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REVIEW

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

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■ Abstract

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

1. Introduction

Dyslipoproteinemia is highly prevalent in diabetes, chronic kidney disease (CKD), and diabetic kidney disease [1-3]. Dyslipoproteinemia is associated with the development of CKD and renal function impairment in the general population and in diabetic patients [4-7]. When renal function declines or proteinuria increases, dyslipoproteinemia becomes severe [8, 9]. However, it is unclear whether dyslipoproteinemia causes end-stage renal disease (ESRD), and whether the treatment of dyslipoproteinemia could prevent ESRD. Recently, the Study of Heart and Renal Protection (SHARP) failed to support that statin treatment can reduce ESRD [10]. The purpose of this review is to describe and analyze carefully the complex association of dyslipoproteinemia with diabetic kidney disease delineated in animal studies, observational studies, and clinical trials.

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/1.73m^2) 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.

Abbreviations:

ACCORD - Action to Control Cardiovascular Risk in Diabetes
ALLIANCE - Aggressive Lipid-Lowering Initiation Abates New Cardiac Events
ApoB-48 - apolipoprotein B 48
ARIC - Atherosclerosis Risk in Communities
CARDS - Collaborative Atorvastatin Diabetes Study
CARE - Cholesterol and Recurrent Events
CKD - chronic kidney disease
CVD - cardiovascular disease
DAIS - Diabetes Atherosclerosis Intervention *Study*
DKD - diabetic kidney disease
eNOS - endothelial nitric oxide synthase
ESRD - end-stage renal disease
FIELD - Fenofibrate Intervention and Event Lowering in Diabetes
GFR - glomerular filtration rate
GREACE - Greek Atorvastatin and Coronary Heart Disease Evaluation
HDL - high-density lipoprotein
HMG-CoA - 3-hydroxy-3-methylglutaryl-coenzyme A
HPS - Heart Protection Study
IDL - intermediate density lipoproteins
LDL - low-density lipoprotein
LIPID - Long-term Intervention with Pravastatin in Ischemic Disease
Lp(a) - lipoprotein(a)
NHANES - National Health and Nutrition Examination Survey
oxLDL - oxidative modification of LDL
PPP - Prospective Pravastatin Pooling
RCT - randomized, controlled trials
RENAAL - Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
SHARP - Study of Heart and Renal Protection
TG - triglycerides
TGF-beta - transforming growth factor beta
TNT - Treating to New Targets
UKPDS - UK Prospective Diabetes Study
VA-HIT - Veterans Affairs High-Density Lipoprotein Intervention Trial
VLDL - very-low-density lipoprotein
WOSCOPS - West of Scotland Coronary Prevention Study

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 eletrophoretic 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 predominates. 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 circulating 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 uni-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 hyperglycema 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 microabluminuric 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 fiborsis.

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 Gubbio 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 194 mg/dl, higher total and LDL-cholesterol and lower HDL-cholesterol were associated with higher risk for ESRD and rapid renal function decline [95].

In the patients with type 2 diabetes with or without CKD, numerous studies have shown that hyperlipidemia is associated with albuminuria and probably with renal function progression and ESRD. Analyses of the 5102 UKPDS participants without albuminuria or with normal plasma creatinine (a mean total cholesterol of 208 mg/dl) showed that higher LDL-cholesterol and triglycerides were associated with albuminuria but not associated with GFR <60 ml/min or doubling of plasma creatinine [96]. In the RENAAL study including 1513 DKD patients with a mean total cholesterol of 228 mg/dl, the relative risk (RR) of reaching the primary composite end point or ESRD among patients in the upper quartile of total and LDL-cholesterol was significantly higher [4]. In our cohort study consisting of 1472 DKD patients with a mean total cholesterol of 198 mg/dl, 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) 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 m^2/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 m^2/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 m^2 [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 m^2 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 m^2/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 m^2/y). This improvement was more apparent in those with albuminuria (0.38 ml/min per 1.73 m^2/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 triglyceride 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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■ References

1. **Parikh NI, Hwang SJ, Larson MG, Meigs JB, Levy D, Fox CS.** Cardiovascular disease risk factors in chronic kidney disease: overall burden and rates of treatment and control. *Arch Intern Med* 2006. 166(17):1884-1891.
2. **Siegel RD, Cupples A, Schaefer EJ, Wilson PW.** Lipoproteins, apolipoproteins, and low-density lipoprotein size among diabetics in the Framingham offspring study. *Metabolism* 1996. 45(10):1267-1272.
3. **Tonelli M, Keech A, Shepherd J, Sacks F, Tonkin A, Packard C, Pfeffer M, Simes J, Isles C, Furberg C, et al.** Effect of pravastatin in people with diabetes and chronic kidney disease. *J Am Soc Nephrol* 2005. 16(12):3748-3754.
4. **Appel GB, Radhakrishnan J, Avram MM, DeFronzo RA, Escobar-Jimenez F, Campos MM, Burgess E, Hille DA, Dickson TZ, Shahinfar S, et al.** Analysis of metabolic parameters as predictors of risk in the RENAAL study. *Diabetes Care* 2003. 26(5):1402-1407.
5. **Gall MA, Hougaard P, Borch-Johnsen K, Parving HH.** Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. *BMJ* 1997. 314(7083):783-788.
6. **Ravid M, Neumann L, Lishner M.** Plasma lipids and the progression of nephropathy in diabetes mellitus type II: effect of ACE inhibitors. *Kidney Int* 1995. 47(3):907-910.
7. **Schaeffner ES, Kurth T, Curhan GC, Glynn RJ, Rexrode KM, Baigent C, Buring JE, Gaziano JM.** Cholesterol and the risk of renal dysfunction in apparently healthy men. *J Am Soc Nephrol* 2003. 14(8):2084-2091.
8. **Kaysen GA, Eiserich JP.** The role of oxidative stress-altered lipoprotein structure and function and microinflammation on cardiovascular risk in patients with minor renal dysfunction. *J Am Soc Nephrol* 2004. 15(3):538-548.
9. **Newman JW, Kaysen GA, Hammock BD, Shearer GC.** Proteinuria increases oxylipid concentrations in VLDL and HDL but not LDL particles in the rat. *J Lipid Res* 2007. 48(8):1792-1800.
10. **Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, et al.** The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011. 377(9784):2181-2192.
11. **Zimmet P, Alberti KG, Shaw J.** Global and societal implications of the diabetes epidemic. *Nature* 2001. 414(6865):782-787.
12. **Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, Ukpds G.** Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int* 2003. 63(1):225-232.
13. **Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR, Group US.** Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. *Diabetes* 2006. 55(6):1832-1839.
14. **Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, Steffes MW, American Diabetes A.** Nephropathy in diabetes. *Diabetes Care* 2004. 27 Suppl 1:S79-S83.
15. **Valmadrid CT, Klein R, Moss SE, Klein BE.** The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. *Arch Intern Med* 2000. 160(8):1093-1100.
16. **MacIsaac RJ, Tsalamandris C, Panagiotopoulos S, Smith TJ, McNeil KJ, Jerums G.** Nonalbuminuric renal insufficiency in type 2 diabetes. *Diabetes Care* 2004. 27(1):195-200.
17. **Kramer HJ, Nguyen QD, Curhan G, Hsu CY.** Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. *JAMA* 2003. 289(24):3273-3277.

18. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis* 2007. 49(2 Suppl 2):S12-S154.
19. **Fioretto P, Mauer M, Brocco E, Velussi M, Frigato F, Muollo B, Sambataro M, Abaterusso C, Baggio B, Crepaldi G, Nosadini R.** Patterns of renal injury in NIDDM patients with microalbuminuria. *Diabetologia* 1996. 39(12):1569-1576.
20. **Osterby R, Parving HH, Hommel E, Jorgensen HE, Lokkegaard H.** Glomerular structure and function in diabetic nephropathy. Early to advanced stages. *Diabetes* 1990. 39(9):1057-1063.
21. **Mauer SM, Steffes MW, Brown DM.** The kidney in diabetes. *Am J Med* 1981. 70(3):603-612.
22. **Dalla Vestra M, Saller A, Bortoloso E, Mauer M, Fioretto P.** Structural involvement in type 1 and type 2 diabetic nephropathy. *Diabetes Metab* 2000. 26 Suppl 4:8-14.
23. **Gambara V, Mecca G, Remuzzi G, Bertani T.** Heterogeneous nature of renal lesions in type II diabetes. *J Am Soc Nephrol* 1993. 3(8):1458-1466.
24. **Olsen S, Mogensen CE.** How often is NIDDM complicated with non-diabetic renal disease? An analysis of renal biopsies and the literature. *Diabetologia* 1996. 39(12):1638-1645.
25. **Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T.** Diabetic nephropathy: diagnosis, prevention, and treatment. *Diabetes Care* 2005. 28(1):164-176.
26. **Moorhead JF, Chan MK, El-Nahas M, Varghese Z.** Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease. *Lancet* 1982. 2(8311):1309-1311.
27. **Fredrickson DS, Lees RS.** A System for Phenotyping Hyperlipoproteinemia. *Circulation* 1965. 31:321-327.
28. **Dalrymple LS, Kaysen GA.** The effect of lipoproteins on the development and progression of renal disease. *Am J Nephrol* 2008. 28(5):723-731.
29. **Tsimihodimos V, Dounousi E, Siamopoulos KC.** Dyslipidemia in chronic kidney disease: an approach to pathogenesis and treatment. *Am J Nephrol* 2008. 28(6):958-973.
30. **Muntner P, Hamm LL, Kusek JW, Chen J, Whelton PK, He J.** The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. *Ann Intern Med* 2004. 140(1):9-17.
31. **Ginsberg HN.** REVIEW: Efficacy and mechanisms of action of statins in the treatment of diabetic dyslipidemia. *J Clin Endocrinol Metab* 2006. 91(2):383-392.
32. **Walzem RL, Watkins S, Frankel EN, Hansen RJ, German JB.** Older plasma lipoproteins are more susceptible to oxidation: a linking mechanism for the lipid and oxidation theories of atherosclerotic cardiovascular disease. *Proc Natl Acad Sci U S A* 1995. 92(16):7460-7464.
33. **Prinsen BH, de Sain-van der Velden MG, de Koning EJ, Koomans HA, Berger R, Rabelink TJ.** Hypertriglyceridemia in patients with chronic renal failure: possible mechanisms. *Kidney Int Suppl* 2003(84):S121-124.
34. **Farbakhsh K, Kasiske BL.** Dyslipidemias in patients who have chronic kidney disease. *Med Clin North Am* 2005. 89(3):689-699.
35. **Ruan XZ, Moorhead JF, Varghese Z.** Lipid redistribution in renal dysfunction. *Kidney Int* 2008. 74(4):407-409.
36. **Ruan XZ, Varghese Z, Moorhead JF.** An update on the lipid nephrotoxicity hypothesis. *Nat Rev Nephrol* 2009. 5(12):713-721.
37. **Kimmelstiel P, Wilson C.** Intercapillary Lesions in the Glomeruli of the Kidney. *Am J Pathol* 1936. 12(1):83-98 87.
38. **Grond J, van Goor H, Erkelens DW, Elema JD.** Glomerular sclerotic lesions in the rat. Histochemical analysis of their macromolecular and cellular composition. *Virchows Arch B Cell Pathol Incl Mol Pathol* 1986. 51(6):521-534.
39. **Lee HS, Lee JS, Koh HI, Ko KW.** Intraglomerular lipid deposition in routine biopsies. *Clin Nephrol* 1991. 36(2):67-75.
40. **Shioi A, Fujimoto T.** Disorganization process in the development of diabetic nodular glomerulosclerosis. *Tohoku J Exp Med* 1989. 159(4):257-275.
41. **Diamond JR, Karnovsky MJ.** Focal and segmental glomerulosclerosis: analogies to atherosclerosis. *Kidney Int* 1988. 33(5):917-924.
42. **Chiang YY, Takebayashi S, Oberley TD.** In vitro analysis of extracellular matrix production by porcine glomerular mesangial and vascular smooth muscle cells. *Am J Pathol* 1991. 138(6):1349-1358.
43. **Zatz R, Meyer TW, Rennke HG, Brenner BM.** Predominance of hemodynamic rather than metabolic factors in the pathogenesis of diabetic glomerulopathy. *Proc Natl Acad Sci U S A* 1985. 82(17):5963-5967.
44. **Kasiske BL, O'Donnell MP, Schmitz PG, Kim Y, Keane WF.** Renal injury of diet-induced hypercholesterolemia in rats. *Kidney Int* 1990. 37(3):880-891.
45. **Hattori M, Nikolic-Paterson DJ, Miyazaki K, Isbel NM, Lan HY, Atkins RC, Kawaguchi H, Ito K.** Mechanisms of glomerular macrophage infiltration in lipid-induced renal injury. *Kidney Int Suppl* 1999. 71:S47-50.
46. **Guijarro C, Kasiske BL, Kim Y, O'Donnell MP, Lee HS, Keane WF.** Early glomerular changes in rats with dietary-induced hypercholesterolemia. *Am J Kidney Dis* 1995. 26(1):152-161.
47. **Witztum JL, Steinberg D.** The oxidative modification hypothesis of atherosclerosis: does it hold for humans? *Trends Cardiovasc Med* 2001. 11(3-4):93-102.
48. **Lee HS, Kim YS.** Identification of oxidized low density lipoprotein in human renal biopsies. *Kidney Int* 1998. 54(3):848-856.
49. **Heeringa P, Tervaert JW.** Role of oxidized low-density lipoprotein in renal disease. *Curr Opin Nephrol Hypertens* 2002. 11(3):287-293.
50. **Chen HC, Guh JY, Shin SJ, Lai YH.** Pravastatin suppress superoxide and fibronectin production of glomerular mesangial cells induced by oxidized-LDL and high glucose. *Atherosclerosis* 2002. 160(1):141-146.
51. **Nosadini R, Tonolo G.** Role of oxidized low density lipoproteins and free fatty acids in the pathogenesis of glomerulopathy and tubulointerstitial lesions in type 2 diabetes. *Nutr Metab Cardiovasc Dis* 2011. 21(2):79-85.
52. **Grone EF, Walli AK, Grone HJ, Miller B, Seidel D.** The role of lipids in nephrosclerosis and glomerulosclerosis. *Atherosclerosis* 1994. 107(1):1-13.
53. **Rayner HC, Ross-Gilbertson VL, Walls J.** The role of lipids in the pathogenesis of glomerulosclerosis in the rat following subtotal nephrectomy. *Eur J Clin Invest* 1990. 20(1):97-104.
54. **Kaplan R, Aynedjian HS, Schlondorff D, Bank N.** Renal vasoconstriction caused by short-term cholesterol

feeding is corrected by thromboxane antagonist or probucol. *J Clin Invest* 1990. 86(5):1707-1714.
55. **Grone HJ, Walli A, Grone E, Niedmann P, Thiery J, Seidel D, Helmchen U.** Induction of glomerulosclerosis by dietary lipids. A functional and morphologic study in the rat. *Lab Invest* 1989. 60(3):433-446.
56. **Keane WF.** Lipids and progressive renal failure. *Wien Klin Wochenschr* 1996. 108(14):420-424.
57. **Albright AL, Johnson PR, Greene S, Stern JS.** Use of glycated hemoglobin to assess Glycemic control in Wistar diabetic fatty rats and Zucker fatty rats. *Obes Res* 1994. 2(6):535-539.
58. **Kasiske BL, O'Donnell MP, Cleary MP, Keane WF.** Treatment of hyperlipidemia reduces glomerular injury in obese Zucker rats. *Kidney Int* 1988. 33(3):667-672.
59. **Kasiske BL, O'Donnell MP, Keane WF.** The Zucker rat model of obesity, insulin resistance, hyperlipidemia, and renal injury. *Hypertension* 1992. 19(1 Suppl):I110-115.
60. **Dominguez JH, Tang N, Xu W, Evan AP, Siakotos AN, Agarwal R, Walsh J, Deeg M, Pratt JH, March KL, et al.** Studies of renal injury III: lipid-induced nephropathy in type II diabetes. *Kidney Int* 2000. 57(1):92-104.
61. **Chapman MJ.** Comparative analysis of mammalian plasma lipoproteins. *Methods Enzymol* 1986. 128:70-143.
62. **Gades MD, Stern JS, van Goor H, Nguyen D, Johnson PR, Kaysen GA.** Estrogen accelerates the development of renal disease in female obese Zucker rats. *Kidney Int* 1998. 53(1):130-135.
63. **Shohat J, Erman A, Zandbank J, Harell D, Boner G.** Renal effects of moderate hypercholesterolaemia in uninephrectomized rats. *Scand J Clin Lab Invest* 1996. 56(4):339-343.
64. **Scheuer H, Gwinner W, Hohbach J, Grone EF, Brandes RP, Malle E, Olbricht CJ, Walli AK, Grone HJ.** Oxidant stress in hyperlipidemia-induced renal damage. *Am J Physiol Renal Physiol* 2000. 278(1):F63-74.
65. **Ellis D, Orchard TJ, Lombardozzi S, Yunis EJ, McCauley J, Agostini R, Diamond JR.** Atypical hyperlipidemia and nephropathy associated with apolipoprotein E homozygosity. *J Am Soc Nephrol* 1995. 6(4):1170-1177.
66. **Suzaki K, Kobori S, Ueno S, Uehara M, Kayashima T, Takeda H, Fukuda S, Takahashi K, Nakamura N, Uzawa H, et al.** Effects of plasmapheresis on familial type III hyperlipoproteinemia associated with glomerular lipidosis, nephrotic syndrome and diabetes mellitus. *Atherosclerosis* 1990. 80(3):181-189.
67. **Matsunaga A, Sasaki J, Komatsu T, Kanatsu K, Tsuji E, Moriyama K, Koga T, Arakawa K, Oikawa S, Saito T, et al.** A novel apolipoprotein E mutation, E2 (Arg25Cys), in lipoprotein glomerulopathy. *Kidney Int* 1999. 56(2):421-427.
68. **Saito T, Ishigaki Y, Oikawa S, Yamamoto TT.** Etiological significance of apolipoprotein E mutations in lipoprotein glomerulopathy. *Trends Cardiovasc Med* 2002. 12(2):67-70.
69. **Liberopoulos E, Siamopoulos K, Elisaf M.** Apolipoprotein E and renal disease. *Am J Kidney Dis* 2004. 43(2):223-233.
70. **Utermann G, Kindermann I, Kaffarnik H, Steinmetz A.** Apolipoprotein E phenotypes and hyperlipidemia. *Hum Genet* 1984. 65(3):232-236.
71. **Araki S, Moczulski DK, Hanna L, Scott LJ, Warram JH, Krolewski AS.** APOE polymorphisms and the development of diabetic nephropathy in type 1 diabetes: results of case-control and family-based studies. *Diabetes* 2000. 49(12):2190-2195.
72. **Eto M, Saito M, Okada M, Kume Y, Kawasaki F, Matsuda M, Yoneda M, Matsuki M, Takigami S, Kaku K.** Apolipoprotein E genetic polymorphism, remnant lipoproteins, and nephropathy in type 2 diabetic patients. *Am J Kidney Dis* 2002. 40(2):243-251.
73. **Hsu CC, Kao WH, Coresh J, Pankow JS, Marsh-Manzi J, Boerwinkle E, Bray MS.** Apolipoprotein E and progression of chronic kidney disease. *JAMA* 2005. 293(23):2892-2899.
74. **Schainuck LI, Striker GE, Cutler RE, Benditt EP.** Structural-functional correlations in renal disease. II. The correlations. *Hum Pathol* 1970. 1(4):631-641.
75. **Ueno M, Kawashima S, Nishi S, Shimada H, Karasawa R, Suzuki Y, Maruyama Y, Arakawa M.** Tubulointerstitial lesions in non-insulin dependent diabetes mellitus. *Kidney Int Suppl* 1997. 63:S191-194.
76. **Mauer SM, Steffes MW, Ellis EN, Sutherland DE, Brown DM, Goetz FC.** Structural-functional relationships in diabetic nephropathy. *J Clin Invest* 1984. 74(4):1143-1155.
77. **Eddy AA.** Interstitial fibrosis in hypercholesterolemic rats: role of oxidation, matrix synthesis, and proteolytic cascades. *Kidney Int* 1998. 53(5):1182-1189.
78. **Grone HJ, Hohbach J, Grone EF.** Modulation of glomerular sclerosis and interstitial fibrosis by native and modified lipoproteins. *Kidney Int Suppl* 1996. 54:S18-22.
79. **Lavaud S, Poirier B, Mandet C, Belair MF, Irinopoulou T, Heudes D, Bazin R, Bariety J, Myara I, Chevalier J.** Inflammation is probably not a prerequisite for renal interstitial fibrosis in normoglycemic obese rats. *Am J Physiol Renal Physiol* 2001. 280(4):F683-694.
80. **Magil AB.** Tubulointerstitial lesions in young Zucker rats. *Am J Kidney Dis* 1995. 25(3):478-485.
81. **Kriz W, Hosser H, Hahnel B, Gretz N, Provoost AP.** From segmental glomerulosclerosis to total nephron degeneration and interstitial fibrosis: a histopathological study in rat models and human glomerulopathies. *Nephrol Dial Transplant* 1998. 13(11):2781-2798.
82. **Gilbert RE, Cooper ME.** The tubulointerstitium in progressive diabetic kidney disease: more than an aftermath of glomerular injury? *Kidney Int* 1999. 56(5):1627-1637.
83. **Gorriz JL, Martinez-Castelao A.** Proteinuria: detection and role in native renal disease progression. *Transplant Rev (Orlando)* 2012. 26(1):3-13.
84. **Okamura DM, Lopez-Guisa JM, Koelsch K, Collins S, Eddy AA.** Atherogenic scavenger receptor modulation in the tubulointerstitium in response to chronic renal injury. *Am J Physiol Renal Physiol* 2007. 293(2):F575-F585.
85. **Fox CS, Muntner P.** Trends in diabetes, high cholesterol, and hypertension in chronic kidney disease among U.S. adults: 1988-1994 to 1999-2004. *Diabetes Care* 2008. 31(7):1337-1342.
86. **Cirillo M, Senigalliesi L, Laurenzi M, Alfieri R, Stamler J, Stamler R, Panarelli W, De Santo NG.** Microalbuminuria in nondiabetic adults: relation of blood pressure, body mass index, plasma cholesterol levels, and smoking: The Gubbio Population Study. *Arch Intern Med* 1998. 158(17):1933-1939.

87. **Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ.** Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. *Kidney Int* 2000. 58(1):293-301.
88. **Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS.** Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med* 2009. 169(4):342-350.
89. **Hunsicker LG, Adler S, Caggiula A, England BK, Greene T, Kusek JW, Rogers NL, Teschan PE.** Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. *Kidney Int* 1997. 51(6):1908-1919.
90. **Greene T, Bourgoignie JJ, Habwe V, Kusek JW, Snetselaar LG, Soucie JM, Yamamoto ME.** Baseline characteristics in the Modification of Diet in Renal Disease Study. *J Am Soc Nephrol* 1993. 4(5):1221-1236.
91. **Syrjanen J, Mustonen J, Pasternack A.** Hypertriglyceridaemia and hyperuricaemia are risk factors for progression of IgA nephropathy. *Nephrol Dial Transplant* 2000. 15(1):34-42.
92. **Samuelsson O, Attman PO, Knight-Gibson C, Larsson R, Mulec H, Weiss L, Alaupovic P.** Complex apolipoprotein B-containing lipoprotein particles are associated with a higher rate of progression of human chronic renal insufficiency. *J Am Soc Nephrol* 1998. 9(8):1482-1488.
93. **Boes E, Fliser D, Ritz E, Konig P, Lhotta K, Mann JF, Muller GA, Neyer U, Riegel W, Riegler P, Kronenberg F.** Apolipoprotein A-IV predicts progression of chronic kidney disease: the mild to moderate kidney disease study. *J Am Soc Nephrol* 2006. 17(2):528-536.
94. **Toth T, Takebayashi S.** Factors contributing to the outcome in 100 adult patients with idiopathic membranous glomerulonephritis. *Int Urol Nephrol* 1994. 26(1):93-106.
95. **Chen SC, Hung CC, Kuo MC, Lee JJ, Chiu YW, Chang JM, Hwang SJ, Chen HC.** Association of dyslipidemia with renal outcomes in chronic kidney disease. *Plos One* 2013. 8(2):e55643.
96. **Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR.** Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. *Diabetes* 2006. 55(6):1832-1839.
97. **Fried LF, Orchard TJ, Kasiske BL.** Effect of lipid reduction on the progression of renal disease: a meta-analysis. *Kidney Int* 2001. 59(1):260-269.
98. **Sandhu S, Wiebe N, Fried LF, Tonelli M.** Statins for improving renal outcomes: a meta-analysis. *J Am Soc Nephrol* 2006. 17(7):2006-2016.
99. **Slinin Y, Ishani A, Rector T, Fitzgerald P, MacDonald R, Tacklind J, Rutks I, Wilt TJ.** Management of hyperglycemia, dyslipidemia, and albuminuria in patients with diabetes and CKD: a systematic review for a KDOQI clinical practice guideline. *Am J Kidney Dis* 2012. 60(5):747-769.
100. **Strippoli GF, Navaneethan SD, Johnson DW, Perkovic V, Pellegrini F, Nicolucci A, Craig JC.** Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. *BMJ* 2008. 336(7645):645-651.
101. **Tonelli M, Isles C, Craven T, Tonkin A, Pfeffer MA, Shepherd J, Sacks FM, Furberg C, Cobbe SM, Simes J, et al.** Effect of pravastatin on rate of kidney function loss in people with or at risk for coronary disease. *Circulation* 2005. 112(2):171-178.
102. **Tonelli M, Moye L, Sacks FM, Cole T, Curhan GC.** Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. *J Am Soc Nephrol* 2003. 14(6):1605-1613.
103. **Collins R, Armitage J, Parish S, Sleigh P, Peto R.** MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003. 361(9374):2005-2016.
104. **Athyros VG, Mikhailidis DP, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, Elisaf M.** The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. *J Clin Pathol* 2004. 57(7):728-734.
105. **Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Charlton-Menys V, DeMicco DA, Fuller JH, Investigators C.** Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). *Am J Kidney Dis* 2009. 54(5):810-819.
106. **Collins R, Armitage J, Parish S, Sleigh P, Peto R, Heart Protection Study Collaborative G.** MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003. 361(9374):2005-2016.
107. **Jun M, Zhu B, Tonelli M, Jardine MJ, Patel A, Neal B, Liyanage T, Keech A, Cass A, Perkovic V.** Effects of fibrates in kidney disease: a systematic review and meta-analysis. *J Am Coll Cardiol* 2012. 60(20):2061-2071.
108. **Tonelli M, Collins D, Robins S, Bloomfield H, Curhan GC.** Effect of gemfibrozil on change in renal function in men with moderate chronic renal insufficiency and coronary disease. *Am J Kidney Dis* 2004. 44(5):832-839.
109. **Group AS, Ginsberg HN, Elam MB, Lovato LC, Crouse JR, 3rd, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, et al.** Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010. 362(17):1563-1574.
110. **Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, et al.** Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008. 358(24):2545-2559.

