Dyslipoproteinemia and Impairment of Renal Function in Diabetic Kidney Disease: An Analysis of Animal Studies, Observational Studies, and Clinical Trials

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1. Introduction

Dyslipoproteinemia is highly prevalent in diabetes, chronic kidney disease, and diabetic kidney disease (DKD). Both diabetes and chronic kidney disease (CKD) are associated with hypertriglyceridemia, lower high-density lipoprotein, and higher small, dense low-density lipoprotein. A number of observational studies have reported that dyslipidemia may be associated with albuminuria, renal function impairment, and end-stage renal disease (ESRD) in the general population, and especially in CKD and DKD patients. Diabetic glomerulopathy and the related albuminuria are the main manifestations of DKD. Numerous animal studies support the finding that glomerular atherosclerosis is the main mechanism of glomerulosclerosis in CKD and DKD. Some randomized, controlled trials suggest the use of statins for the prevention of albuminuria and renal function impairment in CKD and DKD patients. However, a large clinical study, the Study of Heart and Renal Protection (SHARP), does not support that statins could reduce ESRD in CKD. In this article, we analyze the complex association of dyslipoproteinemia with DKD and deduce its relevance from animal studies, observational studies, and clinical trials. We show that special subgroups could benefit from the statin treatment.

Keywords: albuminuria · diabetic kidney disease · dyslipoproteinemia · lipoprotein · lipid · renal disease · type 2 diabetes · triglyceride

2. Diabetic kidney disease versus diabetic nephropathy

Type 2 diabetes is the leading cause of CKD and ESRD in most countries as a consequence of
the global increase in type 2 diabetes and obesity [11]. Our discussion in this article is on type 2 diabetes only. Diabetic nephropathy has been categorized based on the values of urinary albumin excretion as microalbuminuria and macroalbuminuria [12]. However, many data do not support the view that albuminuria and renal function impairment are closely linked in the progression of diabetic kidney disease [13]. Albuminuria can be detected shortly after the diagnosis of diabetes and the prevalence of macroalbuminuria is highly variable, ranging from 5% to 20% in patients with type 2 diabetes [14, 15]. Moreover, in patients with type 2 diabetes in NHANES III (Third National Health and Nutrition Examination Survey), low GFR (<60 ml/min/1.73m²) was present in 30% of patients without albuminuria and retinopathy [16, 17]. Thus, albuminuria and diabetic nephropathy, which is defined by albuminuria, are not consistently correlated with renal function impairment.

Patients with type 2 diabetic nephropathy have more structural heterogeneity than patients with type 1 diabetic nephropathy [18-20]. Type 1 diabetic nephropathy is characterised by glomerular hypertrophy, increased glomerular basement membrane width, diffuse mesangial sclerosis, hyalinosis, microaneurysm, podocyte damage and hyaline arteriosclerosis [20, 21]. Tubulointerstitial fibrosis and tubular atrophy and dedifferentiation are also observed [20]. In diabetic nephropathy, tubulointerstitial fibrosis and atrophy may be present in patients with minimal or mild glomerular lesions [22]. In type 2 diabetic patients who underwent kidney biopsy, the prevalence of non-diabetic renal disease could be 45% to 57% in different reports, depending on selection criteria and population [23, 24]. The term “diabetic nephropathy” should be replaced by diabetic kidney disease (DKD), diabetic CKD, or diabetes and CKD. The terms “diabetic glomerulopathy” or “diabetic nephropathy” should be reserved for biopsy-proven kidney disease caused by diabetes, or for basic studies.

3. Dyslipoproteinemia versus hyperlipidemia as a cause of diabetic kidney disease

Diabetic kidney disease develops in 40% of patients with diabetes, even in some whose glucose levels are well maintained. Microalbuminuria alone may not provide optimal identification of patients with type 2 diabetes at higher risk of renal impairment [13]. The potential initiation and progression factors for DKD, besides hyperglycemia and albuminuria, are heavily researched [25]. Lipid-related nephrotoxicity has been proposed as a cause for the progression of renal disease [26]. Lipoproteins are composed of lipids and apoproteins. Historically, the term “dyslipidemia” was created to refer to abnormal levels of cholesterol, triglycerides (TG), or both. In 1965, Fredrickson et al. translated hyperlipidemia into hyperlipoproteinemia by developing a lipoprotein classification system based on electrophoretic migration of the four major lipoprotein classes [27]. Dyslipoproteinemia includes disorders of lipid levels, abnormalities in lipoprotein structure, and abnormal lipoprotein composition or density [28]. Thus, we
use the term “dyslipoproteinemia-associated nephropathy” to describe the direct or indirect effect of lipoprotein on the kidney.

4. Dyslipoproteinemia is prevalent in DKD and CKD

Before the widespread use of statin, dyslipoproteinemia was frequently detected in diabetes. In the Framingham Offspring Cohort (1983-1987), subjects with diabetes were more likely to have hypertriglyceridemia, lower high-density lipoprotein (HDL)-cholesterol, higher very-low-density lipoprotein (VLDL)-cholesterol, lower apo A1, and higher small dense low-density lipoprotein (LDL) particles than those without diabetes [2]. Observational studies in type 2 diabetes have revealed (i) the association of hypercholesterolemia with the development of diabetic kidney disease, (ii) the decline in renal function, and (iii) ESRD [4-6]. Dyslipoproteinemia is also prevalent in CKD. In the Framingham Offspring Cohort (1998-2001), patients with CKD were more likely to have hypertriglyceridemia, higher TG-rich lipoprotein remnants, lower HDL-cholesterol levels, and higher lipoprotein(a) (Lp(a)) than those without CKD [1, 29]. Total and LDL-cholesterol levels are usually within normal limits or slightly reduced in these individuals. In the NHANES III study, participants with CKD also had higher levels of apo B and lower levels of apo A than those with normal renal function [30]. Whether dyslipoproteinemia in DKD is more severe than dyslipoproteinemia in CKD without diabetes, or in diabetes without CKD, is not well understood. In the Pravastatin Pooling Project, in which baseline lipids were divided by both CKD and diabetes, the CKD/diabetes' group had the lowest HDL- and LDL-cholesterol and highest TG levels [3].

5. Lipid metabolism in diabetes and CKD

Both diabetes and CKD are associated with hypertriglyceridemia, lower HDL-cholesterol, higher VLDL-cholesterol, average levels of LDL-cholesterol, but higher levels of small dense LDL cholesterol. However, diabetes and CKD have a different lipid metabolism [8]. In insulin resistance and type 2 diabetes, increased production of TG-rich lipoproteins predominate. Hepatic VLDL synthesis is increased, driven by an increased flux of free fatty acids. Smaller, denser LDL particles and a decrease in HDL2 subspecies are related to the increase of hepatic lipase activity [31]. In CKD without nephrotic syndrome, decreased disposal of TG-rich proteins predominates [8]. Inhibition of lipoprotein lipase impairs the removal of VLDL and chylomicron remnants, and leads to increased levels of intermediate-density lipoproteins (IDL) [32]. HDL fails to mature normally, and reverse cholesterol transport is inhibited [33]. In CKD with nephrotic syndrome, both an increased production and a decreased catabolism of LDL-cholesterol results in increased total cholesterol and LDL-cholesterol levels as well as an increase in small dense LDL particles [34]. Both proteinuria and hypoalbuminemia can separately contribute to impaired lipoprotein catabolism in these patients [9].

It is possible that serum lipid levels do not reflect the tissue lipid load in some situations. In response to inflammation such as CKD, tissue lipid redistribution from circulation to tissue (renal and vascular) and tissue (adipocytes) to tissue (renal and vascular), and cell lipid accumulation due to increased cellular cholesterol influx and reduced efflux, may occur [35, 36]. Both mechanisms may result in a lower circulating cholesterol levels in patients with chronic inflammatory diseases.

6. Glomerular atherosclerosis

In the kidneys of diabetic humans, intraglomerular lipid deposits were first described in 1936 by Kimmelstiel and Wilson [37]. Intraglomerular lipid accumulations were shown to consist mainly of free and esterified cholesterol, and secondarily of triglycerides and phospholipids in animal models [38]. Lipid accumulation was found in 60% of the mesangial matrix and subendothelial area and in 20% of the intramembranous area and intracellular area in human glomerular disease [39].

The histologic features of focal segmental glomerulosclerosis and diabetic nodular glomerulosclerosis, including glomerular accumulation of serum proteins, lipids, and macrophages, resemble the patterns of the lesions seen in atherosclerosis [38, 40]. Also, the developing atherosclerotic and glomerulosclerotic lesions seem to share certain pathophysiologic mechanisms, including endothelial cell injury, macrophage infiltration, hyperlipoproteinemia, and hypertension (glomerular hypertension) [41]. In 1982, Moorhead proposed that “glomerular atherosclerosis” is the mechanism of glomerulosclerosis, which shares common pathogenetic mechanisms with atherosclerosis.
7. Cell model of glomerular atherosclerosis: the role of mesangial cells and oxidized LDL

Glomerular mesangial cells and vascular smooth muscle cells are closely related in terms of origin, histochemistry and contractility [42]. Glomerular injury could direct lipoproteins into the mesangium [43]. Lipid deposition can stimulate mesangial cell activation and proliferation, similar to smooth muscle cell proliferation in atherosclerosis [44]. Mesangial cells release chemokines and express adhesion molecules which recruit monocytes to the mesangium [45], where they are transformed into resident macrophages that secrete proinflammatory mediators [46]. The macrophages also ingest lipids to become foam cells [46].

Oxidative modification of LDL (oxLDL) plays a pathogenic role in the progression of atherosclerotic lesions [47]. LDL and oxLDL are present in the lesions of glomerulosclerosis [48]. OxLDL exerts cytotoxic, proinflammatory and immunogenic properties [49]. OxLDL, but not native LDL, can be cytotoxic by inducing apoptosis. OxLDL could be proinflammatory by the production of superoxide, cytokines, chemokines and thrombotic factors [50, 51]. The oxLDL produces a number of neo-self determinants that can elicit immune responses such as anti-oxLDL antibody [49]. Lipid and free fatty acid themselves could be causes of lipotoxicity. Fatty acids enter deleterious pathways such as ceramide production, which causes apoptosis [51].

8. Animal and human models of dyslipoproteinemia-associated glomerulosclerosis

Several proposed mechanisms of dyslipoproteinemia-associated glomerulosclerosis are discussed. They are discussed in the following sections.

8.1 High-cholesterol diet rat model of hyperlipidemia with or without hemodynamic factors

Rats fed a diet high in cholesterol develop a higher incidence of glomerulosclerosis after several months [52]. The severity of the hypercholesterolemia correlates with proteinuria and is accompanied by lipid deposits in glomeruli [53]. These rats have increased glomerular capillary pressure, afferent arteriolar resistance, and single nephron filtration fraction [54]. This model augments the glomerular lesions in combination with other insults such as nephrectomy, hypertension, diabetes or obesity [44, 55]. Some studies found that glomerular hemodynamic factor is pathogenetic in this model [55]. The contribution of hypercholesterolemia to the progression of renal disease seems more important than its role in initiating renal disease [56].

8.2 Insulin-resistant rat model of hyperlipoproteinemia independent of hyperglycemia

Increased TG-rich lipoproteins in insulin resistance could be associated with glomerulosclerosis. The obese Zucker rats develop hyperlipoproteinemia, hyperinsulinemia, insulin resistance, and obesity but not hyperglycemia up to one year of age [57]. Albuminuria and spontaneous focal glomerulosclerosis are noted at an early age, despite normal glomerular capillary pressures and nephron plasma flows [58]. Hypertriglyceridemia occurs prior to the development of renal disease and contributes to the observed proteinuria and glomerular injury [59]. Treatment with statin reduces both serum cholesterol and triglyceride levels and also decreases albuminuria, interstitial fibrosis and glomerulosclerosis [58, 60].

8.3 Limitations of animal models

We should notice that the composition, structure, and function of lipoproteins differ between humans and rats [28]. The rat lacks cholesteryl ester transfer protein and Lp(a) [28, 61]. In humans, VLDL secreted by the liver contains ApoB-100 while, in rat, VLDL secreted by rat liver may also contain ApoB-48, which could be taken up by various tissues including mesangial cells [28]. There is also gender difference in the models [62]. The lipid profiles of rats are different from that of humans with very low LDL and higher HDL [61]. A 4-6 fold increase in serum cholesterol is needed to aggravate pre-existing renal injury [63]. In animal models with less pronounced increases in serum cholesterol, other renal injury was applied to exacerbate the disease [64]. This kind of approach could make it difficult to differentiate between hemodynamic and dyslipoproteinemic effect.

8.4 Abnormal lipoprotein structure and glomerulosclerosis

Hyperlipidemia alone does not necessarily result in glomerulosclerosis. Familial type III hyperlipoproteinemia, characterized by elevated levels of...
triglyceride, cholesterol, and xanthomas, has rarely been associated with glomerulopathy [65, 66]. ApoE2/2 homozygosity (familial type III hyperlipoproteinemia-associated glomerulonephropathy) and mutant ApoE (lipoprotein glomerulopathy) could be associated with glomerulosclerosis [65-67]. Abnormal structure of ApoE isoforms may cause aggregated deposits in the glomerulus [68]. Diabetes mellitus is often associated with type III hyperlipoproteinemia. ApoE2 allele, a lipoprotein in chylomicron, VLDL and HDL, is defective in binding to ApoE receptors and associated with type III hyperlipidemia [69, 70]. Many studies suggest that ApoE2 allele is a risk factor for the development of diabetic nephropathy in patients with either type 1 or type 2 DM [71, 72]. In the general population of the Atherosclerosis Risk in Communities (ARIC) study, ApoE2 allele predicts chronic kidney disease progression, independent of diabetes, lipid, and nonlipid risk factors but does not predict hospitalization or ESRD [73]. ApoE2 may affect CKD progression through modulation of circulating lipid levels and through regulation of mesangial and glomerular function [69].

9. Dyslipoproteinemia and tubulointerstitial fibrosis

In glomerular diseases, correlations between histologic variables of tubulointerstitial injury and a decline in renal function have been noted since 1970 [74]. The rate of deterioration of renal function correlates best with the degree of renal tubulointerstitial fibrosis, better than the degree of glomerular injury in type 2 diabetes [75, 76]. The prevalence of tubulointerstitial fibrosis may be as high as 40%, as seen in a study of microalbuminuric type 2 diabetes [19].

Dyslipoproteinemia-associated nephropathy is also proposed in tubulointerstitial disease, in which luminal apoprotein precipitates initiate or aggravate tubulointerstitial disease [26]. Focal staining of neutral lipids and oxidized lipoproteins was seen in tubular epithelial cytoplasm. However, the mechanism is not well studied.

9.1 Dyslipoproteinemia-associated tubulointerstitial fibrosis

Some findings indicate that dyslipoproteinemia could directly contribute to tubulointerstitial fibrosis. Interstitial fibrosis and tubular atrophy have been documented in hypercholesterolemic rats without primary glomerular disease [77, 78]. In obese Zucker rats, the extracellular matrix deposition in the interstitium was evident at 3 months, while macrophage infiltration was noted at 6 months [79]. However, we should note that the animals in some of the studies had very high serum cholesterol levels [77].

9.2 Dyslipoproteinemia superimposed on glomerular injury-associated tubulointerstitial fibrosis

Animal models of the hypercholesterolemic rat showed parallel severity of glomerulosclerosis and tubulointerstitial fibrosis [44, 58, 59, 80]. Tubulointerstitial injury may be secondary to glomerular injury in glomerular diseases [81]. Glomerular proteinuria may increase the protein load of the tubular cells, and misdirection of the glomerular filtrate into the interstitium may induce the interstitial inflammation [81, 82]. Protein filtered by the glomeruli and reabsorbed by proximal tubular cells induce expression of inflammatory and fibrogenic mediators, especially TGF-β [83]. The filtered oxLDL may cause tubular cell apoptosis in diabetic nephropathy [84]. However, it is largely unknown whether glomerular injury or proteinuria in the presence of dyslipoproteinemia further exacerbates tubulointerstitial fibrosis.

10. Dyslipoproteinemia and renal function progression in observational studies

A number of observational studies have reported that dyslipidemia is associated with albuminuria, renal function progression and ESRD in the general population, CKD patients and DKD patients [7]. Some details about these studies should be noted. Firstly, the metabolism of lipoproteins and lipids are altered interdependently in both diabetes and CKD. For example, triglycerides are strongly associated with small, dense LDL and a decrease in the HDL-2. Studies found the association between triglycerides and renal dysfunction without the adjustment of lipoproteins should thus be interpreted carefully [28]. Secondly, there is a decreased trend in the association of CKD and albuminuria with high cholesterol. The prevalence ratio for CKD associated with high cholesterol decreased from 1.58 in NHANES 1988-1994 to 1.2 in NHANES 1999-2004 [85]. Studies in the earlier period may not be up to the current standard of treatment.
In the general population, hyperlipidemia is associated with albuminuria, elevated creatinine but not with ESRD. In the Gubbo Population Study with 1567 nondiabetic adults and a mean total cholesterol of 230 mg/dl, relative risk for microalbuminuria was 1.95 per 40 mg/dl increase in total cholesterol [86]. In the Physician Health Study involving 4483 healthy males with an initial creatinine <1.5 mg/dl and a mean total cholesterol of 234 mg/dl at 1982, total cholesterol >240 mg/dl was associated with an increased risk of elevated creatinine ≥1.5 mg/dl after 15 years [7]. The ARIC study revealed that elevated triglycerides and decreased HDL-cholesterol were associated with an increased risk of rise in serum creatinine [87]. However, in the Kaiser Permanente cohort study, involving 177,570 individuals attending a health check-up with a mean total cholesterol 222 mg/dl at 1964-1973, hypercholesterolemia is not associated with an increased risk for ESRD after 25 years [88].

In the nondiabetic CKD population, studies have shown that hyperlipidemia might be associated with renal function progression and ESRD. In the Modification of Diet in Renal Disease study including 840 nondiabetic CKD patients with a mean total cholesterol of 215 mg/dl, lower HDL-cholesterol predicted a faster decline in GFR [89, 90]. A few studies on glomerulonephropathy have also shown that dyslipoproteinemia was associated with the progression of renal function [91-94]. In our CKD stage 3-5 cohort study consisting of 1931 nondiabetic patients with a mean total cholesterol of 206 mg/dl, showed that high-dose atorvastatin 40 mg/dl and placebo in 18,569 subjects (7% diabetes and a total cholesterol of 234 mg/dl) at high risk for cardiovascular disease (CVD). It was shown that pravastatin reduced the adjusted rate of kidney function loss by 0.08 and 0.22 ml/min per 1.73 m²/y in all subjects and in CKD stage 3 patients, respectively. The pravastatin also reduced the risk of acute renal failure, but did not reduce the frequency of a ≥25% decline in kidney function [101]. A meta-analysis which combined the data from PPP and other 3 RCTs (GREACE, HPS, and ALLIANCE) including 38311 subjects with CVD or at high risk for CVD and a mean total cholesterol of 230 mg/dl showed a benefit of statin therapy (0.93 ml/min per 1.73 m²/yr slower than the control group) [98]. Individual studies (CARE, GREACE and ALLIANCE) have also reported that statin treatment was more beneficial in patients with GFR ≤60 ml/min per 1.73 m² [102-104]. A post hoc analysis of the TNT study, comparing 10 or 80 mg/dl atorvastatin in 9,656 patients (15% diabetes) with coronary heart disease and a total cholesterol of 206 mg/dl, showed that high-dose atorvastatin had an increase in GFR of 1.68 ml/min per 1.73 m² over 5 yr compared with the low-dose group [105].

Statins given to the CKD population has beneficial effects on renal function progression, but not on ESRD. Early small RCTs of lipid reduction in a meta-analysis, including 117 glomeronephritis and 245 diabetic patients carried out in 1990–2000, found that lipid reduction had beneficial effects on the decline of GFR [97]. In another meta-analysis, higher total and LDL-cholesterol and lower HDL-cholesterol were associated with higher risk for ESRD and rapid renal function decline [95].

11. Statin treatment and renal outcomes in randomized controlled trials

Statins that inhibit HMG-CoA reductase have been demonstrated to activate eNOS, maintain glomerular filtration rate and renal cortical blood flow and ameliorate glomerular lesions. Several meta-analyses with different selection criteria about the clinical trials of statin treatment on renal outcomes had been published [97-100]. Statins have been widely tested in cardiovascular disease patients with or without CKD, and showed beneficial effects in slowing renal function progression. Post hoc analysis of data from the Prospective Pravastatin Pooling (PPP) project (including 3 randomized, controlled trials (RCTs), WOSCOPS, CARE, and LIPID) compared pravastatin 40 mg/dl and placebo in 18,569 subjects (7% diabetes and a total cholesterol of 234 mg/dl) in another meta-analysis which combined the data from PPP and other 3 RCTs (GREACE, HPS, and ALLIANCE) including 38311 subjects with CVD or at high risk for CVD and a mean total cholesterol of 230 mg/dl showed a benefit of statin therapy (0.93 ml/min per 1.73 m²/yr slower than the control group) [98]. Individual studies (CARE, GREACE and ALLIANCE) have also reported that statin treatment was more beneficial in patients with GFR ≤60 ml/min per 1.73 m² [102-104]. A post hoc analysis of the TNT study, comparing 10 or 80 mg/dl atorvastatin in 9,656 patients (15% diabetes) with coronary heart disease and a total cholesterol of 206 mg/dl, showed that high-dose atorvastatin had an increase in GFR of 1.68 ml/min per 1.73 m² over 5 yr compared with the low-dose group [105]. Statins given to the CKD population has beneficial effects on renal function progression, but not on ESRD. Early small RCTs of lipid reduction in a meta-analysis, including 117 glomeronephritis and 245 diabetic patients carried out in 1990–2000, found that lipid reduction had beneficial effects on the decline of GFR [97]. In another meta-analysis,
including 3 RCTs, followed up for more than 1 year, with 101 glomerulonephritis patients with a total cholesterol 325 mg/dl, the beneficial effect of statins on GFR was 5.35 ml/min per 1.73 m²/yr [98]. However, in the recent SHARP study, which included 6,247 CKD patients with a mean total cholesterol of 189 mg/dl, simvastatin plus ezetimibe treatment did not produce significant reductions in ESRD, ESRD or death and ESRD or doubling of baseline creatinine [10].

Statins in diabetic patients with or without CKD have a small beneficial effect on renal function progression, but not on albuminuria. Early small RCTs of lipid reduction in 61 diabetic patients did not show significant benefits [98]. In the Heart Protection Study, including 5,963 diabetic patients with a total cholesterol of 224 mg/dl and 5.2% of whom with elevated creatinine, the simvastatin group was associated with a smaller increase in creatinine than the placebo group, with a difference of 0.024 mg/dl [106]. The CARDS study enrolled 2,838 diabetic patients—970 of whom with CKD—with a total cholesterol of 206 mg/dl and no previous CVD. Atorvastatin treatment was associated with a modest improvement in GFR (0.18 ml/min per 1.73 m²/yr). This improvement was more apparent in those with albuminuria (0.38 ml/min per 1.73 m²/yr) [105]. However, atorvastatin treatment did not influence the incidence of albuminuria or regression to normoalbuminuria [105]. 23% of the total participants of the SHARP study were diabetic, but no subgroup analysis was reported [10].

12. Fibrate treatment and renal outcomes in randomized controlled trials

Fenofibrate is a peroxisome proliferator-activated receptor-α activator with pleiotropic effects such as reducing levels of pro-inflammatory markers. Some meta-analyses about the clinical trials of fibrate treatment on renal outcomes have been published [99, 107].

The effect of fibrate on renal function has been less widely studied than that of statin. Early small trials have noted an acute increase in creatinine after fibrate treatment. A post hoc subgroup analysis of 399 CKD men with coronary disease in the VA-HIT study showed that renal function in the gemfibrozil group did not differ from the placebo group after a period of 5 years [108]. Although, the incidence of transient, but unsustained, increases in serum creatinine ≥0.5 mg/dl was significantly greater in the gemfibrozil group [108].

Most of the studies on the effect of fibrate on renal function were carried out in diabetic populations. A meta-analysis, including DAIS, ACCORD, and FIELD, performed on 14,385 patients with mean total cholesterol of 187 mg/dl and mean triacylglyceride of 178 mg/dl showed that fibrate therapy reduced the risk of albuminuria progression (RR: 0.86) [107]. Two trials (DAIS and FIELD) including 2,152 diabetic patients with albuminuria reported that fibrate therapy significantly increased the likelihood of albuminuria regression (RR: 1.19) [107]. The incidence of ESRD was low and no difference was found between the fibrate and control group in the ACCORD and FIELD studies [109]. There was no report for the DKD subgroups in these studies.

13. Summary of findings from studies on diabetic kidney disease

We retain the following main findings and conclusions from the studies on diabetic kidney disease:

1. Diabetic glomerulopathy and the associated albuminuria are present in most, but not all, DKD forms. Both glomerulosclerosis and tubulointerstitial fibrosis are present in DKD.
2. The glomerular atherosclerosis hypothesis, which connects hyperlipoproteinemia, oxidative stress, inflammatory cells, and mesangial cells, is supported by animal models. Association of dyslipoproteinemia with tubulointerstitial fibrosis is less studied.
3. Several observational studies suggest that dyslipoproteinemia is associated with albuminuria in DKD. One RCT (CARDS) does not support the hypothesis that statin treatment decreases albuminuria. Three RCTs (DAIS, ACCORD, and FIELD) support the hypothesis that fibrate treatment reduces the risk of albuminuria progression.
4. Some observational studies suggest that dyslipoproteinemia is associated with renal function progression in DKD. Meta-analyses of RCTs on CVD patients demonstrate a small benefit of statin treatment. One RCT (CARDS) shows a small improvement from statin treatment in diabetes patients, which
was more apparent in those with albuminuria. Fibrate treatment is associated with an acute decrease in GFR, and long-term effects on renal function progression are not clear.

5. Some observational studies suggest that dyslipoproteinemia is associated with ESRD in DKD. The SHARP study of CKD patients treated with simvastatin plus ezetimibe did not show significant reductions in ESRD. The subgroup analysis of DKD has not yet been published. The effect of fibrate treatment on ESRD is not clear.

6. Early studies had higher baseline cholesterol and higher targeted cholesterol levels than later studies. The SHARP study had the lowest baseline cholesterol levels. Thus, it could not be excluded that statin treatment caused benefits on renal outcome in those with high baseline cholesterol levels.

14. Conclusions

Dyslipoproteinemia could cause glomerulosclerosis and tubulointerstitial fibrosis in animal models. Dyslipoproteinemia is associated with albuminuria, renal function progression and ESRD in observational studies of CKD and DKD. In clinical trials, the benefit of statin treatment for renal function progression is small and evident only in the CVD population. There is not enough evidence to recommend the use of statin or fibrate in the treatment of renal function progression and the prevention of ESRD in DKD. Data suggest that certain subgroups such as CVD, CKD stage 3-4, patients with severe hyperlipidemia, and patients with Apo E2 allele may be the candidates for future studies in DKD.

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