Changes of lipoapoproteins and the Role of Statins of Patients with Terminal Chronic Renal Insufficiency treated with repeated hemodialysis

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Abstract— Disorders of lipid metabolism in patients with ESRD for the first time are described in 1827 by Dr. Bright, particularly in patients with nephrotic syndrome [4]. Replacing of physiological apolipoproteins with pathological and high degree of their influence in atherogenity are phenomena still undiscovered and therefore whitening of the above processes are necessary experimental and multicentric numerous studies with the most duration of research. Purpose of research paper is to assess the abnormalities(changes) of apolipoproteins in ESRD patients treated with repeated hemodialysis more than 7 years in Clinical Hospital Tetovo,Hemodialysis Unit,randomized by gender (male or female) and effects of hypolipidemic drugs (statins) on improvement of apolipoproteins abnormalities.Also importance has been given to HDL-ch metabolism disorder which is supposed that is responsible and main factor in controlling the progress and pace of atherogenesis mechanism in uremic patients.

Index Terms— Apolipoproteines, statin, total lipids, total cholesterol, tryglicerides. .

1 INTRODUCTION

It is proved that patients with ESRD treated with repe-ated hemodialysis suffer from a secondary and complex form of dyslipidaemia and are potential candidates for development of atherosclerosis respectively cardiovascular and cerebrovascular complications. Major disorders of apolipoproteins manifested more in the concentration of triglicerides TG, HDL, LDL, remaining particles, small LDL-$_6$. Concentrations of LDL-$_6$ are mostly increasing in patients with ESRD treated with hemodialysis, but the basic responsible disease remains diabetes compared with the others basic disease such HTA, chronic glomerulonephritis, polycystic renal disease. Abnormalities of apolipoproteins during uremic syndrome including all apolipoproteins particles. Due to increasing concentrations of tryglicerides in the compositions of VLDL, IDL, LDL and HDL-ch is dominates hypertrygliceridemia.

Total cholesterol in patients with ESRD treated with hemodialysis not show any significant difference compared with his own values obtained during examination of helthy population.

Replacement of physiological lipo-apoproteins with phatological, high rate of their atherogenesis and additional impact of uremic toxins to the structure and compositions of lipo-apoproteins in uremic medium are phenomena still undiscovered therefore more experimentals and multicentric studies are needed. There are confirmed and documented facts that all values of *LDL-ch, Apo B-$_{100,}$ VLDL, LDL, remnants lipoproteins, LDL-$_6$, IDL, ,LDL-$_{0X}$, lipoapolipoproteins A-$_1$, lipoapoproteins A-$_2$, lipoapoproteins A-$_4$, lipoapoproteins-E polymorphism), lipoapo-proteins - C* are same atherogenic and independent from each other.several studies have verified that qualitative changes in morphology and size of lipoapoproteins particles to patients with ESRD treated with hemodialysis increase their atherogenic impact and have high capability for climbing to arterial subendothel in the presence of oxidized cholesterol LDL-ox (LDL-$_6$) and also have greater predisposition to attacks cardiovascular system.

The most frequent manifestation appear in uremic patients are in these diseases: ischemic heart diseases, acute myocardial infarction, peripheral vascular disease (PVD), peripheral artery occlusive disease (PAOD), cerebrovascular diseases, cerebrovascular accident (CVA). LCAT (Lecithin-Cholesterol- Acyltransferasa) in normal plasma plays role in HDL-cholesterol remodeling and is an enzyme that converts free cholesterol into cholesteryl ester (a more hydrophobic form of cholesterol), which is then sequestred into the core of lipoprotein particle, making the newly synthesized HDL spherical. In uremic patients LCAT activity is reduced 30% and optimal conversion is compromised and reduced [2]. Ex

Perimental clinical investigation (incubation of plasma in

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uremic patients with LCAT inhibitor or without LCAT-inhibitor confirm that atherosclerotic processes are directly dependent from ß1-HDL catabolism disorder . ERSD patients treated with HD due to toxic effects often are treated with hypolipidemic drugs.

In clinical practice more efficient and appropriate hypolipidemic agents are those who are excreted and eliminated via hepar(HMG-CoA reductasae inhibitors-Statins) compared with hypolipidemic drugs who are excreted by the kidneys. Genetic prediction in appearance of early atherosclerosis and familial predisposition is disorders in reverse cholesterol transport (RVS) and disorders of gene encoding LDL receptors.

2 Material and Methods

In our study are included 120 patients (66 male and 54 female) with ESRD treated with hemodialysis in Clinical Hospital in Tetovo, Nephrology and Hemodialysis Unit. The average age of patients treated with HD, gender male is 58.50±15.80 years, while for female gender is 59.80 ± 12.00 years. Controll group consists of 120 helthy individuals with average age for male 57.30 ± 10.80 years and for female 59.00±12.40 years.

Receipt of material (blood) is realized in morning after a minimum of 12 hours not eating in lying position. All the results obtained from the examined patients are compared with obtained results on the control group of helthy individuals according by gender, age and nationality. All patients examined, a minimum of 6 months prior to study were not treated with antihyperlipidemic therapy and have not used drugs that can affect the concentrations of lipids and apolipoproteins.Before the start of the study to all patients was verified normal plasma activity of enzymes such: AP, LDH, ALT, AST, CPK, CK-MB which are marker for muscle and liver diseases. Patients examined are treated with repeated hemodialysis a minimum 7 years.The body weight exceeded normal values of 14 female patients (BMI = 25.0 ± 38.9 kg) while the body weigh exceeded normal values of 18 in male patients (BMI = 45 - 40kg).

In our study we did the division of patients according to renal diseases such as: with chronic glomerulonephritis- 30 patients, diabetic nephropathy - 18 patients, with HTA and nephroarteriosclerosis – 28 ,with autosomal polycystic kidney disease in adults-12 patients, with opstructive nephropathy-7 patients and undifferentiated nephropathies-7 patients (Tab. 1). To all patients before study is made examination of apolipoproteins and then began treatment with Statins (HMG CoA reductase inhibitors) in the duration of 24 weeks. Statins dosage was 20 mg every night before sleeping, while in some cases of extreme hyperlipidemia the dosage was 40 mg.

3 Experimental Results

Achieved results are presented in charts / graphics as follows. Results obtained by patients and control groups to the lab parameters examined such: Total lipids(g/l),Triglycerides (TG), Total cholesterol (TC), LDL-ch, HDL-ch (mmol/l), Apo-A_1, Apo-B_{100}, Apo-C-$_2$, Apo-C- Apo-E (mg/dl), Lipoprotein lipase (LPL (U/I)) and Lipoprotein - a [Lp (a) mg/dl] are presented in tables number 4 and 5 by calculating the average value of three successive measurements.

TABLE 1
DISTRIBUTION OF PATIENTS BY BASIC RENAL DISESASE

Basic Renal Disease	*No. of patients*	*%*
Glomerulopathy	30	25,0
HTA secondary	28	23,3
Diabetes mellitus	18	15,0
Intersticiopathy	16	13,3
RAAP	12	10,0
Nondifferented Nephropathy	9	8
Uroobstructive Nephropathy	7	6

TABLE 2 A
DISTRIBUTION OF PATIENTS BY GENDER AND AVERAGE AGE

Gender	No.	Average age ± SD
Male	66 (55%)	58.40±13.60
Female	54 (45%)	59.80± 12.40

TABLE 2 B
DISTRIBUTION OF CONTROLLS GROUP BY GENDER AND AVERAGE AGE

Gender	No.	Average age
Male	66 (55%)	57.30± 10.80
Female	54 (45%)	59.00±12.40

TABLE 3
NORMAL LEVELS OF LIPIDS AND SERUM APOLIPOPROTEINS

	Values Levels	AUTHORS
LT	4-10 g/l	Zollner & Kirsch
TG	0.68 – 1.70 mmol/l	G. Bucolla & H.David [3]
ChT	3.1 – 5.2 mmol/l	C CAllain et al. [1]
LDL-ch	< 3.4mmol/l,High risk > 4.1 mmol/l	Friedewalde&Frederickson
HDL-ch	1.6 mmol/l, High risk <0,9 mmol/l	G.Warnick et al.
Apo A-I	1.0 – 1.90 g/l	Rifai N.
Apo B-100	0.5 – 1.60 g/l	Rifai N.,
Lp(a)	< 30 mg/dl	Rifai N.,
ApoC-II	1.6 – 3.2 mg/dl	Rifai N.
ApoC-III	5.5 – 9.5 mg/dl	Tilly P.et al[11]
ApoE	2.7 – 4.5 mg/dl	Vincent –Viry M.
LPL	5.6 – 51.3 u/L	Tietz NW

Difference that is registreted with average values of the parameters examined between two groups by gender and nationality belonging is statistically significant p ***< 0.0005*** for the parameters LDL-ch, HDL-ch, ApoA-$_1$, Lp(a), ApoC-$_2$ and TG whereas in the other parameters is not identified any significant difference (table.4)

TABLE 4
VALUES LEVELS ACQUIRED FROM CONTROLL GROUP FROM EXAMINATED PARAMETHERS
(N^O=120)

Parameters	No.	Average	± SD
ApoC-III	120	6.43	0.82
ApoC-II	120	2.83	0.79
Apo E	120	3.59	3.03
LPL	120	24.20	9.21
ApoA-I	120	1.42	0.43
ApoB-100	120	1.05	0.20
LT	120	6.50	0.60
TG	120	1.30	0.63
ChT	120	4.95	1.22
HDL-ch	120	1.60	0.71
LDL-ch	120	2.75	1.03
Lp(a)	120	23.50	7.10

Results show that the concentration of TG, LDL-ch, ApoC-$_{2,3,}$ ApoB-$_{100,}$ Apo-E, Lp(a) , LPL (Lipoprotein Lipasae) were significantly increased while the values of HDL-ch ear ned Apo-A$_{1,2}$ were lower (by reference) to ESRD patients treated with repeated HD compared with control group by gender and age with ***p<0.005.***

TABLE 5
PRESENTATION OF AVERAGE VALUES OBTAINED FROM THE EXAMINED PARAMETERS IN PATIENTS WITH ESRD TREATED WITH HEMODIALYSIS

Parameters	No.	Average	± SD	P
ApoC-III	120	11.06	3.65	0.0001
ApoC-II	120	9.73	4.06	0.0001
Apo-E	120	6.50	2.40	0.0001
LPL	120	20.85	15.20	0.0001
LT	120	7.39	2.00	0.0001
TG	120	3.18	0.80	0.0001
ChT	120	4.95	1.20	0.1980
HDL-ch	120	1.12	0.49	0.4234

LDL-ch	120	3.60	0.50	0.0001
ApoA-I	120	1.04	0.38	0.0001
ApoB-100	120	2.86	0.86	0.0001
Lp(a)	120	48.03	40.10	0.0001

Table 5 present significant diffirence -***p*** between the examined parameters in patients treated with hemodialysis and control group. Difference that is registreted between patients treated with HD and control group is statistically significant for ***p=0.0001*** while no significant difference is registreted only in HDL-ch and Cholesterol (***p=0.4234 and*** p=***0.1938***), table no. 5.Prior treatment with statins HDL-ch concentrations of the examined patients was close to normal values (for men 1.23+-0.40 mmol/l and for women 1.28±0.50 mmol/l), while the reference values of control group for HDL-ch were 1.60±0.71 mmol/l. The others lipoproteinic values obtained from control group and patients with ESRD treated with repeated HD are highlighted in tabeles 4 and 5.Liver-muscle enzyme activities (AP,AST,ALT,CPK,CK-MB) before and after treatment with statins in the same patients group was significantly different with the exception of LDH where the activity of this enzyme was significantly lower after treatment (for men 154.71.40±27.8 vs 133.7±39.5 U/I,p<0.02) and (for women 159.4±38.6 vs 139.6±39.5 U/L, p<0.05).

4 DISSCUSION

Although it is thought that uremic patients in hemodialysis have progressed very fast atherosclerosis and high mortality as a result of complications from it, definitive studies leading to abnormalities apo/lipoproteins and increased frequency of atheromas formation verified with angiography and ultrasono-graphy not yet exist. There is some documented evidence for abnormali-ties of the apolipoproteins values in uremic patients treated with chronic hemodialysis. Patients treated with HD have a reduction in total choleste-rol concentrations and higher concentrations of TG,LDL-ch,ApoB-100, Apo-C2,3, Apo-E, Lp(a), LPL and significantly lower values Apo-A1,2 and HDL-ch [4,7]. In vitro was verified that statin reduce production of oxygen free radicals by interfe-ring 3 with molecules signals NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) transcriptase system by inhibiting the production cascade of inflammatory molecules such a Interleukin 6 (In-6) and CRP. The oxidized LDL-ch (LDLox) realizes its effect via stimulation of NADPH –O2. Because statin gradually reduce the overall amou nt of LDL that is necessary for oxide-tive modification of his own-oxygenation of LDL-choleste-rol, thus practica-lly confirming the way they operate to reduce high concentra-tions of conce ntrations of LDL-ch. All these lipoproteinic particles containing lipoprotein-B therefore conclude most frequently disorders of apolipoproteins are due to increased TG rich with Apo-B. All components of lipoproteinemia and dyslipidemia are atherogenic and independent from each other.

Effects of HMG-CoA reductasae inhibitors-Statins have been shown as the most studied and appropriate medications to apo/lipoproteins disorders in ESRD patients treated with repeated hemodialysis.Effect of statins is blocking the enzyme HMG CoA and reduce the rate of production (synthesis) of LDL-ch. In general population statin arrived reduction LDL-ch for 30-63% and triglycerides 20-40% and raising HDL-ch 10-25% [6] oral published studies on the role of statin have verified that statin had a positive antinflammatory effectby decreasing concentrations of CRP. In many studies statin in patients treated with HD showed higher effect on lowering LDL-ch concentrations up to 43% reduction in total cholesterol (TCH), apolipopro-teins-B and decrease conce-ntrateonsof oxidized cholesterol (LDLox)[8,9].

Early dyslipidemia is highly conditional by the dynamics of changes in choleste-rol between the lipoproteinic particles and the reverse transport. Statins therapy was more effective in comparison with concentrateons of TG and LDL-ch and their concentration was significantly decreased (***p<0.05-0.001)*** as compared with apolipoproteins improvement that is obtained weaker response,because are needed more detailed studies and longer time to be determined with precision the positive effects of statins on improving of apolipoproteins in ESRD patients treated with HD. Progression of cardiova-scular and cerebrovascular diseases, ocular complications in healthy popula-tions significantly reduced by decreasing the high values of LDL-ch and TG in patients with ESRD, uremic syndrome treated with HD. The above findings for uremic patients still are not fully verified with precision. This situation is directly dependent on the specific situation of uremic patients and lipoproteins atherogenesis in ESRD patients treated with repeated HD and is more dependent on the concentration of high densi-ty lipoproteins with Pre-ß (IDL), LDL-6 and not by total fraction of LDL cholesterol. While it is known that the concentration of ApoA-$_1$ and ApoA-$_2$ each time found in serum of healthy patients with ESRD patients treated with reapiting HD, concentration of ApoA-$_1$ ApoA-$_2$ are reduced to increase of the concentration accounts of Apo-B and Apo-E-$_2$ and reducing ApoE-$_4$ and increasing polymorphisms of ApoC-$_1$, ApoC-$_2$, ApoC-$_3$. There are data to support the theory that low values of HDL-ch plasma in patients with ESRD are related to the reduction of synthesis ApoA-$_1$/HDL-ch.

Mentioned effect of HDL-ch against atherosclero-sis comes from the dual role of mechanism reverse cholestererol transport to VLDL and LDL with the help of Cholesteryl Ester Transfer Protein. If creatine kinase (CK)values increased for 10 times then normal value ,the statins therapy should be discontinued was noted that the cholesterol transfer (RCT) from HDL to VLDL / LDL was lower in the serum of patients with ESRD regardless if they are in treatment with dialysis or not. If reverse cholesterol transport is slow then increasing its accu-mulation in tissue, which this breakdown and mechanism helps signifycantly in patients with atherosclerotic processes in ESRD patients and those threated with HD.

5 Conclusion

- Statins in the treatment of dyslipidem-ia and lipoapoproteins aberations pro-ved very secure in our experience with the dosage of 20 mg in the evening every day to redu-ce high concentrations of LDL-ch, TG, IDL, LDL-6, adjusting the concentrateons of Apo-B ,Apo-C, Apo-E and increasing concentrations of HDL-ch, apolipoprotei-nes subfractions and its-Apo-$_{1,2.4}$. Patients treated with HD, considering their rare side effects as rhabdomyoli sis with muscular pain and increase creatine kinase (CK).
- Risk of rhabdomyolisis is larger if statin therapy combined with other additional cyclosporine and fibrates. Application of the statins in the treat-ment of uremic dyslipidemia should be a regular pharmaceutical components applied to patients with chronic uremia treated with repeated HD.
- If taken into consideration all modern theoryes on the treatment of artherosclerotic processes in ESRD patients, drug treatment of apo/lipoproteins abnormalities is thus necessary that will significa-ntly reduce the risk of cardiovascular and cerebrovascular dissease.

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