

APOLIPOPROTEINI E- POLYMORPHOSIS AT UREMIC PATIENTS WITH HEMODIALYSIS

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Abstract:The metabolism disorders of apolipoproteins, recently are considered as one of the most relevant factors in the appearance of atherosclerotic, cardiovascular and cerebral-vascular diseases at the patients with renal chronic insufficiency (RCI) and those treated with chronic hemodialysis (HD) (1,2). The appearance of the dyslipidemia is noticeable since the early stages of the weakening of kidneys, therefore the examination and etio-pathogenesis of the apolipoproteins, in this concrete case the Apolipoprotein – E at these patients, can evidently impact on the prevention of the early cardio-cerebral-vascular and atherosclerosis diseases at the patients with renal chronic terminal insufficiency (RCTI) treated with continual hemodialysis (2). The apolipoprotein – E is a major component of the plasma apoprotein with a large number of biologic actions with a great relevance in the metabolism of lipoproteins. Aside from the known impact of the polymorphism at the apolipoprotein – E in the profile of lipids in the premature pathogenesis of atherosclerosis, and the development of neurodegenerative disorders, apo-E, also plays a great role in the etio-pathogenesis and the acceleration of the renal chronic insufficiency. A large number of studies have verified that the polymorphism of apo-E is and is considered as the main indicator of the levels of plasma lipids at the patients with Renal Chronic Terminal Insufficiency (RCTI) treated with HD. Besides that they can influence in the fast progress of the RCI, the development of diabetic nephropathy, the risk from cardiovascular diseases, also influence the degree of the glomerulopathy, and the mesangial and glomerular functions in a local microcells level of the kidneys at the uremic patients. Lately, it has been proved that certain mutations of apo-E and its polymorphism are closely related with a lipoprotein nephropathy, called *lipoprotein glomerulopathy*. Purpose of the paperThe aim of this research it is to determine the Apolipoprotein-E concentrations and its effects as well as the impact of Apo-E in the appearance of cardiovascular, cerebrovascular and early arteriosclerosis diseases at patients with IRKT treated with repeated hemodialysis. As examination material was used the blood taken from the vein of 120 patients treated with hemodialysis and of the controlling group = 120, taken at the 08:00 o'clock in the morning, in the room temperature from 19-24°C, in lying position. The blood for analysis has always been taken before the sessions of hemodialysis (HD) after a hunger condition of 12 hours, with 5 consecutively measurements and without the usage of the hypolipidemic medications. The attained results present the average values obtained from the five measurements in identical conditions. The obtained blood for examination (3ccm serum) with some drops of heparin has been sent for analysis in the Institution of Clinical Biochemistry at the Clinical Center of the Medical Faculty in Skopje. The profile of apolipoprotein –E was analyzed at 120 patients from whom 66=males and 54=females cured with continuous hemodialysis over 24 months in the Department of Nephrology with Hemodialysis at the Clinical Hospital in Tetovo and the Clinical of Nephrology in the Medical Faculty in Skopje. **GAINED RESULTS** From the Table 4 all the uremic patients treated with HD manifested high values of apolipoproteine-E and, compared to the control group of the healthy persons (apo-E=3.20+- 2.80mg/dl) there was a significant statistic difference with p=0.0001 from all the basic diseases which lead to hemodialysis, but the fact is that patients with diabetes and diabetic neuropathy have shown higher values of apo-E in comparison to other people with basic diseases (renal polycistose=7.68+-3.50 mg/dl etc.) . Higher values were detected in patients with arterial hypertension(6.80+-3.20 mg/dl), values that are in a correlation with many studies concerning apo-E.

Index terms: Apolipoproteina-E (Apo-E); Uremia, Hemodialysis.

1 Introduction

Apolipoproteins are constituent proteins of the lipoprotein macromolecule, specific for each class of them. With the lipids of the lipoprotein molecule they are related by using the hydrophobic peculiarities of the fatty acids from the phospholipids and the polar part of the polypeptide chain (a process of ionic interaction between phospholipids and the pairs of amino acids with an opposed electric load at the alpha helix at the apoproteins. As the essential factor of presenting cardio-cerebral-vascular disease and early atherosclerosis in patients treated with frequentative haemodialysis, metabolism disorder of alipoproteins has an important role.

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Genetic factors for the appearance of cardiovascular, cerebro-vascular and early atherosclerosis diseases in patients are: the disorder of reverse (HDL-ch) transportation, the inappropriated expression of B-receptors comparing with E-receptors, reduced conversion of VLDL to IDL and to LDL-ch. Changes of Apo proteins in patients treated with HD includes all the parts of lipoproteins LPs, hypertriglyceridemia due to redundant amount of triglycerides in the structure of VLDL, IDL, LDL-ch and HDL-ch. Apolipoprotein-E is a component of lipoprotein receptors of liver and it clearly affects the clients of particles of lipoproteins. Apolipoprotein-E is glycoprotein that is found in the structure of α , β , Pre- β lipoproteins. The patients treated with peritoneal dialysis with permanent surgeries are identified low values of apolipoproteins-E compared in patients treated with chronic bicarbonate haemodialysis. Variations of Apo-E significantly affect the metabolism of fats and lipoproteins in patients with IRKT as well as the healthy population. LDL-ch is remarkably increased in carriers of ApoE-4 while the other lipid fractions (TG, HDL-ch and total cholesterol) did not differ in homozygote compared to ApoE-3 and ApoE-4 (12). From all the above we conclude that the use of different modalities of treatment with dialysis significantly affect the metabolism of apoproteins and reduce the progress of the early arteriosclerosis in IRKT patients treated with dialysis. Uremic patients often have high levels of allele of ApoE-4 (in order of indented levels of plasmatic lipids), is closely linked with a prevalence rate of increased accelerated

atherosclerotic processes (atherosclerosis praecox) coronary arteries, cerebral and those peripheral with a high incidence of cardiovascular (acute myocardial infarction, ischemic heart disease, cerebrovascular stroke) and with a high degree of mortality (approximately 60%) of uremic patients treated with haemodialysis (14). Numerous studies have verified that the highest concentrations of Apo-E respectively mostly allele E-4 plays an important role with early onset of Alzheimer's disease. Abnormal metabolism of lipoproteins has an important role in arteriosclerotic process in patients with IRKT. The uremic dyslipidemia is characterized by increased levels of total cholesterol (TCh) triglycerides (TG), LDL-ch increasing the level of oxidative cholesterol (LDox) apolipoproteins-B100 (or B-100), lipoprotein (a), apolipoproteins C while characterized with low levels of HDL-ch proatherogenic, low levels of apolipoproteins A-1 (or A-1) (15). Patients with IRKT are mostly expressed with type IV, of secondary hyperlipoproteinemia (according to Frederickson's classification), in which they dominate the high concentrations of triglycerides (hypertriglyceridemia values of 28-100%) (16). It is assumed that subtle qualitative changes are registered in morphology (size) of lipoproteins' particles, in patients with IRKT, it remarkably increase the impact of the atherogen (increased affinity with adhesion) in subendothelial lateral oxidized LDL-LDlox, LDL, HDL (minor particles) with frequent atherosclerotic injuries of CVS and CBVS, with lethal consequences in medical centres of haemodialysis (17). It is about ischemic heart disease, peripheral cerebro-vascular disease and stroke. B1-HDL is of minor sub fraction that indicates as the initial acceptor of free cholesterol emanates from cells to the liver. In influence of the lecithin-cholesterol-acetyl-transferase (LCAT, B1-HDL passes to LHDL-ch. In normal plasma LCAT affects the maturity of HDL, by converting poor HDL with lipids in HDL spherical enriched with fats. In uremic patients the activity is reduced to 30% and the above described optimum conversion is reduced. Clinical experimental examinations (the incubation of plasma in uremic patients with or without LCAT inhibitor) verify the aforementioned position and certify that early atherosclerosis it is directly dependent upon on disordered catabolism β 1-HDL (18, 19, 20). At patients treated with chronic repetitive haemodialysis the activity of Lipase-Triacylglyceride-Hepatic (LTGH) it is also reduced for 33-45%. The activity of systemic Lipoprotein Lipase (LPL) it is reduced as a result of toxin accumulations or cytokines-Interleukin-1, Interleukin-6, Interleukin-1 α , Interleukin-1 β (21, 22, 23), and it is counted as the cause of pathologic disorders (the concentration of HDL-ch and ApoA-I is reduced while the concentration of triglycerides LDL-ch, ApoB-100, Apo-E, Apo-C, Lp(a) it is increasing) followed by increased prevalence of atherosclerotic vascular disease (24).

2 Methodology and materials

As examination material was used the blood taken from the vein of 120 patients treated with hemodialysis

and of the controlling group = 120, taken at the 08:00 o'clock in the morning, in the room temperature from

19-24°C, in lying position. The blood for analysis has always been taken before the sessions of hemodialysis (HD) after a hunger condition of 12 hours, with 5 consecutively measurements and without the usage of the hypolipidemic medications. The attained results present the average values obtained from the five measurements in identical conditions. The obtained blood for examination (3ccm serum) with some drops of heparin has been sent for analysis in the Institution of Clinical Biochemistry at the Clinical Center of the Medical Faculty in Skopje. The profile of Patient separation according to initial kidney disease it is presented in tabel 1.

apolyprotein –E was analyzed at 120 patients from whom 66=males and 54=females cured with continuous hemodialysis over 24 months in the Department of Nephrology with Hemodialysis at the Clinical Hospital in Tetovo and the Clinical of Nephrology in the Medical Faculty in Skopje. During the exami-nation of apolyproteins, was also analyzed the profile of lipids. During our work, we also separated the patients according to their main-causative disease of the renal chronic terminal insufficiency.

| Patients separation by underlying disease | |
|---|---|
| Total number of patients N^o=120 | Male = 66(55 %), Female= 54(45%) |
| Average age (years) | 59.5±12,8 |
| Glomerulonephritis (GN) | 30(25%) |
| Arterial hypertension with nephroangioscle-rosis sec | 28(23.3%) |
| Diabetes Mellitus (DM) | 18 (15%) |
| Interstitial nephritis (IPN) | 16(13.3%) |
| Adult Renal Polycystosis (ADRP) | 12(10%) |
| Unknown Nephropathy | 9(7.5%) |
| Obstructive uropathy (NUOP) | 7(5.8%) |
| Group controller = 120 (Males =66,Females =54) | Average age (years) =58.5±8,1 |

Hemodialysis frequency was three times per week,for four half past hours(F6 HPS and 5HPS,Fressenius &Hemomed) with $\geq 1-1.3m^2$,sterilized with high pressure steam. Controller group consisted of=120 (males=66 and females 54) healthy people with an average age=58,5±8,1. Together with Apoliproteins-E we designated the lipid profile Apolipoprotein-E of frozen plasma was determined by the help of the method Vincent –Viry M and associates (25, 26).

Reference values of the parameters analyzed are presented in table no.2

| Lipid profile | Reference values | Authors |
|---------------|--|-------------------------|
| LT | 4-10 g/l | Zollner&Kirsch |
| TG | 0,68-1,70 mmol/l | G.Buccola&H.David |
| ChT | 3.1 – 5.2 mmol/l | CC.Allain et al |
| LDL-Ch | < 3.4mmol/l higher risk > 4,1mmol/l | Friedewalde&Fredrickson |
| HDL-Ch | > 1,6mmol/l, higher risk < 0,9 mmol/l | G.Warnick et al |
| Apo-E | 2.7- 4.5 mg/dl | Vincent-Viry M |

3 GAINED RESULTS:The results obtained were processed in a statistical program Windows(Statistics for Windows software) version 6.0 A,Stat soft Inc.Tulsa ,OK,USA) with average values and standard deviation S±SD.
Table number 3. The lipid obtained results of patients with IRKT and controller group are shown in table number 3.The results obtained from the lipid fractions (ChT ,TG,HDL-ch,LDL-ch) for the patients and controller group

| | N°=120 | ChT(mmol/l) | TG(mmol/l) | HDL-ch(mmol/l) | LDL-ch(mmol/l) |
|------------------|--------|-------------|------------|----------------|----------------|
| Patients | 120 | 5.40±1.60 | 3.60±1.20 | 1.02±0.20 | 4.60±0.40 |
| Group controller | 120 | 4.80±1.40 | 1.14±0.80 | 1.50±0.60 | 3.10±0.40 |
| P | | 0.0001 | 0.0001 | 0.0001 | 0.0001 |

From the table is noticed a significant difference between patients treated with HD and the group controller of the values of lipid fractions (ChT,TG,HDL-ch,LDL-ch) with $p < 0.0001$.

Table number 4.The results of the values obtained for Apo-E by patients according to basic disease and group controller

| Total number of patients =120 | Apo-E mg/dl | p |
|---|-----------------|--------|
| Glomerulonephritis (GN) | 7.87±6.08 mg/dl | 0.0001 |
| Arterial hypertension with nephroangiosclerosis | 6.80±3.20 mg/dl | 0.0001 |
| Diabetes Mellitus (DM) | 8.06±3.80 mg/dl | 0.0001 |
| Interstitial nephritis (IPN) | 7.18±3.40 mg/dl | 0.0001 |
| Renal Polycystosis (ADPBB) | 7.68±3.50 mg/dl | 0.0001 |
| Unknown Nephropathy | 7.40±3.45 mg/dl | 0.0001 |
| Obstructive uropathy (NUOP) | 7.60±.60 mg/dl | 0.0001 |

| | | |
|--|------------------------|---------------|
| Group controller N^o= 120 | 3.20±2.80 mg/dl | 0.0001 |
|--|------------------------|---------------|

From the Table 4 all the uremic patients treated with HD manifested high values of apolipoproteine-E and, compared to the control group of the healthy persons (apo-E=3.20+- 2.80mg/dl) there was a significant statistic difference with p=0.0001 from all the basic diseases which lead to hemodialysis, but the fact is that patients with diabetes and diabetic neuropathy have shown higher values of apo-E in comparison to other people with basic diseases (renal polycystose=7.68+-3.50 mg/dl etc.) . Higher values were detected in patients with arterial hypertension(6.80+-3.20 mg/dl), values that are in a correlation with many studies concerning apo-E.

4 DISCUSSION

Dislipidemic factors in patients with ESRD treated with continuous hemodialysis come with different etyologies. The main factors are: reduced activity of the enzyme lipoprotein lipase(LPL), Triglyceride Hepathal Lipase (TGHL),increased accumulation of the uremic toxins, increased concentration of Apo-E, metabolic disorders of lipids and other apolipoproteins (Apo-A,B,C,Lp(a),C-3) and para-tiroidic hormone(31,32,33,-34,35). Apo-E in the plasm circulates like a part of hilocrones (HM),VLDL ,HDL,HDL-ch,HDL-2. It synthesizes with hepatocites (80-90%), macrofags, brain astrocits and the smooth cells of the muscles. Apolipo-proteine-E takes part in transport and distribution of lipids(mainly choles-terolic) in tissues (especially brain tissues) and is an important factor in the catabolisation of lipoproteins (LPS) helped by the receptor cells of HM"remnant" VLDL and ome subclasses of HDL. Apolipoprotein E (apo-E) is a protein of 34.200-kd consisted of 299 amino acids. Apolipoprotein-E is a polymorphic pro-tein which derives from the chromosome 19q13.2, has 3 major alels: Apo-E2,Apo-E3 and Apo-E4. The codes for the 3 main izoforms of Apo-E are: E2 (Arg1583Cys), E3 (maternal isoform), E4 (Arg1123 Cys). All of the three major subclasses: ApoE-4(15%), ApoE-3(77%),AND ApoE-2(8%) form 6 heterozygotic polymo-rphisms of ApoE: ApoE3/3, ApoE4/4, ApoE2/2, ApoE3/2, ApoE4/2 and ApoE4/3. The referent values of ApoE in the plasma are: 2.70-4.5 mg/dl. Low concentrations of ApoE are found in hypercorticisim , meanwhile high concentration of ApoE are evident in hyperlipo-proteinemites of type I,III,IV and V, gravidity, overuse of corticosteroids, treatment with hemodialysis and hepatal stages. Phenotype E 3 /4 and ApoE4/4 are with a higher concentration of cholesterol which makes them causes for origination of coronary diseases, cerebro-vascular and atherosclerosis premature in comparison to phenotypes ApoE2/2 and ApoE2/3. Apolipoproteine E is ligand of lipoproteinemic receptors and affects in the clearance of lipoproteinemic particles (36). Apolipoproteine E with high concentration is found in chylomicrones,in VLDL, remnants of VLDL and in a subfraction of lipoproteins with high density (HDLs), serving as a ligand for receptory-intermediary of their catabolism with the help of lipoproteins with low density(LDL), receptors of Apo-b100/E and apo-e receptors. Different concentrations of apo-E isoforms in uremic patients result with the characteristic model of fractional disorders of lipids and levels of apolipoproteins, the level LDL-ch, levels in ApoE-2 , the transporter of apolipoprotein E3/3 and very high levels of apoE-4. The increase of concentrations of ApoE-4, Total

choletorytes(ChT) and LDL-ch in the process of gravidity is supposed to happen as a consequence of the big increase of cholesterol ,from the gut side disorder of the regulative receptors of LDL in the surface of the hepatic cells which result in a growth of LDL-ch... and the submition of cholesterol to these cells, because of the broaden interaction of Apo-E which contains remaining's of Apo-E receptors. The facts that apolipoproteine-E stimulates the production of triglycerides,VLDL (very low density lipoprotein) and prevents the lipolysis of ApoC-2 are known. Enriched HDL Apo-E can have an important role in the reverse transport of cholesterol in the healthy population; therefore it's easy to understand why patients with uremia since the early stages of the disease are suffering from Hypertriglyceridemia understandably also because of the reverse transport of cholesterol disorders(37,38). Apolipoproteine -E does the transfer of cholesterol in the hepatic tissue with the help of Apo-E receptors, whereas in the extra hepatic tissue with the help of ApoB-E receptors. These are documented facts regarding the huge role of homozygotes E-3 in the development of type III hyper-lipoproteinemia (according to Fredricksons' classify-cation) and the connection of ApoE-4 with the increase of LDL-4 concentrations. The Apo-E gene is divided from the DNA taken of leucocytes. Patients with IRKT treated with repetitive hemodialysis have a decreased prevalence of epsilon-4 allele and a higher concentration of apolipoproteine group. Genetic polymorphism of Apo-E (ApoE-4 allele) in the patients treated with repetitive hemodialysis influences significantly in the appearance of early arterio-sclerosis, cardiovascular diseases, cerebrovas-cular diseases and the levels of Lipoproteins (a) are decreased even after the hemodialysis sessions (17,18,19,22). A large number of studies claim that Apo-E phenotype plays an important role in the lipids catabolism. It's verified that the ApoE-2 and ApoE-4 concentrations in the patients with IRKT are identical, while in the healthy population are different. Some multicentric studies regarding apolipoproteine-E in the patients with IRKT treated with repetitive hemodialysis have found high ApoE-2 and ApoE-3 concentration values. The increased frequency of ApoE-2 phenotype in patients with IRKT is genetically predispositioned.Apolipoproteine-E in its content contains three large iso proteins (ApoE-2, ApoE-3, ApoE-4 with polymorphism and its verified module towards lipids and its effect towards arteriosclerotic diseases as on the patients with IRKT also in the healthy population. (45) ApoE-2 iso protein decreases the lipids affinity and lipoproteinemic receptors while ApoE-4 increases it.

ApoE-4 alleles correspond with high arteriosclerosis prevalence's coronary diseases in the entire population. Apo-E with its polymorphism on the patients with IRKT changes incredibly the level of lipids and patients with increased ApoE-3/4 phenotype have high LPL-ch values and higher index towards arteriosclerosis and lower HD2-ch values. A large number of studies prove that patients with uremia present high Apo-E values which were also verified in the study with our patients and it corresponds with those studies. In the appearance and progress of early arteriosclerosis, coronary diseases, cerebrovascular insult and other different thrombolytic processes except the lipoproteins disorders (hyperlipidemia, dyslipidemia) in the last years an important place is dedicated also to the increased lipoprotein(a)- Lp(a) and total homocysteine (Hcyt) which (besides the already known factors like: heritage, age, gender, high arterial pressure, smoking, diabetes, adiposity, psychological stress, dyslipidemia, decreased physical activity, alter fibrinogen, C-Reactive Protein (CRP)...) in the recent time are counted as new independent factors of early

arteriosclerosis with its consequences towards the cardiovascular system, cerebrovascular system and peripheral arterial diseases (47,55). On the patients with IRKT treated with hemodialysis the affinity of hepatic triglyceride lipase is < than 3% whereas the activity of LCAT is < then 30% compared with the controlling group (56). The comparative studies of apolipoproteines on patients with IRKT treated with different methods of dialysis (chronic dialysis, bicarbonate dialysis and permanent ambulatory peritoneal dialysis) prove that the coronary diseases, cerebrovascular diseases and early arteriosclerosis appear mostly on patients treated with permanent ambulatory peritoneal dialysis (57). The examination of the status parameters of lipo/apoproteines on our patients proved that on these patients dominate high values of TG, TCh, LDL-ch and Apo-E concentrations and low values of HDL-ch concentrations compared with the controlling group, and they match with the researches of authors like: Mathur, Atmann, Odda, Milionis (44,58, 59,60).

5 Conclusion

In conclusion we can say that the mechanisms, epitogenesis, the function and the abnormalities towards polymorphism information's and the negative influence of apolipoprotein E on patients with IRKT treated with repetitive hemodialysis and its role in the appearance of cardiovascular and cardiovascular diseases has an

incredible importance in the appearance of this common occurrence in those patients. Preventive measures like dietary, therapeutic treatment can obviously influence in the reduction, slowing, prevention and treatment of the above mentioned occurrences in patients treated with repetitive hemodialysis.

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