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Preliminary report

Marked decrease of apolipoprotein A-V in both diabetic and nondiabetic patients with end-stage renal disease

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Abstract

Apolipoprotein (apo) A-V has been the focus of significant attention as a potential modulator of plasma triglyceride (TG) in spite of its very low plasma concentration. TG levels are frequently elevated in patients with end-stage renal disease (ESRD), which is associated with a high prevalence of cardiovascular disease among them. We measured plasma apo A-V levels in 20 control subjects and 70 patients with diabetic and nondiabetic ESRD to investigate whether low apo A-V levels could be involved in the pathogenesis of the hyper-TG in ESRD. The plasma TG levels were significantly elevated in diabetic patients with ESRD, whereas those in nondiabetic ESRD patients remained similar to those in the controls. High-density lipoprotein cholesterol levels were significantly lower in the patients with ESRD than in the controls, irrespective of the presence of diabetes. Apo A-V levels measured by an enzyme-linked immunosorbent assay were markedly reduced to 40% to 44% of the control levels in both diabetic and nondiabetic patients with ESRD. The apo A-V levels were not correlated with TG in the overall study population, but they were positively correlated with high-density lipoprotein cholesterol. These results suggest that reduced apo A-V levels do not necessarily lead to hyper-TG in ESRD, but we are unable to exclude the possibility that low apo A-V plays a role in raising the TG level in diabetic ESRD.

Apolipoprotein (apo) A-V has been the focus of significant attention as a potential modulator of plasma triglyceride (TG) in spite of its very low plasma concentration [1]. Plasma TG levels are markedly elevated in apo A-V gene–deficient mice and markedly decreased in human apo A-V gene transgenic mice [2,3]. Human studies have demonstrated associations between several polymorphisms within the apo A-V locus and plasma TG levels [4]. However, it is poorly understood how apo A-V is associated with primary and secondary hypertriglyceridemia in humans. TG levels are frequently elevated in patients with end-stage renal disease (ESRD), which is associated with the high prevalence of cardiovascular disease among them. Our group measured plasma apo A-V levels in patients with ESRD to investigate whether low apo A-V levels could be involved in the pathogenesis of hypertriglyceridemia associated with ESRD.

We studied 20 healthy control subjects and 70 patients with ESRD undergoing hemodialysis (HD) for the treatment of diabetic nephropathy (n = 23) or nondiabetic kidney disease (n = 47). All of the diabetic patients had been diagnosed with diabetes at least 10 years earlier and all had

Table 1
Plasma concentrations in healthy controls and in diabetic (DM) and nondiabetic patients with ESRD on hemodialysis

	Controls	ESRD (DM)	ESRD (non-DM)
n (M/F)	20 (13/7)	23 (18/5)	47 (29/18)
Age (y)	65 ± 11	65 ± 9	61 ± 5
Duration of HD (y)	–	5.8 ± 2.2	6.4 ± 3.0
Creatinine (mg/dL)	0.68 ± 0.15	10.5 ± 1.9*	12.1 ± 2.6*
Albumin (mg/dL)	4.0 ± 0.7	3.7 ± 0.7*	3.7 ± 0.7*
TG (mg/dL)	111 ± 44	178 ± 134*	96 ± 43
LDL-C (mg/dL)	111 ± 44	95 ± 21	79 ± 25*,†
HDL-C (mg/dL)	56 ± 10	39 ± 14*	43 ± 12*
Lp(a) (mg/dL)	13 ± 10	23 ± 20	16 ± 14
Apo A-1 (mg/dL)	136 ± 17	110 ± 21*	112 ± 21*
Apo B (mg/dL)	90 ± 33	85 ± 22	67 ± 20*,†
Apo C-III (mg/dL)	8.5 ± 2.3	13.1 ± 3.1*	10.9 ± 3.7*
Apo A-V (ng/mL)	166 ± 53	67 ± 46*	73 ± 40*

Data are presented as mean ± SD. Apo(a) indicates apolipoprotein(a).
* $P < .05$ compared with the controls.
† $P < .05$ compared with ESRD (non-DM).

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a complication of diabetic retinopathy. There was no significant difference in the mean duration of HD between the diabetic patients (5.8 ± 2.2 years) and nondiabetic patients (6.4 ± 3.0 years). Patients treated with lipid-lowering agents and coronary heart disease cases were excluded. Blood samples were collected after overnight fasting. Plasma apo A-V levels were measured by an enzyme-linked immunosorbent assay using a monoclonal antibody to human apo A-V, as described by Ishihara et al [5]. Informed consent was obtained from each subject, and the study was approved by the local ethics committees.

As shown in Table 1, markedly elevated plasma creatinine and slightly reduced albumin concentrations were found in both diabetic and nondiabetic patients with ESRD at comparable levels. The plasma TG levels were significantly elevated in diabetic ESRD patients, whereas those in nondiabetic ESRD patients remained similar to those in the controls. Low-density lipoprotein cholesterol (LDL-C) and apo B levels were significantly lower in nondiabetic ESRD. Apo C-III levels were higher and high-density lipoprotein cholesterol (HDL-C) and apo A-I levels were significantly lower in the patients with ESRD than in the controls, irrespective of the presence of diabetes. Lipoprotein(a) levels were comparable among the 3 groups. Apo A-V levels were markedly reduced to 40% to 44% of the control levels in both diabetic and nondiabetic patients with ESRD. Apo A-V levels remained unaltered before the HD and 5 hours after the commencement of the HD. The apo A-V levels were not correlated with TG in the overall study population, but they were positively correlated with both HDL-C ($r = 0.53$, $P < .0001$) and apo A-I ($r = 0.42$, $P < .0001$).

Although TG was elevated only in diabetic ESRD, the apo A-V levels were markedly decreased by comparable amounts in both the diabetic and nondiabetic ESRD patients. This suggested that reduced apo A-V levels did not necessarily lead to hypertriglyceridemia. Ishihara et al [5] measured low plasma apo A-V levels in diabetic patients. Their result suggested that diabetes may have been the sole cause of the low apo A-V in the diabetic ESRD patients. However, the similar levels of decline in apo A-V in diabetic and nondiabetic ESRD strongly suggest that renal failure plays a crucial role in the lowering of apo A-V independently of diabetes. The low apo A-V in patients with ESRD was associated with low HDL, although the mild declines in the HDL levels could not fully explain the substantial reduction in apo A-V. Given the wide distribution of plasma apo A-V among TG-rich lipoproteins (TGRLs) and HDL [6], we speculate that the reduction in plasma apo A-V may be mainly due to the reduction in non-HDL. It has been postulated that apo A-V stimulates TGRL catabolism by facilitating the binding between TGRL and lipoprotein lipases bound to the vascular endothelium [7]. We can thus reasonably assume that the apo A-V in TGRL affects the TGRL catabolism more directly than the apo A-V in HDL. Henceforth, it will be important to investigate the distribution of apo A-V in lipoprotein fractions and compare it between diabetic and nondiabetic ESRD patients. Although we found no significant association between TG and apo A-V in our overall population, we were unable to exclude the possibility that low apo A-V plays a significant role in raising the TG level in diabetic ESRD. The regulation of TG levels by apo A-V may take place via different mechanisms in diabetic ESRD and nondiabetic counterparts. Subsequent studies will need to elucidate the mechanism of the low apo A-V in patients with ESRD and the association with the high prevalence of cardiovascular disease in these populations.

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