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# Dyslipidemia and the progression of renal disease in chronic renal failure patients

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**Dyslipidemia and the progression of renal disease in chronic renal failure patients.** Dyslipidemia is a common complication of progressive kidney disease and contributes to the high cardiovascular morbidity and mortality of chronic kidney disease (CKD) patients. Recent evidence also suggests a role for dyslipidemia in the development and progression of renal disease. Experimental studies have demonstrated that lipids may induce glomerular and tubulointerstitial injury, and that lipid-lowering treatments ameliorate renal injury.

Various lipid abnormalities have been associated with the development and progression of renal disease in diabetic and nondiabetic patients. Population-based studies and studies of diabetic patients have reported associations of various lipid abnormalities with the development of renal disease. In patients with CKD, lipid abnormalities have also been associated with renal disease progression. Post hoc analyses of some large clinical trials on patients with vascular disease, diabetes, or dyslipidemia, and a meta-analysis of small, prospective, controlled studies on patients with CKD (diabetics and nondiabetics) suggest that statins may slow the progression of kidney disease. It is unclear whether the beneficial renal effects of statins are due to the reduction of serum cholesterol levels and/or their pleiotropic effects. There is also evidence for synergistic renoprotective effects between statins and renin-angiotensin system inhibitors. According to the results of post hoc analysis of several studies, treatment with fibrates does not seem to confer renoprotection, but evidence is scarce.

In summary, there is growing evidence that lipid abnormalities may be a risk factor for renal disease, and that statins appear to confer a renoprotective effect.

Dyslipidemia is a common complication of progressive kidney disease, which is characterized by high triglyceride and low high-density lipoprotein (HDL) cholesterol levels, accumulation of remnant particles, a predominance of small dense low-density lipoprotein (LDL) particles, and increased levels of lipoprotein A. In patients with advanced chronic kidney disease (CKD), LDL and HDL particles undergo oxidative modification, resulting in the formation of small lipoproteins and enhanced production of oxidized LDL [1]. In the nephrotic syndrome, the lipid profile is highly atherogenic, with increased total and LDL cholesterol, triglyceride, and lipoprotein A serum levels as well as decreased HDL cholesterol.

Dyslipidemia has been hypothesized to cause kidney damage and to play an important role in the progression of renal failure [2]. In animal models, hyperlipidemic diets worsen renal injury, and lipid-lowering strategies ameliorate renal injury [3–6]. Dyslipidemia may damage glomerular capillary endothelial and mesangial cells as well as podocytes. Mesangial cells express receptors for LDL and oxidized LDL, which upon activation induce mesangial cell proliferation, increase mesangial matrix deposition, and enhance the production of chemokines (such as macrophage chemo-attractant protein-1), cytokines (such as interleukin 6), or growth factors. Macrophage chemo-attractant protein-1 enhances the recruitment of macrophages, which can infiltrate the glomerulus and become foam cells that release cytokines. Oxidized LDL increases the adhesion of monocytes to glomerular endothelial cells, favoring monocyte infiltration, and affects tubular epithelial cells [6]. Hypercholesterolemia and hypertriglyceridemia are also associated with podocyte injury, which secondarily leads to mesangial sclerosis [4]. Oxidized LDL induces apoptosis of podocytes and nephrin loss (a key component of the glomerular filtration barrier), and increases albumin diffusion in podocyte monolayers in vitro [7].

The evidence for dyslipidemia as an independent risk factor for renal disease development and/or progression is not as strong in clinical human studies as it is in experimental studies. Existing evidence for the involvement of dyslipidemia in the development and/or progression of CKD and the possible beneficial effects of lipid-lowering therapy on renal disease progression in humans are reviewed in this article.

## DYSLIPIDEMIA AND DEVELOPMENT OF CHRONIC KIDNEY DISEASE

Several studies have shown that dyslipidemia may be a risk factor for renal disease. In the Atherosclerosis Risk in Communities study, high triglyceride and low HDL cholesterol levels were associated with an

**Key words:** chronic kidney disease, dyslipidemia, progression.

increased risk for developing renal dysfunction [8]. Data from the Physicians' Health Study indicated that elevated total cholesterol levels, high non-HDL cholesterol levels, and LDL/HDL cholesterol ratios, as well as low HDL cholesterol levels were all associated with an increased risk of serum creatinine elevation (serum creatinine >1.5 mg/dL) during follow-up in apparently healthy men with normal renal function at baseline [9]. Low HDL cholesterol levels were also an independent risk factor for the development of incident CKD (glomerular filtration rate [GFR] <60 mL/min per 1.73 $m^2$) in the Framingham Offspring study [10]. In middle-aged dyslipidemic men included in the Helsinki Heart Study, lower HDL and higher LDL/HDL cholesterol ratios were associated with a faster decline in GFR over time in hypertensive patients [11]. In an observational study of 1428 hospital-based, ambulatory patients with an estimated GFR >70 mL/min that were followed up for 5 to 6 years, patients with serum cholesterol >350 mg/dL during the follow-up period were more likely to have a decline in renal function than patients with a maximum cholesterol level <250 mg/dL. This observation occurred both in diabetics (relative risk 2.4, 95% confidence interval 1.1–5.2) and in nondiabetics (relative risk 4.0, 95% confidence interval 1.3–12.5) [12]. In a retrospective study on essential hypertensive patients with normal GFR at baseline who were followed up for more than 13 years, baseline systolic blood pressure and mean total cholesterol levels were significant risk factors for developing renal failure (GFR <60 mL/min per 1.73 $m^2$) [13].

A prospective study evaluated 574 patients with type 2 diabetes mellitus of recent onset with normal renal function and urinary albumin excretion rate at baseline who were followed up for a mean of 7.8 years. In the multiple regression analysis, mean blood pressure and levels of total cholesterol and hemoglobin $A_{1c}$ were the main factors associated with a decrease in renal function and with an increase in albuminuria. HDL was also associated with the degree of albuminuria and duration to development of microalbuminuria [14]. In 176 patients with type 2 diabetes and normoalbuminuria, the 5-year cumulative incidence of microalbuminuria was 23%. Risk factors for the development of incipient or overt nephropathy were increased urinary albumin excretion rate, male sex, age, presence of retinopathy, and increased serum cholesterol and hemoglobin $A_{1c}$ concentrations [15]. Among 420 type 1 diabetic patients, the 10-year incidence of overt nephropathy was 12%. The adjusted relative risk for overt nephropathy associated with triglycerides in the range of 150 to 199 mg/dL was 3.2, and 3.0 for values ≥200 mg/dL, compared with baseline triglycerides <100 mg/dL [16]. Similar results were observed in a cohort of 297 type 1 diabetic patients without end-stage renal disease who were followed up for 7 years. Serum triglyceride levels were higher in patients who progressed in nephropathy than in those who did not, both in the whole cohort and in patients with normoalbuminuria at baseline, even after adjustment for systolic blood pressure, diabetes duration, gender, stage of complications at baseline, and hemoglobin $A_{1c}$ [17]. In another study, the 10-year incidence of renal insufficiency in 634 type 1 diabetic patients was associated with age, hemoglobin $A_{1c}$, hypertension, and serum HDL cholesterol levels after adjusting for the presence of microalbuminuria or albuminuria at baseline [18]. Conversely, the World Health Organization Multinational Study of Vascular Disease in Diabetes, which included 959 type 1 and 3558 type 2 diabetic patients with a mean follow-up of 8.4 years, failed to show an association of serum cholesterol with development of renal failure. Serum triglycerides were associated with appearance of renal failure only in type 2 diabetic patients [19]. Other studies have found no association between serum lipid levels and nephropathy in type 1 or type 2 diabetic patients [20–22] (See Table 1).

## DYSLIPIDEMIA AND CKD PROGRESSION

In the Modification of Diet in Renal Disease study, which included patients with moderate-to-severe renal disease of various etiologies, low HDL independently predicted a faster decline in GFR [23]. In a prospective study in 73 nondiabetic patients with primary CKD, total cholesterol, LDL cholesterol, and apolipoprotein B were all significantly associated with a rapid decline in renal function, whereas triglycerides, HDL cholesterol, and apolipoprotein A were not [24]. In another prospective study that assessed the risk of CKD progression to dialysis in a cohort of 138 patients followed up for 12 years, hypertriglyceridemia was of borderline significance for progression to dialysis in the multivariate analysis [25]. Among 104 patients with CKD who were followed up for a mean of 4.1 years, total cholesterol and urinary protein scores were positively related to the progression of renal disease [26]. However, in the Northern Italian Cooperative Study Group trial, plasma lipid levels did not significantly affect the renal outcome in a cohort of 456 patients with CKD [27]. Similarly, a small study failed to show differences in lipid parameters between patients whose renal disease progressed and those whose renal disease did not [28].

In the Early Treatment Diabetic Retinopathy Study, which included 2226 diabetic patients (934 type 1 and 1292 type 2) with retinopathy, the 5-year estimated incidence of renal replacement therapy (RRT) (defined as the need for dialysis or transplantation) was 10.2% and 9.8% for patients with type 1 and type 2 diabetes, respectively. Baseline risk factors for RRT common to type 1 and type 2 diabetes included elevated total cholesterol, serum creatinine, low serum albumin levels, and anemia. In type 2 diabetes, but not in type 1 diabetes,

**Table 1.** Development and/or progression of kidney disease and plasma lipids

| Study | Patients | Number | Follow-up | D/P | Lipid |
|---|---|---|---|---|---|
| ARIC study [8] | Population-based | 12728 | 2.9 yr | D | ↑TG, ↓HDL |
| Physician's Health Study [9] | Healthy men | 4483 | 14 yr | D | ↑TCh, ↑non-HDL, ↑LDL/HDL, ↓HDL |
| Framingham Offspring Study [10] | Population-based | 2585 | 18.5 yr | D | ↓HDL |
| Helsinki Heart Study [11] | Dyslipidemic men | 2702 | 5 yr | D | ↑LDL/HDL and ↓HDL (Only hypertensives) |
| Hsu CY et al [12] | Hospital-based ambulatory population | 1428 | 5.7 yr | D | ↑TCh |
| Segura J et al [13] | Hypertensive (retrospective) | 281 | 13.2 yr | D | ↑TCh |
| Ravid M et al [14] | T2DM | 574 | 7.8 yr | D | ↑TCh MAB and ↓ HDL |
| Gall MA et al [15] | T2DM | 176 | 5.8 yr | D | ↑TCh |
| Orchard TJ et al [16] | T1DM | 420 | 10 yr | D/P | ↑TG |
| Hadjadj S et al [17] | T1DM | 297 | 7 yr | D/P | ↑TG |
| Klein R et al [18] | T1DM | 634 | 10 yr | D/P | Decline GFR and ↑TCh Incidence RI ↓ HDL |
| Watts GF et al [70] | T1DM | 53 | 10 yr | D | Increase albuminuria ↑TCh, LDL, ApoB |
| WHO MSVDD [19] | T1DM | 3558 | 8.4 yr | D | ↑TG in DM-type 2 |
| | T2DM | 959/2559 | | | No association TCh |
| EURODIAB [20] | T1DM | 250 | 7.4 yr | D | No association TCh or TG |
| Wirta OR et al [21] | T2DM | 109 | 5.8 yr | D/P | No association TCh |
| Oue T et al [22] | T2DM | 67 | 10 yr | D/P | No association TCh, HDL, TG |
| MDRD Study [23] | CRF | 840 | 2.2 yr | P | ↓HDL |
| Samuelsson O et al [24] | CRF non-DM | 73 | 3.2 yr | P | ↑TCh, ↑ LDL, ↑Apo B |
| Massy ZA et al [25] | CRF | 138 | 12 yr | P | ↑TG, ↓HDL (univariate) |
| Washio M et al [26] | CRF | 104 | 4.1 yr | P | ↑TCh |
| Locatelli F et al [27] | CRF | 456 | 2 yr | P | No relationship |
| Cappelli P et al [28] | CRF | 52 | 1 yr | P | No relationship |
| Ravid M et al [30] | T2DM with MAB | 94 | 5 yr | P | ↑TCh |
| Solini A et al [31] | T2DM with MAB | 65 | 4 yr | P | ↑TCh and HindIII polymorphism of LPL |
| Yokoyama H et al [32] | T2DM and nephropathy | 182 | | P | ↑TCh |
| Smulders YM et al [33] | T2DM with MAB | 58 | 24 m | P | ↑TG, ↓HDL |
| Nielsen S et al [34] | T2DM normo or MAB | 32 | 5.5 yr | P | No association |
| Krolewski AS et al [35] | T1DM and Nephropathy | 439 | 8 yr | P | ↑TCh |
| EURODIAB [36] | T1DM with MAB | 352 | 7 yr | P | ↑ TG (univariate) |
| Mulec H et al [37] | T1DM and nephropathy | 30 | 2.5 yr | P | ↑TCh, ↑TG, ↑Apo B |
| ETDRS study [29] | DM and retinopathy | T1 934 | 6.5 yr | P | T1DM ↑ TCh |
| | | T2 1232 | 5.9 yr | | T2DM ↑ TCh and TG |

Abbreviations are: D, development; P, progression; ARIC, Atherosclerosis Risk In Communities (study); yr, years; TG, triglycerides; HDL, high-density lipoprotein; TCh, total cholesterol; LDL, low-density lipoprotein; LDL/HDL, ratio LDL/HDL; T2DM, type 1 diabetes mellitus, MAB, microalbuminuria; T2DM, type 2 diabetes mellitus; GFR, glomerular filtration rate; RI, renal insufficiency; Apo B, apolipoprotein B; CRF, chronic renal failure; LPL, lipoprotein lipase; m, months.

elevated triglycerides were also a risk factor for RRT [29]. In other studies of type 2 diabetic patients, baseline levels of serum cholesterol predicted the progression of nephropathy [30–32]. In another study, serum triglyceride and HDL cholesterol levels were associated with progression [33], but another study found no association between renal disease progression and lipid levels in this subset of patients [34]. In type 1 diabetic patients, both serum cholesterol and triglyceride levels have been associated with progression of nephropathy in some studies [35–37] (see Table 1).

The independent association between hypercholesterolemia and/or hypertriglyceridemia and elevated urinary albumin excretion rate in nondiabetic populations is also controversial and inconsistent. Both negative and positive results have been reported, and there is no agreement on the lipid fraction involved [38–42].

These studies indicate an association between hyperlipidemia and renal disease development and/or progression, suggesting that hyperlipidemia is a risk factor for renal disease, although no definitive conclusions can be drawn. It is also not clear whether dyslipidemia increases the renal risk in those without other risk factors for kidney disease, because most studies that have evaluated the effects of dyslipidemia on renal disease have been performed with patients with pre-existing renal disease or other risk factors for renal disease, such as hypertension and diabetes. The risk of loss of renal function associated with dyslipidemia seems to be highest in those with moderate-to-severe renal disease and other renal risk factors, such as hypertension and diabetes. Another aspect that remains unanswered is which lipoprotein or lipoproteins better predict renal disease development and/or progression, because the data are inconsistent regarding the ability of cholesterol (or its fractions) and/or triglycerides to predict the progression of renal disease [43]. Finally, in some of these studies, the possible role of unmeasured confounders, such as the metabolic syndrome,

cannot be ruled out. In fact, the metabolic syndrome, which is associated with high triglyceride and low HDL cholesterol levels, has been recently associated with the development of CKD during follow-up in the Atherosclerosis Risk in Communities study [44].

## RENAL DISEASE PROGRESSION AND LIPID-LOWERING TREATMENT

Although no large, randomized, controlled trials have evaluated the effect of treating hyperlipidemia on the progression of kidney disease, there is an increasing amount of evidence that lipid-lowering agents, particularly statins, may have a renoprotective effect. A post hoc subgroup analysis of the Cholesterol And Recurrent Events study, in a randomized trial of pravastatin versus placebo in patients with a history of myocardial infarction, demonstrated that treatment with the statin was associated with a reduced rate of renal function loss in patients with moderate-to-severe renal failure, especially in those with proteinuria [45]. The MRC/BHF Heart Protection Study was a randomized, placebo-controlled trial that evaluated the effects of lowering serum cholesterol with simvastatin in patients with previous cardiovascular disease or diabetes (5903 diabetic patients and 14,573 nondiabetic patients). Allocation to simvastatin (40 mg/day) was associated with a smaller increase in serum creatinine during a mean follow-up of 4.6 years, both in diabetic and nondiabetic patients. This protective effect was slightly greater in diabetic patients [46]. In the Greek Atorvastatin and Heart Disease Evaluation study, 1600 patients with established coronary heart disease were randomized to atorvastatin or placebo. A post hoc analysis demonstrated that, over the 36 months of follow-up, patients allocated to atorvastatin showed a 12.2% increase in creatinine clearance (CrCl) compared with a 5.2% decrease in statin-free patients; similar results were observed in the subgroup of diabetic patients [47]. Conversely, in a substudy of the Lescol Intervention Prevention Study, which assessed the effect of fluvastatin (80 mg/day) on major adverse cardiac events after a first successful transcatheter therapy in patients with renal dysfunction ($N = 310$) and those without it ($N = 1248$), renal function remained stable throughout the follow-up. The predicted clearance-time profile was not influenced by fluvastatin therapy, regardless of baseline CrCl [48]. In a pooled analysis of data from more than 10,000 hyperlipidemic patients included in the clinical-development program of rosuvastatin, mean GFR was higher when compared with baseline both early and later in the course of rosuvastatin treatment (5–40 mg/day); no change in GFR was observed in the placebo group. Among patients who received long-term rosuvastatin treatment (≥96 weeks), GFR was unchanged or tended to increase, rather than decrease, which suggests that this drug slows the progression of renal disease [49].

A recent meta-analysis of 13 small controlled trials on patients ($N = 384$) with CKD, more than half of whom had diabetes, suggested that lipid-lowering agents, most of which were statins, were renoprotective, as shown by a significantly lower rate of decline in GFR and a reduction in urinary protein excretion [50]. In this meta-analysis, longer follow-up correlated with the amount of improvement in GFR from treatment. However, there was high heterogeneity between the trials, which may be due to the small number of trials, sample size, differences in the etiology of renal disease, duration of treatment, type and dose of statin, severity of albuminuria at baseline, and methodologic differences in GFR and albuminuria measurements. Thus, these data should be interpreted with caution. In hypertensive dyslipidemic patients with mild renal dysfunction, treatment with pravastatin was also associated with a decline in renal function (assessed by serum creatinine) that was slower than that of a matching group given a placebo [51]. In a 1-year prospective, placebo-controlled, open-label study on patients with CKD, proteinuria, and hypercholesterolemia, patients receiving atorvastatin had a small, non-significant decline in CrCl, whereas those receiving placebo showed a significant decrease in renal function [52].

There is also evidence of a synergistic effect between statins and renin-angiotensin system inhibitors on renal protection. In the previously mentioned study, patients had already been treated with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, and allocation to atorvastatin was associated with stabilization of renal function at 1 year compared with a decrease in CrCl in the untreated group [52]. Furthermore, in this and other studies, statins added to angiotensin-converting enzyme inhibitors or angiotensin receptor blocker resulted in further reduction of proteinuria [52–54].

Statins have also been reported to reduce albuminuria in patients with nephrotic syndrome [55] and chronic glomerulonephritis [54, 56], in normolipidemic, well-controlled hypertensive patients [53] and in normotensive and hypertensive type 2 diabetic patients [57–61] in most studies, although negative results have been reported in some studies of type 1 and type 2 diabetic patients [62–64]. Conversely, the Prevention of Renal and Vascular End-stage Disease Intervention Trial failed to show a beneficial cardiovascular or renal effect (reduction in microalbuminuria) of pravastatin in 854 participants with microalbuminuria after 4 years of treatment [65].

Taken together, these studies suggest that treatment with statins may reduce the rate of progression of renal damage in patients with coronary heart disease or other cardiovascular diseases, in patients with diabetes

**Table 2.** Effect of lipid-lowering drugs on renal disease progression

| Study | Drug | Patients | Number | Follow-up | Results |
|---|---|---|---|---|---|
| CARE study [45] | Pravastatin | MI<br>(CRF) | 4159<br>(690) | 58,9 m | ↓Renal loss |
| MRC/BHF HPS study [46] | Simvastatin | CVD or DM | 5903 DM<br>14572 non-DM | 4,6 yr | ↓ Increase in sCr in DM & non-DM |
| GREACE study [47] | Atorvastatin | CHD | 1600 | 3 yr | ↑GFR |
| LIPS study [48] | Simvastatin | CAD and PCA<br>(CRF) | 1558<br>(310) | 3–4 yr | No difference in GFR vs. PLA |
| Vidt DG et al [49] | Rosuvastatin | Hyperlipidemic | 10.000 | Up to 3.8 yr | GFR tendency ↑ |
| Fried LF et al [50] | Mainly statins | Meta-analysis | 384 | | Preserved GFR |
| Imai Y et al [51] | Pravastatin | Hypertensive CKD | 57 | 6 m | No ↑ sCr with treatment |
| Bianchi S et al [52] | Atorvastatin | CKD treated with RAS inhibitors | 56 | 1 yr | Preserved GFR |
| Buemi M et al [56] | Fluvastatin | IgA nephropathy | 21 | 6 m | No Δ GFR but ↓ UAE |
| Lam KS et al [71] | Lovastatin | DM-type 2 | 34 | 2 yr | Lower ↓ GFR |
| VA-HIT [69] | Gemfibrozil | CHD<br>(CRF) | 2532<br>399 | 61 m | None |
| DAIS [68] | Fenofibrate | DM-type 2 + CHD | 312 | 38 m | ↓ Appearance/progression UAE |
| Helsinki Heart Study [11] | Gemfibrozil | Dyslipidemic | 2702 | 5 yr | None |

Abbreviations are: CARE, Cholesterol Amd Recurrent Events (study); MI, myocardial infarction; CRF, chronic renal failure; m, months; HPS, Heart Protection Study; CVD, cardiovascular disease; DM, diabetes mellitus; yr, years; sCr, serum creatinine; GREACE, Greek Atorvastatin and Heart Disease Evaluation (study); CHD, coronary heart disease; GFR, glomerular filtration rate; LIPS, Lescol Intervention Prevention Study; CAD, coronary artery disease; PCA, percutaneous coronary angioplasty; PLA, placebo; RAS, renin-angiotensin system; IgA, immunoglobulin A; Δ, variation; UAE, urinary albumin excretion; VA-HIT, Veterans Affairs High Density Lipoprotein trial; DAIS, Diabetes Atherosclerosis Intervention Study.

and hyperlipidemia, or in those with CKD. Although the possible renoprotective mechanisms of statins may be due to the LDL lowering effect, data suggest that they may be related to their pleiotropic effects. In fact, in a randomized, crossover study that compared the effects of simvastatin and cholestyramine in 26 microalbuminuric type 2 diabetic patients, despite a similar reduction in plasma lipids, only simvastatin reduced urinary albumin excretion rate [58]. Statins prevent the development of glomerular scarring in obese Zucker rats and Dahl salt-sensitive rats. Statins also inhibit the proliferation of several cell lines (mesangial cells, renal, tubular, or vascular smooth muscle cells) and induce apoptosis. Statins inhibit the release of chemokines and cytokines by mesangial cells and monocytes. They also inhibit the production of matrix components, such as collagen or fibronectin, by mesangial cells. In addition, statins improve endothelial function, which may have potentially beneficial hemodynamic renal effects [66]. In patients with polycystic kidney disease, simvastatin treatment for 4 weeks produced a 6.5% and 25% greater increase in GFR and effective renal plasma flow, respectively, compared with placebo [67]. Statins also inhibit oxidized LDL-induced apoptosis, loss of nephrin in glomerular podocytes, and increased albumin diffusion in podocyte monolayers, thus providing a rationale for the antiproteinuric effect of statins [67].

Statins appear to have important potential in the treatment of progressive renal disease, although further studies with humans are required to confirm this. The Study of Heart and Renal Protection (SHARP) may help to elucidate this issue. SHARP is a large-scale, randomized, placebo-controlled trial designed to evaluate the effects of cholesterol-lowering treatment with simvastatin (20 mg/day) plus ezetimibe (10 mg/day) on major cardiovascular events in patients with CKD without known cardiovascular disease. This study will include 9000 patients: 6000 with CKD (serum creatinine ≥1.5 mg/dL in women and ≥1.7 mg/dL in men) and 3000 on dialysis. The primary outcome will be the time to a first cardiovascular event, defined as a composite of myocardial infarction, cardiac death, stroke, or coronary or noncoronary revascularization. Progression of renal disease will be a secondary outcome of the study.

The possible beneficial effect of fibrates on renal function has been evaluated in a few studies, and the results are inconsistent. In the Helsinki Heart study, no beneficial effect of gemfibrozil on renal function during follow-up was observed in male hyperlipidemic patients [11]. In contrast, in a post hoc analysis of data from the Diabetes Atherosclerosis Intervention Study on patients with type 2 diabetes mellitus and coronary heart disease, this randomized trial of fenofibrate versus placebo showed that the progression to microalbuminuria was reduced in the fenofibrate group after 38 months of follow-up [68]. Conversely, in a post hoc analysis of the Veterans Affairs High Density Lipoprotein trial on patients with coronary heart disease and HDL cholesterol complex level ≤40 mg/dL, LDL cholesterol complex ≥140 mg/dL, and triglycerides ≤300 mg/dL who were randomized to gemfibrozil or placebo, 399 patients had moderate chronic renal failure. Gemfibrozil did not significantly modify the rate of change in renal function in these patients compared with the placebo group after a median follow-up of 61.4 months. Furthermore, active treatment did

not significantly affect the likelihood of developing renal failure in patients with baseline GFR ≥60 mL/min per 1.73 m2 [69]. Thus, there is no evidence for a nephroprotective effect of treatment with fibrates (see Table 2).

## CONCLUSION

There is increasing evidence for an association of dyslipidemia and the occurrence and progression of renal disease in both diabetic and nondiabetic patients. Treatment with statins seems to ameliorate the progression of renal disease, although it is unclear whether this is due to the lowering of LDL cholesterol or to the pleiotropic effects of statins. However, these findings require confirmation by large, prospective, randomized trials such as the SHARP trial.

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