Peroxidative Modification of Very-Low-Density Lipoproteins in Chronic Hemodialysis Patients

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Dear Sir,

Atherosclerotic vascular disease is one of the most frequent and serious complications in patients undergoing chronic hemodialysis treatment and lipid metabolism disturbances have been proposed as one potential etiologic factor [1]. However, while it is now well established that elevated serum cholesterol is an important cause of cardiovascular disease [2], the involvement in atherogenesis of hyper-triglyceridemia, which is the prevailing lipid disorder in hemodialysis patients [3], is still controversial. Recently, clinical and experimental studies have emphasized the role of postsecretory modifications of lipoprotein structure and composition as a possible mechanism for accelerated atherosclerosis. Specifically, lipid peroxidation appears to increase the atherogenic potential of lipoproteins. Thus it has been demonstrated that oxidatively modified low-density lipoproteins (LDL) become recognized by a specific scavenger receptor of macrophages resulting in massive, unregulated deposition of cholesterol esters and eventually in the transformation of these cells to the lipid-laden foam cells characteristic of the early atherosclerotic lesion [4]. We therefore attempted to determine whether peroxidative modifications of lipoproteins could also have a role in the pathogenesis of atherosclerosis in hemodialysis patients.

Fifty-eight patients (35 males; 23 females) maintained on regular hemodialysis treatment between 28 and 79 months (mean $\pm$ SD, 48 ± 15 months) and 58 normal subjects (28 males; 30 females) matched for age, sex, smoking habits and plasma lipid levels were selected for this study. None of the patients was suffering from diseases known to enhance lipid peroxidation [5] and none had received lipid-lowering medication for at least 3 months. All patients were dialyzed 3 times a week for 4.0 h on an outpatient basis with standard cuprophane coils (A-15 U, Salvia, Homburg, FRG). Blood specimens from study subjects all were collected after an overnight fast into 10-ml Vacutainers (Fa. Sarstedt, Nümbrecht, FRG) containing EDTA-2Na, at 1.0 mg/ml. Samples from patients were taken immediately before and after 2 h of hemodialysis and administration of 100 U/kg heparin by vein. Plasma was obtained by low-speed centrifugation and isolation of lipoproteins from patients and controls carried out in parallel by gradient centrifugation [6]. Lipoprotein cholesterol, triacylglycerol and protein were measured according to standard

Table 1. TBARs in plasma and lipoprotein fractions of control subjects and hemodialysis patients

Controls
(n=58)
Renal patients (n:
=58)
Statistic

predialysis
postdialysis
significance

	Total plasma	VLDL	LDL	HDL
Controls	0.042	10.018	0.480	10.470
Renal patients	1.114	10.959	0.087	10.113
Significance	0.044	10.016	0.810	11.060
NS	1.185	11.422	0.125	10.219
NS	0.046	10.022	0.440	10.430
NS	1.310	11.520	0.109	10.132

NS p < 0.05
NS NS

Results are expressed as nmol of malondialdehyde/mg of lipoprotein protein and plasma protein, respectively, to account for intradialytic changes of total body fluid and postheparin variations of lipoprotein concentrations. Statistical analysis was performed with Wilcoxon's test. Values are mean ± SD. a Compared to control. b Compared to predialysis value.

procedures [7]. Thiobarbituric acid-reactive substances (TBARs) on total plasma protein and lipoprotein protein as a measure of lipid peroxidation [8] were determined by the method of Warren [9] and Satoh [10] using 1,1,3,3,-tetraethoxypropane, at 0.010 mM in 0.05 M sulfuric acid, as standard. Under these experimental conditions there was no difference in TBARs on total plasma protein, LDL and high-density lipoproteins (HDL) between chronic hemodialysis patients and controls. In contrast, the content of TBARs on freshly isolated very-low-density lipoproteins (VLDL) was significantly higher in patients than in controls. Furthermore, a significant decrease of TBARs on VLDL to the level found in control subjects was observed after 2 h of hemodialysis, while this procedure had no effect on the TBARs content of LDL and HDL of these patients (table 1). Since no statistically significant differences were seen with respect to age, sex distribution or smoking habits between patients and controls and since total plasma cholesterol, triacylglycerol and HDL-cholesterol were also not different, these results strongly suggest that lipid peroxide formation is selectively enhanced in the VLDL fraction of chronic hemodialysis patients. In addition, the demonstration of a significant decrease of TBARs on VLDL after 2 h of hemodialysis is compatible with a heparin-induced acceleration of the catabolism of peroxidized VLDL. On the basis of these results we suggest that lipolytic degradation of oxidatively modified VLDL during hemodialysis possibly targets these lipoproteins for uptake through the scavenger receptor pathway, thereby considerably enhancing their atherogenicity. This mechanism could help to explain the frequent occurrence of cardiovascular disease in chronic hemodialysis patients.

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