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Dyslipidaemia and renal disease - pathophysiology and lipid lowering therapy in patients with impaired renal function

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Dyslipidaemia and Renal Disease – Pathophysiology and Lipid Lowering Therapy in Patients with Impaired Renal Function

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Dyslipidaemia is a consequence of renal disease, especially the nephrotic syndrome, wherein hepatic synthesis of lipoproteins is increased and clearance decreased. The resulting lipoprotein phenotype is highly atherogenic and significantly increases the cardiovascular risk of the patients. Additionally hyperlipidaemia accelerates the progression of human renal disease and therefore its therapeutic control seems to be an important component in the treatment regimen of patients with chronic renal failure. Intensive lipid lowering by LDL apheresis was accompanied by a reduction of proteinuria in diabetic patients with a nephrotic syndrome. Several studies could demonstrate that statins reveal – beside their lipid lowering properties – a renoprotective effect by reducing glomerular cell proliferation and macrophage infiltration. Accumulating data thus indicates that lipid lowering therapy in chronic renal failure is of importance not only with respect to the cardiovascular risk of the patients but also to retard the progression of renal disease. *J Clin Basic Cardiol 2000; 3: 3–6.*

Keywords: dyslipidaemia, renal disease, lipid lowering

Dyslipidaemia reveals a complex relationship to renal disease, because severe lipid disorders can be caused by renal disease, especially the nephrotic syndrome, and hyperlipidaemia itself is not only involved in the cardiovascular risk but also accelerates the progression of glomerular dysfunction. Additionally immunosuppressive therapy after renal transplantation including prednisone and cyclosporine is frequently associated with lipid disorders. Hyperlipidaemia contributes in addition to various other risk factors such as hypertension, hypercoagulopathy, increased plasma homocysteine levels and increased oxidative stress to the significantly increased cardiovascular risk in patients with chronic renal disease [1]. Lipid lowering significantly reduces the cardiovascular risk and also seems to retard the progression of renal disease [2]. The following review summarizes the abnormalities in lipid metabolism associated with renal disease as well as therapeutic procedures for lipid lowering in patients with impaired renal function.

Lipoprotein metabolism and renal disease

Hyperlipidaemia is a striking feature of the *nephrotic syndrome* and is characterized by a significant increase in plasma levels of total cholesterol, LDL-cholesterol and triglyceride, as well as a decrease in HDL2-cholesterol and increase in HDL3-cholesterol (Table 1). Plasma concentrations of apoB, apoCII, apoCIII and apoE are increased, and some patients reveal lipiduria, but without detectable intact immunoreactive apoAI particles. Because serum albumin concentrations are inversely related to serum lipid levels, hypo-albuminaemia, low plasma oncotic pressure and low plasma viscosity have been proposed as possible stimuli that trigger the increased production of apoB [3]. Beside this increased synthesis of apoB containing lipoproteins also the catabolism of triglyceride-rich lipoproteins by lipoproteinlipase was found to be impaired. The diminished clearance of triglyceride-rich lipoproteins is the result of an increase in apoCIII, exerting an inhibitory effect on lipoproteinlipase, and of a reduction of apoCII, an activator of lipoproteinlipase. The reduced activity of hepatic lipase further enhances the impaired removal of remnant particles [4]. Thus *hypertriglyceridaemia* associated with the nephrotic syndrome results from *impaired catabolism of triglyceride-rich lipoproteins,* while *hypercholesterolaemia* is due to *increased hepatic synthesis of apoB-containing lipoproteins* [5].

Table 1. Changes of plasma lipid values in renal disease

	Cholesterol	Triglyceride	VLDL	LDL	HDL
Nephrotic syndrome	++	+	+	++	–
Renal insuffiency	/	++	++	/	/
Renal transplantation	++	+	+	++	/

+ modest increase; ++ significant increase

The decreased serum albumin levels are furthermore associated with an increase in mass and activity of *cholesterol-ester-transfer protein* (CETP) [6], resulting in triglyceride enrichment of HDL- and LDL-particles. Because albumin substitution is able to reverse the increased CETP mass and activity, an increased binding of free fatty acids on lipoprotein particles paralleled by an increase in their native charge was thought to be causal for the CETP abnormalities observed in the nephrotic syndrome.

Patients with renal disease reveal an increase in their *Lp(a) serum level,* and thus a higher cardiovascular risk. Serum levels of Lp(a), composed of an LDL-like particle and apo(a) with a high homology with plasminogen, are for the most part genetically determined, increase with impaired renal function and decrease after renal transplantation [7].

In animal studies a *decline in hepatic LDL-receptor expression* and thus receptor mediated uptake of LDL particles could be demonstrated in the nephrotic syndrome [8]. The impaired receptor mediated uptake of LDL particles results in a prolonged circulation and thus triglyceride enrichment of LDL by the increased CETP activity. After hydrolysis triglyceride enriched LDL become small dense and highly atherogenic lipoproteins [9]. The small dense LDL particles are more prone to oxidative modification than larger LDL subfractions, comparable to the increased oxidizibility of VLDL-subfractions prepared from patients with renal insufficiency [10].

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Lipoproteins and glomerular dysfunction

In *diabetic patients* dyslipidaemia was found to be a predictor of albuminuria in the cause of nephropathy [11]. Treatment of hyperlipidaemia, in addition to an optimized glycemic control and antihypertensive medication, reduced the progression from microalbuminuria to macroalbuminuria in diabetes [12, 13]. A recent study in nondiabetic patients with chronic renal insufficiency showed that elevated LDL cholesterol, total cholesterol, and apoB levels were associated with a more rapid decline in renal function [14].

The harmful effects of lipoproteins on the progression of renal disease could be due to the fact that glomerular mesangial cells express LDL-receptors [15], and that oxidized LDL exerts cytotoxic effects on mesangium cells [16]. Lipid deposition, mononuclear cell infiltration and accumulation of mesangial cell matrix components are early events in the development of glomerulosclerosis, and oxidized LDL and VLDL particles deposit in glomeruli and might thus contribute to renal injury [17].

Lipoproteins as primary initiators of glomerular disease in humans occur in lecithin-cholesterol acyltransferase deficiency and *"lipoprotein glomerulopathy"* with lipoprotein depositions in glomeruli, mesangial proliferation, and glomerulosclerosis [18].

Despite the lack of large scale intervention trials, it appears that hyperlipidaemia accelerates the progression of human renal failure and proteinuria.

Lipid lowering therapy in patients with impaired renal function

Bile acid binding resins

Bile acid binding resins inhibit enterohepatic bile acid re-circulation and thus induce an increase in hepatic bile acid synthesis from cholesterol. The lipid lowering effect of bile acid binding resins is partially compensated by an increased hepatic synthesis of triglyceride rich lipoproteins. Bile acid binding resins are now largely used as adjuncts to statin therapy for patients in whom further lowering of serum cholesterol concentrations is indicated.

Lipid lowering effect: Bile acid binding resins reduce LDL-cholesterol by 15 % and increase HDL-cholesterol by 3–5 %.

Side effects: Gastro-intestinal disorders; hyperchloraemic acidosis in children or in older patients with renal failure because chloride ions are released in exchange for bile acids.

Dose adaption for impaired renal function and drug interaction: The absorption of other drugs is reduced by bile acid sequestrants, including cyclosporine. Bile acid binding resins should therefore not be prescribed after renal transplantation. To avoid a reduced drug absorption by binding to the resin, other substances should be given one hour before or four hours after the resin. Serum triglyceride levels > 200 mg/dl are a relative and > 500 mg/dl a definitive indication against bile acid binding resins.

Statins

Statins (HMG-CoA reductase inhibitors) inhibit the key enzyme of cellular cholesterol biosynthesis, the HMG-CoA reductase. As a consequence cells express more LDL receptors, and serum LDL level decreases (Table 2).

Lipid lowering effect: LDL-cholesterol is reduced by 20–60 %, triglyceride by 15–30 %, HDL-cholesterol increases by 5–10 %.

Side effects: Gastro-intestinal upsets, muscle aches, hepatitis, myopathy, rash, peripheral neuropathy

Dose adaption for impaired renal function and drug interaction: The statins are eliminated in part by the kidneys, and serum concentrations may be higher in patients with renal disease. The predominant route of excretion is through the bile, after hepatic transformation. Patients with hepatic disease should thus be given low doses [15].

Most drug interactions are due to the hepatic metabolism of statins via cytochrome P450, which is shared by many other drugs, including digitalis, marcumar, ketokonazol, methotrexate, macrolides, cimetidine, fibrates. Among the various statins these interactions differ significantly.

None of the statins should be given to pregnant women because they are teratogenic at high doses in animals.

Fibrates

Fibrates inhibit adipose tissue lipolysis, increase lipoprotein-lipase activity, and reduce hepatic synthesis and secretion of triglyceride rich lipoproteins. Fibrates increase fatty acid beta oxidation and inhibit fatty acid synthesis (Table 3).

Most of these effects, like the increase in apoCII and decrease in apoCIII, are due to activation of the nuclear hormone receptor family, peroxisome proliferator activated receptor (PPAR) [19]. Fibrates serve as ligands for these nuclear hormone receptors, and thus regulate apoAI and apoAII transcription.

Lipid lowering effect: Fibrates reduce serum triglyceride levels by up to 50 %, LDL-cholesterol by 10–25 % and increase HDL-cholesterol by 10–30 %.

Side effects: Gastro-intestinal disorders in 2–5 % of all patients, rhabdomyolsyis in combination with statins and gallstone disease.

Dose adaption for impaired renal function and drug interaction: Up to 95 % of fibrates are bound to serum albumin and renal excretion is the main metabolic pathway. Dose adaption is therefore important, when renal function is impaired (serum creatinine 1.5–2.5 mg/dl: reduction by 30 %; serum creatinine: 2.5–5 mg/dl: reduction by 60–80 %). Low elimination of fibrates is found by haemodialysis. Drug interaction with other substances with high protein binding capacity (SH, marcumar, digitoxin) has to be considered.

Fibrates lower fibrinogen and thus exert another favourable effect on the cardiovascular risk [20], while fenofibrate and bezafibrate seem to increase serum homocysteine levels [21].

Table 2. Statin therapy – clinical studies

Substance	Dosage	Hydrophilic/ lipophilic	Studies (cardio-vasular events)
Atorvastatin (Sortis)	10–80 mg	lipophilic	AVERT
Cerivastatin (Lipobay)	0.3 mg	hydrophilic	LDS*, ENCORE
Fluvastatin (Lescol)	20–80 mg	hydrohilic	LCAS
Lovastatin (Mevacor)	20–80 mg	lipophilic	AFCAPS
Pravastatin (Pravachol, Selipran, Sanaprav)	5–40 mg	hydrohilic	WOSCOPS CARE,LIPIDS
Simvastatin (Zocord)	5–40 mg	lipohilic	MAAS,4S

* LDS: Lipids in Diabetes Sudy (results expected for 2005)

Table 3. Fibrate therapy

Substance	Dosage	Studies (cardiovascular events)
Bezafibrate (Bezalip)	400– 600 mg	BECAIT
Clofibrate (Duolip)	250–1500 mg	WHO
Etofibrate (Lipo Merz)	300–1500 mg	
Fenofibrate (Fenolip, Lipcor, Lipsin)	100– 300 mg	LDS
Gemfibrozil (Gevilon)	450–1350 mg	HHS, VA-HIT

Nicotinic acid derivatives

Nicotinic acid inhibits the mobilization of free fatty acids from peripheral tissues, thereby reducing hepatic synthesis of triglyceride and secretion of VLDL [22].

Acipimox (Olbetam) is completely absorbed by the intestinum and renally excreted within 24 hours.

Lipid lowering effect: Curvilinear changes in serum triglyceride and HDL cholesterol concentrations, linear changes in LDL cholesterol. Lowering of Lp(a) by about 30 %.

Side effects: Gastro-intestinal disorders, flush, cephalea, increase in transaminases.

Dose adaption in impaired renal function: serum creatinine 1.5 to 2.5 mg/dl: 1 × 250 mg; serum creatinine 2.5–4.0 mg/dl: 250 mg each second day; serum creatinine > 4 mg/dl: no nicotinic acid derivatives

Dialysis eliminates up to 70 % of acipimox, therefore 100 mg should be given as an additional dosage after dialysis as an additional dosage.

Lipid apheresis

The efficacy and safety of the therapeutic tool which directly removes LDL particles from circulation has already been established for cholesterol-lowering in patients with refractory hypercholesterolaemia.

Lipid lowering effects: LDL reduced by 66–77 %, Lp(a) by 50–73 % [23].

A recent case report suggests that LDL apheresis therapy is a potential new tool for intractable nephrotic syndrome in diabetes due to diabetic glomerulosclerosis, although the mechanisms by which LDL apheresis reduces proteinuria remain unclear [24].

Intervention studies

In none of the recently published large lipid intervention studies was an evaluation and subgroup analysis for patients with impaired renal function performed. The great advantage of lipid lowering drug therapy in reducing the cardiovascular risk was demonstrated for primary (AFCAPS, WOSCOPS) [25, 26], as well as for secondary intervention (BECAIT, VA-HIT, CARE, LIPID) [27–30], especially for high risk subgroups like diabetics or elderly.

Because many patients with impaired renal function also show several cardiovascular risk factors beside dyslipidaemia, like hypertension, hypercoagulopathy, diabetes, hyperhomocysteinaemia, oxidative stress, it seems to be of advantage to treat these patients according to targets in secondary prevention with LDL-cholesterol levels lower than 100 mg/dl (Table 4) [31]. The advantage of intensive LDL lowering in secondary prevention was recently demonstrated by the AVERT and post CABG study [32, 33].

Statins reveal, beside lipid lowering, various other favourable effects for the prevention of atherosclerosis, like plaque stabilization and improvement of endothelial dysfunction [34, 35].

With respect to renal function statins were shown to reduce glomerular cell proliferation and macrophage infiltration (36). These effects may be accomplished by inhibition of isoprenylation of intracellular signalling proteins such as ras protein, causing them to dissociate from the cell membrane and alter their ability to participate in signalling cascades [37]. Statins may augment the action of immunosuppressive therapy after renal transplantation [14], beside the significant improvement of lipid metabolism [38].

Table 4. Lipid targets values for secondary prevention

Cholesterol	< 200 mg/dl
Triglyceride	< 150 mg/dl
LDL	< 100 mg/dl
HDL	> 40 mg/dl
Lp(a)	< 30 mg/dl

Conclusions

Renal disease causes a highly atherogenic lipoprotein phenotype, which results from an increased synthesis of apoB containing lipoproteins and impaired metabolism of triglyceride-rich lipoproteins. With respect to the increased cardiovascular risk of patients with renal disease lipid targets values should be adapted to those for high-risk populations with LDL-cholesterol levels of 100 mg/dl and lower. Lipid lowering drug therapy might also retard the progression of renal disease and improve long-term outcome in renal transplant recipients.

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