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

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Abstract: 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 (1,2,3,4). Cardiovascular diseases (27) 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-III, 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-III levels and the lipidic profile at patients with terminal chronic renal insufficiency treated with HD.Material and methods: the total number of subjects included in the research is N°= 240, 120 subjects are patients diagnosed with terminal chronic renal insufficiency treated with HD, 120 subject are healthy patients that served as a control group. 54 (45%) patients treated with hemodyalisis were female and 64 (55%) patients were male, the average age was 58.00±18.0 (all treated more than 12 years with hemodyalisis in the Nephrology Clinic of Skopje and Clinic Hospital of Tetova). The controlling group of healthy patients was 120 (54 - 45% female and 64-55% 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, Wilcoxon test. The statistical significance of the differences between subjects of the experimented group and control group for the gained parameters of lipids or ApoC-III was analyzed with "Anonova Two Factor " with statistical value for *,,p"* lower than 5% <0.0005 with statistical certansy for "p" smaller then 1% p<0.0001.

Index Terms:: metabolisation of apolypoprotein C -III (ApoC-III), Terminal chronic renal insufficiency, lipidic profile (LT TG Tch LDL-ch), hemodyalisis (HD)

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 TCRI 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)

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Cardiovascular diseases (27) 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 in patients with CRI is the high concen-tration of ApoC-III. ApoC-III is a glycoprotein that weights 8.8 kDa, mainly synthesized in the liver and a small amount is produced by the enterocite of the small intestine(6). Apoliprotein C-III (Apo C- III mRNA) in humans it is coded by the gene APOC3 (38). ApoC-III is a structural component of VLDL, HM and in a small amount it is found in HDL-ch. ApoC-III is a relatively small protein that contains 79 aminoacids it may also have glycolised threons(7). The normal concentration of ApoC-III in the human plasma is 5.5-9.5 mg/dl. There are 3 isomers of ApoC-III in the plasma: ApoC-III_1; ApoC-III_2, ApoC-III_3.
ApoC - III's length is 3.5kb, it consists 4 hexons and 3 introns, its locus is close positioned with the locus of ApoA-I and ApoA-IV.ApoC-III gene it is placed 2.5kb in a distal position form the ApoA-I gene and approximately 5 kb distal from ApoA-IV gene. 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(40.41).The biological half-life of ApoC-III is 2.45±0.33 days (according to other sources 10-18 hours). Earlier studies have verified that the isoform of ApoC-III_1 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 (21,22,24). Metabolic disorders of ApoC-III and dislipidemia at uremic patients treated with chronic HD or patients in preterminal phase are vivid from the initial stages of their wakening, the etiopathiogenesis of these disorders and early tre-atment of Apo-III levels, that may contribute in the prevention of cardiovascular, cerebrovascular and atherosclerotic diseases in this specific group of patients ( ). 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(5). The high concentrations of ApoC-III 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-III is connected to TRL specially with VLDL(8). High levels of ApoC-III contribute on raising the aterogenity of VLDL particles and inhibition of VLDL lipolysis by the help of the inhibition processes of the hepatic clearance it is managed to be blocked the hepatic receptors for VLDL elimination(23). Approximately it is known that 35-75% of ApoC-III it is in VLDL particles. In vitro studies verified that ApoC-III disrupts the secretion and activity of lipo-protein-lipase (LPL), hepatic lipase (HL), and it interferes with the intake of TRLs form the hepatic receptors(5). This apo-protein may trigger the secretion of ApoB and TG, which it means that in an indirect way it contributes in the high levels of VLDL(9,10).High concentra-tions of ApoC-III accumulating on TRLs and their remains associated with impaired catabolism of VLDL is a common occurrence in patients with TCRI (11,12). Metabolic disorders of ApoC -III in patients with TCRI it is an undefined topic but we suspect that patients with TCRI manifest catabolic defects of ApoC-III and VLDL.The majority of stu-dies have verified high correlation between levels of ApoC-III, TRLs a d TG - at patients with CRI and TCRI treated with HD. In vitro studies have proven that transformation of ApoC-III betwe-en VLDL and HDL particles is indirect, and the entire quantity of ApoC-III it is in disposal of the fraction exchange (13).Lately studies have shown that VLDL and ApoC-III have a positive correlation with the frac-tion catabolic rate (FCR) in normoli-pidic or adi-pose subjects(14). The production rate (PR) of ApoC-III 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(23). In Patients with TCRI the fraction of ApoC-III and VLDL complies with the slow catabolic rhythm.

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-III and lipids in the period of 9 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, 120 of them were treated with HD, 120 were healthy that served as a controlling group.

From the patients treated with hemodialysis 54(45%) were females, 64 (55%) were male, the average age was 58.00 ±18.00, treated more than 12 years with hemodyalisis in Clinic of Nephrology - Skopje and Clinical Hospital of Tetovo. The controlling group consists 120 individuals 54 (45%) female and 64 (55%) male (table and graph 2b.) equal as the examined group in age, gender and nationality. In the cohort - prospective study (cross-section) total female participants were 108 (45%) the average age 58.00±12.30, 132 (55%) man with the average age of 57.50 ± 14.00 (table and graph 1a and 2b).

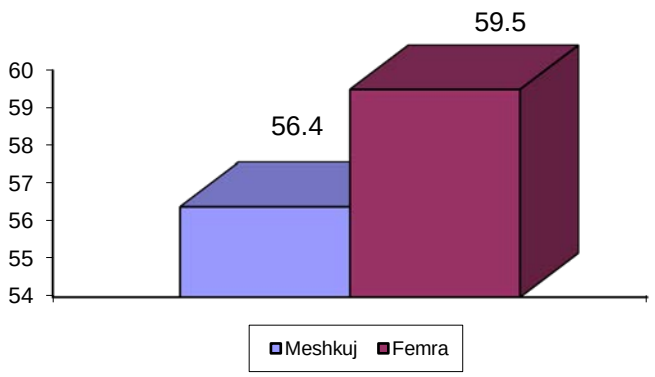
Table number .1-a: Presentation of **patients** with TCRI **according to gender** and **average age**

Gender	Number	Average age ± SD
Male	66 (55%)	57.50 ± 14.00
Female	54 (45%)	58.00 ±12.30

Table number 2b: Presentation of the **controlling** group according to **gender** and **average age**

Gender	Number	Average age± SD
Male	66 (55%)	57.40 ± 10.80
Female	54 (45%)	58.50 ±14.50

Graph number 1-a:



Graph number 2-b:
The average age of male patients was 57.50±14.00 and average age of the female patients was 58.00 ±12.300. The differences of the average age between male and female gender according to statistics was not significant with p=0.0005, that proves a homogeneous group (tab. And graph number 1a and 2b).

Table number 3. Normal parameter of lipids and ApoC-III in the serum, and list of the author's name of the used method.

Parameter	REFERENT VALUES	AUTORET
LT	4-10 g/l	Zollner & Kirsch (49)
TG	0.68 – 1.70 mmol/l	G. Bucolla & H.David (50)
ChT	3.1 – 5.2 mmol/l	CCAllain et al. (51)
LDL-ch	< 3.4 mmol/l, high risk> 4.1 mmol/l	Friedewalde&Frederickson (52)
HDL-ch	1.6 mmol/l, high risk <0.9mmol/l	G.Warnick et a l (53)
ApoC-III	5.5 – 9.5 mg/dl	Tilly P.et al.(54)

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-III 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 U and Wilcoxon test. The differences of the statistical significance between the examined and the contro-ling group for the gained lipidic and ApoC-III 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 apolipoproteine values are presented with graphs, tables, diagram processed with standard statistical program (statistic for windows, version 6.0A, Stat, softinc Tusla, OK USA).

4. GAINED RESULTS

The results from patients and controlling group for ApoC-III and lipid profile (ChT, TG, HDL-ch, LDL-ch) are evidenced in table number 4.

Table number 4:

Examined parameters	TCRI patients 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-ch mmol/l	4.70 ± 0.30	2.90 ± 0.50	<0.0001
HDL-ch mmol/l	0.80 ± 0.50↓↓	1.50 ± 0.80	<0.0001
*Apo C-IIImg/dl	15.80 ± 3.80↑↑	6.50 ± 0.20	<0.0001

From the results of the lipidic profile and ApoC-III of patients with TCRI 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-III in the examined sample containing patients with TCRI were presented with average values 15.80±3.80 mg/dl in their plasma, in the controlling group the average values of ApoC-III were 6.59 ±0.20 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-III in patients with TCRI treated with HD. compared with the results gained from the co controlling group the patients with TCRI have 85% higher levels of ApoC-III.

Table number 5. The average values of the examined parameters from the controlling group didn't show any significant difference between genders that's why we present them in one table (male and female N°= 120)

Parameters	Number	Average	± SD
ApoC-III	120	6.50 ± 0.20	0.83
TG	120	1.14 ± 0.50	0.63
ChT	120	4.30 ± 1.80	1.22
HDL-ch	120	1.50 ± 0.80	0.71
LDL-ch	120	2.90 ± 0.50	1.03

The average values of examined parameters of the controlling group didn't show any significant differences between genders - that's why we present them in one table.

Table number 6. Presentation of average values of the examined patients with TCRI treated with HD **(male + female = N°= 120)**

Parameters	Number	Average	± SD	P
ApoC-III	120	15.80 ↑↑	3.80	0.0001
TG	120	3.90 ↑	0.80	0.0001

ChT	120	5.70	0.90	0.0001
HDL-ch	120	0.80 ↓↓	0.50	0.0001
LDL-ch	120	4.70	0.30	0.0001

Table number 5 and 6 present 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 number 7. tabular presentation of the correlation coefficient of gained parameters.

Rapport	Correlation coefficient	p
LDL-ch/HDL-ch	- 1.27	0.17
LDL-ch/Apo A_1	- 0.11	0.90
Apo A_1/ Apo B_{100}	- 0.22	0.02
Apo A_1/ ApoC_3	0.18	0.66
ApoC_3/Apo E	0.04	0.96

Negative statistical correlation it is noticed between the values of ApoA-I and ApoB-100-0.22 for p=0.02. positive statistical correlation was noticed between values of ApoC-III with ApoE:ApoA1/Apo-C3: 0.18 and p= 0.96.

4 DISSCUTION

Kidneys in a healthy organism have an important role in remodelation of ApoC-III. A various number of studies have suggested(19) for uremic patients with high concentration of ApoC-III to explore on changing the structure of the proteins, change their enzymatic activities and interfere in the activity of the membrane receptors, it means that the change of ApoC-III in structure may contribute in the ApoC-III catabolism in patients with CRI and TCRI treated with HD.Genetics variations of ApoC-III partly are regulated from insulin via the effect of the promoter elements and genetic transcription of insulin responsible for human ApoC-III(28,29). Transcription of ApoC-III gene it is mediated by peroxisomes that serve as an active peroxisome proliferator receptor activator that stimulates the Apoc-III receptors(23,30).In our study we noticed in patients with preterminal CRI and those with TCRI treated with HD high levels of ApoC-III and TG as a result of catabolic disorders of ApoC-III(15). Metabolic disorders of ApoC-III appear since the early stages of CRI without considering the lipid levels. Kimak and Solski (16) have verified that high concentrations of ApoC-III, specially the process of accumulating of ApoC-III in VLDL parti-cles is a common phenomenon in early stages of patients suffering from CRI(17).ApoC-III has the ability to abrogate ApoB-ApoE (39) mediated from lipoproteinic receptors of LDL-ch, or bysymmetrical changes of ApoB and ApoC.The bondage of hylo-microne and VLDL particles in the simulator rece-ptor of lipolysis it is slowed down almost inhib-ited by ApoC-III (18). High levels of ApoC-III at patents with preterminal CRI or uremic patients treated with HD mainly are a consequence of impaired catabo-lism of ApoC-III.Modification of ApoC-III catabolism should be a new therapeutic objective for the experts, this process will minimize the risk for CVD, early atherosclerosis at patients with CRI and TCRI treated with HD(44).The majority of studies (incorporating with our personal multiyear experi-ence) have verified the treatment of dilipidemy (hipertrigliceridemi and hypercholesterolemia) with fibrate, statine, holestiramin, holestipol, niacin may have positive impact in normalization of uremic dislipidemy. ApoC-III lowe-rs and inhibits the acti-vety of Lipoprotein Lipase (LPL) and it stimuli-tes the secretion of Lectin cholesterol acetyl transferase (LCAT). It is supposed that ApoC-III modelates the remain-ning particles rich in TG by hepatic receptors. Recent studies emphasize an important intrace-llular role of ApoC-III 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 cytotoxin accumu-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 (31,32,33).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 biodegenerative bioproce-sses. In the absence of ApoC-III and HDL causes early atherosclerosis and this may happen as a consequence of the movement of ApoA-I; ApoC-III; ApoA-IV locuses or ApoA-I ←→ApoC-III gene inversions.Patients with hiperlipoproteinemy have reduced concentrations of ApoC-III. Functions of ApoC-III 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.

5 CONCLUSION

In this study patients with TCRI treated with HD have high parameters of ApoC-III,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 (110/120 = 95.0%) in samples with TCRI treated with HD-allow necessa-rily should be treated with fibrate, bezafibrate, clof-ibrate not with statine. Concentrations of ApoC-III in the examined group were 6.8 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 liopmetabo-lism. 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 apolipopro-teinic and lipidic concentrations enables preventive measurements for avoiding at least on etiopatho-logical factor for accelerate atheroscle-rosis. That's why we can conclude that examination and treat-ment 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. Hypertri-gliceridemy in uremic patients treated with HD is associated with genetic variations of ApoA-I ; ApoA-III as well as damage in reconstruction of lipoproteins rich in TG or it may be caused by the plasma cleaning damages or hybrid disorder mechanisms.

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