Abstract: It is known that patients with terminal chronic renal insufficiency are presented with early atherosclerosis (atherosclerosis praecox) with serious cardiovascular and cerebrovascular complications and peripheral arterial damages are noticed in a large number of young 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 prevalence of mortality and morbidity compared with patients that suffer from diseases with other etiologies. Patients with TCRi are presented with early atherosclerosis, serious cardiovascular and periph-eral 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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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 cardiovascular diseases in patients with CRI is the high concentration 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 enterocyte 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 LDL-ch. Apo-CIII is a relatively small protein that contains 79 aminocoids it may also have glycolised threon(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-III1; ApoC-III2, ApoC-III3, ApoC - III's length is 3.5kb, it consists 4 hexons and 3 intrones, 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 isoforn of ApoC-III, shows the fastest pass way of triglycerides rich with lipoproteins -
TRLs and fractions 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 etiopathogenesis of these disorders and early treatment of Apo-III levels, may contribute in the prevention of cardiovascular, cerebrovascular and atherosclerotic diseases in this specific group of patients. Form the lipic profile in patients TCRI treated with HD we detect a high level of TG, with elevated growth of atherrogenetic 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 (cardiovascular 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 lipoprotein-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 means that in an indirect way it contributes in the high levels of VLDL (9,10). High concentrations 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 and TG at patients with CRI and TCRI treated with HD. In vitro studies have proven that transformation of ApoC-III between 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 fraction catabolic rate (FCR) in normolipidic or adipose 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 plasma percentage multiplied with 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 varied 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 hemodialysys 54(45%) were females, 64 (55%) were male, the average age was 58.00 ±18.00, treated more than 12 years with hemodysialysis 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>
<thead>
<tr>
<th>Gender</th>
<th>Number</th>
<th>Average age ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>66 (55%)</td>
<td>57.50 ± 14.00</td>
</tr>
<tr>
<td>Female</td>
<td>54 (45%)</td>
<td>58.00 ±12.30</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number</th>
<th>Average age ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>66 (55%)</td>
<td>57.40 ± 10.80</td>
</tr>
<tr>
<td>Female</td>
<td>54 (45%)</td>
<td>58.50 ±14.50</td>
</tr>
</tbody>
</table>
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.

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

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"<

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:

<table>
<thead>
<tr>
<th>Examined parameters</th>
<th>TCRI patients treated with HD</th>
<th>Controlled group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG mmol/l</td>
<td>3.90 ± 0.80†</td>
<td>1.14 ± 0.50</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ChT mmol/l</td>
<td>5.70 ± 0.90</td>
<td>4.30 ± 1.80</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-ch mmol/l</td>
<td>4.70 ± 0.30</td>
<td>2.90 ± 0.50</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-ch mmol/l</td>
<td>0.80 ± 0.50†</td>
<td>1.50 ± 0.80</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>*Apo C-III mg/dl</td>
<td>15.80 ± 3.80†</td>
<td>6.50 ± 0.20</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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 parameters it can be noticed a significant difference 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 (cited 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)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number</th>
<th>Average</th>
<th>± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoC-III</td>
<td>120</td>
<td>6.50 ± 0.20</td>
<td>0.83</td>
</tr>
<tr>
<td>TG</td>
<td>120</td>
<td>1.14 ± 0.50</td>
<td>0.63</td>
</tr>
<tr>
<td>ChT</td>
<td>120</td>
<td>4.30 ± 1.80</td>
<td>1.22</td>
</tr>
<tr>
<td>HDL-ch</td>
<td>120</td>
<td>1.50 ± 0.80</td>
<td>0.71</td>
</tr>
<tr>
<td>LDL-ch</td>
<td>120</td>
<td>2.90 ± 0.50</td>
<td>1.03</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number</th>
<th>Average</th>
<th>± SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoC-III</td>
<td>120</td>
<td>15.80†</td>
<td>3.80</td>
<td>0.0001</td>
</tr>
<tr>
<td>TG</td>
<td>120</td>
<td>3.90†</td>
<td>0.80</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

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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.

<table>
<thead>
<tr>
<th>Rapport</th>
<th>Correlation coefficient</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-ch/HDL-ch</td>
<td>-1.27</td>
<td>0.17</td>
</tr>
<tr>
<td>LDL-ch/Apo A₁</td>
<td>-0.11</td>
<td>0.90</td>
</tr>
<tr>
<td>Apo A₁/Apo B₁₀₀</td>
<td>-0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>Apo A₁/ApoC₃</td>
<td>0.18</td>
<td>0.66</td>
</tr>
<tr>
<td>ApoC₃/Apo E</td>
<td>0.04</td>
<td>0.96</td>
</tr>
</tbody>
</table>

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 DISCUSSION

Kidneys in a healthy organism have an important role in remodeling 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 CR(17). ApoC-III has the ability to abrogate ApoB-ApoE(39) mediated from lipoprotein receptors of LDL-ch, or bysymmetrical changes of ApoB and ApoC. The bondage of hylo-micrones 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 experience) have verified the treatment of dilipidemy (hipertrigliceridermi and hypercholesterolemia) with fibrate, statine, holestramin, 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 stimu-les 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 accumulations (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 plateated growth factors -TGF beta transforming growth factor -TNF alpha tumor necrosis factor -CRP complement reactie protein.

Experimental clinical examination (plasma incubation of uremic patients with and without LCAT inhibitor) 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 accumulation of toxins and weakened immunity 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 accumulation of toxins and weakened immunity 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 accumulation of toxins and weakened immunity 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 accumulation of toxins and weakened immunity 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 accumulation of toxins and weakened immunity 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 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 accumulation of toxins and weakened immunity 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 accumulation of toxins and weakened immunity 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 accumulation of toxins and weakened immunity

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 dislipidemy was hipertrigliceridemy (110/120 = 95.0%) in samples with TCRI treated with HD allow necessa-ryl should be treated with fibrate, bezafibrate, clofibrate 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 apolip-protein means early diagnostification and preven-tion 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

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 dislipidemy was hipertrigliceridemy (110/120 = 95.0%) in samples with TCRI treated with HD allow necessa-ryl should be treated with fibrate, bezafibrate, clofibrate 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 apolip-protein means early diagnostification and preven-tion 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

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