Published in final edited form as:

Contrib Nephrol. 2011 ; 170: 165–171. doi:10.1159/000325654.

Role of Triglyceride-rich Lipoproteins in Renal Injury

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Abstract

Dyslipidemia is implicated as a risk factor for the development of atherosclerosis. Specifically triglyceride-rich lipoproteins (TGRL) and their lipolysis products are shown to be pro-inflammatory and pro-apoptosis in both *in vivo* and *in vitro* studies with endothelium. However the role of TGRL 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.

Introduction

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- β 1 (TGF- β 1) 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 levels and chronic kidney disease (CKD) [1,2]. Dyslipidemia is commonly found among diabetic patients suffering from CKD, which includes elevated levels of triglycerides (TG), atherogenic TG-rich ApoB-containing including very low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), and intermediate-density lipoprotein cholesterol (IDL-C), but lower levels of high-density

lipoprotein (HDL-C). The contribution of these triglyceride-rich lipoproteins (TGRL) 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 apolipoprotein (apo) B [6], apo C-III, and apo (a) [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 non-diabetic CKD. Reduction of HDL-C level also is 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]. These evidences suggest a parallel between the pattern of cardiovascular disease (CVD) and renal diseases. However, the apolipoprotein A5 (apoA5) -1131T-->C polymorphism that affects TG levels has not been correlated with diabetic nephropathy [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 are recently reviewed [3]. Of particular interest is the association between low estimated glomerular filtration rate (eGFR) and dyslipidemia in patients with CKD and CVD. Among patients undergoing exercise therapy, improvements in eGFR are positively correlated with HDL-C level, and negatively correlated with triglyceride level [10].

Most literature has suggested that the elevation of 3-hydroxy-3methylglutaryl 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 glomerular filtration rate [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-alpha (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 TG 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- β 1 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 triglyceride 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, cytokines 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 of free fatty acid metabolites [35]. Very low density lipoprotein (VLDL) has been shown to stimulate cytokine production such as monocyte chemotactic protein-1 (MCP-1) in human mesangial cell culture, resulting in increased monocytes adhesion [20]. Oxidized LDL also increases Lectin-like Oxidized Low-density Lipoprotein Receptor 1 (LOX-1) activity and inflammatory marker Inter-Cellular Adhesion Molecule 1 (ICAM-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, induces 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 (IGF-1), a cytokine that is upregulated in DN, induces foam cell formation in mesangial cells by increasing caveolae-mediated endocytosis with no effect on LDL and scavenger receptors. Mesangial cells are also shown to preferentially accumulate triglyceride and down-regulate 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 (STZ)-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. Sterol Regulatory Element-binding Protein 1 expression increases fatty acid and triglyceride synthesis through up-regulating expression of enzymes such as fatty acid synthase (FAS) 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 triglyceride, 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 STZ-treated rats, a diet high in saturated fatty acid induced SREBP-1 expression in kidney with lipid accumulation in the glomerulus and tubular cells. These rats also had increased plasma TG, 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 triglycerides content and expansion of mesangial matrix [31]. These studies suggest that SREBP-1 expression and its impact on lipid accumulation in 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 (FXR) 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 triglyceride 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 proliferators-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 wildtype 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, another study using Zucker-fatty rats treated with a novel PPAR- γ ligand not only reduces serum triglyceride concentration, but also reduces renal injuries such as glomerular expansion and proximal tubular damage as measured by urine N-acetyl-beta-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 co-delivery 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.

Acknowledgments

This work was supported by Nora Eccles Treadwell Foundation and NIH-HL55667.

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