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LIPID ABNORMALITIES IN UREMIA

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Abstract

Lipid metabolism disorders in patients with end stage renal disease, particularly in patients with nephrotic syndrome were described by Dr Bright in the 1827 year (1).There has been tremendous interest in lipid metabolism in chronic renal failure, that dialysis accelerates atherosclerosis. Cardiovascular disease, still claim many lives on dialysis (2, 3) and after transplantation (4, 5, 6). We realize hyperlipidemia is only one, and may not be the most important one, of the risk factors in the development of ischemic heart disease in patients with uremia and shall restrict ourselves to the review of the current understanding of the pathogenesis of hyperlipidemia in uremic patients with dialysis. Two basic processes regulate plasma triglyceride concentrations: triglyceride production, triglyceride removal.It is known that patients with end-stage renal disease (ESRD) display clinical picture of early accelerated (premature) atherosclerosis with severe cardiovascular and cerebral complications that are very often present even in earlier age compared with the general population.Today, it is considered that uremic dyslipidemia has persisted for many years before chronic dialysis treatment began and presents basic risk factor for early start of atherogenesis processes. That is why the analysis of apolipoprotein and lipid abnormalities as well as their ethiopathogenetic mechanism in patient diseased with ESRD treated with repeated hemodialysis in the initiation phase of dialysis (the first 6 months), can evidently contribute to overtaking timely preventive measures (dietetic, healing) by which the frequency of apolipoprotein and lipid abnormalities will be decreased, which, on the other hand will result in reducing the processes of early atherosclerosis with all its complications in ESRD patients. Disorders of apolipoprotein metabolism are considered as one of the most important factors for early atherosclerosis in patients with ESRD.

*Key-words:*lipid abnormalities, uremia, ESRD.

Introduction

Basic risk factor for early atherosclerosis in patients with end-stage renal disease (ESRD) treated by repeated hemodialysis is the disorder in lipoprotein metabolism(6,7,8) which is described by modified proportion of respective lipids and apoproteins in the composition of lipoprotein (Lp) molecule (so called dyslipidemia(9,10,11,12). Genetic predictors for early predisposition to atherosclerosis are disordered reserve transport of HDL-ch and insufficient expression of B compared to E-receptors, as well as reduced conversion of VLDL in IDL and finally in LDL-ch(13,14).Lipo/apoprotein aberrations in uremia concerns all lipoprotein (Lps) particles.Hypertriglyceridemia predominates due to increased triglyceride content structure of VLDL, IDL, LDL-ch and HDL-ch. ApoA-1 is decreased in the structure of LDL-ch, while ApoA-IV has bigger incidence. The concentration of ApoB-100 is quite increased in VLDL composition. Decreased concentrations of HDL-ch in patients on dialysis reduces the reverse cholesterol transport to the liver which creates conditions for cell accumulation of cholesterol in extrahepatic tissues.Hypertriglyceridemia is the major lipid abnormality and occurs in 70-90% of dialyzed and undialyzed patients with uremia [15,16,17,18). The predominant lipoprotein pattern is type IV according to Frederickson's classification, with elevation of verylow-density lipoproteins (VLDL). Alterations in the composition of major lipoprotein fractions exist with increase in the triglyceride content of VLDL and low-density lipoproteins (LDL) and decrease in the cholesterol content of high-density lipoproteins (HDL). LDL cholesterol, however, remains normal. Because HDL cholesterol has been vincingly to be a "protective" factor against ischemic heart disease in epidemiologic studies [18], the apoprotein composition of HDL has been studied in some detail. Apo-Al, the major apoprotein of HDL, has been reported as normal in patients on maintenance dialysis whereas apoCII, a minor but functionally important apoprotein of HDL, is significantly reduced. The subfractions of HDL, such as HDL2 and HDL3, have not been studied. Influence of underlying renal disease on lipidmetabolism. Patients with uremiare present a heterogenous collection. The etiologies of their

underlying renal disease are diverse. It appears, however, that the cause of renal disease has no significant influence on the lipid abnormalities when the patient reaches ESRD.For example, identical alterations in the composition of individual lipoproteins occur in patients with documented chronic glomerulonephritis and in those with surgicalnephrectomies, and no differences could be detected in serum triglyceride concentrations between patients with chronic glomerulonephritis andpolycystic disease, respectively. Because only patients in end-stage renal failure who are not obviously nephrotic are considered in this review, patients with uremia will be treated as a group to avoid undue repetition when the various pathogenetic factors are discussed. Findings pertinent to a particular group of patients will be indicated wherever appropriate.Triglyceride removal. As mentioned previously, hypertriglyceridemia is the result of increased triglyceride production or decreased triglyceride removal, or both.Removal of Intralipid follows first-order kinetics (20,21,22,24,25) and as the fractional clearance rate of Intralipid is readily obtained from fat tolerance tests, we shall frequently refer to this rate constant in our discussion of triglyceride removal.The correlation is also clearly hyperbolic in hemodialysis patients when intraipid follows first-order kinetics is obtained after heparin administration (19). It therefore appears likely that for patients with a high intraipid follows first-order kinetics, triglyceride removal has to be grossly reduced before there is any appreciable change in serum triglyceride con- centrations. Chylomicrons and VLDL share the same degradative pathway), and it might be argued that the grossly reduced intraipid follows first-order kinetics reflects competition between Intralipid and endogenous VLDL for enzymatic degradation, thereby artefactually reducing intraipid follows first-order kinetics . Such an explanation is difficult to reconcile with the finding of reduced intraipid follows first-order kinetics albeit to a lesser extent, in normotriglyceridemic uremic patients. Furthermore, intraipid follows first-order kinetics and serum triglyceride concentrations do not always undergo reciprocal changes (20,21,22).The patients with ESRD present higher incidence of ApoB/E in the structure of total cholesterol, TG and LDL-ch's compared with their presence in the composition of HDL-ch. Lower concentration of ApoA-1 and increased concentration of Apo-B-100 was detected in all patients. Higher values of ApoB-100 and smaller concentrations of ApoA-1 were found in patients treated of CAPD in comparison with patients treated with chronic hemodialysis. Thus, it can be concluded that various dialysis modalities have influence upon lipoprotein metabolism and evolution of atherosclerotic disease in dialysis patients.

The aim of the study was to determine the concentrations of lipid their abnormalities as well as the lipid profile in patients with ESRD treated with repeated hemodialysis, as well as their role in etiology of premature atherosclerosis in patients with ESRD treated with repeated hemodialysis.**F**actors in the pathogenesis of hyperlipidemia in uremia:decreased triglyceride removal, depressed lipoprotein lipase activity,decreased synthesis of lipoprotein lipase due to insulin resistance,decreased releasable pool of lipoprotein lipase due to repeated heparinization, presence of nonspecific "uremic toxins" as lipoprotein lipase inhibitors,decreased hepatic lipase activity,decreased lecithin-cholesterol-acyl-transferase(LCAT) activity,decreased LCAT conce-ntration,decreased concentration of preferred substrate HDL,decreased activator: apo-Al ,impaired beta-oxidation of free fatty acids due to carnitine deficiency,hormonal factors, for example, hypothyroidism,increased triglyceride production ,dietary carbohydrste,glucose and acetate in dialysis fluid,increased lipolysis due to increased concentrations of glucagon, growth hormone, and insulin resistance; increased hepatic extraction of free fatty acids due to decreased binding capacity of albumin, hyperinsulinemia,decreased beta-oxidation of free fatty acids, drugs, for example, oestrogens and androgens

Materials and methods

Patients' blood and blood of control group of examinees was used for the investigations. The blood was drawn at 08:00 hours in the morning when the room temperature was from 19 to 24^0 C while the patients were in lying position with aim to avoid all possible variations of values in separate lipoprotein fractions (from 9 to 12%) that appear when patients are in standing position. The sample blood was taken immediately prior the beginning of hemodialysis treatment (HD), at least after 12 hours fasting in order to avoid intestinal-absorption effect of food upon serum lipids (postprandial hypercholestero-lemia). Laboratory analyses were determined once a month by three consecutive measurements in all patients. The presented results actually represent mean value of the three consecutive measurements under identical conditions. The obtained blood, preserved by several drops of heparin was sent to the Medical Centre-Tetovo and correspondingly at the Institute of Clinical Biochemistry at the Clinical Centre in Skopje (in 3 ccm serum) in order to organize inspection and calibration of the exactness of the used methods.The lipid profile, ApoA-1 as well as ApoB-100 were analyzed in 120 patients for several months at the Department of Nephrology and Hemodialysis at the Medical Centre in Tetovo and at the Clinic of Nephrology, Medical Faculty – Skopje.
The division of patients according to the basic kidney disease is presented in Table 1.

Table 1.

Division of patients according to the basic nephropathy	
Patients total = 120	**Men = 66 (55%), Women = 54 (45%)**
Mean age (years)	**59.50 ± 12.80**
Glomerulopathies	**30 (25%)**
Arterial hypertension with sec. nephroangiosclerosis	**28 (23,3%)**
Diabetes Mellitus (DM)	**18 (15%)**
Intersticiopathy)	**16 (13,3%)**
Renal policystosis	**12 (10%)**
Nondifferentiated nephropathy	**9 (7,5%)**
Uroobstructive nephropathy (UOP)	**7 (5,8%)**
Control group = 120	**Mean age = 58.50 ± 8.10**

Patients with ESRD treated with repeated hemodialysis were with mean age 59,50 ± 12,80 years. HD frequency was three time a week in duration of 4 hours, while dialyses were carried out by use of biocompatible halfsulphonic capillary membrane (F 6 HPS and F5 HPS, Fressenius&Hemomed) with surface ≥ 1- 1,3 m^2 , sterilized with high pressure steam. Control group of healthy examinees consisted of 120 persons (66 males and 54 females) with mean age 58, 50 ± 8,10 year. The data were processed with standard statistical programme Windows (Statistics for Windows software) version 6.0 A, Stat soft Inc. Tulsa, OK, USA).
Reference values of the examined parameters of lipid profile and apoproteins are presented in Table 2.

Table 2

Lipid profile	Reference values	Authors
TL	**4-10g/l**	**Zollner & Kirsch (60)**
TG	**0,68-1,70 mmol/l**	**G. Buccola & H. David(61)**
TCh	**3,1-5,2 mmol/l**	**CC.Allain et al.(62)**
LDL-Ch	**<3,4mmol/l, increased risk: >4,1 mmol/l**	**Friedewalde&Fredrickson(63)**
HDL-Ch	**>1,6mmol/l,increased risk: <0,9 mmol/l**	**G. Warnick et al.(64)**
ApoA-1 **ApoB-100**	**ApoA-1 = 1.0-1.90g/l** **ApoB-100=0.5-1.60gl**	**Umunoturbidim.-Rifai N (65)**

The obtained lipid results (TCh, TG, HDL-ch, LDL-ch), ApoA-1 and of ApoB-100 from patients with ESRD and those of the control group are presented in Table 3.

Table 3 – Results of laboratory investigations

	N⁰	**TCh Mmol/l**	**TG Mmol/l**	**HDL-ch**	**LDL-ch**	**Apo1-1 mg/l**	**ApoB-100 mg/l**
Patients on HD	**120**	**5.0±1.25**	**2.64±*0.35***	**0.9±*0.35***	3.46±*0.60*	1.04±*0.38*	**2.78±*0.86***
Control group	**120**	**4.95±1.22**	**1.30±*0.63***	**1.6±*0.71***	2.75±*0.75*	1.43±*0.43*	**1.05±*0.20***
p		**0.7541**	**0.0001**	**0.0001**	**0.0001**	**0.0001**	**0.0001**

Table 3 shows significant difference in values of the greater part of tested parameters *[(ApoA-1 (1.04±0.38), ApoB-100 (2.78±0.86), TG (2.64±0.35), LDL-ch (3.46±0.60)]* with ***p<0.0001*** except for TCh, in comparison with the results obtained for the control group.

Discussion

Dyslipidemia is an established cardiovascular (CV) risk factor in the general population. In chronic kidney disease (CKD), however, epidemiologic studies and clinical trials have raised uncertainties regarding the impact of dyslipidemia on clinical outcomes and, consequently, the optimal lipid profile. In this article, we review the pathophysiology of dyslipidemia in CKD and dialysis patients and its association with clinical outcome and the effects of therapy and compare them with those in the general population. Dyslipidemia is empirically defined here as plasma lipid and lipoproteins that are associated with adverse outcomes such as CV disease (CVD) in the general population. Whether this definition is justified in patients with CKD requires further investigations. Etiologic factors for dyslipidemia are numerous in patients with ESRD treated by repeated HD. These factors include declined enzyme activity of lipoprotein lipase (LPL) and triglyceride hepatic lipase (HTGL), accumulation of uremic toxins as well as high serum concentrations of ApoA-III and of parathyroid hormone (PTH)(23-28).There are two big classes in circular lipoproteins that are distinguished on the basis of apolipoprotein composition (ApoA-1 and Apo-B) as basic constituents of apoproteins. The apolipoprotein which mainly contains ApoA-1 is with high density (HDL) and it is antiatherogenic, while Apo-B associates more lipids, it is main constituent in VLDL, IDL and LDL-ch structure and it is considered to be atherogenic apoprotein. LDL lipoproteins, rich with great content of Apo-B, are the most significant factor in the genesis of arterial atherosclerosis. In conditions of uremia, the reduced renal parenchyma cannot synthesize antiatherogenes (ApoA-1) or dissolve proatherogenic apolipoproteins (ApoB-100), which results in increased TG for over 50% (increase of ApoB-100 and ApoC-III), and decrease of HDL-ch for 20% (29,30,31). During the last several years the interest in apolipoproteins (ApoA-1, ApoB-100…) as new risk factors for premature atherosclerosis in patients with ESRD has been increased due to kidneys involvement in metabolism of apoproteins, particularly of Apo(a) and of Lp(a). Frequent and prolonged dialysis does not consistently improve triglyceride removal; nor does chronic hemodiafiltration , a procedure in which substances of higher molecular weight are ultrafiltered across the artificial dialyzer membrane.Dialysis can cause appreciable loss of amino acids and carnitine, a naturally occurring quarternary amine whose major route of excretion is the kidney, appears in significant quantities in the dialysate.Carnitine is important in the transfer of long-chain free fatty acids across mitochondrial membranes to the site of beta oxidation. Conceivably, carnitine deficiency, by reducing the oxidation of FFA, would enhance triglyceride synthesis in the presence of a constant rate of free fatty acid influx. Carnitine can be synthesized in the liver from lysine and methionine. In this regard, it is relevant to note that dialysis patients have low plasma concentrations of lysine, and the myocardial content of carnitine in uremic rats is diminished. Tissue carnitine deficiency due to dietary lysine deficiency resulting in triglyceride accumulation has been reported.Carnitine has been shown to improve hypertriglyceridemia in subjects with normal renal function as well as in dialyzed and nondialyzed uremic patients. Although seemingly promising, in high doses, carnitine can produce severe neuromuscular transmission problems, probably because of its structural similarity to acetylcholine (33,34).The usefulness of this compound in the long-term management of uremic hyperlipoproteinaemia has yet to be evaluated. Hemodialysis also entails the use of heparin. The suggestion that prolonged heparinization in dialysis patients depletes their enzyme stores is an interesting speculation (35-37). This is crucial, because we have previously shown that hypertriglyceridemic and normotriglyceridemic patients differ in their response to heparin.Sequential studies of dialysis with heparin followed by heparin-free dialysis in sepa- rate groups of normo- and hyper-triglyceridemic patients would settle the controversy surrounding the pathogenetic role of heparin in uremic hypertriglyceridemia. The influence of the duration of maintenance dialysis in lipid abnormalities in uremic patients is difficult to determine, for many patients change from one modality of treatment to another, and those who undergo renal transplantation are exposed to large doses of corticosteroids. Our own experience is that the prevalence of lipid abnormalities does not seem to increase with the duration of dialysis, though dialysis patients may have a higher prevalence of hypertriglyceridemia than nondialyzed patients in end-stage renal failure. The reduced lecithin-cholesterol-acyl-transferase (LCAT) activity in uremia is unexpected, because LCAT activity is often raised in hypertriglyceridemic states. It may be due to the low HDL, because HDL is the preferred substrate and one of its apoproteins is an activator of LCAT (38,39).It may also contribute to the defective triglyceride removal, for it has been postulated that LCAT is essential in processing the excess surface material during the breakdown of triglyceride-rich particles. It has been suggested that HDL with the aid of LCAT is responsible for the centripetal transfer of cholesterol from peripheral tissues to the liver (38). HDL has been demonstrated to modify the interaction between endothelial cells and LDL. There is a negative correlation between HDL cholesterol concentrations and the degree of coronary vessel occlusion assessed angiographically. Such studies are most needed in uremic patients.Uremic patients have many factors against them. They are usually hypertensive, and their vessels calcify, probably as a result of hyperparathyroidism. In such a setting, it is perhaps surprising not to find an even higher incidence of coronary heart disease. Thus, the reports of increased availability of prostacyclin to vascular endothelium in uremia are most intriguing. Uremic patients often receive thiazide diuretics and beta-adrenergic receptor blocking agents for the treatment of hypertension.Thiazide diuretics can produce hyperlipidemia, apart from causing impairment in glucose tolerance. The metabolic effects of beta-adrenergic receptor blocking agents are complex, and acute effects may be different from long-term effects; for instance, reduced postheparin lipolytic activity has been

reported in patients with presumably normal renal function after treatment with beta-adrenergic blocking agents. Most dialysis patients can be taken off antihypertensive treatment, and the contribution of these therapeutic agents to their hypertriglyceridemia is probably trivial. The spectrum of dyslipidemia in patients with CKD and dialysis patients is distinct from that of the general population. It involves all lipoprotein classes and shows considerable variations depending on the stage of CKD. There seems to be a gradual shift to the uremic lipid profile as kidney function deteriorates, which is further modified by concurrent illnesses such as diabetes and nephrotic syndrome. Apart from quantitative differences, major qualitative changes in lipoproteins can be observed, such as oxidization and modification to LDL, which render the particles more atherogenic. Plasma triglycerides start to increase in early stages of CKD and show the highest concentrations in nephrotic syndrome and in dialysis patients, especially those who are treated with peritoneal dialysis (PD). Plasma triglycerides are predominantly found in two types of lipoproteins in normal individuals.The reduced fractional catabolic rate is likely due to the decreased activity of two endothelium-associated lipases, namely, LPL and hepatic triglyceride lipase, which have the primary physiologic function of cleaving triglycerides into FFA for energy production or storage. The cause of the decreased lipase activities in uremia is thought to be depletion of the enzyme pool induced by frequent heparinization in hemodialysis (HD) patients, an increase in the plasma apoC-III/apoC-II ratio, and the presence of other lipase inhibitors in plasma. ApoC-II is an activator of LPL, whereas apoC-III is an inhibitor of LPL. The increased apoC-III/apoC-II ratio is usually due to a disproportionate increase in plasma apoC-III. The impaired lipase activities in uremic plasma may also be caused by a decrease in LPL synthesis as a result of secondary hyperparathyroidism or suppressed insulin level. Incomplete catabolism results in the accumulation of remnant particles (chylomicron remnants and IDL) that contribute to the heterogeneity of the plasma pool of triglyceride-rich lipoproteins, with different sites of origin, sizes, compositions, and degrees of atherogenicity). These remnants are rich in apoE, a ligand that is critical for the removal of the particles from the circulation by binding to LRP and perhaps other receptors on the vascular wall (39). The arterial wall therefore is exposed to high plasma levels of remnant lipoproteins for prolonged durations, which may predispose to atherogenesis.Patients with CKD generally have reduced plasma HDL cholesterol concentrations compared with nonuremic individuals. Furthermore, the distribution of HDL subfractions is different.Because of the low apo-AI level and decreased LCAT activity (see the Lipoprotein Pathways section), the esterification of free cholesterol and hence the conversion of HDL_3 to HDL_2 are diminished in uremia. This decreased ability of the HDL particles to carry cholesterol leads to impairment in the reverse cholesterol transport from peripheral cells to the liver, thereby burdening the vasculature with cholesterol and promoting athero-sclerosis.Another important component of HDL is paraoxonase, an enzyme that inhibits the oxidation of LDL. Plasma paraoxonase activity is reduced in patients with CKD, thereby predisposing the LDL and possibly also HDL particles to oxidation. Furthermore, infection-associated or uremia-associated inflammation might convert HDL from an antioxidant into a pro-oxidant particle (40, 41, 42). All of these may contribute to atherogenesis in CKD.Patients with ESRD had decreased values of TCh and HDL-ch and increased values of TG and LDL-h compared with the control group. Thus, it is supposed that low concentrations of TCh could be one of the factors for early premature atherosclerosis in patients with ESRD treated with repeated hemodialysis. There are data supporting the opinion that low plasma concentrations of HDL-ch are in tight correlation with the decreased synthesis of Apo A-1 in patients with ESRD. Protective effect of HDL-ch against early atherosclerosis is a result of its double role in the reserve transport mechanism of cholesterol.HDL-ch removes cell cholesterol and transfers the esterified cholesterol (from LCAT-Lecithin-cholesterol-acyl-transferase) to VLDL and LDL-ch helped by cholesterol ester transfer protein(43,44,45).It was noticed that the transfer of cholesterol (Reverse Cholesterol Transfer, RCT) from HDL-ch to VLDL/LDL is less prevailed in serum of HD patients in comparison with the control group that showed higher values of transport cholesterol.Further studies will confirm whether RCT progressively declines with the increasing of kidney weakness. If RCT reflects effectiveness of reverse transport cholesterol mechanism, then low RCT indicates that HDL-ch in uremic patients can be less effective in cholesterol transfer to remaining lipoproteins and that is why cholesterol demonstrates bigger tissue accumulation potential. This kind of defect can lead to accelerated atherosclerosis in ESRD. Statin therapy partially increased the level of serum HDL-Ch (10-15%), so it probably improves RCT in patients with ESRD treated with repeated hemodialysis. In patients undergoing hemodialysis, HTGL has significantly reduced activity for 33% while the activity of LCAT is reduced for 30% when compared with the control group (46, 47).The concentration of ApoA-1 in patients on HD is decreased as a result of the increased catabolism, while that of ApoA-2 due to decreased production. Several studies have shown that the two groups of patients (chronic hemodialysis program, CAPD) have significantly increased concentrations of Apo-B-100 that contains ApoC-3(ApoB:C-3) while the concentrations of TG, TCh, LDL-ch, ApoB-100 in patients treated with CAPD are higher in comparison with those in patients treated with chronic hemodialysis program. Patients with ESRD treated with repeated HD have markedly increased concentrations of TG, total Apo-E, ApoC, ApoB-100, ApoCnonB, Lp(a) and LDL-ch/HDL-ch, but they demonstrate significant decline of ApoA-1, HDL-ch, HDL-ch/ApoA-1, ApoA-1/ApoB and ApoA-1/ApoC-3 in comparison with the control group of healthy examinees. The comparative studies of lipo/apoprotein parameters in patients treated with different dialysis modalities (CAPD, HHDP) indicate that patients treated with CAPD are more concerned by atherosclerosis, which is not confirmed by other authors (48,49).Additional studies are required with greater number of patients with aim to precisely ascertain the way, frequency of cholesterol transport as well as its connection with chronic renal insufficiency. The analysis of parameters of lipo/apoprotein status in our patients demonstrated that they had

increased values of TG, ApoB-100 while decreased values of ApoA-1 and of HDL-ch in comparison with the control group. Many researchers such as Atmann, Oda, Mathur, Prichard, Milionis confirmed disorder of apo/lipoprotein status of HD and increased oxided LDL-ch (50-54).The decreased concentrations of Apo-A1 in patients with ESRD treated with repeated HD are in tight link with the decline of HDL-ch and with the increase of ApoB-100 concentrations that is followed by accumulation and increase of concentrations of VLDL and IDL.The initial stadium for development of early atherosclerosis depends only on serum values of LDL-ch and ApoB-100 as well as declined values of ApoA-1. Atherogenic effect of dyslipidemia in uremic patients is pointed out due to increased peroxidation of LDL-ch.The use of biocompatible dialysis membranes ("High flux", *Polysulfon, PAN-AN69),* enables bigger membrane absorption of atherogenic apolipoproteins and improvement of lipid profile as a result of decreasing concentrations of total ApoB-100 (for 30%) and AOPP (Advance Oxided Protein Products) in uremic patients (55-57).Lipid abnormalities in uremic and dialysis patients are due to multiple factors. Defective triglyceride removal as a result of decreased enzyme/activator or increased inhibitor concentrations plays an important role. Increased triglyceride production probably also occurs in some patients. Insulin resistance may contribute to both decreased removal and increased production of triglycerides.Whether this resistance could be ascribed to a reduced number of cellular receptors for insulin (58, 59) remains to be clarified. High dietary carbohydrate and fat intake undoubtedly impose further burdens on the defective triglyceride removal mechanism. Contributions due to dialysate glucose will assume greater proportions now that CAPD is widely practised.Further insight into the pathogenesis of uremic hypertriglyceridemia is likely to come from measurements of plasma lipoprotein lipase activator concentrations with parallel determinations of in vivo triglyceride clearances and in vitro postheparin lipolytic activities, particularly in normotriglyceridemic and hypertri-glyceridemic patients studied as separate groups. The contribution of hypertrigly-ceridemia and low HDL concentrations to the incidence of coronary heart disease has to be carefully assessed in the light of other risk factors such as hypertension, left ventricular hypertrophy, hyper- uncemia, and smoking habits. Until such work is done, attempts to correct the lipid abnormalities on a long-term basis with potentially toxic therapeutic agents are probably not warranted. After renal transplantation, increased triglyceride production due to hyperinsulinemia resulting from peripheral insulin resistance owing to high steroid therapy plays the dominant role. Although the search for a nonsteroidal immunosuppressive agent continues, the most reasonable approach to correct hyperlipidemia after renal transplantation appears to be calorie restriction. Whether the correction of lipid abnormalities reduces cardiovascular mortality in these patients remains to be seen.

Conclusion

In conclusion, we can point out that the knowledge of etiopathogenetic mechanisms of apo/lipoproteins and lipid abnormalities in patients with ESRD treated by repeated hemodialysis as well as revealing their role in early atherosclerosis may contribute to undertaking timely preventive measures (dietetic, healing, therapeutic) by which the incidence of dyslipidemia will be declined, the process of atherogenesis will be slowed down and finally, the onset of cardiovascular and cerebrovascular disorders will be reduced. However, the fact is evident that additional long-term investigations with greater number of patients are required, when by use of less traumatic methods (for instance Doppler measurements of lipid plaque of carotid arteries and other blood vessels) will confirm or discard their role as new, independent risk factors for development of early atherosclerosis in patients with ESRD. Recognition of their physiologic functions, incomparable genetic polymorphism, broad inter-individual variations in plasma concentrations of ApoA-1 and ApoB-100 can evidently contribute to preventing or postponing premature atherosclerosis mainly presented as coronary and/or cerebral disease in uremic population.The optimal targets for plasma lipids in patients with CKD and dialysis patients are unknown. The commonly used clinical assays to measure triglycerides and total, LDL, and HDL cholesterol may not capture the clinically relevant lipid abnormalities of uremia, such as elevated Lp(a), IDL cholesterol, modified LDL cholesterol, and alterations in HDL cholesterol subfractions. *Post hoc* analyses of large clinical trials support the beneficial effects of statins in early stages of CKD, whereas there is a lack of data on the use of statins in stages 4 and 5 CKD. Data in patients who are treated by PD as well as in nondiabetic HD patients are too sparse to draw any conclusion on these subpopulations. Statins are generally ineffective in correcting the elevated plasma concentrations of triglycerides and Lp(a) as well as decreased plasma concentrations of HDL cholesterol, which are the major lipid abnormalities seen in uremia. Although there is a trend toward benefits of the 4D. Study did not provide definitive evidence for statins to improve CV outcomes in HD patients with diabetes. Nicotinic acid derivatives and, to a lesser extent, fibrates may be more suitable to treat uremic dyslipidemia, but there are no studies on the efficacy of these agents to improve CV outcomes in CKD.

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