Management of hyperlipidemia in CKD

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MECHANISMS OF DYSLIPIDEMIA IN CKD

Table 3: Mechanisms of Dyslipidemia in Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Protein</th>
<th>Change</th>
<th>Effect on Plasma Lipids or LP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoA-1</td>
<td>↓</td>
<td>HDL</td>
</tr>
<tr>
<td>LCAT</td>
<td>↑</td>
<td>HDL-C, HDL-2/HDL-3</td>
</tr>
<tr>
<td>CETP</td>
<td>↑</td>
<td>HDL-C</td>
</tr>
<tr>
<td>ACAT</td>
<td>↑</td>
<td>VLDL-C, ↓ HDL-C</td>
</tr>
<tr>
<td>LPL</td>
<td>↑</td>
<td>Trig (↑ delipidation of VLDL and CM)</td>
</tr>
<tr>
<td>VLDL receptor</td>
<td>↑</td>
<td>VLDL, Trig</td>
</tr>
<tr>
<td>Hepatic lipase</td>
<td>↑</td>
<td>IDL, CM remnants, HDL-TG, Trig, LDL-TG</td>
</tr>
<tr>
<td>LRP</td>
<td>↑</td>
<td>IDL, CM remnants</td>
</tr>
<tr>
<td>ApoCII/CIII ratio</td>
<td>↓</td>
<td>Trig (↑ LPL activity)</td>
</tr>
<tr>
<td>Pre-β HDL</td>
<td>↑</td>
<td>Trig (↑ LPL activity)</td>
</tr>
</tbody>
</table>

Adapted from Vaziri (4).

↓ = decreases; ↑ = increases; ACAT = acyl-CoA (cholesterol acyl) transferase; Apo = apoprotein; CETP = cholesterol ester transferase protein; CM = chylomicron; DGAT = acyl-CoA diacylglycerol acyl transferase; HDL = high-density lipoprotein; HDL-C = high-density lipoprotein cholesterol; HDL-TG = high-density lipoprotein triglyceride; IDL = Intermediate-density lipoprotein; LCAT = lecithin cholesterol acyl transferase; LDL-TG = low-density lipoprotein triglyceride; LP = lipoproteins; LPL = lipoprotein lipase; LRP = low-density lipoprotein receptor-related protein; Trig = triglyceride; VLDL = very-low-density lipoprotein; VLDL-C = very-low-density lipoprotein cholesterol; VLDL-TG = very-low-density lipoprotein triglyceride.
Background on Dyslipidemia in CKD

In advanced chronic kidney disease (CKD), the lipid profile is characterized by the following:

- Markedly elevated triglycerides and triglyceride-rich apoB-containing lipoproteins
- Decreased HDL-cholesterol (HDL-C)
- Minimal to no change in LDL-cholesterol (LDL-C)

This profile has been linked to high incidence of cardiovascular (CV) morbidity and mortality

**Table 2. Secondary Causes of Dyslipidemia**

<table>
<thead>
<tr>
<th>Medical Conditions</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>The nephrotic syndrome</td>
<td>13-cis-retinoic acid</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Highly active antiretroviral therapy</td>
</tr>
<tr>
<td>Excessive alcohol consumption</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Liver disease</td>
<td>β-Blockers</td>
</tr>
<tr>
<td></td>
<td>Androgens</td>
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<tr>
<td></td>
<td>Oral contraceptives</td>
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<td></td>
<td>Corticosteroids</td>
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<tr>
<td></td>
<td>Cyclosporine</td>
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<tr>
<td></td>
<td>Sirolimus</td>
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</table>

* Reproduced from reference 30.
The major determinants of dyslipidemia in CKD patients

- GFR,
- The presence of diabetes mellitus,
- Severity of proteinuria,
- Use of immunosuppressive agents,
- Method of renal replacement,
- Comorbidity
- Nutritional status
Management of hyperlipidemia in CKD
Clinical guidelines

Guidelines for the management of chronic kidney disease

Adeera Levin MD, Brenda Hemmelgarn MD PhD, Bruce Culleton MD MSc, Sheldon Tobe MD, Philip McFarlane MD PhD, Marcel Ruzicka MD PhD, Kevin Burns MD, Braden Manns MD MSc, Colin White MD, Francoise Madore MD MSc, Louise Moist MD MSc, Scott Klarenbach MD MSc, Brendan Barrett MD MSc, Robert Foley MD MSc, Kailash Jindal MD, Peter Senior MBBS PhD, Neesh Pannu MD MSc, Sabin Shurrarow MD, Ayub Akbari MD, Adam Cohn MD, Martina Reslerova MD PhD, Vinay Deved MD, David Mendelsohn MD, Gihad Nesrallah MD, Joanne Kappel MD, Marcello Tonelli MD SM, for the Canadian Society of Nephrology

See related commentary by Eknoyan, page 1107
Recommendations for Monitoring Dyslipidemia in CKD

Lipid profiles should be measured after an overnight fast (ideally ≥ 12 h duration)

Total cholesterol, LDL-C, HDL-C and triglycerides should be measured

Fasting lipid profiles should be measured no sooner than 6 weeks after initiation or change in pharmacologic therapy

Thereafter, lipid profiles should be monitored every 6–12 months if the results could influence subsequent therapeutic decisions

**Recommendations for Monitoring for Adverse Effects of Medication**

Serial monitoring of creatinine kinase and alanine aminotransferase:

- Not required for asymptomatic patients with CKD taking a low to moderate dose of statin (≤20 mg/d of simvastatin or atorvastatin, or an equivalent dose of another statin)
- Should be measured every 3 months for patients with stage 4 CKD who are taking a moderate to high dose of statin (≥40 mg/d of simvastatin or atorvastatin, or an equivalent dose of another statin)

A statin and fibrate should not be coadministered to patients with stage 4 CKD because of the risk of rhabdomyolysis

Treatment
The Unique Character of Cardiovascular Disease in Chronic Kidney Disease and Its Implications for Treatment with Lipid-Lowering Drugs

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Abstract

Although the risk for cardiovascular disease (CVD) is high in individuals with chronic kidney disease (CKD), there are very limited data to guide the use of lipid-lowering drugs (LLDs) in this population because the major trials of LLDs in the general population have included very few individuals with CKD. The pathophysiologic and epidemiologic differences of CVD in the CKD population suggest that the study findings derived in the general population may not be directly applicable to those with CKD, and the few trials that have been directed at patients with kidney disease have not shown clear clinical benefits of LLDs. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDQI)
### Evidence for Lipid-lowering Therapy in CKD: Subgroup Analyses of Major Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin pooling project</td>
<td>4491 patients with eGFR 30-60 mL/min</td>
<td>Pravastatin reduced risk of composite endpoint (time to MI, coronary death or revascularization; HR 0.77)</td>
<td>Suggested benefit in secondary prevention setting</td>
</tr>
<tr>
<td>Heart Protection Study</td>
<td>375 patients with serum creatinine 1.25 – 2.28 mg/dL (women), 1.48 – 2.28 mg/dL (men)</td>
<td>Simvastatin reduced risk of first major vascular event (HR 0.70)</td>
<td>Supports benefit of treatment with statins in relatively mild CKD</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>6517 hypertensive adults with undefined &quot;renal dysfunction&quot;</td>
<td>Atorvastatin lowered the risk of nonfatal MI and fatal CHD (HR 0.61)</td>
<td>Further supports a role for statins in relatively mild CKD</td>
</tr>
</tbody>
</table>

Updated Recommendations for Lipid-lowering Therapy in CKD

It is advisable to aggressively treat individuals who have an eGFR of 30 to 60 mL/min/1.73 m² and have known CHD.

Updated Recommendations for Lipid-lowering Therapy in CKD

It may be advisable to treat those with high risk for atherosclerotic cardiac events regardless of initial LDL level to achieve a marked (at least 30 to 40%) reduction in LDL.

A lower goal LDL of 70 mg/dL may be a reasonable therapeutic option in patients with CKD.

The increase in mortality in hemodialysis patients at lower cholesterol levels demands caution within this population.

KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease
In adults aged ≥50 years with eGFR <60 ml/min/1.73 m² but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), is recommended treatment with a statin or statin/ezetimibe combination. (1A)
In adults aged 18-49 years with CKD but not treated with chronic dialysis or kidney transplantation, is suggested statin treatment in people with one or more of the following (2A):

- Known coronary disease (myocardial infarction or coronary revascularization)
- Diabetes mellitus
- Prior ischemic stroke
- Estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%
In adults with dialysis-dependent CKD, is suggested that statins or statin/ezetimibe combination not be initiated. (2A)

In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, is suggested that these agents be continued. (2C)

In adult kidney transplant recipients, is suggested treatment with a statin. (2B)
Lipid Management Guidelines for Adults with Chronic Kidney Disease

May 31, 2016 | Lara Kovell

Overview

Chronic kidney disease (CKD), defined by at least 3 months of impaired kidney function or albuminuria, has been shown in multiple studies to be associated with an increased risk of cardiovascular disease (CVD).1 While CKD is often the result of hypertension and diabetes, both impaired kidney function and albuminuria are CVD risk factors independent of the presence of hypertension and diabetes.

In a meta-analysis of over 1.4 million people, there was a linear increase in cardiovascular mortality seen with decreasing estimated glomerular filtration rate (eGFR) below a threshold eGFR of 75 mL/min/1.73 m², with mortality rates twice as high in stage 3 CKD (eGFR 30-59 mL/min/1.73 m²) and three times as high in stage 4 CKD (eGFR 15-29 mL/min/1.73 m²).2 Patients with CKD have also been shown to have similar rates of myocardial infarction (MI) or coronary heart disease (CHD) compared to those with diabetes, which is why it is considered a CHD equivalent by many thought leaders.3
Pharmacotherapy and Dosing of Statins in Adults With CKD adults ≥50 years

In more advanced stages of CKD (Stage 3-5, eGFR <60 mL/min/1.73 m²) more than 50 years old, treatment with combination statin plus ezetimibe is recommended.
Pharmacotherapy and Dosing of Statins in Adults With Stage 1 or 2 CKD (eGFR > 60 mL/min/1.73 m²)

Since drug toxicity is less of a concern with better renal excretion, those with Stage 1 or 2 CKD (eGFR > 60 mL/min/1.73 m²) can be treated in the same way as the general population.
Baseline transaminase levels should be measured in all CKD patients prior to starting statin therapy, though routine transaminase for CK levels is not recommended in the absence of clinical evidence of hepatotoxicity or myopathy.
Dyslipidemia of kidney disease

Attman, Per-Ola; Samuelsson, Ola
Why Aren't Statins Powerfully Effective in Stage 4 CKD?

Statins are not very effective in reducing triglyceride-rich apoB- and apoC-containing lipoproteins.

This is the major lipoprotein abnormality of advanced renal failure.

We should therefore not expect statins to significantly attenuate renal dyslipidemia in advanced CKD.

Risk Reduction with Statins in Renal Dyslipidemia

Cardiovascular risk reduction by statins?

Renoprotection by statins?

Study of Heart and Renal Protection (SHARP)

What Do We Know About the Impact of LDL-lowering in CKD?

LDL may not play as large a role in mediating CV risk in CKD as it does in the general population.
**Objectives:** To assess the effects of lowering cholesterol on major vascular events and on the rate of progression to ESRD among patients with CKD

**Subjects:** ~9,000 patients with CKD (6,000 pre-dialysis, 3,000 on dialysis)

**Interventions:** Simvastatin / ezetimibe combination vs. placebo

**Assessments:**
- Effect of LDL lowering on time to first vascular event (primary)
- Effect of treatment on progression to ESRD
- Effect of treatment on various mortality and morbidity endpoint

Association Between Cholesterol and CV Mortality

General population

<table>
<thead>
<tr>
<th>Total cholesterol, mmol/L</th>
<th>CV mortality, % per annum</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.7</td>
<td>1</td>
</tr>
<tr>
<td>4.7 - 6.2</td>
<td>10</td>
</tr>
<tr>
<td>&gt; 6.2</td>
<td>100</td>
</tr>
</tbody>
</table>

Hemodialysis patients

<table>
<thead>
<tr>
<th>Total cholesterol, mmol/L</th>
<th>Total mortality, % per annum</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.6</td>
<td>1</td>
</tr>
<tr>
<td>2.6 - 3.8</td>
<td>10</td>
</tr>
<tr>
<td>3.9 - 5.1</td>
<td>100</td>
</tr>
<tr>
<td>5.2 - 6.3</td>
<td>100</td>
</tr>
<tr>
<td>6.4 - 7.7</td>
<td>100</td>
</tr>
<tr>
<td>7.8 - 9.0</td>
<td>100</td>
</tr>
<tr>
<td>&gt; 9.0</td>
<td>100</td>
</tr>
</tbody>
</table>

Causes of CV Mortality in CKD

~25%: Directly attributable to MI (potentially avoidable with cholesterol reduction)

~75%: Other causes (cardiac arrest, arrhythmia, heart failure)
Not as dependent on cholesterol reduction

Efficacy analysis of the lipid-lowering and renoprotective effects of rosvastatin in patients with chronic kidney disease

Masanori Abe\textsuperscript{1)}, Noriaki Maruyama\textsuperscript{1)}, Yoshinori Yoshida\textsuperscript{1)}, Midori Ito\textsuperscript{1)}, Kazuyoshi Okada\textsuperscript{1)} and Masayoshi Soma\textsuperscript{1), 2)}

\textsuperscript{1)} Division of Nephrology, Hypertension and Endocrinology, Department of Internal Medicine, Nihon University School of Medicine, Tokyo, 173-8610, Japan
\textsuperscript{2)} Division of General Medicine, Department of Internal Medicine, Nihon University School of Medicine, Tokyo, 173-8610, Japan

Abstract. We aimed to assess the effects of rosvastatin treatment on lipid levels, albuminuria, and kidney function in patients with chronic kidney disease (CKD). We conducted a prospective, open-label, study of 91 patients with CKD, low-density lipoprotein cholesterol (LDL-C) levels > 120 mg/dL, and well-controlled blood pressure who were undergoing treatment with renin-angiotensin system inhibitors. Subjects were treated with 2.5 mg/day rosvastatin, which was...
Conclusion

Rosuvastatin administration reduced albuminuria, serum cystatin C levels, and inflammation, and improved lipid profiles, regardless of the presence or absence of DM, and the degree of the eGFR.
Rosuvastatin

Rosuvastatin is a high potency, efficacious and generally well tolerated statin indicated for the management of a variety of dyslipidemic states.

It is the most effective statin currently available for reducing LDL-C and non-HDL-C and increasing HDLC.

It has been shown to be safe and efficacious in women, and children with heterozygous familial hypercholesterolemia.

Expert Opin. Drug Saf. (2011) 10(6)
The adverse event rate of rosvastatin is comparable to other statins. Unlike statins that depend on CYP450 3A4 for metabolism, rosvastatin has low risk for interacting with azole antifungal medications, macrolide antibiotics, calcium channel blockers (verapamil, diltiazem) and other drugs.

Expert Opin. Drug Saf. (2011) 10(6)
Nephrotoxicity and proteinuria??

Rosuvastatin drew controversy because its use was associated with proteinuria in some patients. This was subsequently shown to be due to increased tubular secretion of low molecular weight proteins which was neither associated with nor promoted glomerulotoxicity or nephrotoxicity.

The FDA subsequently agreed that rosuvastatin within its approved dosage range of 5 - 40 mg/day did not induce renal toxicity.

Expert Opin. Drug Saf. (2011) 10(6)
Disorders of lipid metabolism in nephrotic syndrome: mechanisms and consequences

Nosratola D. Vaziri

1 Division of Nephrology and Hypertension, Departments of Medicine, Physiology, and Biophysics, University of California, Irvine, Irvine, California

Nephrotic syndrome results in hyperlipidemia and profound alterations in lipid and lipoprotein metabolism. Serum cholesterol, triglycerides, apolipoprotein B (apoB)–containing lipoproteins (very low-density lipoprotein [VLDL], immediate-density lipoprotein [IDL], and low-density lipoprotein [LDL]), lipoprotein(a) (Lp(a)), and the total cholesterol/high-density lipoprotein (HDL) cholesterol ratio are increased in nephrotic syndrome. This is accompanied by significant changes in the composition of various lipoproteins including their cholesterol-to-triglyceride, free cholesterol-to-cholesterol ester, and

glomerular proteinuria ≥3.5 g/day in adults or a urine protein/creatinine ratio of 2 to 3 mg/mg creatinine or greater in children results in nephrotic syndrome, which is characterized by the tetrad of proteinuria, hypalbuminemia, edema, and hyperlipidemia. The magnitude of hyperlipidemia and the associated alteration in lipoprotein metabolism in nephrotic syndrome parallels the severity of proteinuria. Plasma concentrations of cholesterol, triglycerides, apolipoprotein B (apoB)–containing lipoproteins (very low-density lipoprotein [VLDL], immediate-density lipoprotein [IDL], and low-density lipoprotein [LDL]), and
Triglyceride enrichment of HDL deficiency and hypo-
cet of cholesterol from per-
cETP, which increases the
cargo to IDL/LDL, work in
tement of HDL in nephrotic
duction of hepatic HDL
ed by downregulation of
bad its cholesterol cargo in
alities result in accumula-
and severe impairment of
or transport, thereby
ffect of proteinuria.

es in nephrotic syndrome
polism in nephrotic syn-
use serious consequences:
that can result in the loss of nephrons and development and
progression of chronic kidney disease\textsuperscript{21,105-107}; and an in-
crease in plasma LP(a) in nephrotic patients increases the risk
of the thromboembolic and cardiovascular complications.

Treatment of nephrotic dyslipidemia
The conventional and potential novel therapeutic strategies
for the management of dyslipidemia in kidney disease were
addressed in previous reviews in detail\textsuperscript{21,108} and are only
briefly described here. Given the central role of proteinuria in
the pathogenesis of lipid disorders in nephrotic syndrome, the
ideal target of therapeutic intervention is reversal or attenu-
ation of proteinuria.

Statins. Because upregulation of HMG-CoA reductase
contributes in part to hypercholesterolemia in nephrotic
syndrome, statins are generally effective in attenuating hy-
percholesterolemia in these patients. However, use of rosu-
fastatin should be avoided in patients with kidney disease
because it can intensify proteinuria and impair renal function.\textsuperscript{108,109}

**PCSK9 inhibitors.** As mentioned earlier in this review, the underlying mechanism of upregulation of HMG-CoA reductase and impaired clearance of LDL in nephrotic syndrome is PCSK9- and IDOL-mediated degradation of the LDL receptor. Therefore, therapeutic interventions aimed at inhibiting PCSK9 or IDOL can be highly effective in reducing LDL cholesterol in nephrotic patients. A recent clinical trial of the monthly subcutaneous administration of human monoclonal antibody against PCSK9 (Evolocumab, AMG 145) demonstrated a >50% reduction in LDL cholesterol in a large cohort of hypercholesterolemic patients.\textsuperscript{110,111} Although the study did not include patients with kidney disease, upregulation of PCSK9 and its central role in the pathogenesis of LDL receptor deficiency and increased LDL cholesterol in patients and animals with nephrotic syndrome\textsuperscript{60,61} point to the potential efficacy and specificity of the PCSK9 inhibitors in the nephrotic population. Future studies are needed to explore this possibility.

proteinuria and no evidence of renal insufficiency.

**Conclusions**

Studies conducted to evaluate the use of lipid disorders in nephrotic syndrome suggest that dysregulation of a variety of sterol biosynthesis, transport, and metabolic proteins. These findings indicate the potential for development and clinical use of therapies that can control nephrotic complications with high-resolution imaging.

**DISCLOSURE**

The author declared no conflicts of interest.

**REFERENCES**

1. Vaziri ND. Molecular obesity syndrome. Kidney Int

2. Joven J, Villabona C, metabolism in patients with...
Ezetimibe Treatment in Hypercholesterolemic Kidney Transplant Patients is Safe and Effective and Reduces the Decline of Renal Allograft Function: a Pilot Study

Ezetimibe in Hypercholesterolemic Kidney Transplant Patients

Objective: To prospectively investigate the effect of ezetimibe on renal function in kidney transplant recipients

Subjects: 56 patients with statin-resistant hypercholesterolemia (total cholesterol >200 mg/dL) after renal transplantation

Methodology:
- Study patients received additional ezetimibe therapy (10 mg/day) for 12 months (n=56)
- A group receiving statin therapy (n=28) alone served as controls
- Investigators assessed changes in total cholesterol and LDL-C concentrations, as well as in creatinine clearance.

Changes in Total Cholesterol: Statin ± Ezetimibe in Kidney Transplant Patients

Changes in LDL-C: Statin ± Ezetimibe in Kidney Transplant Patients

Changes in Creatinine Clearance: Statin ± Ezetimibe in Kidney Transplant Patients

Other Observations with Ezetimibe in Kidney Transplant Patients

The investigators reported that:

- Ezetimibe therapy was “nearly without side effects” in this population.
- Ezetimibe’s positive effects on endothelial function may be an explanation for the drug’s positive effects on renal function.
- Previous studies have indicated a direct positive effect of ezetimibe on endothelial function.

Other drugs

Sevelamer

L-carnitine
Elder et al., A meta-analysis of randomized controlled trials comparing Sevelamer vs CBBs

**Results**

- **All cause mortality** *(sevelamer vs CBBs)*
  
  13 studies, \( n=3799 \); significantly lower (46% reduction) in Sevelamer Group
  
  **RR 0.54, 95% CI 0.32–0.9**

- **Cardiovascular mortality** *(sevelamer vs CBBs)*
  
  4 studies showed \( n=2712 \); RR 0.33, 95% CI 0.07–1.64

- **Pleiotropic effects**
  
  - **Total cholesterol**
    
    Sevelamer significantly lower versus CBB recipients (MD –20.22 mg/dL, 95% CI –25.95 to –14.50 mg/dL when pooled 14 studies \( n=2039 \)).

  - **Low-density lipoprotein cholesterol**
    
    Sevelamer significantly lower versus CBBs, based on 12 studies \( n=1171 \); MD –21.64 mg/dL, 95% CI –27.88 to –15.41 mg/dL
Conclusion

Studies published from **March of 2009 to March 31, 2015** were searched in PubMed and the Cochrane Central Register of Controlled Trials.

This meta-analysis, combining **25 studies** and **4770 participants**, shows a **46% reduction** in all-cause mortality risk for sevelamer.

Sevelamer was also associated with **lower** serum Ca, higher iPTH, lower total and LDL-C, a reduced risk of hypercalcemia versus CBBs, and a marginally increased risk of combined gastrointestinal adverse events.
Triglyceride-lowering treatment in adults
KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease
In adults with CKD (including those treated with chronic dialysis or kidney transplantation) and hypertriglyceridemia, we suggest that therapeutic lifestyle changes (TLC) be advised.
Non-pharmacological treatment of high triglycerides

**TLC (therapeutic lifestyle changes):**

- Dietary modification,
- Weight reduction,
- Increased physical activity,
- Reducing alcohol intake,
- Treatment of hyperglycemia (if present).
Dietary changes that may reduce serum TGs:

- low-fat diet (≤15% total calories),
- reduction of monosaccharide and disaccharide intake
- reducing the total amount of dietary carbohydrates and use of fish oils to replace some long-chain TGs
Pharmacological treatment of high triglycerides: effects on risk of pancreatitis

Fibric acid derivatives could be considered for the rare patients with CKD and markedly elevated fasting levels of serum TG (411.3 mmol/l [>1000 mg/dl]).

If such therapy is prescribed, fibric acid derivatives must be dose-adjusted for kidney function.
Which fibric acid derivative is better?

There is limited evidence to recommend one fibric acid derivative over another in the setting of CKD and therefore any of the alternatives may be used.
Nicotinic acid has not been well studied in advanced CKD and therefore is not recommended for treatment of severe hypertriglyceridemia, given the risk of toxicity (especially flushing and hyperglycemia).
Fenofibrate and the kidney: an overview

Michael S. Kostapanos, Matilda Florantin and Moses S. Elieaf
Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece

ABSTRACT

Background Fenofibrate has been used for the management of atherogenic dyslipidaemia for many years. Reports of fenofibrate-associated increases in serum creatinine (SCR) levels raised concerns regarding deleterious effects on renal function.

Design In this narrative review, we discuss available literature on the effect of fenofibrate on the kidney.

Results Most clinical studies showed a rapid (within weeks) raising effect of fenofibrate on SCR levels. This was often accompanied by declined estimated glomerular filtration rate. Risk predictors of this adverse effect might include increased age, impaired renal function and high-dose treatment. Also, the concomitant use of medications affecting renal hemodynamics (e.g., angiotensin-converting enzyme inhibitors [ACE] and angiotensin receptor blockers) may predispose to fenofibrate-associated increased SCR levels. Interestingly, SCR increases by fenofibrate were transient and reversible even without treatment discontinuation. Furthermore, fenofibrate was associated with a slower progression of renal function impairment and albuminuria in a long-term basis. Also, fenofibrate might be protective against pathological changes in diabetic nephropathy and hypertensive glomerulosclerosis. In this context, it is uncertain whether fenofibrate-associated increase in SCR levels mirrors true renal function deterioration. Several theories have been expressed. The most dominant one involved the inhibition of renal vasodilatory prostaglandins reducing renal plasma flow and glomerular pressure. Increased creatinine secretion or reduced creatinine clearance by fenofibrate was also suggested. These hypotheses should be settled by further studies.

Conclusions Fenofibrate may not be a nephrotoxic drug. However, a close monitoring of SCR levels is relevant especially in high-risk patients. Increases in SCR levels > 30% can impose treatment discontinuation.

Keywords Albuminuria, estimated glomerular filtration rate, fenofibrate, kidney, renal function, serum creatinine.

Fenofibrate and the kidney: an overview

- Clinicians should be cautious when fenofibrate is coadministered with antihypertensive drugs that affect renal hemodynamics.

- Fenofibrate may reduce vasodilatation of the afferent arteriole, thus decreasing glomerular capillary pressure and perfusion of the kidneys.

- If this effect is combined with the vasodilatory actions of ACEi on the efferent arteriole, glomerula pressure might be further reduced resulting in prerenal azotemia.
Fenofibrate and the kidney: an overview

- Another important issue is that the nephrotoxic effect of fenofibrate might be dose dependent.
- This may be associated with the accumulation of its active metabolite fenofibric acid.
- Inappropriate use of fenofibrate in patients with impaired renal function (creatinine clearance < 50 mL/min) can result nephrotoxicity.
Fenofibrate and the kidney: an overview

- Increases in SCr levels are transient and reversible even without treatment discontinuation,
- Fenofibrate can limit proteinuria, which is an independent risk factor for both CV events and CKD,
- Fenofibrate was associated with long-term benefits on renal function. However, a close monitoring of SCr levels is relevant especially in high-risk patients.
- Increases in SCr levels 30% can impose treatment discontinuation.
**Risk predictors of raising serum Cr level**

- increased aged
- impaired renal function
- high dose treatment
Fibrate treatment can increase serum creatinine levels

Sir,

We read with great interest the recently published article by Broeders et al. with regard to the fibrate-induced increase in blood urea and creatinine [1]. Taking into account these findings, we retrospectively reviewed the charts of patients treated with fibrates, in the lipid clinic of our university hospital. In the study we included patients without any evidence of renal dysfunction, not receiving nephrotoxic agents or drugs that could affect renal function (such as angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory drugs, aminoglycosides etc), with available serum urea and creatinine levels before and after treatment with fibrates.

Interestingly, in accordance to the results of Broeders et al., a significant increase in serum creatinine levels was observed after ciprofibrate and fenofibrate administration (Table 1). In addition, similar elevations were observed in serum urea levels after the administration of both drugs (by 17% and 8%, respectively). These increases in serum urea and creatinine patients also receiving drugs that may affect renal function, such as kidney transplant recipients.

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Ioannina Greece

levels after the administration of both drugs (by 177% and 37%, respectively). These increases in serum urea and creatinine levels were evident at the patients’ first visit (after a mean period of 6 weeks of therapy) and remained unchanged or slightly elevated during a follow-up period of 8 months (3–18 months). However, as shown in Table 1, no significant change in serum creatinine levels was observed after gemfibrozil administration.
One possible explanation for these diverse effects of fibric acid derivatives could be the hypothesis that fibrates, such as fenofibrate, ciprofibrate and bezafibrate, impair the generation of vasodilatory prostaglandins, probably because of the activation of peroxisome proliferator-activated receptors (PPARs), which can down-regulate the expression of the inducible COX-2 enzyme [2–4]. Gemfibrozil, in contrast to the other fibrates, fails to bind and activate PPARs, which may account for the absence of nephrotoxicity observed [5].

We conclude that fibrates, possibly with the exception of gemfibrozil, can cause a small though significant increase in serum creatinine levels, which should be taken into account, especially in patients with underlying renal disease or in
Table 1. Effect of fibrates on serum creatinine levels (expressed in mg/dl)

<table>
<thead>
<tr>
<th>Fibrates</th>
<th>Serum creatinine levels</th>
<th>% change</th>
<th>Range of increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td></td>
</tr>
<tr>
<td>Fenofibrate ($n = 60$)</td>
<td>0.92 ± 0.12</td>
<td>1.03 ± 0.14*</td>
<td>12</td>
</tr>
<tr>
<td>Ciprofibrate ($n = 55$)</td>
<td>0.88 ± 0.14</td>
<td>1.03 ± 0.17*</td>
<td>17</td>
</tr>
<tr>
<td>Gemfibrozil ($n = 15$)</td>
<td>0.96 ± 0.13</td>
<td>1.02 ± 0.16</td>
<td>6</td>
</tr>
</tbody>
</table>

Values represent mean ± SD. Statistical analysis was performed using paired $t$-test and a $P$ value of less than 0.05 was considered to be significant. $^*P < 0.0001$ compared to the pretreatment values.
Alterations in Lipid Profiles in CKD

<table>
<thead>
<tr>
<th>Generally Increased Levels</th>
<th>Generally Decreased Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerids</td>
<td>Total cholesterol</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td>LDL-C</td>
</tr>
<tr>
<td>Apoprotein B</td>
<td>HDL-C</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>Apoprotein A1</td>
</tr>
<tr>
<td>IDL-C</td>
<td></td>
</tr>
</tbody>
</table>

Lipid Management in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2013 Clinical Practice Guideline

Marcello Tonelli, MD, SM; Christoph Wanner, MD; for the Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members (1)

Article, Author, and Disclosure Information

Abstract

Description: The Kidney Disease: Improving Global Outcomes (KDIGO) organization developed a clinical practice guideline in 2013 on lipid management and treatment of all adults and children with chronic kidney disease (CKD). All forms of CKD are included (non–dialysis-dependent, dialysis-dependent, and kidney transplant recipients).

Methods: The KDIGO Lipid Guideline Development Work Group defined the scope of the guideline and the evidence hierarchy, identified and appraised the evidence, determined the recommendations, and prepared the draft guideline. The guideline was then reviewed by the KDIGO members and by external experts, and the final guideline was approved by the KDIGO Executive Committee.

Related Articles

Update in Nephrology
Annals of Internal Medicine, 152 (11): 721-725

Management of Dyslipidemia for Cardiovascular Disease Risk Reduction: Synopsis of the 2014
From: Lipid Management in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2013 Clinical Practice Guideline


Figure Legend:
Algorithm for cholesterol-lowering treatment in persons with CKD.
Boxes represent recommendations about whether to prescribe a statin regimen. Boxes with dark and medium green fill represent strong recommendations; lighter green and white boxes represent weak recommendations. Recommended statin regimens are shown in Table 1 and include statin monotherapy or statin/ezetimibe for those with CKD stage 3a to 5 and statin monotherapy for all other CKD populations. CKD = chronic kidney disease; HD = hemodialysis; PD = peritoneal dialysis.
Thanks for your attention