

Chapter 2

Lipid Nephrotoxicity: New Concept for an Old Disease

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Introduction

In 1982 Moorhead and colleagues published the “Lipid Nephrotoxicity Hypothesis” in *Lancet* [1], which stimulated lipid studies in the context of kidney diseases. This chapter was the first to introduce the concept that the compensatory hepatic synthesis of lipoproteins in response to urinary loss of albumin could cause progressive kidney disease and that pathogenesis of atherosclerosis and renal injury and glomerulosclerosis could have a common pathway. In this “two-hit” model, the original disease could coexist or be replaced by lipid-mediated damage. Persistent albuminuria stimulates excess lipoprotein synthesis by the liver, thereby maintaining the lipid injury cycle. It also proposed that many of the features of progressive glomerular and tubulo-interstitial diseases share biological mechanisms with those of atherosclerosis, including dyslipidemia, oxidative stress, inflammatory stress, and genetic factors. The term glomerular atherosclerosis was proposed. Lipid-loaded cells derived from macrophages and mesangial cells (MCs), which share many properties of vascular smooth muscle cells (VSMCs) and take up both unaltered and altered LDL cholesterol, should be considered in the context of lipid-mediated vascular and renal injury. Against this background, it is not surprising that cardiovascular disease (CVD) is the most important cause of morbidity and mortality at all stages of progressive kidney disease and that chronic kidney disease (CKD) is now considered as a risk factor for CVD.

Since then, many laboratory and clinical studies [1, 2] have supported the hypothesis that hyperlipidemia resulting from compensatory hepatic synthesis of lipoproteins in response to urinary loss of albumin contributed to the progression of both atherosclerosis and glomerulosclerosis. However, kidney injury does not always

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occur in the presence of hyperlipidemia alone; for example, the higher risk of cardiovascular death in dialysis individuals is associated with low plasma cholesterol (reverse epidemiology), suggesting that multiple factors accompanying with CKD may interfere lipid-mediated kidney injury. In this chapter, we will discuss the promises and exceptions to the original hypothesis, updating the lipid nephrotoxicity hypothesis by analyzing dyslipidemia of CKD, the renal pathophysiological changes induced by dyslipidemia, recent developments of and some apparent exceptions to the hypothesis, and how inflammatory stress alters lipid homeostasis.

Original Lipid Nephrotoxicity Hypothesis: Promises and Exceptions

Intensive laboratory studies have demonstrated that dyslipidemia in CKD can be both consequence [3] and cause [1] of the progression of CKD and CVD, a disease spectrum offering a substantial study platform for the original hypothesis. Although many studies support the hypothesis that lipid abnormalities contribute to renal injury, the latter does not occur in the presence of hyperlipidemia alone [4]. For example, the Watanabe heritable hyperlipidemic (WHHL) rabbit model, which is characterized by a deficiency of low-density lipoprotein (LDL) receptors and hypercholesterolemia, develops atherosclerosis but not renal lesions [5]. There is also no evidence of kidney disease in the hypercholesterolemic Nagase analbuminemic rat model [6]. In humans familial hypercholesterolemia is not usually associated with renal failure, and kidney disease rarely occurs in patients with primary hyperlipidemias [7]. In contrast normolipidemic patients with kidney disease often develop both glomerulosclerosis and atherosclerosis [8, 9]. Interestingly, while atherosclerosis regresses with reduction of serum cholesterol, human kidney disease does not. In other words, the plasma level of cholesterol per se does not correlate with glomerulosclerosis.

Since renal injury does not always occur in the presence of hyperlipidemia alone [4], and glomerulosclerosis can occur without lipid deposition, a precursor condition such as intra-renal hypertension, increased glomerular capillary shear stress, hyperfiltration, decreased nephron mass, or inflammatory stress appears to be required for the induction and progression of lipid-induced renal dysfunction.

Atherogenic Dyslipidemia in CKD: Enhanced Disease Progression

The lipid profile of CKD patients is typified by high circulating levels of very low-density lipoprotein (VLDL) triglycerides, intermediate-density lipoprotein (IDL) and chylomicron remnants (CM), and low plasma high-density lipoprotein (HDL) cholesterol. Reduced clearance and increased plasma levels of small dense LDL

particles aid easier entrance into arterial walls where faster oxidation causes renal and vascular damage [10]. The LDL cholesterol level is not usually increased and may even be reduced. A higher risk of death from CVD is associated with low plasma cholesterol (reverse epidemiology) [8, 11]. In addition to causing quantitative reductions in HDL cholesterol and apoA-1 concentrations, CKD results in deficiency of HDL-associated enzymes (paraoxonase, glutathione peroxidase, and lecithin:cholesterol acyltransferase (LCAT)) and conversion of HDL from an antioxidant/anti-inflammatory agent to a prooxidant and pro-inflammatory agent [12, 13]. These abnormalities can compound the effects of HDL deficiency in promoting an atherogenic diathesis in this population. Lp(a), and apolipoprotein (apo)A-IV are also increased. This lipid profile is similar to the atherogenic dyslipidemia of diabetics, and may sometimes be observed in early stages of primary kidney disease when measured glomerular filtration rate (GFR) is normal [14].

Renal Injury

It has long been established that cholesterol supplementation of the diets of several animal species leads to focal and segmental glomerulosclerosis (FSGS). French et al. showed that feeding guinea pigs a diet containing 1 % cholesterol caused severe glomerular disease [15, 16]. Peric-Golia et al. have demonstrated that feeding normal male Sprague–Dawley rats with a 3–4 % cholesterol diet resulted in hypercholesterolemia accompanied by aortic damage and renal glomerular abnormalities including lipid droplets, hyalinosis, glomerulosclerosis, and interstitial fibrosis [17, 18]. The severity of glomerular injury is greatly increased if dietary-induced hyperlipidemia is combined with either a loss of functioning nephrons, partial nephrectomy, or hypertension [18, 20]. Rats that had a unilateral nephrectomy at 1 month that were fed a diet consisting of 4 % cholesterol developed significantly higher glomerular scarring than cholesterol-fed rats with two kidneys. Chronic renal failure induced by 5/6 nephrectomy results in accumulation of lipids in the remnant kidney, which is associated with upregulation of receptors involved in the influx of oxidized lipids and lipoproteins, activation of fatty acid biosynthesis, and inhibition of pathways involved in fatty acid oxidation [19]. Studies using the puromycin amino nucleoside (PAN) nephrotic rat model have also shown that cholesterol feeding increases the severity of proteinuria and FSGS [18, 20]. Apo B and apo E were encountered in increased amounts in the mesangium and co-localized with Oil Red O-positive lipid deposits [21]. Animals with endogenous hyperlipidemia [22] also develop progressive glomerular damage. Such models include the hyperlipidemic Sprague–Dawley rat developed by Imai et al. [23], the spontaneously hypertensive rat described by Koletsky [24], and the obese Zucker rat [22]. Glomerular injury is also greater when systemic hypertension is combined with hyperlipidemia [25].

Several clinical studies have documented an association between dyslipidemia and the progression of CKD. Atherosclerosis risk in communities (ARIC) [26] with low HDL cholesterol and increased non-HDL cholesterol was associated with

increased risk of developing a reduced GFR (≤ 55 mL/min/1.73 m²). In the ARIC study, higher HDL cholesterol levels were associated with a decreased risk of progression of CKD, although one study showed an association between high LDL cholesterol levels and progression of kidney disease [27]. The weight of evidence, therefore, suggests that hypertriglyceridemia, accumulation of LDL cholesterol and low HDL cholesterol are associated with increased risk of progression of CKD. Survival statistics in renal transplant patients have also demonstrated that survival with declining renal function is far superior in patients with normalized lipid profiles [28, 29].

Foam cells and lipid deposits are found in FSGS in human renal biopsies [30]. Patients with hereditary LCAT enzyme deficiency are unable to esterify cholesterol normally, and their abnormally large lipid-laden HDL has a defective maturation pattern. In these individuals, lipid deposition in the glomerulus is associated with progressive renal insufficiency. Some patients with hepatorenal syndrome who have lipoproteins with abnormal compositions have been reported to have progressive glomerular damage. A unique form of the nephrotic syndrome was reported in Japanese patients, where mesangial proliferation, mesangial expansion, glomerular deposition of lipoproteins, and FSGS were associated with high levels of circulating apoE [31]. Lee et al. found that 8.4 % of 631 CKD patients had ultrastructurally detectable extracellular lipid in non-sclerotic glomeruli, which suggests that there may be an early pre-sclerotic stage of lipoprotein-mediated damage [30]. Takemura also demonstrated that predominant deposition of apo B and apo E in the mesangial area in mesangial proliferative types of glomerulonephritis and that the distribution and staining intensity of these apolipoproteins correlated with the grade of mesangial proliferation and proteinuria, but were independent of plasma lipid levels [32].

Vascular Injury

The term glomerular atherosclerosis was proposed, because atherosclerosis shares similar pathogenesis with glomerular sclerosis. CVD risk is increased in chronic inflammatory states, up to 33-fold in patients with renal failure and allografts compared to non-uremic subjects. Patients with an “inflammation profile” including CKD, SLE, rheumatoid arthritis, psoriasis, and diabetes are especially prone to this problem. On the face of it, these data could suggest that a relatively normal cholesterol level in inflammatory conditions argues against a causative connection with cardiovascular mortality, which may explain why the phenomenon is often ignored by the atherosclerosis research community. The explanation for this may lie in the fact that the clinical setting responsible for previously “hidden” mechanisms of lipid-mediated vascular damage and cytotoxicity is more complex in CKD than in the general population; the question one should ask is why cholesterol levels are relatively normal or low under inflammatory stress?

Renal Pathophysiological Changes Driven by Atherogenic Dyslipidemia

Lipid-loaded foam cells in the kidney and atherosclerotic plaques support pathophysiological roles for lipids in the progression of both CKD and CVD.

Oxidative Stress

Though initial events involved in lipid-mediated renal damage are unclear, oxidative stress is thought to be especially important. Hyperlipidemia causes significantly higher rates of monocyte reactive oxygen species (ROS) generation, which is strongly associated with impairment of endothelium-dependent relaxation and elevated plasma levels of Ox-LDL. Arteries from hypercholesterolemic animals produced significantly higher rates of oxygen radical than control arteries.

The mechanisms by which hyperlipidemia contributes to systemic oxidative stress in CKD remain unclear. Plasma HDL-cholesterol with its important antioxidant function is reduced in CKD [33]. Inflammatory mediators, including TNF α and IL-1 β , are ROS-activating factors in the kidney and may induce oxygen radical production by MCs. Immune-mediated mesangial injury causes increased oxygen radical and eicosanoid production [34]. An important source of ROS is NAD(P)H-oxidase (NOX). The NOX family comprises seven members, Nox1–Nox7. Nox1 and Nox2 (gp91phox-containing NADPH oxidase), together with Nox4 and Nox5, have been identified in the cardiovascular–renal systems and have been implicated in oxidative stress [35] in kidney disease. In addition, the leukocyte-derived enzymes myeloperoxidase (MPO) and xanthine oxidoreductase (XOR) may contribute to oxidative stress pathways in end-stage renal disease (ESRD) with a role in cardiovascular dysfunction [36, 37].

Inappropriate ROS generation may contribute to tissue dysfunction in three ways: (1) dysregulation of redox-sensitive signalling pathways; (2) oxidative damage to biological structures including DNA, proteins, and lipids; and (3) activation of macrophages [38]. Lipid peroxidation is the first step in the generation of Ox-LDL, which can accumulate in renal mesangial cells [39]. The process of lipid peroxidation itself generates free radicals and ROS.

The cytotoxic effects of Ox-LDL, produced *in vitro* by incubating LDL with CuSO₄ include induction of podocyte [40] and endothelial cells apoptosis, which may influence cellular turnover in vascular and renal injuries. All major cell types in the artery wall and kidney, including endothelial cells, SMCs, monocyte–macrophages, and MCs, have been shown to cause oxidative modification of LDL *in vitro* [41, 42]. Oxidative stress decreases renal NO production and availability [43] and stimulates angiotensin II synthesis, suggesting that activation of the renin-angiotensin system (RAS) may contribute to lipid-induced renal injury. It has been demonstrated that angiotensin II increases TGF- β and plasminogen activator inhibitor-1 (PAI-1) expression, thereby propagating glomerular fibrosis [44]. Oxidized LDL has also been identified in the lesions of FSGS *in vivo* [45].

Endoplasmic Reticulum Stress

Metabolic stress within the endoplasmic reticulum (ER) induces a coordinated unfolded protein response (UPR), which helps the ER to cope with the accumulation of misfolded proteins. UPR is initiated by three ER transmembrane proteins (namely, PKR-like ER-regulated kinase (PERK), inositol-requiring enzyme-1 (IRE-1), and activating transcription factor-6 (ATF-6)) [46]. Recent studies report that intracellular accumulation of saturated fatty acids and cholesterol results in ER stress, resulting in apoptosis in macrophages; macrophage scavenger receptor type A is essential in regulating ER stress-induced apoptosis [47]. Palmitate also induces ER stress by increasing IRE1 protein levels and activating the c-Jun NH₂-terminal kinase (JNK) pathway [48]. In both cultured cells and whole animals, ER stress leads to activation of the JNK and IKK/NFκB pathways, promoting an inflammatory response. ER stress, in turn, leads to dysregulation of the endogenous sterol response mechanism and concordantly activates oxidative stress pathways [49].

Inflammatory Stress

The presence of oxidative and ER stress activates the NF-κB pathway, which has been associated with inflammatory events in glomerulonephritis, as well the progression of CKD [50]. In addition, lipids may act as pro-inflammatory mediators. At certain concentrations LDL, VLDL, and IDL enhanced the secretion of inflammatory cytokines by MCs, including IL-6, PDGF, and TGFβ. Since HDL down-regulates VCAM-1 and E-selectin on endothelial surfaces and reduces NFκB, low HDL cholesterol levels may augment inflammatory responses [51]. In apoE KO mice [52], blocking the IL-6 receptor prevented progression of proteinuria and renal lipid deposition, as well as the mesangial cell proliferation associated with severe hyperlipoproteinemia. These results strongly support the role of pro-inflammatory cytokines in the pathogenesis of hyperlipidemia-induced glomerular injury. Inflammation also enhances both medial and intimal calcification, which contribute to vascular, and perhaps also renal injury [53, 54].

Ox-LDL binds preferentially to the glomerulus when injected intra-arterially in the rat and to mesangial cells in vitro [55]. Ox-LDL is a potent proinflammatory chemoattractant for macrophages and T lymphocytes with a role in the recruitment of circulating monocytes either directly or by inducing SMC, MCs, and/or endothelial cells to produce chemotactic and adhesive factors such as MCP-1, monocyte colony-stimulating factor (m-CSF), and IL-1β [56, 57]. Modified LDL may also inhibit the motility of resident monocytes once they have differentiated into macrophages within the site [58]. Both oxidized LDL and minimally oxidized LDL stimulated TNF-α secretion by MCs by activating the NFκB pathway [50].

Mesangial Cell Proliferation and Matrix Expansion

MCs have been shown to bind LDL and Ox-LDL, leading to more cell proliferation via multiple downstream effects. LDL also stimulates the expression of extracellular matrix proteins including fibronectin. Furthermore, glomerular macrophages obtained from hypercholesterolemic animals displayed higher expressions of TGF- β mRNA, which contributes to glomerular matrix expansion [59].

Inflammatory Stress Modifies Lipid Homeostasis

CKD is associated with a low-grade, long-term, and chronic inflammatory stress characterized by elevated plasma CRP levels [60]. Inflammatory stress may modify lipid homeostasis, thereby causing tissue lipid accumulation [61].

Inflammation Changes Lipid Composition

Inflammation alters HDL structure and removes its anti-inflammatory functionality. HDL levels are decreased in inflamed individuals without renal failure, and SAA replaces the apo A-I that normally composes about half of the proteins in HDL [36]. The resulting loss of HDL's protective ability during inflammatory stress renders LDL prone to oxidation from increased activity of MPO, an abundantly expressed enzyme of activated neutrophils that chlorinates a tyrosine residue on apo B100 [62]. Inflammation could be responsible for an increase in triglyceride levels in CKD [63]. Ettinger showed that human recombinant TNF- α , IL-1 β , and IL-6 resulted in dose-related reductions in the concentrations of apoA-I, apoB, and LCAT activity in HepG2 cells, which may contribute to the hypocholesterolemia of acute inflammation.

Inflammation Causes Cholesterol Redistribution

Recently, kinetic analysis of TG fractional catabolic rates (FCR) and production rates (PR) demonstrated that CKD is associated with decreased clearance of TG-rich lipoproteins without change in synthesis. However, catabolism of LDL cholesterol is increased significantly [64], suggesting that both cholesterol production and degradation are modified in CKD. LDL is the major carrier of cholesterol in humans and plays a more important role than other lipids in forming foam cells. However, the plasma LDL cholesterol level is not increased in CKD and hemodialysis patients

and the relationship between cardiovascular mortality and plasma cholesterol levels is reversed [8]. In this section, we will focus on recently observed connections between inflammatory stress, cholesterol homeostasis, and renal injury.

In a retrospective study of nephrotic patients with progressive kidney disease, heavy proteinuria and hypercholesterolemia accompanied kidney disease progression, but plasma cholesterol gradually fell to normal levels as patients approached ESRD [65]. Recently, Liu et al. evaluated the association between plasma cholesterol levels and mortality in 823 dialysis patients from 79 clinics in the United States. They divided the patients into inflamed and non-inflamed on the basis of inflammation markers (CRP and IL-6). The non-inflamed dialysis patients showed a linear relationship between cholesterol levels and mortality and behaved like the normal population in that higher cholesterol was associated with higher mortality. In contrast the higher mortality in inflamed dialysis patients was inversely associated with lower cholesterol levels (J-shaped curve) [8], suggesting that inflammation may divert plasma cholesterol to the tissue compartments, increasing cardiovascular mortality.

We have demonstrated that inflammatory cytokine IL-1 β increases intracellular cholesterol influx into VSMCs, MCs, and macrophages by inducing scavenger receptor expression, disrupting LDL receptor feedback regulation and causing unrestrained LDL receptor-mediated uptake [39, 66, 67]. Pro-inflammatory cytokine IL-1 β also inhibits ATP-binding cassette A1 (ABCA1)-mediated cholesterol efflux from mesangial cells [68]. Furthermore, *in vitro* studies have shown that IL-1 β increases intracellular cholesterol synthesis in MCs, HepG2 [69], and VSMCs by increasing HMG-CoA reductase transcription and activity, thereby enhancing inflammation-mediated intracellular cholesterol synthesis and inhibiting HMG-CoA reductase degradation. *In vivo*, chronic systemic inflammation induced by 10 % subcutaneous casein in apoE KO mice and characterized by increased serum SAA and TNF- α , lowered plasma LDL cholesterol and HDL cholesterol levels, and enhanced lipid accumulation in the liver, vessels, and kidneys, promoting nonalcoholic fatty liver disease (NAFLD), atherosclerosis, and renal injury [70]. However, cholesterol biosynthesis and fatty acid oxidation were reported to be reduced in a remnant rat kidney model [19, 71]. The possible reasons for the differences are that inflammatory stress may differ between nephrectomy rat models (unilateral and 5/6th) and systemic casein-induced inflammatory stress in a mouse model. The nephrectomy rat model is characterized by heavy proteinuria, marked elevation of plasma total cholesterol, LDL cholesterol, triglyceride, and free fatty acid concentrations. While suitable for the investigation of renal pathophysiological changes, this model does not adequately mirror lipid homeostasis in CKD patients whose LDL cholesterol level is not increased; nor is the casein-induced systemic inflammatory stress model affected by uremia-related factors. These points reinforce views that across-species cholesterol homeostasis may be differently regulated according to the type and stage of kidney disease as well as variations in inflammatory stress. HMG-CoA reductase-mediated cholesterol synthesis in kidney may be decreased in the CRF nephrectomy rat model but increased in the presence of serious inflammatory stress or in the early stages of CKD.

Zhao et al., using a unilateral nephrectomy model, showed adipose tissue redistribution to kidney from the peri-renal capsule, omentum, mesentery, and abdominal wall, suggesting that lipid redistribution may also take place between tissues [72, 73]. Furthermore, we and others have shown that inflammatory stress causes cholesterol accumulation in the normally cholesterol-poor ER, indicating that cholesterol redistribution can occur intracellularly between organelles. Cholesterol relocation at this level could potentially trigger lipid-induced apoptosis or ER stress [74].

Hence, inflammatory stress accompanied by CKD modifies cholesterol homeostasis by diverting cholesterol from blood to tissues, which causes cholesterol to accumulate in peripheral tissues such as kidney, vessel wall, and liver, lowering circulating cholesterol levels. Tissue cholesterol redistribution and accumulation in response to inflammation may occur at several levels and sites: from circulation to tissue, tissue to tissue, and organelle to organelle. Therefore, plasma LDL cholesterol in patients with CKD may be a poor marker of the risk of lipid-mediated vascular or renal injury and unhelpful or even misleading in the evaluation of the clinical efficacy of lipid-lowering drugs.

The Impact of Statins on CKD

Statins have revolutionized the treatment of high plasma cholesterol and atherosclerosis, confirming their benefits in vascular disease [75]. They are effective in correcting dyslipidemia and are relatively safe [76]. Statin prescription is now common in patients with CKD, an approach endorsed by the recent Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, although its value in preventing the progression of CVD and CKD is not yet clear.

Effect of Statins on Renal Protection: Evidence from CVD Trial

The majority of clinical trials in statins excluded patients with kidney disease as judged by serum creatinine (Cr), which leaves large subgroups of patients with normal Cr but abnormal estimated glomerular filtration rates (eGFR) using the modification of diet in renal disease (MDRD) calculation. A post hoc subgroup analysis of the Cholesterol and Recurrent Events trial (CARE) study [77] demonstrated that pravastatin may slow renal function loss in individuals with moderate to severe kidney disease, especially in those with proteinuria. The GREACE study, performed to evaluate the effect of atorvastatin on renal function [78], demonstrated that statin treatment prevented decline in renal dysfunction based on eGFR and potentially improved renal function, offsetting an additional factor associated with CHD risk. A pooled analysis of data demonstrated that among patients who received long-term

rosuvastatin treatment (>96 weeks), eGFR was unchanged or tended to increase rather than to decrease when compared with baseline [79]. Furthermore, a post hoc subgroup analysis of data from three randomized double-blind controlled trials (LIPID, CARE, and WOSCOPS) demonstrated that pravastatin (40 mg/day) reduced the adjusted rate of kidney function loss by 34 % in patients with moderate CKD [80]. These data suggest a protective effect of statins on renal function, though the value may be limited due to the fact that the patients in these studies had preexisting cardiac disease.

Effect of Statins on Renal Protection: Evidence from CKD Trials

The first meta-analysis of 13 controlled prospective studies demonstrated a lower, though small, rate of decline in eGFR with treatment compared with controls [81]. In a second meta-analysis of 27 studies comprising 39,704 participants, 21 studies included data for eGFR and 20 for proteinuria. Overall, the change in the weighted mean differences for eGFR and reduction in proteinuria were significant in statin recipients. Both analyses, together with small prospective controlled studies [82, 83], support emerging trial evidence that treatment with statins reduces proteinuria and possibly the rate of kidney function loss. However, recently the randomized, double-blind, controlled SHARP trial involving patients with advanced CKD demonstrate no benefit on renal protection [84]. The controversy may result from various complicated conditions in CKD patients, such as the stages of the disease or presence or absence of other disorders. The types or doses of statin may also affect the renal outcome.

The Pleiotropic Effects of Statins

In addition to lowering lipids, statins may provide renal protection via pleiotropic effects. Statins act by blocking 3-hydroxy-3-methylglutaryl coenzyme A reductase, thereby inhibiting synthesis of mevalonic acid, a precursor of many nonsteroidal isoprenoid compounds such as farnesyl pyrophosphate and geranylgeranyl-pyrophosphate involved in subcellular localization and intracellular trafficking of several membrane-bound proteins involved in oxidative stress injury (Rho, Ras, Rac, Rab, Ral, and Rap). An important source of ROS is NOX. Statins inhibit the activation of Rac1, which is involved in the activation of NOX by preventing the geranylgeranyl-dependent translocation of Rac1 from the cytosol to the cell membrane thereby reducing ROS generation [85, 86]. By blocking geranylgeranylation of Rho GTPase, statins also decrease the levels of the surface protein endothelin-1, a potent vasoconstrictor and mitogen, which might play a role in retarding

glomerulosclerosis [87]. Statins also prolong eNOS mRNA half-life and upregulate eNOS expression, reducing hypertension-induced glomerular injury by inhibiting the expression of Rho [88]. Statins also reduce LDL oxidation via the above mechanisms. Statins suppress receptor CD36 expression on monocytes, which may inhibit the uptake of Ox-LDL and their subsequent conversion to macrophage foam cells [89]. Furthermore, statins have been shown to reduce levels of MCP-1, TNF- α , TGF- β , IL-6, PDGF, and NF κ B [89–91], and reduce the proliferation of renal tubular epithelium by impairment of activator protein-1 (Ap-1) [92] as well as by preventing monocytes from maturing into macrophages, inducing apoptosis of these cells [93].

Statin Resistance Under Inflammatory Stress

Some recent experimental evidence showed that statins in therapeutic concentrations failed to prevent cholesterol synthesis in these cells under inflammatory stress, causing statin resistance [69]. The recent TNT study suggests a dose-related effect of atorvastatin on GFR, with 80 mg/day eliciting a greater beneficial effect than 10 mg/day [94]. This raises the possibility that a variable response to statins may be due to statin resistance in some patients, which higher statin doses and anti-inflammatory treatments might overcome. A further point requiring investigation is the presently unknown ability of statins to reduce apo B concentrations in many clinical trials of CKD patients. Peripheral statin resistance might partly explain why statins at ordinary doses did not reduce cardiovascular events or contributed to the residual risk in large randomized trials (4D and AURORA) in dialysis patients [95, 96].

How Long a Low LDL Cholesterol Status Should be Maintained?

It seems that duration for cholesterol lowering is a very important issue. Recently, it has been demonstrated that lifelong history of reduced LDL cholesterol in patients with PCSK9 mutation was associated with a 28 % reduction in mean LDL cholesterol and an 88 % reduction in the risk of CHD [97, 98], compared to only 40 % reduction normally observed in most of the clinical trials completed in 5 years. These data indicate that moderate lifelong reduction in the plasma level of LDL cholesterol is associated with a substantial reduction in the incidence of coronary events, even in populations with a high prevalence of non-lipid-related cardiovascular risk factors. It may imply that long-term use of lipid-lowering treatment may be important, especially for the patients with chronic inflammatory stress, such as CKD or dialysis.

Conclusion

Clinical and experimental evidence suggest that dyslipidemia promotes progression of CKD by activating inflammatory, oxidative, and ER stress. Inflammation also fundamentally modifies lipid homeostasis by diverting cholesterol from plasma to tissue compartments. Thus, the level of circulating cholesterol is not on its own a reliable predictor of cardiovascular and renal risks in patients with inflammatory stress. Therefore, we suggest that in kidney disease emphasis should be placed on the role of inflammatory cytokines on cholesterol redistribution together with plasma cholesterol levels or hypercholesterolemia. Increased understanding of the pathogenesis of lipid-mediated renal and vascular injury will encourage a search for reliable methods of risk assessment in at-risk patients in whom higher doses of statins for longer periods, carefully monitored for side effects on liver, muscle, and myocardium, may be required to prevent lipid-mediated renal and vascular injury.

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