DISTURBANCE OF APOLIPOPROTEIN IN UREMIC PATIENTS TREATED WITH DIALYSIS

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Abstract: Abnormalities in lipid metabolism occur in patients with all stages of chronic kidney disease (CKD) (1-7). The most common dyslipidemia in CKD and dialysis is hypertriglyceridemia, whereas the total cholesterol concentration can be high, normal, or low, perhaps due in part to malnutrition (8). In contrast, the nephrotic syndrome is typically associated with hyper-cholesterolemia and hypertriglyceridemia.The pathogenesis of most lipid abnormalities in pati-ents with CKD primarily involves defective removal from the circulation. The diminished clearance of triglycerides, which can lead to hypertriglyceridemia, stems both from an alteration in the composition of circulating triglycerides (which become enriched with apolipoprotein C-III) and, perhaps later, from reductions in the activity of lipoprotein lipase and hepatic triglyceride lipase, which are involved in triglyceride removal (9). Why lipoprotein lipase activity is reduced in CKD is not well understood, but has been thought to reflect increased inhibitor activity. The associated secondary hyperparathyroidism may play a contributory role, perhaps by increasing calcium accumulation within the cells in the liver and adipose tissue. Studies in humans and experimental animals with CKD suggest that parathyroidectomy can normalize serum triglyceride levels and hepatic lipase activity (10,11,12). In experimental animals, benefit can also be achieved with verapamil by a similar mechanism , although this has not been confirmed in humans.Another possible mechanism for hypertriglyceridemia in CKD is retention of a circulating inhibitor of lipoprotein lipase, such as pre-beta-high density lipoprotein (HDL) (13-16). Pre-beta-HDL is a form of apolipoprotein A-I found in the non-lipoprotein fraction of normal plasma.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: Lipoproteines, statin, total lipids.

1 INTRODUCTION

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). Patients with ESRD are at a particularly high risk for coronary artery disease (CAD) or atherosclerotic coronary heart disease (ASCHD). There are traditional and nontraditional risk factors that contribute to the high incidence of CAD in this population Chronic kidney disease (CKD) is a significant health problem. It was estimated that the prevalence of CKD among the USA population between 1999-2004 was 15.3% (1). On the other hand, it is well documented that cardiovascular disease (CVD) is a major cause of morbidity and morta-lity in patients with CKD (2,3,4,5,6). Thus, although some patients with CKD will ultimately develop end stage renal disease (ESRD), most patients with CKD will die of CVD before dialysis becomes necessary (7). Mild chronic impaired renal function contributes actively to the development of CVD, so the American Heart Association has recommended that these patients should be classified in the highest risk group for developing cardiovascular events (5). Even microalbuminuria in the absence of apparent deterioration in renal function or diabetes predicts more CVD and deaths (8). In patients who finally advance to ESRD and especially dialysis patients, the prevalence of clinical coronary heart disease is 40% and CVD mortality is 10 to 30 times higher than in the general population of the same gender, age and race (9,10). CKD is characterized by specific metabolic abnormalities of plasma lipoproteins (27,28 ,29). These abnormalities involve all lipoprotein classes and shows variations depending on the degree of renal impairment, the etiology of primary disease, the presence of nephrotic syndrome (NS) and the method of dialysis [hemodialysis (HD) or peritoneal dialysis (PD)] for patients undergoing renal replacement therapy.It is

proved that patients with ESRD treated with repe-ated hemodialysis suffer from a secondary and complex form of dyslipidaemia and are potential candi-dates for development of atherosclerosis respectively cardiova-scular and cerebro-vascular 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 dise-ase. 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 domina-ntes 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 additionnal 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 lipo-proteins, LDL-6 , IDL, ,LDL-0X, lipoapolipoproteins A-1, lipoapoproteins A-2, lipoapoproteins A-4, lipoapo-proteins-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, cerebrovas-cular accident (CVA). LCAT (Lecithin Cholesterol- Acyl transferasa) in normal plasma plays role in HDL-choles-terol 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 (31). Ex Perimental clinical investigation (incubation of plasma in uremic patients with LCAT inhibitor or without LCATinhibitor 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 hypo-lipidemic 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 58.40±13,60 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 nephroarterio-sclerosis – 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 exam-ination of apolipoproteins and then began treatment with HMG CoA reductase inhibitors in the duration of 24 weeks. Statins do sage 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), ApoA1, Apo-B100, Apo-C-2, Apo-C- Apo-E (mg/dl), Lipoprotein lipase (LPL (U/l)) 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 no. 1: Distribution of patients by basic renal disease

Basic Renal	N°. 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	8	8.0
Uroobstructive Nephropathy	7	6

Table no 2a: Distribution of patients by gender and average

Gender	N° 120	age ± SD
Male	66 (55%)	58.40± 13.60
Female	54 (45%)	59.80± 12.40

Table no. 2 b: Distribution of controls group by gender and average age

Gender	N° 120	age ±SD
Male	66 (55%)	57.30 ± 10.80
Female	54 (45%)	59.00± 12.40

Table no. 3: Normal levels of lipids and apolipoproteins values level and authors

	REFERENCE VALUES	AUTHORS
LT	4-10 g/l	Zollner & Kirsch (12)
TG	0.68 – 1.70 mmol/l	G. Bucolla & H.David (32)
ChT	3.1 – 5.2 mmol/l	CCAllain et al. (31)
LDL-ch	< 3.4 mmol/l, High risk > 4.1 mmol/l	Friedewalde&Frederickson (41)

HDL-ch	1.6 mmol/l, High risk <0.9mmol/l	G.Warnick et a l (42
Apo A-I	1.0 – 1.90 g/l	Rifai N.(43)
Apo B-100	0.5 – 1.60 g/l	Rifai N.(43)
Lp(a)	< 30 mg/dl	Rifai N.(43)
ApoC-II	1.6 – 3.2 mg/dl	Rifai N.(43)
ApoC-III	5.5 – 9.5 mg/dl	Tilly P.et al.(40)
ApoE	2.7 – 4.5 mg/dl	Vincent –Viry M, et al.44)
LPL	5.6 – 51.3 u/L	Tietz NW et al.

Table no. 4: Values Levels acquired from control group from ezamined parameters (N^{O}=120)

Parametheres	N^{o}	Average ± SD
LT g/l	120	6.20 ± 0.50
TG mmol/l	120	1.50 ±0.60
ChT mmol/l	120	5.60±1.40
HDL-ch mmol/l	120	1.70 ±0.80
LDL-ch mmol/l	120	2.90±1.1.20
Apo-A-I mg/dl	120	1.46 ±0.60
ApoB-100 mg/dl	120	1.10 ± 0.40
Apo-E mg/dl	120	3.60 ±0.08
ApoC-II mg/dl	120	2.70 ±0.60
ApoC-III mg/dl	120	6.20 ±0.50
LPL u/L	120	25.00± 8.50
Lp(a) mg/dl	120	26.00 ±12.00

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 paramet LDL-ch, HDL-ch, ApoA-$_1$,Lp(a),Apo-C-2 and TG whereas in the other parameters is not identified any significant difference (table.4). Results show that the concentration of TG, LDL-ch, LPL ApoC-II,III, Apo-B100, Apo-E, Lp(a) , were significantly increased while the values of HDL-ch ear ned Apo-AII.III were lower (by reference) to ESRD patients treated with repeated HD compared with control group by gender and age with p<0.005.

Table no. 5. Presentation of average values obtained from the examined parameters in uremic patients treated with dialysis

Parametheres	Pati.N^{o}	Average ± SD	*p*
LT g/l	120	7.60 ± 2.40	0.0001
TG mmol/l	120	3.80 ± 0.90	0.0001
ChT mmol/l	120	5.60 ± 1.40	0.0001
HDL-ch mmol/l	120	1.08 ± 0.50	0.0001
LDL-ch mmol/l	120	4.60 ± 0.60	0.0001
Apo-A-I mg/dl	120	1.03 ± 0.40	0.0001
ApoB-100 mg/dl	120	2.90 ± 0.80	0.0001

Apo-E mg/dl	120	6.80 ± 2.60	0.0001
ApoC-II mg/dl	120	9.70 ± 4.20	0.0001
ApoC-III mg/dl	120	12.00 ± 4.60	0.0001
LPL u/L	120	23.60± 14.50	0.0001
Lp(a) mg/dl	120	48.70 ± 36.80	0.0001

Difference that is registreted between patients treated with HD and control group is statistically significant for p=0.0001 table no. 5. Liver-muscle enzyme activities (AP,AST,ALT, CPK,CK-MB) before and after treatment with statines 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/l,p<0.005).

Table no. 6: Presentattion of Mann-Whitney U test parameter values displayed examine female patients and male patients treated with dialysis

Paramethers	U	Z	p-level
ApoC-III	1630.80	-0.84	0.50
ApoC-II	1698.00	0.47	0.75
Apo-E	1680.00	-0.46	0.80
LPL	1650.00	0.87	0.50
LT	1348.50	2.70	0.08
TG	1730.50	0.48	0.70
Ch	1670.00	-0.68	0.49
HDL-ch	1720.00	0.50	0.70
LDL-ch	1674.00	0.62	0.54
ApoA-I	1568.00	1.24	0.28
ApoB-100	1740.50	0.40	0.72
Lp(a)	1650.50	-0.76	0.45

The difference between the value that was recorded average patients treated with dialysis in both sexes (tab. no. 6) is josignifikant for p <0.005.

4 DISSCUSION

In patients with ESRD hypertriglyceridemia is due to increased production of concentartion Apo-B with a significant decrease in VLDL metabolism, mainly as a result of the collapse of endothelial cells delipidation of VLDL .Main cause lipoproteinemic metabolism is supposed bereduced catabolism and cleaning of Apo-B containing lipoprotein rich in TG). The main factors that contribute to the reduction of catabolism include a reduced activity of lipolytic enzyme, compositional lipopro-teinemic abnormalitiesare also diminished lipolisis, and a receptor- which mediates in obtaining lipoproteins.Main characteristic disiplidemia of renal patients treated with HD is hipertriglyceridemia. There are documented facts that different modalities play important role in correcting dyslipidemia by reducing uremic toxicity. Thus, it is shown that the use of polysulfone or cellulose triacetate membranes with high flux instead of membrane withdecreased flux was associated with a significant reduction in triglyceride levels of serum, as well as an increase of apolipoproteines AI and levels of HDL-ch .Another factor that could potentially influence lipoprotein metabolism in HD patients is repeated use of heparin as an anticoagulant. Heparin releases LPL from endothelial surface and thus its chronic use may result in depletion of lipoprotein lipase anddamaged lipoprotein catabolism. However, few studies that tested the role of heparin in the pathogenesis of uremic dyslipidemia have shown conflicting results. 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 (33 34). In vitro was verified that statin reduce production of oxygen free radicals by interfe-ring 3 with molecules signals NF-κB (nuclear factor kappa-lightchain-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 LDLch (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 ownoxygenation 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% 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)[(35,36)]. 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<0.005.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 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 accumulation in tissue, which this breakdown and mechanism helps signifycantly in patients with atherosclerotic processes in ESRD patients and those threated with HD. Heart disease is a major cause of morbidity and mortality among patients with renal failure. Premature atherosclerotic coronary heart disease is driven by multiple risk factors, including dyslipidemia and oxidative stress. In the nondialysis population, there is overwhelming evidence that treatment of dyslipidemia can significantly improve cardiovascular outcomes. Accumulating data indicate that dialysis patients have atherogenic lipid abnormalities. Although LDL-ch levels in patients who undergo hemodialysis are normal or near normal, increased oxidized LDL-C, triglycerides, and lipoprotein (a) [Lp(a)]; decreased HDL-ch, and triglyceride-rich VLDL have been noted. Patients who receive peritoneal dialysis have a more atherogenic lipid profile with increased LDL-ch, apolipoprotein B, oxidized LDL-Ch(LDLchox, triglycerides, and Lp(a) and decreased HDL-C. Furthermore, the LDL particles of peritoneal dialysis patients are small and dense. However, there is a dearth of information regarding the goals, efficacy, and safety of dyslipidemia treatment among dialysis patients. Given the strong evidence of risk reduction and the benefits of lipid-lowering treatment in the nondialysis population, the emerging consensus is that dialysis patients should be treated aggressively for dyslipidemia to an LDL-Ch goal below 100 mg/dl. Although physicians and patients may be reluctant to add medications because of concerns about polypharmacy, potential decreased compliance, and increased cost, the use of agents such as sevelamer that can serve multiple functions, including phosphate control, lipid lowering (decreased LDL-ch and total cholesterol), and anti-inflammatory effects (decreased high-sensitivity C-reactive protein), should be explored and considered for patients who would benefit from such treatment.

5 CONCLUSION

Dyslipidemia is a very common complication of CKD. Disturbances in lipoprotein metabolism are evident even at the early stages of CKD and usually follow a downhill course that parallels the deterioration in renal function. Recently published studies indicate that dyslipidemia in these patients may actively participate in the pathogenesis of CVD as well as in the deterioration of renal function. Thus, we believe that the current evidence dictates the use of statins in patients with mild to moderate CKD. 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-I,II,IV. Patients treated with HD, considering their rare side effects as rhabdomyoli sis with muscular pain and increase creatine kinase (CK). A number of other hypolipidemic drugs that are increasingly used in the general population (such as niacin, omega-3 polyun saturated fatty acids and ezetimibe) may also have important roles in the management of uremic dyslipidemia. However, although small studies have documented the biochemical efficiency and the tolerability of these substances in patients with chronic kidney disease, no prospective studies with clinical end-points have proved their efficiency in terms of cardiovascular morbidity and mortality

reduction. Further studies are needed to delineate the role of these drugs in the treatment of dyslipidemia in individuals with CKD. On the other hand, in subjects with ESRD the decision for the institution of lipid-lowering therapy should be individualized. Thus, in individuals with established CVD as well as in those who run a high risk for acute pancreatitis due to severe hypertriglyceridemia the administration of hypolipidemic drugs (Statins, Gemfibrozil, Cholestipol, Holestyramine,Niacin) is a safe and reasonable approach. However, it should be kept in mind that further studies are needed to delineate the clinical efficacy of these intervene tions. 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 abnor malities is thus necessary that will significantly reduce the risk of cardiovascular and cerebrovascular disease.

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