DYSLIPIDEMIA IN UREMIC PATIENTS TREATED WITH INTERMITTENT DIALYSIS

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Abstract :It is known that uremic patients present clinical atherosclerosis mirror the earlier representation and serious complications of cardiovascular, cerebrovascular with peripheral arterial injuries more frequently with many more younger compared with the healthy population. Recent years has been verified that uremic dyslipidemia persists that in the early stages of kidney weakness, prior to treatment with hemodialysis (HD) and is one of basic factors of the beginning of atherogenic processes in uremic patients. Lipid metabolism disorders in patients with ESRD is first described in 1827 by Dr. Bright, especially in patients with nephrotic syndrome. Replacingphysiological lipoapoproteins with those pathological and effect of their high atherogenic impact phenomena are still undiscovered. Metabolism disorders of HDL-ch is the main factor responsible for checking the progress and pace of atherogenesis in uremic patients.The purpose of this paper research is to evaluate the anomalies of lipids and apolipoproteins inuremic patients treated with hemodialysis over 7 years in the Department of Haemodialysis at the Clinical Hospital of Tetovo, randomized by gender, age and underlying disease that has led to uremia. Matherial 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. 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. Conclusion: statins in the treatment of dyslipidemia and lipoapoproteins aberations proved very secure in our experience with the dosage of 20 mg in the evening every day to reduce 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, apolipoproteines subfractions and its-Apo-1,2.4. Patients treated with HD, considering their rare side effects as rhabdomyolisis with muscular pain and increase creatine kinase (CK). Risk of rhabdomyolisis is larger if statin therapy is combined with other additional cyclosporine and fibrates. Application of the statins in the treatment of uremic dyslipidemia should be a regular pharmaceutical components applied to patients with chronic uremia treated with repeated HD.

Term Index: uremia, lipid profile, apolipoproteines, hemodialysis.

1 Introduction

It is proved that patients with ESRD treated with repeated 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.

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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 (LecithinCholesterol-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). Experimental clinical investigation (incubation of plasma inuremic 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 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.The pathogenesis of a large number of lipid abnormalities in patients with CKD mainly includes removal of the damaged lipid from circulation.Reduced cleaning of the triglycerids, which may lead to hypertriglyceridemia, stems from a change in the composition ofcirculating triglycerides (which become enriched with apolipoprotein C-III) and, perhaps later, the curtailment of activity for the operation of lipoprotein lipase and triglyceride hepatic lipase, which are involved in the removal of triglycerides (3,4,5).The mechanism of activity of lipoprotein lipase reduced in patients with CKD still is not well known, but it is assumed that the activity of reduced LPL is due to the activity of so-called inhibitors of LPL. [4]. In this mechanism important role can play the secondary hyperparathyreoidism connected possibly by increasing calcium inside the cells collected in the liver and adipose tissue. Studies in humans and experimental animals with CKD suggest that parathyroidectomia can normalize serum TG levels and hepatic lipase activity (6,7). There are experimental animal studies that a benefit can be achieved with verapamil treatment, although this has not been confirmed in humans. Another possible mechanism for hypertriglyceridemia of CKD is to maintain a circulating inhibitor of lipoprotein lipase, an increase of HDL-ch concentration and pre beta HDL who mostly is found in the composition of Apo-A (8,9). Disorder of lipid metabolism indiabetic patients and with uremia manifested by increased VLDL, IDL fractions, which are mainly due to a defect in the catabolism of triglyceride-rich lipoproteins (3) and reducing the fraction of HDL-ch (10, 11). Variations of the locus of APO-E, affecting the level of fats and lipoproteins in the population and also early conditional presentation of coronary disease. LDL-ch significantly increased in carriers of ApoE4 locus, and other lipid fractions as triglycerides, HDL-ch and total cholesterol (CHT), they do not differ in homozygotes compared with locus of ApoE-ApoE-III and IV. Is concluded that the level of LDL-ch patients with terminal chronic renal failure (CRF) is closely connected with the carrier ApoE-IV and may be the cause of early atherosclerosis of this group of patients. Apolipoprotein-E is is ligand for Livelipoproteinicreceptors andaffects cleaning of lipoprotheinic particles. Aproximately 50% of ESRD patients die from a cardiovascular disease that shows cardiovascular mortality is 30 times higher in dialysis patients than population general, and is associated with characteristic changes in lipid and lipoprotein metabolism (12,13). Uremic patients treated with chronic hemodialysis suffer from a large number of biochemical abnormalities of lipids and apolipoproteineins. As the main cause of the high rate of mortality in uremic patients treated with hemodialysis (HD) still accounted cardiovascular diseases (14). In patients with chronic renal terminals (IRKT) to treat HD mostly appear with the type IVsecondary hyperlipoproteinemia (by classification Fredericks-on-it) in which they dominate higher concentrations of triglycerides (hypetreglyceridemia dominates with the value of 28-100%} (15,16,17). Renaldysiplidemia is reflected disorders of lipid fractions associated with disorders of apolipoproteinsfamilies (APO) individually. (18,19)It is characterized byreduced concentrations of apolipoproteines-A (Or-A) and high density cholesterol (HDL-ch) and concentrations of elevated triglyceride rich in apolipoprotein-B (APO-B) with lipoprotein VLDL, IDL and LDL-ch IDL and small dense LDL [20,21,22). The hyperlipidemia in patients with uremia treated with HD is incriminated as a senior risk factor for the appearance of atherosclerotic disease of the blood vessels of heart, brain and peripheral arteries. (23).Treatment with HD is connected and closely correlated positively with higher concentrations of triglycerides (hypertriglyceridemia) while concentrations of LDL-ch are not usually raised (24,25,26). Five year examination of 220 patients with CRF has not verified growthtrend and progression of hypertriglyceridemia (27). It is assumed that subtle, qualitative changes registered in morphology (size) of the particles of (particles) of lipoproteins in patients with chronic renal failure (CRF) increasetheir atherogenic impact (affinity increased with fastening (climbing) inarterial subentotelin of oxidized LDL-LDlox, small LDL, HDL minor particles) with frequent atherosclerotic damage to the cardiovascular system and cerbrovascular fatal consequences for treatment centers with hemodialysis(28). It is about ischemic heart disease, peripheral vascular disease and stroke.Pre β1-HDL is minor subfraction which acts as a acceptor of free cholesterol which emanates from the cells and their transport to the liver. Under the influence of lecithin-cholesterol-acetyl-transferase (LCAT), β1-HDL-ch is transformed in αHDL-ch. LCAT in normal plasma affectsHDL maturity, while transforming HDLwith spherical HDL enriched with fats. In uremic patients LCAT activity is reduced for optimal 30% and the above described conversion is compromised and reduced. Experimental clinical examinations (incubation of uremic patients with plasma LCAT inhibitor or

without inhibitor of LCAT) verify the above-mentioned position and prove that atherosclerosis earlier representation is dependent directly from the disordered catabolism of β1-HDL (29,30). The patients treated with HD activity of triglyceride-hepatic lipase (TGHL) is also reduced by 33-45% (31)Activity of systemic lipopoprotein lipase (LPL) is reduced because of the (collection) cumulation of toxins or cytokines-interleukin-1, interleukin-6, Interleukin- 1α, Interleukin-1α(32,33,34)and counts as the cause of pathological disorders of lipids and apolipoproteins of uremic patients (concentration in HDL-ch and ApoA-I are reduced, while the concentrations of triglycerides, LDL-ch, ApoB-100, Apo-E, Apo-C, Lp (a) are increased) followed with increasing prevalence of atherosclerotic vascular disease (35,36).Cholesterol and triglycerids actually are not hydrosolubile fats, but their solubility in water is significantly increased and IMPROVED if they are connected to specific plasmacarrier known as APOPROTEINS that enable their transport through the blood in the form of molecules called lipoproteins (37). Most frequent disorders of apoliporoteins are manifested byhigh concentrations of triglycerides TG, LDL cholesterol, the remaining small particles of LDL-6. The concentrations of LDL-6 are mainly grown in patients with ESRD and treated with hemodialysis, but this growth is faced most often in diabetes compared with other basic diseases such as hypertension, chronic glomerulonephritis, polycystic kidney disease, etc. Apolipoprotein abnormalities during uremic syndrome include all particles and fractions of lipids. Due to increased concentration of the TG component of VLDL, IDL, LDL and HDL-ch mostlydominates hypertriglyceridemia in uremic patients. Total cholesterol in patients with ESRD treated with HD does not show any significant changes compared with the comparative values in general population (38,39,40). Replacement of thosephysiological lipoproteins with pathological and high rate of atherogenesis and impact of uremic toxins in structure andlipoapoprotein fractions inuremicenvironment are still undiscovered phenomenon therefore multicentric experimental studies are necessary. There are not documented and confirmed facts that all values of LDL-ch, Apo B-100, VLDL, LDL, lipoproteinemicremnants, LDL-6, IDL, LDL-ox, lipoapolipoprotein A-1, Apo-2, ApoA- 4, Apo-E with all of its fractions, Apo-C in atherogenic processes are equally atherogenic and independent of one another. Numerous studies have proven that the qualitative changes in the morphology and particle size of lipoapoproteins in patients with ESRD treated with HD and increase their atherogenic influence and have high ability for climbing or fixing thesubendotelialarterial wall in the presence ofoxidated cholesterol (LDL-6) and also have very high predisposition for atherogenity in cardiovascular system. Frequent manifestations that occur in uremic patients as a result of the atherogenic disorders of lipids and apolipoproteins are: ischemic heart disease, acute myocardial infarction, peripheral vascular disease, peripheral artery occlusive disease, cerebrovascular stroke etc. LCAT (LecithinCholesterol- acyltransferase) in normal plasma plays an important role in remodeling of HDL cholesterol and is an enzyme which converts free cholesterol to cholesteryl ester which is then basically asequestered lipoproteinemic particle, synthesizing spherical HDL.In uremic patients LCAT activity is reduced to 30-45% and the optimum conversion is compromised (42,43,44,45).

2 Matherial 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 apolipo-proteins.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 nephro-pathies-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 m

3 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 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

Basic Renal Disease No. of patients %	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	**12**	**10,0**
Nondifferented Nephropathy	**9**	**8**
Uroobstructive Nephropathy	**7**	**6**

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

Gender	No	± SD
Male	66 (55%)	57.30 ± 10.
Female	54 (45%)	59.00 ± 12.4

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 < 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

Paramthers	Values Levels	Author
LT	4-10 g/l	Zollner & Kirsch
TG	0.68 – 1.70 mmol/l	G. Bucolla & H.David [46]
ChT	3.1 – 5.2 mmol/l	C CAllain et al. [47]
LDL-ch	< 3.4mmol/l,High risk > 4.1 mmol/l	Friedewalde&Frederickson
HDL-ch	1.6 mmol/l, High risk < 30 mg/dl	Rifai N
Apo A-I	1.0 – 1.90 g/l	Rifai N
Apo $B\text{-}_{100}$	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[48]
LPL 5.6 – 51.3 u/L	5.6 – 51.3	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 (NO=120)

Paramthers	**No**	**Average ± SD**
LT	**120**	6.50 ± 0.60
TG	**120**	1.30 ± 0.63

ChT	**120**	4.95 ± 1.22
LDL-ch	**120**	2.75 ± 1.03
HDL-ch	**120**	1.60 ± 0.71
Apo A-I	**120**	1.42 ± 0.43
Apo B_{-100}	**120**	1.05 ± 0.20
Lp(a)	**120**	23.50 ± 7.10
ApoC-II	**120**	4.95 ± 1.22
ApoC-III	**120**	6.43 ± 0.82
LPL	**120**	24.20 ± 9.21

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-A1,2 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

Paramthers	**No**	**Average ± SD**	***p***
LT	**120**	7.39 ± 2.00	0.0001
TG	**120**	3.18 0.80	0.0001
ChT	**120**	4.95 1.20	0.0198
LDL-ch	**120**	3.60 0.50	0.0001
HDL-ch	**120**	1.12 0.49	0.4234
Apo A-I	**120**	1.04 0.38	0.0001
Apo B_{-100}	**120**	2.86 0.86	0.0001
Lp(a)	**120**	48.03 40.10	0.0001
ApoC-II	**120**	9.73 4.06	0.0001
ApoC-III	**120**	11.06 3.65	0.0001
LPL	**120**	20.85 15.20	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/l,and (for women 159.4±38.6 vs 139.6±39.5 U/L, $p<0.005$

4 Discusion

In patients with ESRD hypertriglyceridemia is due to increased production of konentracioneve 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 triglycerides (TG). The main factors that contribute to the reduction of catabolism include a reduced activity of lipolytic enzyme, compositional lipopro-teinemicabnormalitiesare 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 -cholesterol [49,50,51).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 (52,53,54).In addition, controversies exist if

the low molecular weight heparins have a favorable effect on the lipid profile of patients treated with HD compared to standard molecularhigher weight heparin. (55,56).Recent studies show that the use of phosphate -binder sevelamer hydrochloride significantly reduces total cholesterol and apolipoprotein-B in HD patients.Studies have shown that renal dyslipidemia characteristic features remain unchanged with a long duration period HD (57). In uremic dyslipidemia manifestations an important role have the apolipoprotein aberations (Apolipoproteina-A with its five subclasses: ApoA-I, II, IV, V Apolipoproteina-B (Apo -B) with its two subclasses: ApoB-100 , ApoB-48); Apolipo protein-C (Apo-C) represented by three supclasses: APOC-I, II, III; Apolipoprotein-E (APO E) with its four varieties: (Or EI, II, III, IV); Apolipopproteina-D (APO-D); Apolipoproteina F (Apo-F); Apolipoproteina -G (Apo G); Apolipoproteina H (Apo H), and Apolipoproteina-S (Apo-S).In uremic dyslipidemia appearance an important role has Lipoprotein (a) (Lp / a /) which is synthesized in the liver and intracellulary through disulfide bonds is associated with ApoB-100. For the first time Lp (a) Berger discovered in 1963 and is presumed to be LDL-ch and is quantitative marker for the risk of atheromatosis .Concentrations of Lp (a) in the body are controlled genetically (58).Some studies have shown that Lp (a) has two effects that atherogenic and thrombogenic, the latter is due to the impact of Lp (a) plazminogenic changes. Last years is counted as an independent main risk to myocardial infarction (59-64) Lipidic and apolipoproteinic profile definition in particular their abnormalities in patients with renal chronic terminalsinsufficiency (CRF) in the early stages of the disease, and enlighting etiopathogenetic mechanisms can significantly assist in the proposal of preventive measures (dietary, treatment) which will reduce the frequent appearance of dyslipidemia, atherosclerotic lessions and reduce the incidence of atherosclerosis in patients with TerminalChronic Renal Insufficiency randomized by gender and age (65)Patients with terminal chronic renal failure (CRF) mostly appear with the type of type IV secondaryhyperlipoproteinemia(according to Frederickson's classification) in which they dominate high concentrations of triglycerides (hypetregliceridemia values of 28-100%)(66). 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-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% [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 ($p<0.005$-0.0001) 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 dyslipidemia and lipoapoproteins aberations proved very secure in our experience with the dosage of 20 mg in the evening every day to reduce 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, apolipoproteines subfractions and its-Apo-1,2.4. Patients treated with HD, considering their rare side effects as rhabdomyolisis with muscular pain and increase creatine kinase (CK). Risk of rhabdomyolisis is larger if statin therapy is combined with other additional cyclosporine and fibrates. Application of the statins in the treatment 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 theories on the treatment of artherosclerotic processes in ESRD patients, drug treatment of apolipoproteins abnormalities is thus necessary that will significa-ntly reduce the risk of cardiovascular and cerebrovascular dissease.

Literature

1..Chan MK,Varghese Z, Moorhead JF. Lipid abnormalities in uremia, dialysis and transplantation. Kidney Int. 1981;(19): 119- 625.

2. Wanner C, Zimmermann J, Quaschning T, Galle L. Inflammation, dyslipidemia and vascular risk factors in hemodialysis patients. *Kidney Int Suppl. 1997; 62:S53-5.*

3.Sentí M, Romero R, Pedro-Botet J, et al. Lipoprotein abnormalities in hyperlipidemic and normolipidemic men on hemodialysis with chronic renal failure. Kidney Int 1992; 41:1394.

4.Attman PO, Samuelsson O, Alaupovic P. Lipoprotein metabolism and renal failure. Am J Kidney Dis 1993; 21:573.

5.Arnadottir M, Thysell H, Dallongeville J, et al. Evidence that reduced lipoprotein lipase activity is not a primary pathogenetic factor for hypertriglyceridemia in renal failure. Kidney Int 1995; 48:779.

6. Lacour B, Roullet JB, Liagre AM, et al. Serum lipoprotein disturbances in primary and secondary hyperparathyroidism and effects of parathyroidectomy. Am J Kidney Dis 1986; 8:422.

7. Liang K, Oveisi F, Vaziri ND. Role of secondary hyperparathyroidism in the genesis of hypertriglyceridemia and VLDL receptor deficiency in chronic renal failure. Kidney Int 1998; 53:626.

8. Akmal M, Perkins S, Kasim SE, et al. Verapamil prevents chronic renal failure-induced abnormalities in lipid metabolism. Am J Kidney Dis 1993; 22:158.

9.Cheung AK, Parker CJ, Ren K, Iverius PH. Increased lipase inhibition in uremia: identification of pre-beta-HDL as a major inhibitor in normal and uremic plasma. Kidney Int 1996; 49:1360.

10. Attman, PO, Samuelsson, O, Alaupovic, P: Lipoprotein metabolism and renal failure. *Am J Kidney Dis* 1993 21:573 592,

11. Wanner, C, Frommherz, K, Hörl, WH: Hyperlipoproteinemia in chronic renal failure: Pathophysiological and therapeutic aspects. *Cardiology* 199178:202 217,

12.Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998; 32: S112-S119.

13.Attman P-O, Samuelsson O, Alaupovic P. Lipoprotein metabolism and renal failure. Am J Kidney Dis 1993; 21: 573–591.

14. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998; 32: S112-S119.

15. Ponticelli C.et al. Lipid abnormalities in maintenance dialysis patients and renal transplant recipients.*Kidney Int Suppl. 1978; 8: S 72.*

16. Haas LB,Wahl PW, Sherrard DJ. A longitudinal study of lipid abnormalities in renal failure.*Nephron 1983;* 33:*145.*

17. Somer JB. Et al.B. Lipoprotein lipids in chronic renal failure and hemodialysis: the influence of etiology and implication for atherogenesis. *Atherosclerosis 1979; 34:353.*

18. Attman P-O, Samuelsson O, Alaupovic P. Lipoprotein metabolism and renal failure. Am J Kidney Dis 1993; 21: 573–591..].

19. Alaupovic P. Apolipoprotein composition as the basis for classify-ing plasma lipoproteins. Characterization of apoA- and apoB-con-taining lipoprotein families.Prog Lipid Res 1991; 30:105–138.

20. Attman P-O, Alaupovic P, Tavella M, Knight-GibsonC.Abnor-mal lipid and apolipoprotein composition of major lipoprotein density classes in patients with chronic renal failure.Nephrol Dial Transplant

1996; 11: 63–69.
21. Rajman I, Harper L, McPake D, et al. Low-density lipoprotein subfraction profiles in chronic renal failure. Nephrol Dial Trans plant 1998; 13: 2281–2287].

22.Attman PO, Samuelsson OG, Moberly J, Johansson AC, Ljungman S, Weiss LG, Knight-Gibson C, Alaupovic P. Apolipoprotein B-containing lipoproteins in renal failure: the relation to mode of dialysis. Kidney Int 1999; 55:1536-1542.

23. Keane WF, Oda H. Lipid abnormalities in end stage renal disease. Nephrol Dial Transplant 1998; 13 [suppl 1] : 45.49.

24. De Gomez NT, Giammona AM, Touceda LA, Raimondi C. Lipid abnormalities in chronic renal failure Patients undergoing hemodialysis. Medicina (Buenos aires) 2001; 61: 142.146.
25. Quashing T, Krane V, Metzger T, Warner C, Abnormalities in Uremia lipoprotein metabolism and its impact on Cardiovascular disease. Am J Kid Dis 2001; 38(4): 514.S19.
26. Mbewu AD, Durrington PN. Lipoprotein(a): structure, properties and possible involvement in thrombogenesis and atherogenesis. Atherosclerosis 1990; 85: 1-14.

27. Haas LB,Wahl PW, Sherrard DJ. A longitudinal study of lipid abnormalities in renal failure.*Nephron 1983;* 33:*145*.

28. Agarwal SK. et al. Prevalence of Chronic Renal Failure in adults in Delhi,India. *Nephrol Dial Transplant 2005; (20) :1638-42.*

29. Miida T, et al. LCAT-dependent conversion of pre β1-HDL intoα-migrating HDL is severely delayed in haemodialysis patients. *J Am Soc Nephrol.2003;14:732-8.*

30.Attman PO, Alaupovic P. Lipid abnormalities in chronic renal insufficiency. *Kidney Int.1991;39:16.*

31. Okubo K, et al. Abnormal HDL apolipoprotein A-I and A-II kinetics in haemodialysis patients: a stable isotope study. *J Am Soc Nephrol. 2004;15:1008-15.*

32. Agarwal SK. et al. Prevalence of Chronic Renal Failure in adults in Delhi,India. *Nephrol Dial Transplant 2005; (20) :1638-42*

33. Neiss G. Effect of iron treatment on circulating cytokine levels in ESRD patients receiving recombinant human erythropoetin. *Kidney Int 2003;(64) :572-8.*

34.Parsy D, Dracon M, Cachera C, et al. Lipoprotein abnormalities in chronic hemodialysis patients. *Nephrol Dial Transplant. 1988;3:51-6.*

35. Rao P, Reddy GC and Kanagasabapathy AS. Malnutition-Inflammation-Atherosclerosis Syndrome in Chronic Kidney Disease.*Indian Journal of Clinical Biochemistry,2008 (23) 209-217.*

36 Webster JR et al. The association of common genetic variants in the ApoA-V, LPL and GCK genes with longitudinal changes in metabolic and cardiovascular traits.*Diabetologija 2009 ;52:106-114.*

37. Somer JB. Et al.B. Lipoprotein lipids in chronic renal failure and hemodialysis: the influence of etiology and implication for atherogenesis. *Atherosclerosis 1979; 34:353*

38. Kwan BC, Kronenberg F, Beddhu S, Cheung AK. Lipoprotein metabolism and lipid management in chronic kidney disease. J Am Soc Nephrol 2007; 18:1246.

39. Arnadottir M, Thysell H, Dallongeville J, et al. Evidence that reduced lipoprotein lipase activity is not a primary pathogenetic factor for hypertriglyceridemia in renal failure. Kidney Int 1995; 48:779.

40. Yamamoto S, Kon V. Mechanisms for increased cardiovascular disease in chronic kidney dysfunction. Curr Opin Nephrol Hypertens 2009; 18:181.

41. Lo JC, Go AS, Chandra M, et al. GFR, body mass index, and low high-density lipoprotein concentration in adults with and without CKD. Am J Kidney Dis 2007; 50:552.

42.Shlipak MG, Fried LF, Cushman M, et al. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. JAMA 2005; 293:1737.

43. Chawla V, Greene T, Beck GJ, et al. Hyperlipidemia and long-term outcomes in nondiabetic chronic kidney disease. Clin J Am Soc Nephrol 2010; 5:1582.

44. Sarnak MJ, Bloom R, Muntner P, et al. KDOQI US commentary on the 2013 KDIGO Clinical Practice Guideline for Lipid Management in CKD. Am J Kidney Dis 2015; 65:354.

45. Arnadottir M, Thysell H, Dallongeville J, et al. Evidence that reduced lipoprotein lipase activity is not a primary pathogenetic factor for hypertriglyceridemia in renal failure. Kidney Int 1995; 48:779

46. Bucola G., David H, Quantitative determination of serum triglycerides by use of enzymes. Clin.Chem, 19, 476- 482 (1973).

47. Allain CC., Poon LS., Chan CS., Richmond W, Enzymatic determination of total serum cholesterol, 6th Edition Clin. Chem, 20,470- 475(1974).

48. Tilly P, et al. Biological and genetic determinants of serum apo CIII concentration: reference limits from the STANISLAS cohort study. J Lipid Res. 2003;44 :430-6.

49. Docci D, Capponcini C, Mengozzi S, Baldrati L, Neri L, Feletti C. Effects of different dialysis membranes on lipid and lipoprotein serum profiles in hemodialysis patients. Nephron 1995; 69: 323-326.
50. Jung K, Scheifler A, Schulze BD, Scholz M. Lower serum high-density lipoprotein-cholesterol concentration in patients undergoing maintenance hemodialysis with acetate than with bicarbonate. Am J Kidney Dis 1995; 25: 584-588.

51. Seres DS, Strain GW, Hashim SA, et al. Improvement of plasma lipoprotein profiles during high-flux dialysis. J Am Soc Nephrol 1993; 3: 1409–1415.

52. Shoji T, Nishizawa Y, Nishitani H, Yamakawa M, Morii H: Impaired metabolism of high density lipoprotein in uremic patients. Kidney Int 1992; 41: 1653-1661.
53. Huttunen JK, Pasternack A, Vanttinen T, Ehnholm C, Nikkila EA: Lipoprotein metabolism in patients with chronic uremia. Effect of hemodialysis on serum lipoproteins and postheparin plasma triglyceride lipases.Acta Med Scand 1978; 204: 211-218.
54. Katopodis KP, Elisaf M, Balafa O, Nikolopoulos P, Bairaktari E, Katsaraki A, Siamopoulos KC: Influence of the type of membrane and heparin on serum lipid parameters during a dialysis session: a pilot study. Am J Nephrol 2004; 24: 469-473.
55. Schrader J, Stibbe W, Armstrong VW, Kandt M, Muche R, Kostering H, Seidel D, Scheler F. Comparison of low molecular weight heparin to standard heparin in hemodialysis/hemofiltration. Kidney Int 1988; 33: 890-896.
56. Chertow GM, Burke SK, Raggi P: Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 2002; 62: 245-252.

57. Shoji T, Nishizawa Y, Kawagishi T, et al. Atherogenic lipoprotein changes in the absence of hyperlipidemia in patients with chronic renal failure treated by hemodialysis. Atherosclerosis 1997; 131: 229–236.

58. Utermann G, Menzel HJ, Kraft HG, Duba HC, Kemmler HG, Seitz C. Lp(a) glycoprotein phenotypes: inheritance and relation to Lp(a)-lipoprotein concentration in plasma. I Clin Invest 1987; 80: 458-65.

59. Miles LA, Fless GM, Levin EG, Scanu AM, Plow EF. A potential basis for the thrombotic risks associated with lipoprotein (a). Nature 1989; 339: 301-3.
60. Hajjar KA, Garish D, Breslow JL, Nachman RL. Lipoprotein(a) modulation of endothelial cell surface fibrinolysis and its potential role in atherosclerosis. Nature 1989; 339: 303-5.
61. Association of levels of lipoprotein Lp(a), plasma lipids and other lipoproteins with coronary artery disease documented by angiography. Circulation 1986; 74: 758-63.
62. Detection and quantification of lipoprotein(a) in the arterial wall of 107 coronary bypass patients. Arteriosclerosis 1988; 9: 579-92.
63. cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. Nature 1987; 330: 132-7.
64. Rhoads GG, Dahlen G, Berg K, Morton NE, Dannenberg AL. Lp(a) lipoprotein as a risk factor for myocardial infarction. JAMA 1986; 256: 2540-24.

65. Wanner C, Zimmermann J, Quaschning T, Galle L. Inflammation, dyslipidemia and vascular risk factors in hemodialysis patients. *Kidney Int Suppl. 1997; 62:S53-5*.

66.Ponticelli C.et al. Lipid abnormalities in maintenance dialysis patients and renal transplant recipients.*Kidney Int Suppl. 1978; 8: S 72*

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