

## Apolipoprotein c-iii (apo-c<sub>3</sub>) Metabolism in Patients with End Stage Renal Disease Treated with Long Term Hemodialysis

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### Abstract

Background: End Stage Renal disease (ESRD) as it was historically termed is a term that encompasses all degrees of decreased renal function, from damaged-at risk through mild, moderate, and severe chronic kidney failure. ESRD is a worldwide public health problem. In the United States, there is a rising incidence and prevalence of kidney failure, with poor outcomes and high cost (see Epidemiology).

Material and Methods: 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 chylomicrons. In all samples regardless of their group, the concentration of ApoC-II and lipids were analyzed in a period of 12 months in a period of 12 months (the measurements were made every three months, it means we totally made 3 measurements in 9 months).

Results: The results from patients and controlling group for Apo-C<sub>3</sub> and lipid profile (ChT, TG, HDL-ch, LDL-ch) are given in table number 3. A significant statistical difference with  $p < 0.0001$  is found from the results of the lipidic profile and ApoC-III of patients with ESRD treated with HD compared with the results of the controlling group for the same parameters.

Conclusion: In this study patients with ESRD treated with HD have high parameters of ApoC-III, TG, LDL-ch but low concentrations of HDL-ch due to impaired catabolism of apolipoproteins in this specific group of patients. In all patients symptoms of CDV (myocardial infarction, angina pectoris, ischemia), acute coronary syndrome were noticed.

**Key words:** Apolipoprotein-C<sub>3</sub> (Apo-C<sub>3</sub>), End stage renal disease.

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## Introduction

Lipid metabolism disorders in patients with chronic terminal renal insufficiency were prescribed for first time in 1827 by Dr Bright, especially in the patients with nephrotic syndrome (10). It is a known fact that patients with chronic renal terminal insufficiency (CTRI) present clinically with early atherosclerosis and serious cardio-vascular complications, cerebro-vascular and peripheral arterial injuries more frequently in very large number in younger population compared to the healthy population. Recently it 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 analysis of ethiopathogenic mechanisms can significantly help in proposing preventive measures (dietary, treatment) with which there will be reduced visible frequent appearance of dyslipidemia, atherosclerotic lesions and reduced incidence of atherosclerosis in patients with CTRI randomized by gender and age (11). Patients with terminal chronic renal failure (TCRF) mostly appear with the type IV type of secondary hyperlipoproteinemia (according to Frederickson's classification) where high concentrations of triglycerides dominates (hypetriglyceridemia values of 28-100%) (12,13). Apolipoprotein-C<sub>3</sub> also known as apo-CIII is a protein that in humans is encoded by the Apo-C<sub>3</sub> gene. Apo-CIII is a component of very low density lipoprotein (VLDL). Apo-C<sub>3</sub> is a relatively small protein containing 79 amino acids that can

be glycosylated at threonine-74. The most abundant glycoforms are characterized by an O-linked disaccharide galactose linked to N-acetylgalactosamine (Gal-GalNAc), further modified with up to 2 sialic acid residues. Less abundant glycoforms are characterized by more complex and fucosylated glycanmoieties.

Apolipoprotein C-III (apo-C<sub>3</sub>) is an 8.8 kDa glycoliprotein synthesized by the liver and intestines. APOC3 inhibits lipoprotein lipase and hepatic lipase; it is thought to inhibit hepatic uptake of triglyceride-rich particles. The Apo-A<sub>1</sub>, Apo-C<sub>3</sub> and Apo-A<sub>4</sub> genes are closely linked in both rat and human genomes. The Apo-A-1 and Apo-A-4 genes are transcribed from the same strand, while the A-1 and C-III genes are convergently transcribed. An increase in apoC-III levels induces the development of hypertriglyceridemia. Recent evidences suggest an intracellular role for Apo-C<sub>3</sub> in promoting the assembly and secretion of triglyceride-rich VLDL particles from hepatic cells under lipid-rich conditions.

However, two naturally occurring point mutations in human apo C<sub>3</sub> coding sequence, namely Ala23Thr and Lys58Glu have been shown to abolish the intracellular assembly and secretion of triglyceride-rich VLDL particles from hepatic cell. ApoC-III is highly associated with hypertriglyceridemia and is a powerful independent predictor of CVD risk in subjects without renal disease. In the circulation, apoC-III is associated with TRL and HDL exchanging rapidly between these lipoproteins. In vitro studies demonstrate that apoC-III inhibits LPL and HL activities and the uptake of TRL and their remnants by hepatic lipoprotein receptors (14,15). ApoC-III may also stimulate apoB and triglyceride synthesis and, hence, drive hepatic overproduction of VLDL particles. Elevated plasma apoC-III concentration, specifically its accumulation in TRL and their remnants, is a consistent feature of dyslipidemia in

CKD (16,17). Of note, we recently reported that moderate CKD is associated with hypertriglyceridemia related to delayed catabolism of triglyceride-rich VLDL and IDL particles. In CKD subjects, plasma apoC-III concentration was significantly elevated and was an independent predictor of impaired VLDL catabolism (18,19). The underlying mechanism for the increased plasma apo-C<sub>3</sub>I concentration in these CKD subjects, however, has not been examined. A better understanding of the metabolism of apoC-III may clarify the association between dyslipidemia and CVD, with implications for better therapeutic management in the CKD population. In the present study, we investigated the kinetics of plasma apo-C<sub>3</sub> in predialysis, moderate CKD subjects (defined as those with an estimated glomerular filtration rate [eGFR] of 30–60 ml/min). We hypothesized that subjects with moderate CKD would exhibit catabolic defects in apo-C<sub>3</sub> metabolism. We also explored associations between the kinetics of plasma apo-C<sub>3</sub> and VLDL apoB and other markers of TRL metabolism, including apoA-V.

## Material and Methods

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 of their group, the concentration of ApoC-II and lipids were analyzed in a 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  $58.00 \pm 18.00$ , treated more than 12 years with hemodialysis 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  $59.60 \pm 12.80$ , 102 (55%) man with the average age of  $58.70 \pm 14.60$  (Table 1).

| <b>Gender</b> | <b>Nr.</b>  | <b>Average age<br/>± SD</b> |
|---------------|-------------|-----------------------------|
| <b>Male</b>   | 55<br>(55%) | $59.60 \pm 12.80$           |
| <b>Female</b> | 45<br>(45%) | $58.70 \pm 14.60$           |

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

| Parameter       | Reference values                    | Autors                          |
|-----------------|-------------------------------------|---------------------------------|
| <b>LT</b>       | 4-10 g/l                            | Zollner & Kirsch (20)           |
| <b>TG</b>       | 0.68 – 1.70 mmol/l                  | G. Bucolla & H.David (21)       |
| <b>ChT</b>      | 3.1 – 5.2 mmol/l                    | CCAllain et al. (22)            |
| <b>LDL-ch</b>   | < 3.4 mmol/l, high risk> 4.1 mmol/l | Friedewalde & Frederickson (23) |
| <b>HDL-ch</b>   | 1.6 mmol/l, high risk <0.9mmol/l    | G.Warnick et a l (24)           |
| <b>ApoC-III</b> | 5.5 – 9.5 mg/dl                     | Tilly P.et al.(25)              |

Table 2. Normal parameter of lipids and Apo-C<sub>3</sub> in the serum, and list of the author's name of the used method.

### Statistical processing of the examined materials

From the basic statistical methods we have used: average arithmetical value and standard deviation  $X \pm SD$ . Statistical comparison of parameters of lipids and ApoC-III between two groups was analyzed with "Studentov t" test, while for the dependent 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 controlling 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).

### Results

The results from patients and controlling group for Apo-C<sub>3</sub> and lipid profile (ChT, TG, HDL-ch, LDL-ch) are evidenced in table 3.

| <i>Examined parameters</i> | <i>ESRD patients treated with HD</i> | <i>Controlle d group</i> | <i>p</i>          |
|----------------------------|--------------------------------------|--------------------------|-------------------|
| <b>TG mmol/l</b>           | <b>3.90 ± 0. 80↑</b>                 | <b>1.14 ± 0.50</b>       | <b>&lt;0.0001</b> |
| <b>ChTmmol/l</b>           | <b>5.70 ± 0.90</b>                   | <b>4.30 ± 1.80</b>       | <b>&lt;0.0001</b> |
| <b>LDL-chmmol/l</b>        | 4.70 ± 0.30                          | 2.90 ± 0.50              | <0.0001           |
| <b>HDL-chmmol/l</b>        | 0.80 ± 0.50↓↓                        | 1.50 ± 0.80              | <0.0001           |
| <b>Apo C-III mg/dl</b>     | 12.80 ±3.80 ↑↑                       | 5,80± 0.90               | <0.0001           |

Table 3

From the results of the lipidic profile and ApoC-III of patients with ESRD 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 ESRD were presented with average values  $12.80 \pm 3.80$

mg/dl in their plasma, in the controlling group the average values of ApoC-III were  $5,80 \pm 0.90$  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 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-III. Table 4. Statement of Mann-Whitney U test parameter values displayed examine female patients and male patients treated with HD.

| Parameters      | U              | Z            | p-level     |
|-----------------|----------------|--------------|-------------|
| <b>ApoC-III</b> | <b>1896.00</b> | <b>0.80</b>  | <b>0.65</b> |
| <b>LT</b>       | <b>1345.50</b> | <b>2.30</b>  | <b>0.02</b> |
| <b>TG</b>       | <b>1701.50</b> | <b>0.42</b>  | <b>0.67</b> |
| <b>Ch</b>       | <b>1651.00</b> | <b>-0.69</b> | <b>0.48</b> |
| <b>HDL-ch</b>   | <b>1705.00</b> | <b>0.40</b>  | <b>0.68</b> |
| <b>LDL-ch</b>   | <b>1676.50</b> | <b>0.55</b>  | <b>0.58</b> |

The difference between the value that was recorded average patients treated with dialysis in both sexes (Table 4) is not significant for  $p < 0.005$  for larger number of parameters examined, significant statistical difference was verified only at LT with  $p = 0.0213$

| Report                                     | The correlation coefficient | p           |
|--------------------------------------------|-----------------------------|-------------|
| <b>LDL-ch/HDL-ch</b>                       | <b>- 1.27</b>               | <b>0.17</b> |
| <b>LDL-ch/Apo A<sub>1</sub></b>            | <b>- 0.11</b>               | <b>0.90</b> |
| <b>Apo A<sub>1</sub>/ ApoC<sub>3</sub></b> | <b>0.04</b>                 | <b>0.66</b> |
| <b>Apo A<sub>1</sub>/ ApoC<sub>2</sub></b> | <b>0.08</b>                 | <b>0.42</b> |
| <b>Apo A<sub>1</sub>/Apo E</b>             | <b>0.01</b>                 | <b>0.28</b> |
| <b>ApoC<sub>3</sub>/Apo E</b>              | <b>0.04</b>                 | <b>0.96</b> |
| <b>ApoC<sub>2</sub>/Apo E</b>              | <b>0.19</b>                 | <b>0.03</b> |

*Table 5. The correlation coefficient between the examined parameters*

Statistically significant positive correlation between the value recorded ApoC-III with Apo-E: ApoC<sub>2</sub> / ApoE: 0.96.

## Discussion

Moderate chronic kidney disease (CKD) (defined by an estimated glomerular filtration rate of 30–60 ml/min) is associated with mild hypertriglyceridemia related to delayed catabolism of triglyceride-rich lipoprotein particles. Altered apolipoprotein C-III (apoC-III) metabolism may contribute to dyslipidemia in CKD. Dysregulation of lipoprotein metabolism may develop early in CKD with altered apolipoprotein concentrations despite normal plasma lipid concentrations. Of note, Kimak and Solski (25) reported that elevated plasma apoC-III concentrations, particularly the accumulation of apoC-III in VLDL particles, occur in moderate CKD (26).

Compositional changes in apoB-containing lipoprotein may render these particles less suitable as substrates for hepatic receptor-mediated uptake (27). Consistent with this notion, cellular studies report that apoC-III can abolish apoB- and apoE-mediated binding of lipoproteins to the LDL receptor, either by masking or altering the conformation of apoB and apoE (28,29). Elevated apoC-III concentration in moderate CKD was primarily a function of impaired apoC-III fractional catabolism. Holdsworth et al. (30) showed that renal impairment was associated with excess sialylation of apoC-III, which may render apoC-III-containing TRL particles less suitable as substrates for lipolytic degradation. Furthermore, the kidney is partly involved in the removal of apoC-III from plasma.

Decreased apoC-III fractional catabolism was associated with decreased VLDL particle catabolism in moderate CKD. The potential coupling of apoC-III and VLDL apoB metabolism is consistent with the role of apoC-III as a key regulator of apoB transport, as shown by recent studies using anti-apoC-III immunoaffinity chromatography that demonstrates kinetic and structural heterogeneity of apoB-containing lipoproteins, based on apoC-III content.

Hence, the reduction in apoC-III fractional catabolism could partly be a consequence of moderate CKD. Pooled analysis of controls and CKD subjects showed a strong positive association between apoC-III catabolism and eGFR ( $r = 0.569$ ,  $P < 0.0001$ ). Similar associations were observed in CKD subjects but failed to reach statistical significance. In addition, protein carbamylation and accumulation of advanced glycation end products in the setting of CKD have been shown to alter protein structure, enzymatic activities, and binding to cell surface receptors. Hence, modification of apoC-III structure and binding could contribute to altered apoC-III catabolism in CKD (31,32). Elevated apoC-III concentration is a common feature of dyslipidemia in CKD subjects. In addition, it is increasingly recognized as an important risk factor for CVD in the general population and may be an important target in CKD subjects. Moderate CKD subjects have elevated plasma apoC-III concentrations, a consequence of delayed apoC-III catabolism. Altered apoC-III catabolism in moderate CKD may also impair apoB metabolism, resulting in decreased catabolism and accumulation of TRL and their remnants *in vivo*. Modification of apoC-III catabolism may be a new therapeutic target for reducing CVD risk in moderate CKD. Future studies to assess the effects of statins and/or fibrates on apoC-III metabolism will provide better understanding of the

cardiovascular benefits of such interventions in moderate CKD. A decrease in apolipoprotein-C-II/C-III ratio due to a disproportionate increase in plasma apolipoprotein-C<sub>3</sub> is a possible cause of lipoprotein lipase inactivation in uremia. 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. 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 hypertriglyceridemia in patients with CKD. Hypertriglyceridemia [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. Synthesis of apolipoprotein it is directly impacted and controlled by genes unlike lipidic components that directly depend on the food consumption and lipometabolism.

## Conclusion

In this study patients with ESRD 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 CVD (myocardial infarction, angina pectoris, ischemia), acute coronary syndrome. Most common dyslipidemia was hypertriglyceridemia 90.0-

95.0%) in samples with ESRD treated with HD-allow necessarily should be treated with fibrates, bezafibrate, clofibrate not with statins. Concentrations of ApoC-III in the examined group were 5-6 times higher compared to the controlling group. The role and clinical examination of apolipoprotein means early diagnosis and prevention of visceral and peripheral atherosclerosis as accelerator for cardiovascular diseases. Determination of apolipoprotein and lipid concentrations enables preventive measurements for avoiding at least one etiopathological factor for accelerate atherosclerosis. That's why we can conclude that examination and treatment of apolipoprotein in the early stages of the diseases should be the first postulate in the treatment of CKD patients, this approach to the disease significantly will reduce the risk for CVD. Hypertriglyceridemia in uremic patients treated with HD is associated with genetic variations.

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