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Effects of lipid-lowering drugs on intermediate-density lipoprotein in uremic patients

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Background. Patients with chronic renal failure often have alterations in lipoprotein profile including elevated very-low density lipoprotein (VLDL) and intermediate density lipoprotein (IDL), and reduced high density lipoprotein (HDL) levels. Among these changes, raised IDL has been shown as an independent risk factor for atherosclerosis in hemodialysis patients. There are a limited number of studies reporting pharmacological approaches to IDL reduction in a uremic population.

Methods. We therefore summarize the effects of lipid-lowering drugs on IDL levels in patients with chronic renal failure treated by hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD).

Results. First, a nicotinic acid analog niceritrol was given to hemodialysis patients. The drug increased HDL-cholesterol by 11%, but the reductions in VLDL-, IDL- and LDL-cholesterol were not significant. Second, CAPD patients were treated with a fibric acid derivative clinofibrate, which was excreted mainly into bile unlike other drugs in this class. The fibrate resulted in a remarkable reduction in VLDL-triglycerides, although it did not reduce IDL-cholesterol. Finally, an HMG-CoA reductase inhibitor (statin) pravastatin was used in HD and CAPD patients. Pravastatin reduced IDL- and LDL-cholesterol to the same extent (by 31%). None of these treatments caused serious adverse effects.

Conclusions. We propose that IDL is an important target in the management of uremic dyslipidemia. To date, statins have been shown to be suitable for this purpose, although it remains to be clarified whether such an intervention reduces the risk for atherosclerotic vascular events in the uremic population.

Patients with chronic renal failure show hypertriglyceridemia due to raised levels of very-low density lipoprotein (VLDL) and intermediate density lipoprotein (IDL) [1]. Low density lipoprotein (LDL) concentration is not usually elevated but rather lower than that of nonuremic control subjects [1]. High density lipoprotein levels are reduced in renal failure [1, 2]. *In vivo* kinetic studies in renal failure patients [3, 4] indicated normal VLDL production, delayed catabolism of VLDL into IDL, suppressed conversion of IDL to LDL, and reduced clearance of LDL from the circulation. These metabolic alterations are attributable to suppressed lipolysis mediated by lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL), and to decreased activity of the LDL receptors as outlined in Figure 1.

ATHEROGENIC LIPOPROTEINS IN DIALYSIS PATIENTS

Atherosclerosis is more advanced in uremia. Intima-medial thickness of carotid and femoral arteries is greater in hemodialysis patients than in the age- and gender-matched healthy controls [5]. The sclerotic changes of the aorta are also more advanced in hemodialysis patients [6]. Although uremic dyslipidemia is believed to contribute to an increased risk for atherosclerosis, it is not known which lipoprotein abnormality is most closely related to atherosclerosis. Our recent study indicated that IDL is a significant and independent risk factor for sclerotic changes of the aorta in the hemodialysis population [6]. Raised IDL is an important risk factor not only in dialysis patients but also in the general population [7]. In our previous study, 45% of nondiabetic hemodialysis patients exceeded 15 mg/dl of IDL-cholesterol, the 95th percentile level of nonuremic healthy population [1].

STRATEGIES TO REDUCE THE IDL LEVEL

Theroretically, the following approaches could reduce plasma IDL levels: (*1*) suppression of hepatic production of VLDL, the precursor of IDL; (*2*) promotion of IDL-to-LDL conversion; and (*3*) enhancement of the LDL receptor activity. Nicotinic acid, fibrates, and HMG-CoA reductases (statins) are suitable for these purposes, respectively. There are only a limited number of studies that examined the effects of lipid-lowering drugs on raised IDL in patients with chronic renal failure (Table 1).

Key words: cholesterol, uremia, statin, nicotinic acid, hemodialysis, fibrate, CAPD.

Table 1. Reports on the effects of lipid-lowering drugs on intermediate density lipoprotein (IDL) levels in uremic patients

Drug name	Daily dose	Subjects	IDL-cholesterol		Reference
			Baseline level	Reduction	
Niceritrol	750 mg	HD (N = 17)	12.4 mg/dl	19%[a]	[9]
Clinofibrate	600 mg	CAPD (N = 12)	21.1 mg/dl	9%[a]	[10]
Pravastatin	10 mg	HD (N = 11)	14.3 mg/dl	34%	[11]
	10 mg	CAPD (N = 8)	22.8 mg/dl	29%	[11]
	10 mg	HD+CAPD (N = 19)	17.9 mg/dl	31%	[11]

Abbreviations are: HD, hemodialysis; CAPD, continuous ambulatory peritoneal dialysis.
[a]Not statistically significant

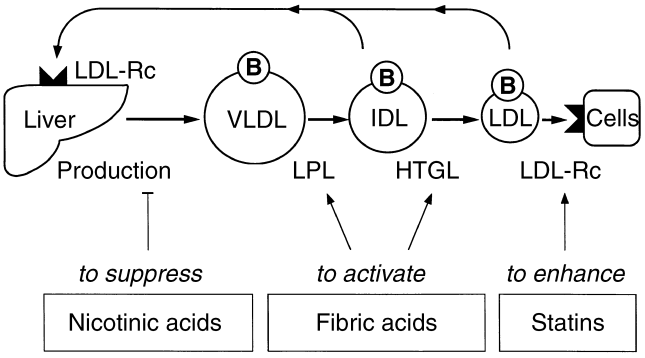

Fig. 1. Metabolic pathway of intermediate density lipoprotein (IDL) and strategies to reduce IDL level. Very-low density lipoprotein (VLDL), the precursor of IDL, is produced by the liver. VLDL is metabolized to IDL by the action of lipoprotein lipase (LPL). IDL is further converted to low density lipoprotein (LDL) by hepatic triglyceride lipase (HTGL). LDL and a portion of IDL particles are cleared from the circulation via the LDL receptors (LDL-Rc) expressed in the liver (70%) and other cells (30%). Patients with chronic renal failure show normal VLDL production, delayed catabolism of VLDL into IDL, impaired conversion of IDL to LDL, and reduced clearance of LDL from the circulation. As a result, they have a raised level of VLDL and a decreased level of LDL. IDL concentration is markedly elevated in renal failure. There are three approaches to the reduction of IDL: (1) suppression of hepatic production of VLDL; (2) promotion of IDL-to-LDL conversion; and (3) enhancement of the hepatic LDL-Rc activity. Nicotinic acid, fibrates, and HMG-CoA reductases (statins) are suitable for these purposes, respectively.

EFFECTS OF NICOTINIC ACIDS ON IDL

Nicotinic acids suppress hepatic secretion of VLDL. When a nicotinic acid analog niceritrol was administrated to hemodialysis patients at a daily dose of 750 mg, IDL-cholesterol was decreased by 19%, but this was not statistically significant [8]. Interestingly, it decreased lipoprotein(a) [Lp(a)] concentration by 33% and increased HDL-cholesterol by 11%.

EFFECTS OF FIBRATES ON IDL

In contrast to most other fibrates that are metabolized by the kidney, clinofibrate is excreted primarily into bile [9]. This unique property of clinofibrate makes it suitable for use in patients with impaired renal function. The usual dose of clinofibrate (600 mg/day) reduced VLDL-triglycerides by 48% in patients on CAPD [9]. LDL-cholesterol increased following clinofibrate treatment, suggesting that the VLDL-IDL-LDL delipidation cascade might improve with this treatment. However, no change was observed in IDL-triglycerides or IDL-cholesterol.

EFFECTS OF STATINS ON IDL

HMG-CoA reductase inhibition by statins results in suppressed cholesterol biosynthesis, reduced intracellular cholesterol pool, and up-regulation of the LDL receptor expression. The LDL receptor recognizes not only LDL, but partly delipidated VLDL and IDL as well. Treatment with 5 to 10 mg pravastatin per day in hemodialysis and peritoneal dialysis patients resulted in marked reduction in VLDL-, IDL-, and LDL-cholesterol levels [10]. The reduction of IDL by 31% was as great as that of LDL-cholesterol. Simvastatin, another HMG-CoA reductase inhibitor, was also shown to be effective in decreasing cholesterol-rich fraction of VLDL, presumably VLDL-remnant.

CONCLUSIONS

We propose that the reduction in IDL should be an important target in the management of uremic dyslipidemia, because IDL was shown to be an independent risk factor for atherosclerosis in uremic patients as well as in the general population. To date, the only drugs clearly shown to reduce IDL levels in chronic renal failure effectively and safely are statins. It remains to be clarified whether such an intervention reduces the risk for atherosclerotic vascular complications in the uremic population.

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