Dyslipidemia Associated with Chronic Kidney Disease

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Abstract: Cardiovascular disease is a major cause of morbidity and mortality in patients with impaired renal function. Dyslipidemia has been established as a well-known traditional risk factor for cardiovascular disease (CVD) in the general population and it is well known that patients with chronic kidney disease (CKD) exhibit significant alterations in lipoprotein metabolism. In this review, the pathogenesis and treatment of CKD-induced dyslipidemia are discussed. Studies on lipid abnormalities in predialysis, hemodialysis and peritoneal dialysis patients are analyzed. In addition, the results of the studies that tested the effects of the hypolipidemic drugs on cardiovascular morbidity and mortality in patients with CKD are reported.

INTRODUCTION

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 mortality in patients with CKD [2-6]. 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 [5, 9, 10].

Several factors contribute to atherogenesis and CVD in patients with CKD [11]. Although most of the cases of coronary heart disease in the general population can be explained by traditional, Framingham risk factors [12], in patients with CKD, uremia related, non-traditional risk factors, such as, inflammation, oxidative stress, anemia, malnutrition, vascular calcification (due to alterations in calcium and phosphorus metabolism) and endothelial dysfunction have been proposed to play a central role [13]. However, studies investigating the usefulness of current CVD biomarkers have concluded that they add only moderately to traditional risk factors for risk assessment in individuals with almost normal

renal function [14] as well as patients with mild to moderate CKD [15, 16].

Notable among the traditional risk factors for CVD in the general population is dyslipidemia. Several observational studies have shown that total and LDL-cholesterol values are two of the most important independent predictors of cardiovascular morbidity and mortality [17]. Also, it is well known that patients with impaired renal function exhibit significant alterations in lipoprotein metabolism, which in their most advanced form may result in the development of severe dyslipidemia. However, the precise role that these alterations play in the pathogenesis of atherosclerosis in individuals with CKD remains controversial. In this review studies on the pathogenesis of CKD-induced dyslipidemia in predialysis and dialysis patients with impaired renal function and the results of drug therapy are discussed.

PATHOPHYSIOLOGY OF CKD-INDUCED DYSLIPIDEMIA

CKD is characterized by specific metabolic abnormalities of plasma lipoproteins [18, 19]. 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.

ALTERATIONS OF TRIGLYCERIDE-RICH LIPOPROTEIN METABOLISM IN PREDIALYSIS AND DIALYSIS PATIENTS WITH CKD

Hypertriglyceridemia is one of the most common quantitative lipid abnormalities in patients with CKD [20-22]. The concentrations of triglyceride-rich lipoproteins [very-low-density lipoprotein (VLDL), chylomicrons, and their remnants] start to increase in early stages of CKD and show the highest values in NS and in dialysis patients, especially those who are treated with PD.

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Several studies have shown that patients with impaired renal function exhibit increased concentrations of triglycerides even though serum creatinine levels are within normal limits [23, 24]. Also, individuals with CKD usually display abnormal increases in serum triglyceride levels after a fat meal (postprandial lipemia) [25]. The predominant mechanism responsible for increased concentration of triglyceride-rich lipoproteins in predialysis patients is one of delayed catabolism [26]. The reduced catabolic rate is likely due to diminished lipoprotein lipase activity as a consequence of the downregulation of the enzyme gene [27] and the presence of lipase inhibitors [28]. Apolipoprotein C-III is a potent inhibitor of lipoprotein lipase whereas apolipoprotein C-II is an activator of the same enzyme. A decrease in apolipoprotein C-II/C-III ratio due to a disproportionate increase in plasma apolipoprotein C-III is a possible cause of lipoprotein lipase inactivation in uremia [29-32]. It was also suggested that secondary hyperparathyroidism is involved in the impaired catabolism of triglyceride-rich lipoproteins, provided an additional mechanism by which CKD may raise plasma triglyceride concentrations [33, 34]. Except of the low catabolic rate, the increased hepatic production of triglyceride-rich lipoproteins may also play a contributory role in the pathogenesis of dyslipidemia in renal disease [26]. It is well known that CKD causes insulin resistance which can, in turn, promote hepatic VLDL production [23-25]. Thus, it could be hypothesized that the insulin resistance-driven overproduction of VLDL may significantly contribute to the development of hypertiglyceridemia in patients with CKD.

Hypertiglyceridemia [due to accumulation of VLDL and remnant lipoproteins such as intermediate-density lipoprotein (IDL)], is also the predominant lipoprotein abnormality in a considerable number of cases with nephrotic range proteinuria [35]. This dyslipidemia results from a combination of increased production and reduced clearance of VLDL [36]. It is well known that the progressive delipidation of triglyceride-rich lipoproteins is facilitated by the action of two different enzymes namely endothelial-bound lipoprotein lipase and hepatic lipase. The expression of the genes of these enzymes has been found to be downregulated in patients with NS [37]. In addition, other factors such as hypoalbuminemia and proteinuria may further decrease the efficiency of lipoprotein lipase-induced lipolysis of triglyceride-rich lipoproteins by interfering with the endothelial binding of the enzyme and by changing the composition of VLDLs in a way that reduces their suitability as lipoprotein lipase substrates, respectively [38].

The initiation of renal replacement therapy, as well as the choice of dialysis modality, may also influence the levels of triglyceride-rich lipoproteins in ESRD patients [39]. The pathophysiological mechanisms responsible for these alterations seem to be generally similar with those described in predialysis patients with CKD. However, factors related to the procedure of renal replacement therapy seem to contribute to the increased levels of triglycerides observed in this patient group. In HD patients the repeated use of low-molecular heparins for anticoagulation may lead to a defective catabolism of triglyceride-rich lipoproteins as heparin releases lipoprotein lipase from the endothelia surface and thus its chronic use may result in lipoprotein lipase depletion. However, the studies that tested the role of heparin in the pathogenesis of HD-induced dyslipidemia revealed con-

tradictory results [40-42]. In addition, controversy exists as to whether low-molecular weight heparins have a more favorable effect on the lipid profile of HD patients compared to standard unfractionated heparin [43, 44]. Also, studies on the influence of the type of membrane used in HD yielded conflicting results. It has been shown that the use of high-flux polysulfone or cellulose triacetate membranes is accompanied by a significant reduction in serum triglyceride. This improvement could, at least in part, be attributed to an increase in the apolipoprotein C-II/CIII ratio which increases the activity of lipoprotein lipase and facilitates the intravascular lipolysis of triglyceride-rich lipoproteins [45]. However, other studies suggest that the type of dialysis membrane does not influence the characteristics of dyslipidemia [46].

In contrast to HD patients, hypertiglyceridemia is more prevalent in continuous ambulatory peritoneal dialysis (CAPD) patients [47]. Although the pathophysiological mechanisms are not clear, it has been suggested that the significant absorption of glucose from the dialysis fluid may play a significant role as it can lead to an increase in insulin levels and may enhance the hepatic synthesis and secretion of VLDL [48]. Although no direct correlation has been observed between peritoneal glucose absorption and serum lipid levels in peritoneal dialysis patients, recent studies indicate that the reduction of glucose load with the use of less absorbed icodextrin-containing dialysis solution instead of glucose for the overnight dwell, sufficiently improves the lipid profile of these patients [49, 50].

ALTERATIONS IN LOW DENSITY LIPOPROTEIN (LDL) METABOLISM IN PREDIALYSIS AND DIALYSIS PATIENTS WITH CKD

Plasma total cholesterol is usually normal or reduced and occasionally elevated in ESRD patients. A significant factor which determines the levels of plasma cholesterol-rich lipoproteins, except of the deterioration in renal function, is the degree of proteinuria. Chronic kidney disease in the absence of heavy proteinuria does not significantly affect gene expressions of either hydroxyl-3-methylglutaryl-CoA reductase (HMG-CoA reductase) which is the rate-limiting enzyme for cholesterol biosynthesis, or that of cholesterol 7a-hydroxylase which is the rate-limiting enzyme for cholesterol catabolism and conversion to bite acids [51]. Also, LDL receptor-mediated cholesterol uptake plays an important role in cholesterol homeostasis. CKD in the absence of heavy proteinuria or significant glomerulosclerosis does not alter hepatic LDL receptor gene expression [51]. In contrast, patients with nephrotic range proteinuria, exhibit an acquired LDL-receptor deficiency [52]. Although the nature of this deficiency has not been fully characterized, studies in experimental animals have shown that the inefficient translation and/or the increased LDL-receptor protein turnover may represent the most important causes for its development [53, 54]. In addition to these mechanisms, conformational changes in the apolipoprotein B moiety of LDLs may further reduce the affinity of LDL particles for LDL receptor thus contributing to the elevated LDL-cholesterol levels that represent the prominent feature of nephrotic dyslipidemia [55]. The reduced receptor-mediated catabolism of LDL particles along with the upregulation of acyl-coenzyme A: cholesterol acyltransferase (ACAT) gene (the enzyme responsible for

cholesterol esterification in hepatocytes) that has been observed in individuals with NS [56] may reduce the free cholesterol content of hepatocytes and thus may lead to the dysregulation of the key enzymes that are involved in cholesterol homeostasis. Indeed, studies in animals with experimental nephrosis revealed an upregulation of HMG-CoA reductase [57] as well as a relative reduction of cholesterol 7α-hydroxylase [58]. All the aforementioned mechanisms in concert may result in the increased concentration of LDL-cholesterol in individuals with NS.

Chronic kidney disease patients, with or without heavy proteinuria, display important qualitative alterations in LDL metabolism. The proportion of small dense LDL particles, which is considered to be highly atherogenic, is increased [59, 60]. Small dense LDL is a subtype of LDL that has high propensity to penetrate the vessel wall, becomes oxidized and triggers the atherosclerotic process.

In HD patients the serum lipid concentrations resemble those of predialysis patients with CKD, which means that total and LDL cholesterol levels are generally normal, whereas the subfractionation of apolipoprotein B-containing lipoproteins usually reveals a predominance of small dense particles [60, 61]. On the other hand, CAPD patients exhibit a more atherogenic lipid profile that is characterized by higher total and LDL cholesterol values and increased concentrations of small dense LDL and apolipoprotein B [47, 60, 62]. A number of possible factors associated with the PD treatment may explain those alterations in lipoprotein metabolism. It is known that CAPD patients lose substantial amounts of plasma proteins into the peritoneal dialysate. This protein loss may, in turn, stimulate the hepatic synthesis of albumin and other liver-derived proteins, including cholesterol-enriched lipoproteins [63-65]. It should be also mentioned that, in CAPD patients, substantial amounts of apolipoproteins and intact lipoproteins are lost via the peritoneal cavity. However the pathophysiological significance of these loses remains unclear [66, 67].

Finally, recent studies have investigated the role of the administration of the phosphate-binding resin sevelamer hydrochloride in the levels of plasma cholesterol and apolipoprotein B in HD and PD patients. It has been shown that sevelamer hydrochloride significantly reduces the concentrations of total cholesterol and apolipoprotein B in HD patients [68]. Obviously, the cholesterol-lowering properties of this compound are irrelevant to phosphate reduction and can be mainly attributed to its bile acid sequestrating properties, resembling cholestyramine effect. It is likely that the use of sevelamer would result in a similar effect in CAPD patients.

LIPOPROTEIN (a) (LP(a)) AND CKD

Lp(a) represents an LDL-like particle distinguished from LDL by the presence of apolipoprotein(a) [apo(a)], which is attached to apolipoprotein B-100 molecule through disulfide linkage [69]. Apo(a) is highly homologous to the plasma protease zymogene plasminogen and thus it has been suggested that Lp(a) may promote thrombogenesis by inhibiting fibrinolysis [69]. Studies in healthy individuals and in patients with CKD have shown that serum Lp(a) levels are strongly and negatively associated with apo(a) isoform size. Indeed, subjects who have low molecular weight (LMW) apo(a) isoforms show on average higher Lp(a) concentra-

tions compared to those who have high molecular weight (HMW) isoforms [70]. The large concentration gradient of Lp(a) between aorta and the renal vein [71] as well as the identification of apo(a) fragments in urine [72] suggest that the kidney may actively participate in the degradation of Lp(a). Thus, it is not surprising that patients with primary kidney diseases (even those with normal GFR values) usually exhibit markedly elevated concentrations of Lp(a) [73, 74] as well as increased concentrations of LDL-unbound apo(a) [75]. However, recently published studies indicate that the negative association between renal function and Lp(a) levels is phenotype-specific. Thus, predialysis CKD patients with HMW apo(a) isoforms tend to have much higher Lp(a) values than apo(a) phenotype-matched healthy controls, whereas patients with kidney diseases who exhibit LMW apo(a) isoforms have similar Lp(a) concentrations with phenotype-matched healthy individuals, who already have high Lp(a) levels [69, 76]. It is worth mentioning that prospective studies identified small apo(a) isoform size and not Lp(a) level as an independent predictor of total and cardiovascular mortality in patients with CKD [77, 78].

The isoform-specific increase in plasma Lp(a) was also observed in HD patients [79, 80]. The malnutrition and inflammation and, mainly, the decreased clearance of apo(a) in HD patients, have been implicated in this procedure [80-83]. In contrast, in CAPD patients, increases in plasma Lp(a) levels occur in all apo(a) isoform groups, probably as a consequence of the pronounced protein loss and the subsequently increased production of this lipoprotein in the liver [79, 84, 85]. Similarly to CAPD patients, individuals with nephrotic range proteinuria exhibit increased concentrations of Lp(a) that is not phenotype-specific [86, 87].

HIGH DENSITY LIPOPROTEIN (HDL) AND CKD

The main function of HDL is the transport of surplus cholesterol from the arterial wall to the liver for excretion. This process, which is commonly called 'reverse cholesterol transport', is critical for cellular cholesterol homeostasis and protection against atherosclerosis. Moreover, HDL serves as a potent endogenous inhibitor of inflammation, platelet adhesion and LDL oxidation, because of a number of HDL associated apolipoproteins (mainly apolipoprotein AI) and enzymes (paroxonase-1, platelet-activating factor acetylhydrolase and lecithin-cholesterol acyltransferase (LCAT) [88]. Several epidemiological studies have demonstrated that HDL cholesterol is a negative risk factor for atherosclerosis [89]. Patients with CKD have, generally, reduced plasma HDL-cholesterol levels compared to individuals with normal renal function [19, 90, 91]. This can be attributed to several mechanisms. Thus, patients with impaired renal function usually exhibit decreased levels of apolipoproteins AI and AII (the main protein constituents of HDL) [91], diminished activity of LCAT (the enzyme responsible for the esterification of free cholesterol in HDL particles) [92, 93], as well as increased activity of cholesteryl ester transfer protein (CETP) [94] that facilitates the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins thus reducing the serum concentrations of HDL-cholesterol. In addition to their reduced efficiency as cholesterol acceptors, HDL particles from individuals with impaired renal function have less effective antioxidative and anti-inflammatory function. This impairment can, at least in part, be attributed to the reduction

in the activities of HDL-associated enzymes, such as paraoxonase (an enzyme that inhibits the LDL oxidation) [95, 96].

Hemodialysis and PD procedure may also have a contributory role in the reduced HDL cholesterol levels of dialysis patients [39, 47]. Thus, in dialysis patients the type of membrane and dialysate used in HD procedure may influence the HDL-cholesterol levels. It has been shown that the use of high-flux instead of low flux membranes is associated with an increase in apolipoprotein AI and HDL-cholesterol values. [97, 98]. In addition, the type of dialysate may also significantly affect the serum levels of lipoproteins in HD patients. Indeed, it has been shown that the use of bicarbonate dialysate may result in higher HDL-cholesterol concentrations than the use of acetate dialysate [99].

DYSLIPIDEMIA AS A RISK FACTOR FOR CARDIO-VASCULAR DISEASE IN CKD

It is well known that dyslipidemia represents an important (maybe the most important) risk factor for the development of cardiovascular disease (CVD) in the general population. Indeed, large-scale epidemiological studies revealed a lineal relationship between total and LDL-C values and the incidence of ischemic events in both primary and secondary prevention individuals, whereas the reduction in the concentrations of these parameters by means of diet, drug therapy or surgery is followed by an impressive reduction in the future cardiovascular risk [17]. On the other hand, the role of dyslipidemia in the pathophysiology of atherosclerotic disease in patients with impaired renal function remains controversial. Thus, some studies have shown a positive association between cholesterol values and the risk for cardiovascular events in CKD individuals [100], whereas others failed to find any significant correlation [101, 102]. Finally, some other studies suggested an inverse relationship between serum cholesterol values and mortality in ESRD individuals, a phenomenon also known as "reverse epidemiology" [101, 103, 104]. Although the precise causes of this significant deviation from what is observed in the general population have not been established, it has been proposed that the presence of phenomena such as inflammation or protein energy wasting (conditions very common in ESRD patients) may significantly confound the relationship between the traditional risk factors for CVD and mortality in this patient population [105, 106]. In other words, ESDR patients free of these complications behave exactly as individuals with normal renal function, whereas in the presence of these conditions low rather than high cholesterol values predict a poor outcome. [105, 106]. In agreement with this hypothesis the statistical adjustment for markers of inflammation and/or malnutrition in some studies restores the positive association between serum cholesterol values and mortality in CKD individuals[105, 106]. However, it must be mentioned that the aforesaid assumptions were not confirmed by the results of recent studies. Indeed, Kilpatrick *et al.* [107] in a cohort of 15.859 HD patients showed that the positive relationship between cholesterol values and cardiovascular death risk may be confined to certain racial subgroups such as black HD patients. These discrepancies clearly show that further studies are needed to delineate the impact of lipoprotein concentrations on total and cardiovascular risk in individuals with ESRD.

DYSLIPIDEMIA AS A THERAPEUTIC TARGET IN CKD

Despite the uncertainty that surrounds the role of dyslipidemia in the pathogenesis of atherosclerotic disease in CKD individuals, based on the extremely high cardiovascular mortality that characterizes this patient population, the Work Group for Kidney Disease Outcomes Quality Initiative (K/DOQI) proposed the adoption of Adult Treatment Panel (ATP) III LDL-cholesterol targets for individuals with ESRD and suggest the aggressive treatment of lipid disorders [108, 109]. However, recent studies indicate that the use of lipid-lowering medications in individuals with impaired renal function is limited, whereas a small minority of those receiving hypolipidemic drugs achieves therapeutic targets [110, 111]. It is possible that the most important factor that limits the use of hypolipidemic drugs in individuals with CKD is the contradictory results of the studies that tried to delineate the effects of statins on total and cardiovascular mortality in this patient population. It is well known that statins are by far the most commonly prescribed hypolipidemic drugs in the general population and numerous large, randomized, prospective studies have shown that their use is accompanied by an impressive reduction in the incidence of cardiovascular events [112]. On the other hand, the beneficial effect of statin administration on cardiovascular morbidity and mortality in individuals with CKD seems to be related to the severity of renal dysfunction. Indeed, in several large, prospective, placebo-controlled trials of statins, post hoc analyses of subgroups with mild to moderate CKD (stages 1-3) revealed a significant reduction in cardiovascular morbidity and mortality independently of the baseline lipid values and the presence or the absence of diabetes and coronary artery disease [113-118]. The same results were also obtained by the study of the prespecified subgroups of individuals with impaired renal function in the HPS [109, 119] and ASCOT-LLA [120] studies that utilized simvastatin and atorvastatin, respectively. A recently published metaanalysis that included 26 studies (about 25.000 participants) revealed that the use of statins in predialysis individuals with CKD is followed by a significant reduction in all-cause and cardiovascular mortality by approximately 20%[121]. Interestingly, the rate of adverse events was similar in patients receiving statins and placebo. These results suggest that the use of statins for the prevention of ischemic events in dyslipidemic individuals with early CKD seems to be a safe, reasonable and evidence-based approach.

Although epidemiological studies have shown that the use of statins in individuals receiving maintenance hemodialysis is accompanied by a reduction in cardiovascular mortality [122-124], the prospective, randomized trials that tested the potential beneficial effect of statins in this patient population revealed disappointing results. The 4D (Die Deutsche Diabetes Dialyse) trial enrolled 1255 diabetic subjects who had been on maintenance HD for less than 2 years and were randomized to receive either placebo or 20 mg/day of atorvastatin [125]. Overall, after a mean follow-up period of 2.4 years atorvastatin did not significantly reduce the risk of the composite primary end point (cardiovascular death, nonfatal myocardial infarction and stroke), despite a significant 42% reduction in LDL-cholesterol concentration [126]. Although this study had several potential limitations [the

majority of cardiovascular events were possibly non-ischemic in nature, a significant proportion of individuals in the placebo arm (about 15%) also received a non-study statin, the study was conducted exclusively in patients with diabetes mellitus and the extrapolation of its findings to non-diabetic subjects was questionable etc], it raised important concerns about the efficacy of statin administration in individuals with ESRD. Similar findings were also reported in a small Scandinavian study that showed a significant decrease of cardiovascular end points after atorvastatin administration in predialysis patients with CKD but no effect in individuals who were on maintenance HD [166].

The publication of the results of AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) study few months ago [127], led to the conception of "a point of no return", i.e. a point in the deterioration of renal function beyond which the beneficial effect of statins in cardiovascular morbidity and mortality is offset by the uremic environment. AURORA study was a prospective, double-blind trial involving 2775 individuals on maintenance HD who were randomized to receive 10 mg of rosuvastatin per day or placebo. After a median follow-up period of 3.8 years, and despite the impressive reduction in LDL-C and C-reactive protein concentrations (by 43 and 11.5%, respectively), rosuvastatin administration had no effect on the primary composite end-point (nonfatal myocardial infarction, nonfatal stroke and cardiovascular death) or the individual components of the primary end-point. There was also no significant effect on all-cause mortality while none of the pre-specified secondary outcomes was influenced by active treatment.

Several mechanisms have been proposed for the explanation of the failure of statins to improve cardiovascular outcomes in individuals with advanced CKD. Thus, it has been suggested that the initiation and progression of atherosclerotic disease in this population may have a different pathophysiological basis (arterial wall calcification, inflammation etc), whereas other investigators emphasize that lipoproteins other than LDL (such as Lp(a), IDL etc) may play significant role in the initiation and progression of coronary atherosclerosis [22, 128, 129]. Whatever the cause, it seems that in this patient population the decision for the administration of statins should be individualized.

Fibric acid derivatives (fibrates) represent another important class of hypolipidemic medications. These drugs modify the expression of genes involved in lipoprotein metabolism and thus they reduce the concentrations of triglycerides, increase the serum concentrations of HDL-cholesterol and induce a shift in LDL subfraction distribution towards larger and more buoyant particles [130]. Thus, theoretically, these drugs could represent an ideal option for the treatment of uremic dyslipidemia. However, it has been shown that the administration of fibrates (possibly with the exception of gemfibrozil) in individuals with impaired renal function is associated with an extremely high risk of muscular toxicity [131, 132]. In addition, these drugs also significantly increase serum creatinine values. Although it has been proposed that this increase does not represent a true deterioration in renal function but rather is due to increased metabolic production of creatinine, cases of nonreversible renal failure

have been reported after fibrate administration [131]. In addition, the effect of fibrates on cardiovascular morbidity and mortality in individuals with impaired renal function has not been extensively studied. Thus, although an observational study suggested that the use of fibrates in patients with impaired renal function does not reduce total mortality [122], a post hoc analysis of the secondary prevention VA-HIT study revealed that the administration of gemfibrozil in individuals with moderate CKD reduced the risk of the primary end point (coronary death or nonfatal myocardial infarction) by 27% [133]. For these reasons, it seems reasonable that fibrates should be used only in the subpopulation of patients with CKD who exhibit extremely high triglycerides values (greater than 500 mg/dl)[131]. In these cases, the risk of acute pancreatitis justifies the use of gemfibrozil that is the fibrate of choice in individuals with impaired renal function [131]. The administration of omega-3 polyunsaturated fatty acids may also have a role in the management of this extremely rare condition [134].

A number of other hypolipidemic drugs that are increasingly used in the general population (such as niacin, omega-3 polyunsaturated 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.

CONCLUSIONS

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. 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 and gemfibrozil, respectively) 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 interventions.

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