Lipid profile was determined by standard routine methods.

Tabela 3: Reference Values and methods by authors whose blood Hcyst are determined, and Lidids profiles are Presented in table 3.

Lipid profile	Normal values	Authors
LT	4-10g/l	Zollner & Kirsch [22]
TG	0,68-1,70 mmol/l	G. Buccola& H. David [24]
TCh	3,1-5,2 mmol/l	CC. Allain et al [25]
LDL-ch	<3,4mmol/l, high risk: >4,1 mmol/l	Friedewalde&Fredrickson [23]
HDL-ch	>1,6mmol/l, high risk: <0,9 mmol/l	G. Warnick et al [26]
tHcy	5-13 µmol/L	*Miller JW* [27]

3 Statistical processing of material examined

Values obtained of the total homocystein and lipids (Kol.Total, TG, HDL-ch, LDL-ch) and control group are presented with mean values and standard deviation X ±SD. In the results were also calculated correlation coefficient “r "statistical value of *p* ,," less that1% (p <0.0001). Statistics comparative lipid parameters between the two groups were analyzed to test the so-called Studentov ,, t "while for examples dependent or independent and non-parametric tests were used tests: Mann-Whitney-U. significant statistics differrences between the group of patients and control group obtained values of the parameters of lipids, and Hcyt were analyzed to test the so-called ,, Anova Two-Factor "statistical Worth ,, *p* ” lesser of 5 %, namely p<0.0005.

Results obtained

Table 4: Obtained results from patients and control group for Hcyt and lipid profile (ChT,TG,HDL-ch,LDL-ch).

	N°	ChT mmol/l	TG mmol/l	HDL-chmmol/l	LDL-ch mmol/l	tHcy µmol/L
Experimental group	80	5.00 ± 1.20	2.60 ±0.30	0.90 ± 0.30	3.95 ± 0.80	19.50±7.40 ↑↑
Control Group	80	4.90 ± 1.20	1.10 ± 0.40	1.60 ± 0.70	2.80 ± 0.60	9.60 ± 5.80
p		*0.7500*	*0.0001*	*0.0001*	*0.0001*	*0.0001*

In table 4 is noticed difference with statisticall significance for analyzed parameters. [*TG(2.60±0.30),HDL-ch(0.90±0.35),LDL-ch(3.95±0.80) and Hcyt (19.50 ± 7.40 µmol/L*) with *p<0.0001* exept for ChT where results from experimental group and control group doesnt show significant difference (in patients with coronary diseases *ChT=5.00±1.20 mmol/l* whereas in control group *=4.90±1.20 mmol/l* with *p=0.7500*. TG concentrations between two groups show significant difference with *p=0.0001*, in patients with coronary diseases TG concentration was elevated=*2.60 ± 0.30 mmol/l* whereas in the control group TG=*1.10 ± 0.40 mmol/l,* expected results and verified in many other multicentric studies. High concentrations were obtained for other fractions also: *LDL-Ch* in patients=*3.95±080mmol/l* while in control group=*2.80±0.60 mmol/l* with *p<0.0001*. *HDL-Ch* fraction in patients with coronary diseases =*0.90 ± 0.30 mmol/l,* compared with the control group =*1.60 ± 0.70 µmmol/ L* with *p<0.0001*. Total Hcy in experimental group = *19.50±7.40 µmol/L* with statisticall significance of *p<0.0001* compared with the control group =*9.60 ± 5.80 µmol/L,* which is in line with other authors conclusions (17,18,19,20,21).

4 DISCUSION

In recent years, attention of nephrologists is concentratet in examination of metabolism of homocysteine as new risk factor for cascular diseases of cerebral, coronary and periferic arteries with early manifestation of arteriosclerosis (artherosclerosis praecox) in patients with renal insuficiency in terminal stage. Disorders of homocysteine metabolism and other sulfuric amino acids in patients with esrd for first time were described in 1980 Wilcken et al. who saw accumulation of excess homocysteine and cysteine in uremic patients treated with HD (28). Some studies has shown taht in uremic patients every elevation of Hcyt for 1 µmol/L increases the risk of CVD for 1% (29). Yet reaminsun know the impact and arteriosclerotic effect of high concetrations of Hcyt in early manifestations of CVD, but it is believed that is a result of endothelium malfunction or abnormalities in coagulation factors and platelets (30). In healthy individuals, Hcy concentrations can be decreased by using folic acid. This B vitamine is converted in 5-methyltetrahydrofolate and gives one methyl group to homocysteine. In patients with CVD, a dose of 400-600mg does rapid decline of 20-30% of plasmatic concentrations of Hcyt whereas in patients with ESRD despite application of high doses folic acid doesnt show decrease of Hcyt concentrations in blood (31). Coreleation between hyperhomocysteinemia and CVD in uremic patients began to be investigated 25 years ago when scientists discovered with a rare disease

called *homocysteinuria as result of high concetrations of homocysteine in urine and blood* are potential candidates for developing atheromatous processes of coronary arteries in young age (before puberty). In these cases it is verified abscence of enzymes which mediates Hcyt metabolism, therefore we have accumulation of excess homocysteine in blood and urine (32).

Homocysteine is amino acid, product of Demethyltion-Methionin and precursor of Cysteine-Byosinthases (17). It was believed that homocysteineisnt present in blood, but it was supposed that Hcyt in humans exists as substrate with unknown origin. Later it was discovered that 70% of homocysteine together with plasmatic proteins form a complex homocysteine-albumine. Nowadays studies have verified that 15-30% of coronary diseases are tightly linked with high concetrations of Hcy in blood, where important role play: genetic predisposition, folate, pyridoxine, cyanoco-balamin and vitamine E deficiency (33,34,35). High concentrations of Hcy can be normalized by compensating the component which is deficient.

Homocysteinuria is inhereted disease. If the patients iherits two alleles from each parent, the risk for coronary disease will be higher comapred with patients who inherits only one allele. Nair et al. in one study with indian population have verified that genetic mutations in Methylen-tetra-hydrofolate-reductase is main reason of hyperhomocysteinuria in this population (18,19).

Many studies have documented that high levels of Hcy are counted as new risk factor for onset of arteriosclerotic processes in coronary, cerebral and perfieric arteries. It is verified that in hyperhomocysteinemia activity of *cystathionine-Beta-synthetasae*is increased and this enzyme is responsible and important factor in metabolism and levels of Hcy in blood. Another study has found that eleveation of homocysteine for 5 µmol/L above normal levels is associated with consequences and CVD for 20-25%. A new study which included more than 80.000 female individuals with duration of 14 years, found that incidence of arteriosclerosis is lower in those females who consumed vitamins or high doses of folic acid and pyridoxine in daily meals compared with females which in theri daily meals havent consumed enough of above mentioned vitamins (36). Victor and Hebert in theri study have proved that low concentration of folic acid is result of malabsorbtion of B12 which is corelated with eldery people. It is proved that by decreasing concenctrations of Hcyt in serum in same time decreases the risk of artheriosclerosis in patients with homocysteinuria. Despite many studies about hyperhomocysteinemia, experts still are not ready to make final conclusion that any decrease of homocysteine levels decreases the possibility of stroke and cardiac accidents in patients with mild elevation of homocysteine (13,37). Another four year study with 101 patients with CVD who consumed everyday folic acid, pyridoxine and cyanocobalamin by usin ultrasonography of carotid arteries was discovered a reduction of

ateromatous- plaques. Cause of hyperhomocysteinemia in patients with esrd is still unknown, and appropriate therapy for reducing Hcyt levels still isnt found. Supossedly that the disorder of Hcyt metabolism in to patient with ESRD is signifycantly because is known the convertation of Hcyt in Methionin is delaydet and reductet more than 30 %. Experts suggestions are that individuals with CVD which cant be explained by inhereted factors or other risk factors, and with positive anamnesis for early arteriosclerosis should be investigated for Hcyt levels, and between 9-10 µmol/L should be treated with therapy at least one month, a therapy that shows great results. Another contemporary study regarding positive effects of B6 and B12 substi-tution in patients with hyperhomocysteine-mia found that by substituting B6 and B12 (combined or separately) helps the organism for correcting high levels of Hcyt. In USA, Canada and Europe (a study including 60.000 individuals, which is still ongoing) are studied effects of high Hcyt levels, onset od myocardial infarction, thromboembolia and possible ways reducing Hcyt (20). Some studies suggest that hyperhomocysteinemia is result of conversion of hydrogen peroxide into oxygen radicals and by so converting oxidized Hcy in bisulfidHcy (21). Raisd levels of oxidized LDL-ch can be explained by increasing activity of oxidized Hcy from hydrogen peroxide. Hydrogen peroxide affects endothelial desquamation of blood vessels with inhibitory effect on prostacyclines and prostaglandins, antagonists of platelets aggregation (21,38,39,40). Many studies have found that in patients after angyoplastic procedures by normalizing Hcy levels decreases consequences of ateromatous plaques also compared to patients with high Hcy. One most recent study shows that patients treated with vit. B6, vit.B12 and folic acid have decreased risk for new cardiac attacks and need for repeteti vere vascularisation by 1/3 compared with patients who have not consumed abovementioned therapy (41). High levels of Hvyt can be associated with cyanocobalamindefficiency which occurs as result of vit b12 malabsorbition in individuals with gastric atrophy. B12 defficiency causes anemia, if is let untreated causes heavy damage in nervous system and early arteriesclerosis. Patients above 50 years of age who consume folic acid daily (1mg) are advised to consume 25mg Vit.B12 also because after 50 years of age incidence of gastric atrophy is increased. One multicentric study found that females after menopause have higher levels of homocysteine and therefore higher risk of coronary artery diseases compared to females before menopause (42).From all what is above mentioned, a question arises: which are mechanismis that definietly will normalize Hcy concentrations and how can we prevent and cure hyperhomocysteinemia and hyperhomocysteinuria as new independent risk factor of early arteriosclerosis. We can easily answer first question: by substitutive therapy with B6,B12, folic acid, and tocoferol. Regarding to second question, it is harder to answer because the

onset of early arteriosclerosis is corelated with known and unknown factors which are hard to be controled, therefore more studies have to be made, in many countries, with longer duration and with more patients. Negative effects of hyperhomocysteinemia on coronary arteries are incresed if it is associated with elevation of triglycerides and cholesterol, especiallt LDL-ch and LDL-ox. Corelation between hyperhomo-cysteinemia and folate, pyridoxine andcyano-cobalamin deficiency has been established (43). Consulted literature and many other studies have found that ethiology of coronary arteriosclerosis is multifactorial and as result of interaction between genetic predispositon, environment, life style, obesity etc. Therefore experts of this subject with the help of modern laboratory and genetic technology will try to put light on the exact mechanisms on how Hcy affects etheiopa-thogenesis of arteriosclerosis of coronary arteries so in the near future adequate preventive measures can be proposed. There are conclusions of many studies that by suplementing B12 vitamine has decreesed homocysteine levels for 17-30%, also intravenous application of acetylcysteine has showen results on decreasing Hcy levels and correcting dyslipidemia and therefore improving periferic circulation. Use of different modalities of dialysis (high flux membranes covered with tocoferol) have showenexellent results on lowering homocysteine concentrations (44-49). Scholze et al. in uremic patients used 5g acetylcysteinei.v during dialysis sessions and found remarkable decrease of Hcy from 20 µmol / L before HD to 2,2 µmol / L after HD. Acetylcysteine effect remained till the dose of next dialysis. Many studies have verified that use of folic acid, B12 vitamine and pyridoxine decreases Hcyt levels in nearly 35%, also the degree of reobstruction of coronary artery decreases and revascularisation is improved (51). In one larger study it was found that patients with coronary artery disease which have taken folic acid and have been followed nearly 2 years, homocysteine level was decreased for 18% but mortality from CVD did not show siginificant decrease despite lowering of Hcy (52). Other studies in uremic patients terated with HD have verified that despite positive effects on lowering homocystene levels, folic acid can improve the fundtioning of vlood vessels with the help of mechanisms which are not corelated with the Hcyt levels (53). To verify abovementioned results or to chalange them many other studies need to be made, with more patients and countries so final conclusions on the effect of folic acid, cyanocobalamie and acetylcysteine can be made regarding to the endothelial improvment of blood vessels (54,55).

5 CONCLUSION

We can conclude that in our paer obtained results form uremic patients with CVD treated with HD and are in line with many other multicenctric studies, on the role of Hcyt as new indipendend risk factor for early arteriosclerosis of coronary arteris. In abovementioned patients it is prefered substitution of folic acid, pyridoxine, cyanocobalamine, tocoferol,acetylcysteine and other antioxidative agents which obviously can prevent praecox arteriosclerosis as result of hyperhomocysteinemia in uremic patients treated with chronic HD and in patients after: PTCA, CARB, myocardial infarction, angina pectoris, Stening and prevention of stroke.

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