METABOLISM OF APOLIPOPROTEIN C-II (ApoC-II) IN UREMIC PATIENTS TREATED WITH CHRONICAL HEMODIALYSIS

1. Dr. DritonSelmani [1], 2.Prof. Dr. Sci. Med. LutfiZylbeari[1,2], 3. Mr Chemistry Hamdije Memedi [1],,4. Mr. Dr, Gazmend Zylbeari1[,2], 4.Zamira Bexheti[1,2]

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

2. Private Special Hospital For Nephrology and Hemodialysis "Vita Medical Group" - Tetova, Macedonia

Abstract :The high incidence of arteriosclerotic disease in patients with chronic renal failure seems to be due to certain peculiarities in their lipid metabolism. These are principally a disorder in the transportation of lipoproteins and a concomitant defect in triglyceride metabolism causing an accumulation of triglyceride-rich-lipoproteins which predispose to early atherosclerosis (1).We studied the disturbances in concentration of apolipoproteins, notably Apo C-II which modulate the activity of lipoprotein lipase (LPL), in patients with chronic renal failure (CRF) without replacement therapy and in hemodialysis patients with and without hyperlipidemia. LPL hydrolyses triglycerides in the lipoprotein-triglyceride (LPRTG) core. The main lipid parameters were measured in patients with ESRD in comparison with healthy controls. We found that the lipolytic activity index (A-I/C-II) was decreased, and Apo C-II levels were increased, in patients with CRF and patients on HD patients. We conclude that high Apo C-II levels are found in uremic patients before starting dialysis and do not change during dialysis treatment. This increase could be one of the initial causes of impaired triglyceride catabolism and LPRTG accumulation even in normolipidemic patients with CRF and may be one explanation of the high mortality from cardiovascular disease in these patients.Apolipoprotein C2 or apolipoprotein C-II is a protein that in humans is encoded by the APOC2 gene (2)The protein encoded by this gene is secreted in plasma where it is a component of very low density lipoproteins andchylomicrons. This protein activates the enzyme lipoprotein lipase in capillaries (3,4) which hydrolyzes triglycerides and thus provides free fatty acids for cells. Mutations in this gene cause hyperlipoproteinemia type I-B, characterized by xanthomas,pancreatitis, and hepatosplenomegaly, but no increased risk for atherosclerosis. Lab tests will show elevated blood levels of triglycerides, cholesterol, and chylomicrons. It is known that patients with terminal chronic renal insufficiency are presented with early atherosclerosis (atherosclerosis praecox) with serious cardiovascular and cerebrovaskular complications and peripheral arterial damages are noticed in a large number of yang patients compared with the healthy ones (5-8). Cardiovascular diseases (9) and disorders of metabolism of apolipoproteins are the main cause of morbidity and mortality in patients with uremia. In patients with terminal chronic renal insufficiency the lipoprotein disorders are present in early stages associated with metabolic disorders of Apo-C-II, hypertriglyceridemia as well as increased aterogen concentrations of triglycerides rich with lipoproteins-TRLs- Triglyceride-Rich- Lipoprotein. Aim of the paperwork: the aim of our study is examination, kinetics and evaluation of Apo C-II levels and the lipidic profile at patients with end stage renal disease treated with HD. Material and methods: the total number of subjects included in the research is N°= 200, 100 subjects are patients diagnosed with ESRD treated with HD, 100 subject are healthy patients that served as a control group. 45 patients treated with hemodyalisis were female and 55 (55% the average age was58.70 ±14.60 years) patients were male, the average age was 59.60±12.80 (all treated more than 12 years with hemodyalisis in the Clinic Hospital of Tetova. The controlling group of healthy patients was 100 (45 female and - 55 male) identical with the experimental subject according to demographic data.Statistical elaboration: the basic statistical method used in this study were: arithmetical average value, standard deviation X±SD, Studentov “t” test, Mann Whitney U test. The statistical significance of the differences between subjects of the experimented group and control group for the gained parameters of lipids or ApoC-II was analyzed with “Anonova Two Factor ” with statistical value for ,,p” smaller then 1% p<0.0001.

Index Terms: metabolisation of apolypoprotein C-II (ApoC-II),Lipidi profile (EndSage Renal Disease (ESRD).

1 INTRODUCTION

Chronic renal insufficiency it represents a clinical state with progressive and irreversible damages of the kidney tissues during various diseases of the kidneys and the urinary tract. Many studies have shown that the cardiovascular complications at patients with CRI (without considering the stages) are the most common factors with higher prevale-nce of mortality and morbidity compared with patients that suffer from diseases with other etiolo-gies. Patients with ESRD are presented with early atherosclerosis, serious cardiovascular and peri-pheral artery complications in the mayor number of the patients in a younger age compared to the control group (1,2,3,4) Cardiovascular diseases and dyslipidemia are the main cause of morbidity and mortality at uremic patients. Disorders of lipidic profile at CRI patients are always associated from the early stages of the disease with high levels of triglyceride rich lipopro-teins, high level of VLDL and IDL concentrations. One of the main factors that in the last years is classified as a high risk factor for cardio vascular diseases and early atherosclerosis in patients with CRI is the high concentration of ApoC-II.

Apolipoprotein C-II (Apolipoprotein glutamic acid, Or Lp-Glu; Apoc-II) is a small protein and easy shifting with determined genetic and proteinemic sequence. *Apolipoprotein C-II is the basic component of HM, VLDL and HDL-ch* **(10)**

Mainly synthesized in the liver and a small part in enterocite. APOC-II mRNA produces protein which in itself contains 101 amoniacidic sequences with signaling peptide containing 22 aminacidic waste. Through Process of O-glycolization and signalisation by endoplasmatic reticulum and Golgi apparatus is obtained basic peptide which in itself contains 70 amino-acids. Because of inefficientglycolisation the prothein is secreted in disignalised form of the (APOC-II $_{s2)}$ and in the form of notsignalised APOC-II in a ratio of 1: 1. APOC-II $_{s2}$ in plasmas is further disignalised in the form of asignalised APOC-II. In the content of lipoproteinemic particles is recorded presence of Apo-B, APOC-I, II ApoC-, APOC-III (IPR: C, E), but without specifying and defining their function and physiological role. APOC-II comprises 33, namely 22 acid residue between nucleotides 1 8-50 and 51 - 72. The secondary analysis of APOC-II (by Chou & Fasman) provides residue α amphipathic -helix between waste:13-22, 28-39 The 42-50 β - Amongst waste: 9-12, 23-26 and 52-55 and β -pli between waste (residues) 60-74.Variant APOC - II with phospholipids increases content of α - helix from 35% to 59%. The bond of the APOC-II with lecitine forms particles disc shaped of double dimensions (with smaller shafts = 4nm and great shafts = 20 nm). Constant dissociation (dK) is = 45 – 1.07 μ M, while the number of saturation (number of apoproteinemic molecules related to 1000 fosfolipidic molecules) is = 8.3 drei in 11.8. *Molecular Weight of APOC-II is 8824 D calculated based on the content of amino-acid sequences. ApolipoproteinaC-II is activator of LPL (Lipo-protein Lipase-a) with maximum effect and the mass is equimolarto the mass of the enzyme (ratio 1: 1).* Constant dissociation reference of this complex is between 10^{-8} - 10^{-10} M. The maximum dissociation environments is for APOC-II when there are high concetrations of NaCl. Position 43-79 which is bonded to phospholipids and VLDL-vesicle is very sufficient for maximum activation of LPL, while the C-terminal position 55-79 comprises 90% of catalyzes capacity of LPL.LPL catalyses hydrolysis of treglycerides from HM and VLDL. *The function of APOC-II in activation of LPL are reported in patients with inherited deficit (shortage) of APOC-II, to which cleaning (clearing) of lipoprotein rich treglycerides is difficult.* Natural Mutations of C-terminal APOC-II region enable(facilitate) the ability of the mutante protein to activate LPL **(10-15)** . *Mutations in the structure of APOC-II are major factors which condition and determine occurrence of hyperlipoproteinemia.* APOC-I more and APOC-II lesser inhibite binding of lipoproteins that contain Apo-E eg β - VLDL) with LRP and LDLreceptors **(16).** A part of APOC-II is removed from circulation through the capture by hepatocites as integral components of VLDL, IDL and HDL subfraction. The composition of APOC-II by hepatocytes is assisted by means of LDL / LPR receptors during high ratio between Apo-E: APOC-II.A smaller percentage of the apolipoproteines C-II from circulation is removed with the help of proteolysis of cDNA and genetic sequence of apolipoprotein C-II human, documented facts. *The gene for the synthesis of APOC-II is closely linked with genes that produce apolipoprotein E and apolipoprotein CI. Group of the aforementioned genes (,,cluster ") is located and placed in the long arm of chromosome XIX.* Proteinemic analysis of patients with absence of APOC-II with the help of PAGE-twodimensional verifies the presence of the small forms of apoproteinesvariant .Sequentional analysis of nucleotides of genes of this group of patients showed changes which had numerous mutations associated with a lack of APOC-II and Type-I hyperlipoproteinemia. Plasma time (T / 2) of ApoC-II is 2.90 $\pm$ 0:24 day (or according to

some scientific sources is 10-18 days) .Density of ApoC II means presence of fraction of HDL and it is = 1063-1210 g / ml in normolipemic patients analyzed hunger situation whereas in individuals with hyperlipidemia is found in VLDL fraction from 0.950 to 1006 g / ml. With the help of isoelectric focusing it is isolated a genetic variant (pI5.0). Reference values of concentrations of APOC-II are: 0.02-00:08 g / l (for men) and 0:06 0.01- g / l (for the female gender). Lower concentrations of APOC-II appear in lack of APOC-II, nephrotic syndrome, Tangier disease and hypo-alfahyperlipo-proteinemia. Elevated concentrations APOC-II are registered in patients with chronic renal failure *and those with CRF preterminal treated with hemodialysis as well as the --Type I, Type-III, Type IV and TypeV*. All three groups of ApoC-III (ApoC-III1; ApoC-III2 and ApoC-III3) are placed in the long arm of a the 11th chromosome in the regi-on 11q-13q(17-22). Earlier studies have verified that the isoform of ApoC-II shows the fastest pass way of triglycerides rich with lipoproteins -TRLs and fracti-ons of HDL-ch. These are documented facts that patients with CRI are 10 times higher in a risk for cardiovascular diseases compared to the healthy subjects (23-26). Hypertriglyceridemia is one of the most common quantitative lipid abnormalities in patients with CKD (27-30). The concentrations of triglyceride-rich lipoproteins [very-low-density lipoprotein (VLDL), chylomicrons, and their remnants] start to increase in early stages of CKD and show the highest values in NS and in dialysis patients, especially those who are treated with PD.Several studies have shown that patients with impaired renal function exhibit increased concentrations of triglycerides even though serum creatinine levels are within normal limits (24,25). Also, individuals with CKD usually display abnormal increases in serum triglyceride levels after a fat meal (postprandial lipemia) . The predominant mechanism responsible for increased concentration of triglyceride-rich lipoproteins in predialysis patients is one of delayed catabolism(26). The reduced catabolic rate is likely due to diminished lipoprotein lipase activity as a consequence of the downregulation of the enzyme gene and the presence of lipase inhibitors(27,28).Apolipoprotein C-III is a potent inhibitor of lipoprotein lipase whereas apolipoprotein C-II is an activator of the same enzyme. A decrease in apolipoprotein C-II/C-III ratio due to a disproportionate increase in plasma apolipoprotein C-III is a possible cause of lipoprotein lipase inactivation in uremia (29-32). It was also suggested that secondary hyperparathyroidism is involved in the impaired catabolism of triglyceride-rich lipoproteins, provided an additional mechanism by which CKD may raise plasma triglyceride concentrations (33, 34). Except of the low catabolic rate, the increased hepatic production of triglyceride-rich lipoproteins may also play a contributory role in the pathogenesis of dyslipidemia in renal disease . It is well known that CKD causes insulin resistance which can, in turn, promote hepatic VLDL production. Thus, it could be hypothesized that the insulin resistance-driven overproduction of VLDL may significantly contribute to the development of hypertiglyceridemia in patients with CKD.Hypertiglyceridemia [due to accumulation of VLDL and remnant lipoproteins such as intermediate-density lipoprotein (IDL)], is also the predominant lipoprotein abnormality in a considerable number of cases with nephrotic range proteinuria (35). This dyslipidemia results from a combination of increased production and reduced clearance of VLDL (36). It is well known that the progressive delipidation of triglyceride-rich lipoproteins is facilitated by the action of two different enzymes namely endothelial-bound lipoprotein lipase and hepatic lipase. The expression of the genes of these enzymes has been found to be downregulated in patients with NS (37). In addition, other factors such as hypoalbuminemia and proteinuria may further decrease the efficiency of lipoprotein lipase-induced lipolysis of triglyceride-rich lipoproteins by interfering with the endothelial binding of the enzyme and by changing the composition of VLDLs in a way that reduces their suitability as lipoprotein lipase substrates, respectively (38).The initiation of renal replacement therapy, as well as the choice of dialysis modality, may also influence the levels of triglyceride-rich lipoproteins in ESRD patients (39). The pathophysiological mechanisms responsible for these alterations seem to be generally similar with those described in predialysis patients with CKD. However, factors related to the procedure of renal replacement therapy seem to contribute to the increased levels of triglycerides observed in this patient group. In HD patients the repeated use of low-molecular heparins for anticoagulation may lead to a defective catabolism of triglyceride-rich lipoproteins as heparin releases lipoprotein lipase from the endothelia surface and thus its chronic use may result in lipoprotein lipase depletion. However, the studies that tested the role of heparin in the pathogenesis of HD-induced dyslipidemia revealed contradictory results (40-44). In addition, controversy exists as to whether low-molecular weight heparins have a more favorable effect on the lipid profile of HD patients compared to standard unfractionated heparin (45, 44). Also, studies on the influence of the type of membrane used in HD yielded conflicting results. It has been shown that the use of high-flux polysulfone or cellulose triacetate membranes is accompanied by a significant reduction in serum triglyceride. This improvement could, at least in part, be attributed to an increase in the apolipoprotein C-II/CIII ratio which increases the activity of lipoprotein lipase and facilitates the intravascular lipolysis of triglyceride-rich lipoproteins. However, other studies suggest that the type of dialysis membrane does not influence the characteristics of dyslipidemia (46-55).Form the lipidic profile in patients TCRI treated with HD we detect a high level of TG, with elevated growth of atherogenetic particles of TG rich in lipoproteins TRLs, VLDL and IDL. The high concentrations of ApoC-II at uremic patients are associated with high levels of TG, and they are a independent powerful factor for CVD (cardiovas-cular diseases- acute myocardial infarction, acute coronary syndrome, cardiac ischemia, angina pectoris) In the blood stream apoC-II is connected to TRL specially with VLDLN. Lately studies have shown that VLDL and ApoC-II have a positive correlation with the frac-tion catabolic rate (FCR) in normoli-pidic or adi-pose subjects. The production rate (PR) of ApoC-II it is calculated as a product of FCR and the synthesis quantity that it is equal with the plas-matic percentage multiplied with the plas-ma volu-me -the plasma volume it is calculated as 4,5% of the body weight. In Patients with TCRI the fraction of ApoC-III and VLDL complies with the slow catabolic rhythm. Thus, some studies have shown a positive association between cholesterol values and the risk for cardiovascular events in CKD individuals (56), whereas others failed to find any significant correlation (57,58).

Finally, some other studies suggested an inverse relationship between serum cholesterol values and mortality in ESRD individuals, a phenomenon also known as "reverse epidemiology" (59,60). Although the precise causes of this significant deviation from what is observed in the general population have not been established, it has been proposed that the presence of phenomena such as inflammation or protein energy wasting (conditions very common in ESRD patients) may significantly confound the relationship between the traditional risk factors for CVD and mortality in this patient population (61,62). In other words, ESDR patients free of these complications behave exactly as individuals with normal renal function, whereas in the presence of these conditions low rather than high cholesterol values predict a poor outcome. In agreement with this hypothesis the statistical adjustment for markers of inflammation and/or malnutrition in some studies restores the positive association between serum cholesterol values and mortality in CKD individuals (63).

2 MATERIALS AND METHODS USED

The blood sample for routine analysis (lipidogram) and specific analysis was taken at 08 o'clock in the morning with the room temperature that variated from 19 to 24°C, before the hemodialysis session, minimum 12 hours of fasting - with tendency to avoid the absorption effect of food by the intestine as well as avoid absorption of lipids and formation of hilomicrones. In all samples regardless in which group they are, controlling or examined from their blood sample was analyzed the concentration of ApoC-II and lipids in the period of 12 months (the measurements were made every three months, it means we totally made 3 measurements in 9 months). In the study we had totally 240 subjects, 100 of them were treated with HD, 100 were healthy that served as a controlling group.From the patients treated with hemodialysis 45(45%) were females, 54 (55%) were male, the average age was 58.00 ±18.00, treated more than 12 years with hemodyalisis in Clinical Hospital of Tetovo. The controlling group consists 100 individuals 45 (45%) female and 55 (55%) male (table nr.1.) equal as the examined group in age, gender and nationality. In the cohort - prospective study (cross-section) total female participants were 100 (45%) the average age 59.60±12.80 , 102 (55%) man with the average age of58.70 ±14.60 (table number1).

Table number .1: Presentation of **patients** with ESRD**according to gender**and **average age**

Gender	Number	Average age ± SD
Male	55 (55%)	59.60±12.80
Female	45 (45%)	58.70 ±14.60

Table number 2.Normal parameter of lipids and ApoC-II in the serum, and list of the author's name of the used method.

Parameter	REFERENT VALUES	Autors
LT	4-10 g/l	Zollner & Kirsch (64)
TG	0.68 – 1.70 mmol/l	G. Bucolla & H.David (65)
ChT	3.1 – 5.2 mmol/l	CCAllain et al. (66)
LDL-ch	< 3.4 mmol/l, high risk> 4.1 mmol/l	Friedewalde&Frederickson (67)

HDL-ch	**1.6 mmol/l, high risk <0.9mmol/l**	**G.Warnick et a l (68)**
ApoC-II	***1.6–3.2mg/dl***	**Tilly P.et al.(69)**

3 STATISTICAL PROCESSING OF THE EXAMINED MATERIALS

From the basic statistical methods we have used: average arithmetical value and standard deviation X±SD. Statistical comparation of parameters of lipids and ApoC-II between two groups was analy-zed with "Studentov t" test, while for the depe-ndent or independent examples as well as for the nonnumeric tests we used: Mann-Whitney test. The differences of the statistical significance between the examined and the contro-ling group for the gained lipidic and ApoC-II values were analyzed with Anonova Two - Factor test, with statistical value for "p"< 5%=0.0005.The statistical dependence between the examined parameters were calculated with the linear regression formula (y=A+B) with statistical accuracy for "p" <1%= p<0.0001. The results of lipidic profile and apolipo-proteine values are presented with graphs, tables, diagram processed with standard statistical program (statistic for windows.

4 GAINED RESULTS

The results from patients and controlling group for ApoC-II and lipid profile (ChT, TG, HDL-ch, LDL-ch) are evidenced in table number 3.

Examined parameters	ESRDpatienients treated with HD	Controlled group	*p*
TG mmol/l	3.90 ± 0. 80↑	1.14 ± 0.50	**<0.0001**
ChTmmol/l	5.70 ± 0.90	4.30 ± 1.80	**<0.0001**
LDL-chmmol/l	4.70 ± 0.30	2.90 ± 0.50	**<0.0001**
HDL-chmmol/l	0.80 ± 0.50↓↓	1.50 ± 0.80	**<0.0001**
Apo C-II mg/dl	**9.73±5.20 ↑↑**	**2.86±0.79**	**<0.0001**

From the results of the lipidic profile and ApoC-II of patients with ESRD treated with HD and from the results of the controlling group for the same para-meters it can be noticed a significant differences with p<0.0001. The concentration of ApoC-II in the examined sample containing patients with ESRD were presented with average values 9.73±5.20 mg/dl in their plasma, in the controlling group the average values of ApoC-II were 2.86±0.79 mg/dl. The difference between these two groups has a significant statistical meaning for p<0.0001. Facts that dovetail with various number of studies (citated in the study) of the metabolic disorders and high concentration of ApoC-II in patients with ESRD treated with HD. compared with the results gained from the co controlling group the patients with ESRD have 82- 85% higher levels of ApoC-II.

Table number 4. Presentation of average values of the examined patients with ESRD treated with HD (male + female = N°= 100)

Parameters	**Number**	**Average**	**± SD**	**P**

ApoC-II	100	8.96 ↑↑	4.80	0.0001
TG	100	3.90 ↑	0.80	0.0001
ChT	100	5.70	0.90	0.0001
HDL-ch	100	0.80 ↓↓	0.50	0.0001
LDL-ch	100	4.90↑↑	0.80	0.0001

Table number 4present the significant differences between examined parameters of the patients treated with HD and the controlling group. The evidenced differences between these groups has a significant difference for p=0.0001.

Table.5. Staetmentof Mann-Whitney U test parameter values displayed examine female patients and male patients treated with HD

Parametrat	U	Z	p-level
ApoC-II	1696.00	0.45	0.65
LT	1345.50	2.30	0.02
TG	1701.50	0.42	0.67
Ch	1651.00	-0.69	0.48
HDL-ch	1705.00	0.40	0.68
LDL-ch	1676.50	0.55	0.58

The difference between the value that was recorded average patients treated with dialysis in both sexes (tab. No.5) is nosignifikant for p <0.05 for larger number of parameters examined, significant statistical difference was verified only at LT with p = 0.0213

Table number 6. The correlation coefficient between the examined parameters

Report	The correlation coefficient	*p*
LDL-ch/HDL-ch	- 1.27	0.17
LDL-ch/Apo A_1	- 0.11	0.90
Apo A_1/ ApoC$_3$	0.04	0.66
Apo A_1/ ApoC$_2$	0.08	0.42
Apo A_1/Apo E	0.01	0.28
ApoC$_3$/Apo E	0.04	0.96
ApoC$_2$/Apo E	***0.19***	***0.03***

Statistically significant positive correlation between the value recorded ApoC-II with Apo-E: ApoC$_2$ / ApoE: 0.03.

4 DISCUSSION

Disorder of lipid metabolism in patients with chronic terminal renal insufficiency are prescribed for first time in 1827 by Dr Bright, especially in the patients with nephrotic syndrome **(70).** It is known fact that patients with chronic renal Terminal insufficiency (CTRI) present clinics with Early atherosclerosis and serious cardiovascular complications, cerebrovascular with peripheral arterial injuries more frequent in very large number in younger population compared to the healthy population. Recent years has been verified that uremic hyperlipidemia persists in the early stages of kidney weakening, prior to treatment with hemodialysis (HD) and it is presented as basic factor of the beginning of atherogenic processes in patients with chronic terminal renal insufficiency. Determination of lipid and apolipoproteins profile in particular of their abnormalities in patients with chronic terminal renal insufficiency (CTRI) in the early stages of the disease, and analizeethiopathogenic mechanisms can significantly help in proposing preventive measures (dietary, treatment) with which there will be reduced visible frequent appearance of dyslipidemia, atherosclerotic lesions and reduce the incidence of atherosclerosis in patients with CTRI randomized by gender and age **(71).** Patients with terminal chronic renal failure (TCRF) mostly appear with the type IV type of secondary hyperlipoproteinemia (according to Frederickson's classification)where they dominate high concentrations of triglycerides (hypetriglyceridemia values of 28-100%} **(72).** Five year examination of 220 patients with CTRI does not verify the trend of permanent growth and progression of hypertriglyceridemia **(73).** It is assumed that the subtle qualitative changes, registered in morphology (size) of the particles of lipoproteins in patients with chronic renal terminals insufficiency (CRTI) , increase extraordinary their atherogenic impact (increased affinity with fixation (adhesion) in the arterial *subendothel of LDL oxidized LDL-ox, small LDL, HDL minor particles)* with frequent atherosclerotic damage to the cardiovascular and cerebrovascular system with fatal consequences for treatment centers with hemodialysis **(74).** It is about ischemic heart disease, peripheral vascular disease and cerebrovascular stroke. Pre b 1 HDL is a minor subfraction which acts as the initial acceptor of free cholesterol emanated from cells and transport to liver. Under the influence of lecithin-cholesterol-acetyl-transferase (LCAT), *b ₁HDL passes in migrating- a HDL.* LCAT in normal plasma affects HDL maturity, *while* transforming *HDL with poor lipids in spherical HDL lipid enriched with fats. In uremic patients LCAT activity is reduced to "30% and the optimal conversion of the above described process is reduced.* Experimental clinical examinations (incubation of uremic patient plasma with inhibitor or without inhibitor of LCAT) verify of the abovementioned stance and certify that the early representation of atherosclerosis is directly dependent from

distorted catabolizing of b 1-HDL **(75).** *In patients treated with chronic hemodialysis-repetitive activity of triglycerides-hepatic lipase (LTGH) also is reduced for* 33-45%. *Lipopoprotein activity of systemic lipase (LPL) is reduced because of cumulation (collection) of toxins or cytokines-Interleukin-1, Interleukin-6, Interleukin-1 α, Interleukin-1 b and are counted as* the cause of pathological distortions of lipids and apolipoproteins in uremic patients(concentrations of HDL-ch and ApoA-I are reduced, while the concentrations of triglycerides, LDL-ch, ApoB-100, Apo-E, Apo-C, Lp (a) are increased) followed by increasing prevalence of atherosclerotic vascular diseases **(76).** Genetic prognosis of presentation of early family disposition to atherosclerosis is distortion of transport regulation of reverse of HDL-C $_h$and insufficient expression of receptor B and E with the reduction in conversion of VLDL to IDL and finally in LDL-ch. The abovementioned distortions (> Ch total,> LDL-C$_h$ and **<HDL-C** $_{h)}$)enable increased lipid and apoproteins (hiperlipemi) in serum with increased risk of early atherosclerosis. With the term ,, distortion" of lipid metabolism and apolipoproteins we mean, hypolipoproteinemia, hyperlipoproteinemia and normolipidemia (eulipidemia) with the presence of qualitative-quantitative changes (dyslipoproteinemia) to subfractions of different lipoproteins and normal concentrations of fundamental components lipoproteins. Therefore a large number of authors believe that normalization of serum lipoproteins stagnates progress of atherosclerosis. Stamler and associates believe that the risk of atherosclerosis is high if total cholesterol is above 5.7 mmol / l, while for the normal cholesterolemia propose values = 4.0-5.5 mmol / l. Abnormalities of lipo / apoproteins during the uremia comprise all particles of the lipoproteins (Lp). Because of the high values of triglycerides (TG) dominates hypertreglyceridemia in the composition of structure of VLDL, IDL, LDL and HDL-ch. Cholesterol in patients with uremia does not show a significant difference compared with the values of the examined trailer in the healthy population. Cholesterol is more present and increased in VLDL fraction while is reduced in the composition of structural HDL. *Carriers of molecules called lipid-apolipoproteins enter the class A, B and C. In the structure of LDL-ch, concentration of AI (ApoA-I) apolipoprotein is reduced while the presence of apolipoproteine A-IV (ApoA-IV) is higher (increased). Concentrations of apolipoproteins B-* $_{48}$ *(Apo-B*$_{48)}$ *and apolipoproteins B-* $_{100}$ *in the composition of the VLDL are elevated, while APOC* $_2$ */ C* $_3$ *respectively in the composition of VLDL are reduced while in the structure of LDL-ch are increased.* In post dialysed patients APOC-III concentrations are easily changed while APOC-II concentrations did not change. Apo-CI concentrations are extremely reduced with the help of the HD in the composition of VLDL while APOC-I concentrations are not changed in the composition of the HDL lipoproteins. Apolipoproteina C-II is specific uncompetitive inhibitor of Lipoprotein lipase (LPL). Concentration in plasma of Apolipoprotein C-II correlates strongly with treglyceridemia. Increased concentration of ApolipoproteinesC-II in plasma leads to the cumulation of treglycerides rich with lipoiprotein ***(TRLs-Tryglicerid-Rich-Lipoprotein),*** which is manifested by hypertreglyceridemia and fast progress of atherogenesis of the renal, coronary and cerebral vessels. ***The term accerelated atherosclerosis*** is used by Lindner, who thought that the early atherosclerosis (early accerelated) **(77), in** the patients with terminal chronic renal insufficiency begins before the onset of chronic hemodialysis treatment **(78-81)** . *It is verified that in the patients with uremia, the occurrence of myocardial infarction is 10 times more frequent than in patients with another primary disease.* Statistical studies published in the US in 1997 on the introduction of mortality in patients with chronic terminal renal insufficiency treated with hemodialysis showed 53% mortality caused due to cardiovascular disease, 16% due to infections, 4% of carcinomas and 27% from other causes in patients up to age 64 years.

ApoC-II lowe-rs and inhibits the activety of Lipoprotein Lipase (LPL) and it stimuli-tes the secretion of Lectin cholesterol acetyl transferase (LCAT). It is supposed that ApoC-II modelates the remain-ning particles rich in TG by hepatic receptors. Recent studies emphasize an important intrace-llular role of ApoC-II related to TG secretions and VLDL secretion in hepatocites in an a lipidemic intra organic environment.the subtly quality changes registered in the morpho-logy (size) of lipoprotein particles in patients with TCR, increases the aterogen impacts of LDL-ox as well as making them more able to hitch in arterial subendotel, transformed in LDL-ox creating atherosclerosis and CVD contributing on

fatality of the patients that are treated with HD.ApoA; ApoC; LDL-ch cause functional insufficiency that manife-sts with deficit of LPL synthesis, whereas low activity of LACT and low levels of HDL-ch condition the impaired use of Ch from the liver. LCAT in a healthy patient contributes in HDL-ch maturity, converting a small HDL poor in lipids in to a mature HDL rich in fat.In patients with TCRI treated with HD the activity of hepatic triglyceride lipase HTGL and LCAT is lowered for 33-45%, and the activity of LPL is lowered due to toxin or cytotoxinaccumu-lations (interleukin I, Interleukin I beta, interleukin VI, interleukin I alpha), malnutrition - inflammation and atherosclerosis syndrome MIA that

verified the fact that TCRI is an inflammation. TCRI patients treated with HD have high level of LDL-ox,VLDL and IDL accelerate the inflammatory cytokine secretion such as:

-PDGF platelated growth factors

-TGF beta transforming growth factor

-TNF alpha tumor necrosis factor

-CRP complement reactive protein.

Experimental clinical examination (plasma incubation of uremic patients with and without LCAT inhibitator) have proven that early athero-sclerosis with consequences over cardio-vascular system directly it is dependent from the metabolic disorders of bet 1- HDL-ch, PCR, MIA syndrome, accumulation of toxins and weakened immunity (82-84).Abnormality of lipids or lipoproteins during uremia include all lipoprotein particles. High levels of ApoC-III; PCR and uremic toxins increase mortality for 25% of patients with TCRI from CDV compared to the controlling group.ApoC-III has a defined rapport of particles in composition of lipoproteins and lipids (LpB:C-III; LpBE:C-III; LpBAIII:C-III; LpA-I:A-II:C-III) as a active substance it also has strict rapports in joint complexes with ApoC-I;II and ApoC-III.ApoC-III prevents the function of LPL and enzymes that hydrolyze the separation of HM and VLDL, they block the conjugation of complex lipoproteins of ApoE with TG and LDL receptors.High levels of ApoC -III are associated with high values of trigly-cerides that proves its blocking role for rich TG-lipoprotein uptake.The destruction of basal part from the structure of ApoC-III happens in the liver its fractions may turn in VLDL, IDL or HDL-ch subtractions. Hepatic extraction of ApoC-III it is helped by LDL-ch. LPP receptors give high correla-tions between: ApoC-III and E. A part of ApoC-III is eliminated by different biodegenerativebioproce-sses. In the absence of ApoC-II and HDL causes early atherosclerosis and this may happen as a consequence of the movement of ApoA-I; ApoC-II; ApoA-IV locuses or ApoA-I ←→ApoC-II gene inversions.Patients with hiperlipoproteinemy have reduced concentrations of ApoC-II. Functions of ApoC-II partly are unknown , for their specific function and role multi-centric researches should be developed, including different regions and an enormous number of subjects.In uremic patients it is important to reduce the concentration of HTG for about 33% and LCAT activity to be reduced for 35-45% compared to the controlling group. Concent-ration of ApoC-III in VLDL+LDL it's a significant indicator for progression of coronary atheroscle-rosis, verified and documented with angiograpgy.Apolipoproteines C blood level-II (ApoC-II) = V.R = 1.8-3.2mg/l) of the patients examined were presented with significant value too high. Nephrpathy of the undifferentiated ekzaminedwith concentration of Apo-C-II were maximum = 9.73 ± 5.20 mg / l, while the minimum value of 6.18-3.78 mg / l were verified to chronic glomerulonephritis.

5 CONCLUSION

In this study patients with ESRD treated with HD have high parameters of ApoC-II,TG,LDL-ch but low concentrations of HDL-ch approve for impaired catabolism of apolipoproteins in this specific group of patients.In all patients we had symptoms of CDV (myocardial infarction, angina pectoris, ischemia), acute coronary syndrome. Most common dislipide-my was hipertrigliceridemy 90.0- 95.0%) in samples with ESRDI treated with HD-allow necessa-rily should be treated with fibrate, bezafibrate, clofibrate not with statine. Concen-trations of ApoC-II in the examined group were 5- 6 times higher compared to the controlling group.Synthesis of apolipoprotein it is direct impacted and controlled by genes unlike lipidic components that directly depend on the food consumption and liopmetabolism. The role and clinical examination of apolipo-protein means early diagnostification and preve-ntion of visceral and peripheral atheroscle-rosis as accelerator for cardio/neuro vascular diseases. Determination of apolipoproteinic and lipidic concentrations enables preventive measurements for avoiding at least on etiopatho-logical factor for accelerateatheroscle-rosis. That's why we can conclude that exami-nation and treatment of apolipoproteine in the early stages of the diseases should be the first postulate in the treat-ment of CRI patients, this approach to the disease significantly will reduce the risk for CDV. Hypertrigliceridemy in uremic patients treated with HD is associated with genetic variations of ApoA-I.

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Adress of autors

Dr. DritonSelmani

E-mail:driton.selmani@unite.edu.mk

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Adress of the author

Doc. Dr. Sci. Med. LutfiZylbeari, MD, PhD.

Spec. IntenalMedicne-Nefrologist

E-mail: dr-luti@hotmail.comTel.00389/72/658-402