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NEPHROLOGY - REVIEW

The impact of dyslipidemia and oxidative stress on vasoactive mediators in patients with renal dysfunction

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Abstract
Hyperlipidemia and oxidative stress are indispensable features of chronic kidney disease (CKD) that favor the development of atherogenic plaques and cardiovascular disease (CVD). A number of vasoactive mediators including proprotein convertase subtilisin–kexin type 9 (PCSK9), endothelin-1, nitric oxide, and angiotensin II have fundamental roles in the pathophysiology of atherosclerotic events; moreover, their levels are affected by dyslipidemia and oxidative stress due to renal dysfunction. Therefore, therapeutic measures aimed at correcting dyslipidemia and alleviating oxidative stress could potentially protect against CVD in CKD patients. In this review, we discuss the relation between dyslipidemia, oxidative stress, and vasoactive mediators as well as the available treatment options against these disturbances in CKD patients.

Keywords Hyperlipidemia · Oxidative stress · Atherosclerosis · Vasoconstrictors · Chronic kidney disease

Introduction

Hyperlipidemia and dyslipidemia are important risk factors for the development and progression of atherosclerosis [1] and hyperlipidemia could result in renal dysfunction and chronic kidney disease (CKD) in long term [2]. Moreover, lipid metabolism is often disturbed in CKD patients [2]. Increased incidence of cardiovascular events in CKD patients could be attributed to elevated production of reactive oxygen species (ROS), electrolyte imbalances, proteinuria, and inflammation [3].

It is now known that hypercholesterolemia induces oxidative stress in the endothelial cells [4], initiating the peroxidation of cell membranes and unsaturated free fatty acids [5]. Furthermore, free radicals alter the composition of lipoproteins, producing oxidized low-density lipoproteins (Ox-LDL) inside the blood vessels. Ox-LDL has multiple biological functions and favors increased expression of pro-inflammatory cytokines, adhesive molecules, and growth factors. Foam cell are formed by the accumulation of cholesterol inside the macrophages, favoring the development of atheromatous plaques which leads to glomerulosclerosis [5]. Atherogenic Ox-LDLs disturb the function of various vasoactive molecules such as nitric oxide (NO), endothelin 1 (ET1), angiotensin II, transforming growth factor beta (TGF-β), causing pathologic changes in the kidneys [6]. The impact of lipid accumulation in the kidneys could be observed both in glomeruli and in tubules, resulting in the development of glomerulosclerosis, fibrosis, tubular atrophy, and mesangial expansion [7].

Lipid abnormality in CKD

Dyslipidemia is generally observed in CKD patients. The pattern of abnormal lipid profile is different between various degrees and groups of CKD patients, depending on the renal function, underlying disease, and the severity of the proteinuria [8]. Elevations in apoprotein B (apoB), apoCIII, and apoE-containing lipoproteins, together with decreased levels of lipoproteins that contain apoAI, and

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apoAII like HDL-C are the most salient abnormalities in CKD patients [9]. HDL-C has anti-inflammatory and anti-oxidant properties, preventing the conversion of macrophages to foam cells by reverse transport of cholesterol to the liver [10]. Anti-oxidant actions of HDL-C are effected by the activity of paraoxonase 1 (PON1) and glutathione peroxidase (GPx); and both enzymes are reduced in CKD patients, leading to relentless oxidative changes in the proteins and lipids and formation of Ox-LDL [11]. In addition to the prevention of atherosclerosis, HDL-C is able to decrease the expression of anti-inflammatory molecules, including monocyte chemoattractant protein 1 (MCP1), E-selectin, and NF-kB expression, and thereby, reduces the infiltration of monocytes into the vessel walls [10]. Consequently, reduced levels of HDL-C contribute to the progression of atherosclerotic plaques in the subjects with renal disease. Albumin-associated transportation of free cholesterol is decreased due to hypoalbuminemia in patients with nephrotic syndrome or CKD. Urinary loss of LCAT impedes the conversion of HDL3 into HDL2 and the levels of apoA1 are reduced [12]. Engagement of HDL-C to the ATP-binding cassette transporter A-1 (ABCA1) is facilitated by apoA1; therefore, apoA1 deficiency favors the formation of foam cells and atherosclerotic plaques [13].

Total cholesterol levels might be higher than normal in CKD patients and its levels have inverse relation with mortality due to cardiovascular complications [10]. Highly atherogenic, small and dense LDL-C particles (sdLDL) are also formed in these patients [14]. By contrast, in ESRD patients undergoing dialysis hyperlipidemia is associated with improved survival that is termed "reverse epidemiology" or "risk factor paradox". Short-term risk factors including malnutrition and inflammation are found to relate more to the poor outcomes in dialysis patients than conventional risk factors including obesity, hyperlipidemia, and hypertension [15].

CKD patients have higher levels of glycerolipids, free fatty acids, and glycerophospholipids, and as GFR decreases, the levels of saturated fatty acids are increased in these individuals [16]. Moreover, the levels of sulfatide, plasmenyl ethanol amine, ceramide and phosphatidyl choline are decreased in the LDL-C particles; alterations that increases the risk of CVD in CKD patients [17].

Lipoprotein lipase (LPL) has a unique role in transforming IDL-C to the LDL-C. In proteinuric patients, the enzymatic function of LPL is decreased due to increased ratio of apoCIII (LPL deactivator) to apoCII (LPL activator) [2]. Defects in LPL and hepatic lipase disrupt the clearance of IDL-C, VLDL-C, and chylomicrons, leading to the elevation of atherogenic IDL-C levels in serum [18]. Therefore, accurately evaluating lipid profile and fatty acids levels are important for determining the risk of atherosclerosis in CKD patients.

Oxidative stress in CKD

Hyperlipidemia-associated oxidative stress changes the proteins in the vascular walls, contributing to the development of atherosclerosis in CKD patients [19]. When encountered with ROS, the LDL-C particle turns into oxidized low-density lipoprotein (Ox-LDL) that itself favors the generation of ROS, intensifying oxidative stress [20]. Apart from promoting the motility and chemotactic activity of macrophages, Ox-LDL induces cholesterol accumulation inside macrophages, giving rise to the formation of foam cells and atherosclerotic plaques [21]. Additionally, Ox-LDL induces apoptosis in various cells including renal glomerular and tubular cells through increasing the expression of CHOP and the activity of C-Jun kinase-1 signaling pathway [22]. Moreover, Ox-LDL-induced inflammation in the kidneys causes glomerular sclerosis and renal fibrosis [23].

Nitric oxide

Nitric oxide (NO) is a vasodilator, generated from L-arginine by NO synthase (eNOS), and is secreted from renal macula densa and vascular cells. It modulates the function of glomerular and tubular function [24]. It seems that nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and xanthine oxidase are the main sources of ROS generation in hypercholesterolemia and promote the formation of peroxynitrite [19, 25], that reduces the bioavailability of NO, a protective agent against endothelial atherosclerotic lesions [26]. This is a fundamental process that aids to the progression of endothelial dysfunction, increasing the risk of CVD in CKD patients [26]. Moreover, production of NO reduces in CKD patients [27] and these reductions in NO contribute to the pathologic changes in the kidneys including mesangial expansion, glomerulosclerosis, and renal fibrosis [28]. ADMA is an important biomarker for atherosclerosis that possibly favors endothelial dysfunction [26].

ADMA is a competitive inhibitor of eNOS and, therefore, reduces NO production [29]. Under pathologic states like dyslipidemia, and CKD, increased levels of ADMA lead to endothelial dysfunction [30]. ADMA levels might be increased due to reductions in the function of dimethyl arginine aminohydrolase (DDAH) which metabolizes ADMA [31]. Moreover, its levels might be elevated because of the increases in the function of protein-arginine methyl

transferase (PRMT) that augments methylation of arginine residues and increases the production of ADMA [30].

While ADMA levels are increased in CKD patients, it has no correlation with eGFR and Cr and only serves as the predictor of CVD [32, 33]. Zoccali et al. stated ADMA as a potent predictor factor for heart attack and death in CKD patients [34]. As a result, ADMA could be implemented as a novel biomarker in detection of CKD (Fig. 1).

Angiotensin II

Angiotensin II (Ang II) has two receptors: Ang II receptor type 1 (AT_1) and Ang II receptor type 2 (AT_2). Many physiologic and pathophysiologic functions of Ang II are mediated via AT_1 and the expression of AT_1 is induced by hypercholesterolemia [35].

LDL-C and Ox-LDL increase Ang II levels and facilitate the progression of atherosclerosis [36]. Ang II induces the formation of superoxide anions by activating NADPH oxidase in the vascular smooth muscle cells (VSMC) and mesangial cells; as a result, the production of pro-fibrotic mediator TGF-β is increased, activating the intracellular Smad via ERK [37]. In addition to increasing the expression of plasminogen activator inhibitor-1 (PAI-1), platelet-derived growth factor (PDGF), vascular cell adhesion molecule 1 (VCAM-1), and intercellular adhesion molecule 1(ICAM-1) in the vascular walls, Ang II induces the expression of extracellular matrix proteins including fibronectin and type IV collagen, facilitating glomerular fibrosis in the kidneys [37].

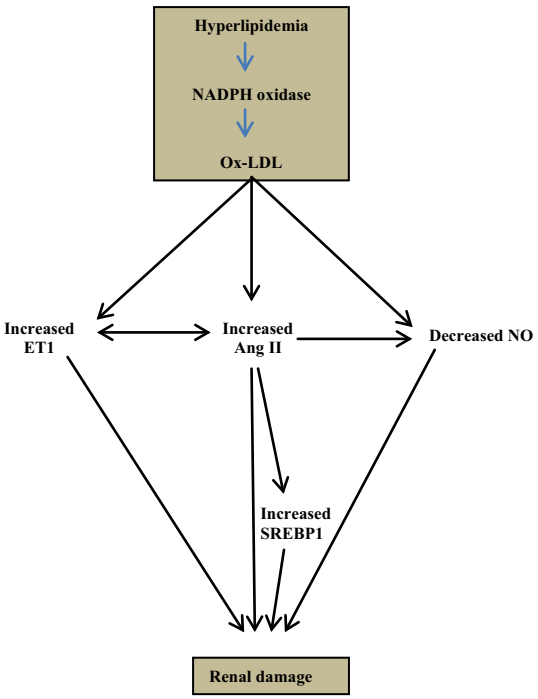

Fig. 1 Hyperlipidemia and Ox-LDL increase the production of vasoactive factors that induce renal injury by endothelial dysfunction

Bianche et al. showed that the inhibition of Ang II could lower the progression of CKD and mitigate hypercholesterolemia and proteinuria [38].

Angiotensin-converting enzyme (ACE) inhibitors not only decelerate the progression of CKD but also alleviate hypercholesterolemia. Furthermore, these agents are effective therapeutic measures in reducing the risk of CVD [39].

Endothelin 1

Endothelin 1 is a vasoconstrictor synthesized in the glomerular and tubular cells [40]. In the kidneys, ET1 regulates local blood flow, podocyte function, and mesangial constriction [41]. Under hypercholesterolemic states, when the levels of LDL-C are increased and the levels of HDL-C are reduced, ET1 levels have demonstrated to be elevated which participate in the development of atherosclerosis [42]. Ox-LDL is also able to increase the production of ET1 [43]. ET1 acts as a chemoattractant molecule for macrophages and monocytes; it, moreover, functions as a mitogenic factor for the smooth muscle cells [41, 42]. In CKD patients with hypercholesterolemia, circulating levels of ET1 are increased [44]. ET1 has a major role in the development of proteinuria and renal fibrosis in CKD patients by disturbing the integrity of podocytes [45]. Furthermore, ET1 increases the production of other vasoconstrictors and growth factors such as angiotensin II [46]. Hence, ET1 blocked improves vascular endothelial and renal function in CKD patients [47].

Sterol regulatory element-binding proteins

Sterol regulatory element-binding proteins (SREBPs) are transcription factors that belong to the basic helix–loop–helix–leucine zipper family, with crucial roles in lipid homeostasis, acting as the main regulators of cholesterol and fatty acid synthesis in the liver [48]. SREBP-1a and -1c activate the genes involved in the synthesis of fatty acids including acetyl-CoA carboxylase and fatty acid synthase; by contrast, SREBPs-2 is involved in the induction of the expression of the genes that participate in cholesterol synthesis including HMG-CoA reductase, dihydroxymethyl glutaryl-CoA reductase, farnesyl diphosphate synthase, and squalene synthase [49]. Under high glucose levels of glucose in streptozotocin-induced diabetic mice, the expression of SREBPs-1a and -1c are increased in the renal cortex, elevating the expression of fatty acid synthase and acetyl-CoA carboxylase which culminated in the accumulation of triglycerides in the renal cells [50]. Ang II is also able to

activate SREBP-1, augmenting extracellular matrix synthesis through upregulating TGF-β [51]. Elevations in the SREBP-1 and triglyceride content of the kidneys increase the expression of fibrotic factors like TGF-β and vascular endothelial growth factor (VEGF) [51]. TGF-β increases the production of extracellular matrix through activating ERK and Smad in the mesangial cells, aggravating renal fibrosis [52].

Proprotein convertase subtilisin–kexin type 9

Proprotein convertase subtilisin-kexin type 9 (PCSK9) is a serine protease produced in the kidneys [53]. PCSK9 binds to low-density lipoprotein receptor (LDL-R, aiding to the destruction of LDL-R inside lysosomes; and therefore, by reducing LDL-C catabolism elevates LDL-C levels [53]. PCSK9, moreover, increases the expression of oxidized low-density lipoprotein receptor-1 (LOX-1) in VSMCs [53]. PCSK9-associated reductions in low-density lipoprotein receptor-related protein 1(LRP-1) interferes with LPa catabolism, elevating its serum levels and the risk of atherosclerosis [54]. PCSK9 levels are increased in CKD patients that contribute to the development of dyslipidemia [55]. Moreover, PCSK9 serum levels are elevated in patients with hypercholesterolemic nephrotic syndrome [56]. No relation, however, has been observed between eGFR and PCSK9 levels in CKD patients [57]. Treatment with statins in CKD patients activates SREBP-2 that in addition to increasing the expression of PCSK9, elevates the expression of LDL-R, improving the clearance of LDL-C from serum [58]. Monoclonal antibodies targeted against PCSK9 have been found to be effective in reducing LDL-C levels in patients with hypercholesterolemia [59]. The outcome of ODYSSE1/COMBO clinical trial denoted that alirocumab significantly decreased LDL-C levels in serum compared with placebo, as well as ezetimibe plus statin. However, its efficacy in reducing serum triglyceride levels was controversial and further studies need to be conducted to assess its efficacy and safety in CKD patients [60]. Thereby, PCSK9 can use as a new biomarker for lipid metabolism and is a new medicine target for hypercholesterolemia. Inhibition of PCSK9 not only decreases LDL-C levels but also reduces the risk of cardiovascular diseases [59].

Treatment of dyslipidemia in CKD

Currently, statins are the most common agents used in the treatment of hyperlipidemia in patients with CKD. Statins inhibit HMG-CoA reductase and decrease hepatic production of cholesterol, reducing cholesterol levels by 20–50% [61]. Moreover, these agents possess anti-inflammatory properties and decrease the expression of TNF-α, IL-6, TGF-β, VCAM, and fibronectin in the renal mesangial cells. Apart from increasing NO synthesis, statins prevent LDL-C oxidation by alleviating oxidative stress. This antioxidant property of statins improves endothelial function [62]. Statins can ameliorate the outcomes of the CAD and CKD patients and reduce the rate of cardiovascular disease mortality [63]. The findings regarding statin effects on renal function are disparate. Some studies have shown that statin therapy can be effective in improving renal function and increasing eGFR in patients [64, 65]; however, another study has demonstrated that statin therapy has no beneficial effect on renal function [66]. Accordingly, more in-depth studies are required to clarify the exact benefit of statins in CKD patients (Table 1).

Most statins are mainly metabolized in the liver; therefore, dose adjustment in early CKD is typically not needed when eGFR is more than 30 ml/min. However, the maximum dose of these agents need to be restricted in more advanced CKD with eGFR less than 30 ml/min. Atorvastatin, fluvastatin, lovastatin, and simvastatin are metabolized almost exclusively by the hepatic routes; consequently, minimal dose restrictions would suffice in CKD patients. By contrast, pitavastatin, pravastatin, and rosuvastatin are metabolized both in the liver and in the kidney, making dose restrictions imperative in CKD patients [67].

Nicotinic acid derivatives including niacin reduced triglyceride synthesis by inhibiting diacylglycerol transferase and hormone-sensitive lipase. They, moreover, inhibit VLDL-C secretion and thus, reduce LDL-C production. Additionally, nicotinic acid is able to decrease Apo A1 clearance and increase HDL-C synthesis; overall, these agents reduce cardiovascular events [68].

Fibric acid derivatives such as fenofibrate and gemfibrozil are agonists of transcription factor peroxisome proliferator-activated receptor alpha (PPAR-alpha). Despite beneficial effects of fibrates and niacin in treating hyperlipidemia, their adverse effects in patients with renal dysfunction could be unfavorable [68]. Therefore, further studies are needed for their effects in patients with CKD and their side effects.

Literature is scant regarding the use of non-statin lipid-lowering agents in CKD patients. Niacin has equivalent lipid-lowering effect in CKD patients as compared to non-CKD individuals; moreover, its use has gained interest in CKD patients for its phosphorus-lowering properties [69]. By contrast, fibrates are metabolized in the kidneys and thus generally contraindicated in patients with CKD [67].

Bile acids including colesevelam, colestipol, cholestyramine and colestimide are involved in the cholesterol catabolism and have as important role in the absorption of the fats [61]. The adverse effects of these drugs in the gastrointestinal tract, however, limit their clinical utility [70].

Table 1 Summary of the factors that affect renal function in CKD

Factor	Experimental model	Study duration	Main findings	References
1-SREBP inhibition	Unilateral ureteral obstruction (UUO) mice	21 days	Fatostatin inhibitsactivation of SREBP Upregulation of collagen types I and III are inhibit by Fatostatin Activation of smad3 is attenuated TGF-β signalling and fibrosis are inhibited	Mustafa et al. [52]
2-Angiotensin II	Nephrectomyfollowed by AngII infusion mice	8 weeks	Ang II activates SREBP1 and increases ER stress SREBP1 upregulates TGFB1 and fibronectin synthesis	Wang et al. [51]
3-Renin –angiotensin inhibitors	Nephrotoxic nephritis(NTN) mice	11 weeks	Albuminuria is reduced.Renal accumulation of collagen III is reduced Infiltrations of leukocytes are decreased	Ougaard et al. [39]
4-Nitric oxide	Patients with various stages of CKD		Patients in all stages of CKD have lower plasma NO levels ADMA levels are increased in all stages of CKD L-arginine/citrullin ratio is higher in patients with stage 3, 4, and 5 of CKD	Reddy et al [27]
5-ET-1	Obese rats induced by high fat-diet	8, 12 weeks	Endothelin decreased in groups treated with silver nanoparticles and rosuvastatin in compared with atherogenic group Positive correlation between Endothelin and TC, TG, LDL and VLDL and negative correlation with HDL	Al-Dujaili et al. [42]
6-Monoclonal antibody against PCSK9	Randomized controlled ODYSSEY trial	24–104 weeks	Alirocumab reduces LDL-C as compared to placebo or ezetimibe Alirocumab decreases apoB, non-HDL-C lipoproteins, triglycerides, and Lp(a); and increases HDL-C Alirocumab does not affect eGFR levels, renal function, and hsCRP	Toth et al. [59]
7-Statins	CKD patients with CVD	4 years	Statin therapy is much more effective in CKD patients with CVD than CKD only patients	Shen et al. [63]
8-Rusavastatin and atorvastatin effects on renal function	Meta-analysis		Rusavastatin and atorvastatin improve eGFR Atorvastatin is better than rusavastatin at reducing proteinuria	Wu et al. [65]

Ezetimibe is the first member of the cholesterol absorption inhibitors that selectively prevent intestinal absorption of cholesterol and phytoesterols; therefore, reduce LDL-C levels without affecting lipid-soluble vitamins. Ezetimibe is used for the treatment of hyperlipidemia in patients who do not tolerate statin therapy [71].

Since oxidative stress has a substantial role in the progression of CKD, anti-oxidants could be regarded as novel therapeutic agents in these group of patients. Several lines of evidence have shown that anti-oxidants and vitamin E improve lipid profile in patients undergoing hemodialysis and have protective effects on cardiovascular complications

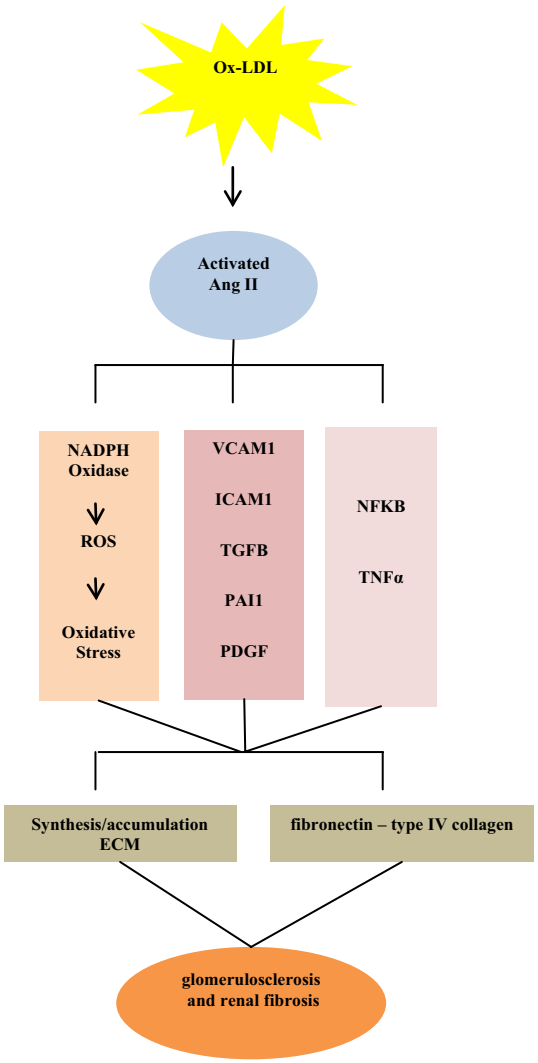

Fig. 2 Renal injury and fibrosis. Under hyperlipidemic states, the production of Ang II is increased with the formation of Ox-LDL particles, activating the inflammatory factors such as tumor necrosis factor-alpha and NF-kB. Moreover, the production of fibrotic factors such as VCAM, ICAM, PDGF, and TGF-B are increased that culminate in the accumulation of type IV collagen and fibronectin in the extracellular spaces and renal fibrosis

[72, 73]; however, their effects in long term should be well investigated. CKD patients have high risks of developing cardiovascular events even in the early stages [74]. Therefore, identification and treatment of dyslipidemia prior to the development of ESRD is inevitable (Fig. 2).

Conclusion

Cardiovascular complications are common causes of mortality in CKD patients. Decreased HDL-C levels in patients with CKD are an important contributing factor for the development of atherosclerosis. Moreover, hyperlipidemia-associated oxidative stress and inflammation have detrimental effects in various organs including the kidneys. Ox-LDL disturbs endothelial function and increases the risk of atherosclerosis. In addition, oxidative stress reduces NO synthesis and simultaneously promotes Ang II production. Under hyperlipidemic states, increased production of Ang II might aggravate renal injury. ET-1 levels are elevated due to hyperlipidemia in CKD patients, accelerating the progression of proteinuria and renal dysfunction. Evidences still denote that CVD is the main cause of mortality in CKD patients and collectively identification and management of lipid abnormalities in CKD patients is of vital value.

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Compliance with ethical standards

Conflict of interest All the authors declare no conflict of interest.

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