Abstract

Dyslipidemia is implicated as a risk factor for the development of atherosclerosis. Specifically triglyceride-rich lipoproteins and their lipolysis products are shown to be proinflammatory and proapoptosis in both in vivo and in vitro studies with endothelium. However, the role of triglyceride-rich lipoproteins in the progression of kidney diseases is not clear. Epidemiology studies demonstrated a correlation between renal disease and blood lipids. Recent evidence suggests that the mechanism may involve cellular uptake of lipid and de novo lipogenesis. Further studies are needed to establish the relevance of these mechanistic studies in human pathophysiology.

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Clinical and experimental studies have suggested that lipids and/or lipoproteins promote glomerular and tubulointerstitial injury through mediators such as reactive oxygen species, chemokines, cytokines, increased renal transforming growth factor-β1 (TGF-β1) gene expression, and macrophage extravasations into the glomeruli and tubules. In this review, we will examine the pathogenic mechanisms for lipid and lipoprotein-induced renal injury.

Epidemiology Linking Renal Disease with Elevated Blood Triglycerides

Several epidemiology studies have suggested a positive correlation between serum cholesterol, triglyceride (TG) levels and chronic kidney disease (CKD) [1, 2]. Dyslipidemia is commonly found among diabetic patients suffering from CKD, which includes elevated levels of TGs, atherogenic TG-rich apolipoprotein (apo) B-containing very-low-density lipoprotein cholesterol, low-density
lipoprotein cholesterol, and intermediate-density lipoprotein cholesterol, but lower levels of high-density lipoprotein (HDL-C). The contribution of these TG-rich lipoproteins towards diabetic nephropathy (DN) has recently been reviewed [3]. Dyslipidemia has been suggested as a risk factor for the progression of renal insufficiency through development of glomerulosclerosis and tubulointerstitial lesions with concomitant accelerated atherosclerosis [4, 5], and is often found in patients with microalbuminuria and overt proteinuria. These patients also are noted for their elevated plasma level of circulating apoB [6], apoC-III, and apoA [7]. Cardiovascular risk factors such as elevated levels of circulating cell-adhesion molecules and systemic inflammatory markers can be found in the early stages of diabetic and nondiabetic CKD. Reduction in HDL-C level is also associated with an increased risk of DN as lower levels of HDL-C have been shown to predispose type 1 diabetics to suffer from renal injury more than those with higher levels of HDL-C [8]. This evidence suggests a parallel between the pattern of cardiovascular disease and renal diseases. However, the apoA5 –1131T→C polymorphism that affects TG levels has not been correlated with DN [9], although this may be the result of the differences between measurements of fasting and postprandial TG levels.

Clinical studies have also demonstrated lipid-lowering treatment can affect progression of renal diseases. Studies examining the effects of lipid-lowering drugs on diabetic kidney disease have recently been reviewed [3]. Of particular interest is the association between low estimated glomerular filtration rate (eGFR) and dyslipidemia in patients with CKD and cardiovascular disease. Among patients undergoing exercise therapy, improvements in eGFR are positively correlated with HDL-C level, and negatively correlated with TG level [10].

Most literature has suggested that the elevation of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity and severity of albuminuria are markers of DN [11]. Large post-hoc data analyses show that HMG-CoA reductase inhibitors (statins) improved both lipid profile and renal function in patients with CKD [12, 13]. A meta-analysis study also showed that lipid and lipoprotein reduction decreases proteinuria in patients with CKD by preserving GFR [14]. However, the mechanism is still unknown, and it is possible that the renal protection conferred by statins is lipid independent. Fenofibrate, a TG-lowering drug that is also a peroxisome proliferator-activated receptor-α (PPAR-α) agonist, has been shown in the FIELD Helsinki substudy to decrease eGFR with a concomitant increase in plasma creatinine, complicating the analysis. Therefore, the benefit of this TG-lowering drug in improving renal function is still unclear [15]. Further studies will be needed to separate out the effect of lowering TGs and activating PPAR-α. Although the mechanism of lipid-induced renal injury remains to be determined in these human studies, they nonetheless showed benefit from lipid lowering and improvement in the prognosis of renal diseases.
Experimental Models of Renal Disease and Hypertriglyceridemia

Animal studies have corroborated the evidence from human studies and demonstrated benefit of lipid lowering therapy in experimental renal and metabolic diseases. For example, diabetic rats treated with a lipid-lowering statin drug, lovastatin, for 8 weeks showed significantly preserved GFR compared to untreated diabetic rats [16]. In addition, 12 months of lovastatin treatment suppressed glomerular TGF-β1 gene expression, albuminuria, and preserved renal mass and glomerular volume in diabetic rats [17]. Similar observations were made in statin-treated nondiabetic rats with kidney disease with the additional benefits of decreased glomerular and tubulointerstitial macrophage accumulation and reduced renal injury [18]. Zucker fatty rats treated with pioglitazone, an insulin sensitizer, have reduced serum TG levels and basement membrane thickening [19]. These studies suggest that the lipid profile improvement correlates with attenuation of classical renal disease symptoms.

The question remains, however, whether dyslipidemia is a cause or metabolic sequelae of renal diseases and the mechanism remains unclear. Cell culture studies have shown that plasma lipids are injurious to many renal cell types, leading to inflammation, cytokine production, increased lipid accumulation, and in some cases foam cell formation. The toxic effects of lipid accumulation are thought to be mediated through the increase in free fatty acid metabolites [see 35]. Very-low-density lipoprotein has been shown to stimulate cytokine production such as monocyte chemotactic protein-1 in human mesangial cell culture, resulting in increased monocyte adhesion [20]. Oxidized LDL also increases lectin-like oxidized low-density lipoprotein receptor 1 activity and inflammatory marker inter-cellular adhesion molecule 1 expression in the rat renal epithelial cell line NRK52E [21]. There is also evidence that saturated free fatty acids, a major class of lipolysis products, induce apoptosis in mesangial cells and podocytes [22, 23]. Low-density lipoprotein and scavenger receptors are also found on mesangial cells that can preferentially bind to atherogenic oxidized LDL and lead to cellular lipid accumulation. Recently, Berfield et al. [24] has demonstrated that insulin growth factor-1, a cytokine that is upregulated in DN, induces foam cell formation in mesangial cells by increasing caveola-mediated endocytosis with no effect on LDL and scavenger receptors. Mesangial cells are also shown to preferentially accumulate TG and downregulate PPAR-δ which decrease fatty acid oxidation [25]. These observations confirm in vivo observations of lipid accumulation in renal injuries.

However, it is also increasingly clear that increased lipid uptake is not solely responsible for lipid accumulation in mesangial cells. Studies have also pointed out increased cellular lipid content can be due to de novo lipogenesis. A series of experiments done by the Levi group have demonstrated the importance of sterol regulatory element-binding protein 1 (SREBP-1) in renal lipid accumulation. Using streptozotocin-treated rat as a type 1 diabetes model [26], FVB db/db mice
as type 2 diabetes model [27], and diet-induced obese C57BL/6J mice as a metabolic syndrome model [28], they have demonstrated that increased renal expression of SREBP-1 leads to increased lipid accumulation. SREBP-1 expression increases fatty acid and TG synthesis through upregulating expression of enzymes such as fatty acid synthase and acetyl-CoA carboxylase. These animal models developed classical manifestations of DN such as lipid droplet formation in the mesangium and tubules, increased TGF-β synthesis, and mesangium expansion, further demonstrating the correlation between glomerulus foam cell formation and early signs of renal failure. Of particular interest is that these changes might not associate with changes in serum TG, except in the case of the type 2 diabetes FVB \( db/db \) mice model [29].

Dietary lipid studies have also demonstrated the link between renal SREBP-1 expression and high fat diet. In streptozotocin-treated rats, a diet high in saturated fatty acid induced SREBP-1 expression in the kidney with lipid accumulation in the glomerulus and tubular cells. These rats also had increased plasma TGs, albuminuria, and renal TG content [30]. In the same study, a polyunsaturated fatty acid (PUFA) diet seemed to normalize this SREBP-1 expression. The same SREBP-1 normalization can be seen in \( db/db \) mice fed with PUFA, resulting in reduced renal TG content and expansion of mesangial matrix [31]. These studies suggest that SREBP-1 expression and its impact on lipid accumulation in the kidney may be diet induced. Interestingly, SREBP-1 expression might also be related to age, as aging C57BL/6 mice have increased renal SREBP-1 expression that can be reversed by caloric restriction [28]. Modulating SREBP-1 expression using a farnesoid X receptor-activating ligand reverses deleterious effects in the kidney of Western diet-fed mice, including proteinuria, podocyte loss, mesangial expansion, and renal lipid accumulation [29]. In another study, feeding homozygous LDL receptor mice a Western diet with an apoA-1 mimetic peptide reduced renal SREBP-1c mRNA levels and TG levels, without changes in the serum level of lipids and lipoproteins levels [32]. Thus, targeting SREBP-1 may prove to be an effective treatment to lipid-induced renal injuries and warrants further clinical studies.

Another signaling pathway that plays an important role in lipid-induced renal disease is the peroxisome proliferator-activated receptor pathway. Clinical studies using fenofibrate, which is a PPAR-α agonist, have demonstrated some success in attenuating the progression of renal failure. A study comparing wild-type and heterozygous PPAR-γ mice, both fed a high-fat diet, has demonstrated that PPAR-γ insufficiency attenuates renal injury, lipid accumulation, and abnormal lipid metabolism [33]. On the other hand, in another study using Zucker fatty rats, treatment with a novel PPAR-γ ligand not only reduced serum TG concentration, but also reduced renal injuries such as glomerular expansion and proximal tubular damage as measured by urine N-acetyl-β-D-glucosaminidase [34]. Thus far, the results have been inconclusive about the PPAR-γ pathway, and further studies are needed to clarify its role.
Finally, lipids could damage the proximal tubules by codelivery with filtered albumin as described in the ‘Trojan horse’ hypothesis [35]. It is well known that albumin is capable of absorbing blood substances such as toxins and particularly free fatty acid. Elevated filtration of serum albumin is common in patients with renal diseases and can therefore increase exposure of albumin-bound free fatty acid to the proximal tubules which causes inflammation and injuries [36]. Oxidizable lipoproteins are also found in the urine of proteinuric subjects, and therefore it is possible for atherogenic lipid to injure proximal tubules in this way as well.

Conclusion

These epidemiological and animal studies suggest an association between concentration of plasma lipoproteins and lipids and development and progression of CKD. However, the renal injury could also involve de novo lipogenesis. Lipid control appears to be important in prevention and treatment of CKD, but further large-scale, prospective, randomized and controlled studies are still needed to confirm the benefits of lipid-lowering treatment in human as well as to clarify the mechanisms involved.

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References


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