REVIEW ARTICLE

Dyslipidemia in chronic kidney disease

Pathogenesis and intervention

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KEY WORDS

coronary heart disease, dyslipidemia, lipoprotein(a), renal failure, statins

ABSTRACT

Dyslipidemia is a known cardiovascular risk factor in subjects without kidney disease. In patients with kidney disease, however, the relation of dyslipidemia to cardiovascular risk is confounded and the underlying pathomechanisms are complex. Statins have proven to be highly effective in patients with initial stages of chronic kidney disease (CKD). Definite evidence from prospective controlled trials in hemodialyzed (diabetic) patients and transplanted patients is not available. Although no significant impact on the primary composite endpoint was observed, significant effects on secondary endpoints were noted. In our opinion, in view of excessive cardiovascular risk statins should be administered in patients with advanced CKD as well.

In 1836, Richard Bright commented on the "milky serum" of patients with (what today would be called) end-stage renal disease (ESRD) – almost certainly the first recognition of hyperlipidemia. The relation between heavy proteinuria with dyslipidemia had been noted at the beginning of the 20th century and indeed dyslipidemia in patients with nephrotic proteinuria differs in many respects from dyslipidemia in patients with chronic kidney disease (CKD) with non-nephrotic proteinuria, i.e. <3 g/day. Proteinuria *per se* is associated with dyslipidemia as discussed in detail by Kaysen.[1,2] A more detailed discussion of the situation in nephrotic proteinuria is beyond the scope of this contribution.

The causes of dyslipidemia are undoubtedly complex. An interesting new hypothesis states that prenatal programming[3], e.g. the result of intrauterine malnutrition, causes obesity, dyslipidemia, type 2 diabetes, and a deficit in nephron numbers, thus increasing in parallel cardiovascular and renal risks (FIGURE)[4]. A potential further contributor is impaired insulin resistance, a known component of metabolic syndrome and type 2 diabetes, both of which are associated with dyslipidemia and kidney disease. Dyslipidemia in type 2 diabetes has recently been reviewed by Jandeleit-Dahm[5] and by Krane[6]. Dyslipidemia[7,8], and particularly the role of lipogenesis[9] in non-diabetic CKD, have recently been reviewed by Rutkowski.

In the following we shall discuss:

1 the lipid profile in chronic kidney disease
2 the association of dyslipidemia with cardiovascular disease in CKD
3 the potential impact of dyslipidemia on progression of CKD
4 the available evidence from lipid lowering interventions in CKD.

Lipid profile and kidney disease (TABLE 1) In chronic kidney disease total cholesterol and low-density lipoprotein (LDL) cholesterol, the routine lipid parameters, are usually in the normal range or even low. Behind this apparently benign spectrum, a whole range of abnormalities are hidden.

Triglyceride concentrations are high. This is the main dyslipidemic disturbance. It is already seen in early stages of CKD and present in up to 70% of ESRD patients, but hemodialysis tends to improve triglyceridemia at least in nondiabetic patients.[10] High-density lipoprotein (HDL) cholesterol is subnormal in the majority of patients. Low HDL cholesterol has been ascribed to low activity of lecithin-cholesterol acyltransferase which normally increases the uptake of esterified

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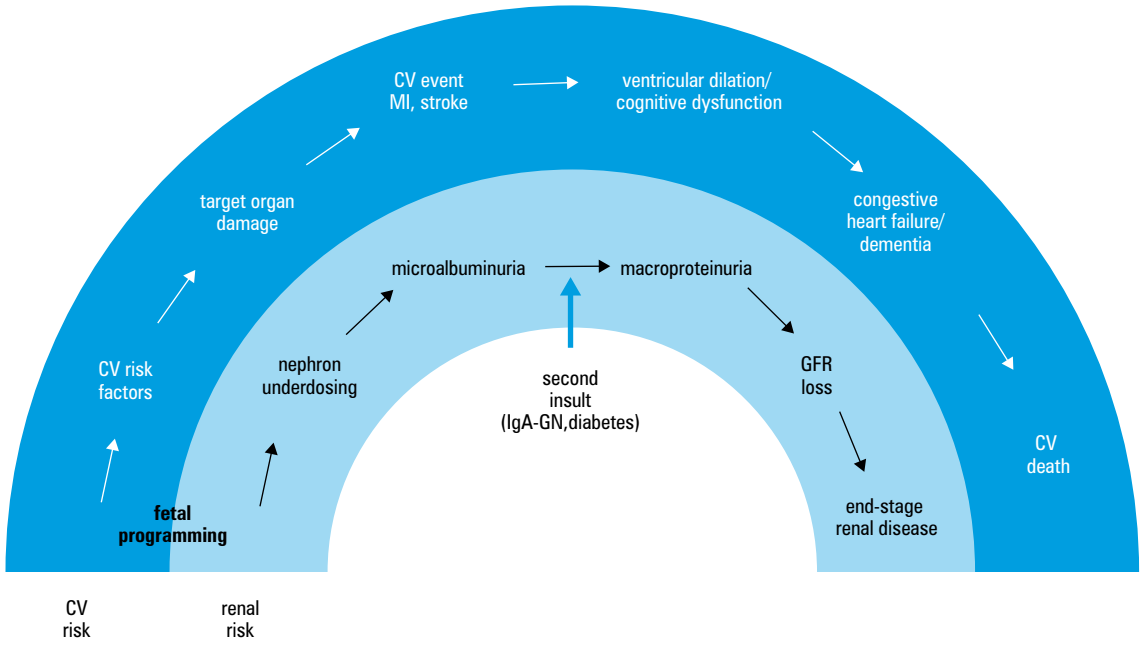

FIGURE Coevolution of cardiovascular and renal risk at adult age in individuals with intrauterine malnutrition
Abbreviations: CV – cardiovascular, GFR – glomerular filtration rate, IgA-GN – immunoglobulin A glomerulonephritis, MI – myocardial infarction

cholesterol by HDL. The change in HDL concentration is favored by the common presence of microinflammation in uremic patients.[11]

Even more marked changes are seen in the lipoprotein profile, the result of changes in lipid catabolism and to some extent lipogenesis. Decreased lipolysis is primarily the result of diminished activity of lipoprotein-lipase and hepatic lipase. Because of decreased catabolism of lipoproteins[12] and chylomicrons[13], intermediates such as chylomicron remnants and very LDL (VLDL) remnants as well as intermediate density lipoproteins accumulate and their concentrations are elevated. Because of their prolonged half-life, this is particularly true for the atherogenic small dense LDL.[14,15] LDL particles tend to be smaller, denser and more atherogenic.[16] It is important that the plasma concentration of lipid subfractions may not fully reflect the cardiovascular risk because the turnover (and by implication the residence time of lipoproteins in the circulation) are significantly altered[12]; this exposes the lipoproteins to the risk of post-ribosomal modification. Postribosomal modifications acquired during the prolonged residence time in the circulation include glycation[17], oxidation[18] and carbamylation[19]. As a result, the affinity for the classic LDL receptor is diminished and such modified lipoproteins are taken up by the scavenger receptor[20] which is increased in uremia[21] and, among others, favors the development of foam cells in atherosclerotic plaques. The normally protective HDL are to some extent transformed by incorporation of serum amyloid A (SAA) into inflammatory acute phase HDL.[22] Finally, depending on the lipoprotein(a) [Lp(a)], phenotype Lp(a) concentrations are elevated. Both Lp(a) concentration and Lp(a) phenotype, particularly small lipoprotein(a), are predictive of cardiovascular events including in renal patients.[23,24]

As indicated above the concentrations of total cholesterol and LDL cholesterol are deceivingly unremarkable. Japanese authors proposed to calculate the concentration of non-HDL cholesterol which reflects the sum of LDL and VLDL cholesterol[25] and is a clinically useful predictor of cardiovascular risk in CKD. **TABLE 2** illustrates the discrepancy between normal total cholesterol and pathological non-HDL cholesterol, based on the data of the 4D study.[26]

Lipid abnormalities are seen in the earliest stages of CKD. In the MMKD study (Mild and Moderate Kidney Disease) we followed 227 patients with primary kidney disease for 7 years, measuring Iohexol clearance at baseline and assessing doubling of serum creatinine and/or ESRD as the endpoint.[27] The study documented a progressive decrease of HDL cholesterol in the earliest stages of primary kidney disease accompanied by a continuous increase in triglycerides and a significant decrease of average Lp(a). As in nonrenal patients, Lp(a) of the low molecular weight variety increased the risk of cardiovascular events.[24]

TABLE 1 Dyslipidemia in dialysis patients

	Lipids	Lipoproteins
abnormal	low HDL-cholesterol	VLDL-remnants/IDL
	high triglyceride	chylomicron-remnants
		small dense LDL
		modifications (glycation-oxidation-carbamylation)
		AGE-ApoB
		high lipoprotein(a)
		acute-phase HDL
normal	total cholesterol	
	LDL cholesterol	

Abbreviations: AGE-ApoB – advanced glycation end product-modified apolipoprotein B, HDL – high-density lipoprotein, IDL – intermediate-density lipoprotein, LDL – low-density lipoprotein, VLDL – very LDL

TABLE 2 Non HDL-cholesterol (results of 4D study)

	Mean ±SD (mg/dl)	
cholesterol	221 ±42	
triglyceride	257 ±157	
LDL cholesterol	128 ±30	sum: 185 mg/dl (target:130 g/dl)
VLDL cholesterol	57 ±34	
HDL cholesterol	37 ±18	

Abbreviations: see TABLE 1

Association of lipid changes with cardiovascular disease Clinical observations[28] and experimental data document accelerated atherogenesis in early stages of renal damage and in ESRD. In our experimental study using the model of the apoE-/- mouse, the rate of aortic plaque growth was elevated even after uninephrectomy and this was not explained by the changes in routinely measured lipid parameters.[29]

The findings on the association of dyslipidemia with cardiovascular events in patients with ESRD has not been uniform. Obviously, the relation is confounded and the most potent confounder apparently is microinflammation.[30] Indeed, following the studies of Degoulet[31] and Lowrie[32], numerous authors found that low total cholesterol and LDL cholesterol, admittedly not measured under standard (fasting) conditions, are strong predictors of mortality in hemodialyzed patients and in these short follow-up studies only a trend was seen for increased mortality at very high cholesterol concentrations. This finding is conventionally explained as the effect of "reverse causality" or confounding by disease, specifically microinflammation). Indeed, Liu[33] found a relation overall between low serum-cholesterol and higher mortality. As observed in the general population, however, in patients without elevated CRP a consistent positive relation between serum-cholesterol and mortality was found, although this finding has not been uniformly confirmed.[34]

Dyslipidemia and progression of kidney disease In the MMKD study, 177 patients completed follow-up and the endpoint (doubling of serum-creatinine and/or ESRD) was reached in 65 patients.[27] It was found that the concentration of apolipoprotein (apo) A-IV was correlated to the presence of CKD: the hazard ratio per 1 mg/dl was 1.06 (CI 1.018–1.108). The mechanism underlying this relationship is unclear: apo A-IV activates lipoprotein lipase, has antioxidative properties and is anti-atherogenic (apo A-IV transgenic mice); in nonrenal patients low concentrations are associated with coronary heart disease.

TABLE 3 Causes of death in the 4D study

coronary heart disease	9%	
sudden death	26%	
heart insufficiency	6%	sum: 35%
other cardiovascular causes	3%	
stroke	6%	
non-cardiovascular causes	6%	

For every 1 mmol/l of low-density lipoprotein cholesterol lowering:
– 19% reduction in coronary death – as in individuals without chronic kidney disease
– 7% reduction in sudden death

Evidence from lipid lowering interventions In view of the constellation of lipid parameters with early hypertriglyceridemia described in TABLE 1, fibrates would appear to be logical candidates for the treatment of dyslipidemia in CKD, but they are not frequently used because of the substantial risk of rhabdomyolysis in such patients.[35] Alternative interventions such as dietary changes[36] or switching to polyunsaturated fatty acids[37] carry a significant risk of malnutrition and have not become popular.

In contrast, statins are widely used. In early stages of CKD, there is remarkable evidence from a metaanalysis[38] and post-hoc analyses of large cardiovascular statin trials: cardiovascular patients who had been included in the classical cardiovascular trials and who happened to have low estimated glomerular filtration rate (GFR) (CKD 2 or 3) derived similar, if not higher, cardiovascular benefit from statin therapy.[39] This was complemented by a minor but significant, retarding effect on progression of CKD.[40] This is in line with the observation in the TNT study where high dose atorvastatin had a greater impact on change in GFR than low dose atorvastatin. Cardiovascular events were reduced in diabetic and nondiabetic patients.[41]

In patients with ESRD and after transplantation the evidence is less straight forward. An observational study showed improved survival in hemodialyzed patients put on statins.[42] In contrast, however, an Australian study compared the effect of lipid lowering on carotid intima-media thickness as a readout.[43] With similarly aggressive lowering of LDL cholesterol, the maximum intima-media thickness was reduced only in cardiac patients without CKD but remained unchanged in patients with CKD.

The prospective randomized 4D study in hemodialyzed type 2 diabetic patients[26] showed that despite lowering of LDL cholesterol by up to 20 mg/day of atorvastatin to approximately 70 mg/dl, i.e. aggressive treatment targets[44], no significant effect on the primary composite endpoint (death from cardiac causes, nonfatal myocardial infarction, stroke) was seen (relative risk reduction 8% (CI 0.77–1.10). It is of note, however, that coronary heart disease accounted only for 9% (TABLE 3), while sudden death and heart failure as well as other cardiac causes for 35%. In nonrenal patients, autopsy studies showed that coronary heart disease was the major cause of sudden death. Apparently, the mechanisms of sudden death in patients with ESRD differ from those in nonrenal patients. Remarkably, the decrease of adjudicated deaths from coronary heart disease per 1 mmol lowering of LDL cholesterol was exactly the same

as found by the Collaborative Cholesterol Trialists in nonrenal patients.[45] It is of interest that the study of United States Renal Data System as well as the Dialysis Outcomes and Practice Pattern Study showed that the hazard ratio for cardiovascular death in statin treated dialysis patients was 0.63 (0.44–0.91) and 0.77 (0.61–0.97) respectively (as in the study of Seliger)[42]. We agree with the statement of Kwan[46] that statins should be administered to all CKD and ESRD patients because of their extremely good safety profile and the presumably beneficial effect, although benefit has admittedly not yet been shown in a prospective trial. The final answer will be provided in ongoing studies (Aurora, SHARP).[47,48]

A final comment on patients after renal transplantation. The ALERT (Assessment of Lescol in Renal Transplantation) study[49] failed to show a significant impact on the composite cardiac endpoint, but extended observations and analyses of specific endpoints pointed to a beneficial effect. We and others concluded[50] that – given the high rate of coronary events in transplanted patients compared to the background population – statins should be routinely administered after kidney transplantation.

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ARTYKUŁ POGLĄDOWY

Dyslipidemia u osób z przewlekłą chorobą nerek

Patogeneza i leczenie

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SŁOWA KLUCZOWE

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STRESZCZENIE

Dyslipidemia jest uznanym czynnikiem ryzyka sercowo-naczyniowego u osób bez choroby nerek. U osób z przewlekłą chorobą nerek (PChN) związek pomiędzy dyslipidemią a ryzykiem sercowo-naczyniowym jest bardziej skomplikowany, a leżące u jej podstawy patomechanizmy złożone. Skuteczność statyn w początkowych stadiach PChN jest potwierdzona. Natomiast dane z prospektywnych badań klinicznych z grupą kontrolną u chorych dializowanych i po przeszczepieniu nerki nie są rozstrzygające – chociaż nie zaobserwowano istotnego wpływu na główny złożony punkt końcowy, to jednak zaobserwowano istotny wpływ na dodatkowe punkty końcowe. W opinii autorów, ze względu na zwiększone ryzyko sercowo-naczyniowe, osoby z zaawansowaną PChN powinny być również leczone statynami.

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