Intermediate-Density Lipoprotein as an Independent Risk Factor for Aortic Atherosclerosis in Hemodialysis Patients

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Abstract. Patients with chronic renal failure often show accumulation of intermediate-density lipoprotein (IDL). Because recent studies have emphasized the atherogenicity of IDL in the general population, we evaluated the relationship between this lipoprotein and aortic atherosclerosis in uremic patients treated with hemodialysis. Aortic pulse wave velocity (PWV) was measured as a noninvasive index of sclerotic change of aorta in 205 hemodialysis patients and 184 age- and gender-matched healthy subjects. Fasting plasma lipoproteins were fractionated by ultracentrifugation into very low-density lipoprotein (VLDL), IDL, LDL, and HDL. Plasma lipoprotein (a) (Lp(a)) was measured by a latex immunoturbidimetric assay. Aortic PWV was significantly higher in the hemodialysis patients than in the control subjects. The hemodialysis group showed a significant increase in VLDL and IDL cholesterol, whereas their LDL and HDL cholesterol were lower than the control levels. Lp(a) levels did not differ between the two groups. In the hemodialysis population, VLDL, IDL, and LDL cholesterol correlated positively with aortic PWV adjusted for age, gender, smoking, and BP, whereas Lp(a) did not. Multiple regression analyses indicated that plasma triglycerides, independent of HDL cholesterol, had a significant association with aortic PWV in the hemodialysis patients but not in the control subjects. Further analyses revealed that aortic PWV in the hemodialysis patients had a significant and independent association with IDL cholesterol, whereas aortic PWV in the control subjects had significant and independent associations with HDL cholesterol and Lp(a). These results demonstrate that IDL is the lipoprotein fraction most closely associated with aortic PWV in the hemodialysis patients.

Atherosclerotic vascular disease is a major cause of death in uremic patients treated with hemodialysis (1,2), and they have increased intima-medial thickness of carotid and femoral arteries as shown by our previous study (3). Uremic patients have a unique lipoprotein profile called uremic dyslipidemia (4), characterized by hypertriglyceridemia (5), elevated very low-density lipoprotein (VLDL), accumulated intermediate-density lipoprotein (IDL), or remnant particles (6–8), and decreased HDL (9,10). LDL cholesterol is usually within the normal range (11,12). As we have recently surveyed (13), the average level of IDL cholesterol in the hemodialysis population is two-to threefold higher than that of the healthy subjects. Also, IDL accumulation is found at a markedly higher prevalence. Furthermore, lipoprotein (a) (Lp(a)) has been shown to be elevated in chronic renal failure in many (14,15), but not all, studies (16,17). To date, however, little is known about what is the most atherogenic change in the lipoprotein abnormalities in hemodialysis patients.

Epidemiologic studies in the general population have established the roles of LDL and HDL as a positive and negative risk factor, respectively, for ischemic heart disease (18–20). Traditionally, LDL cholesterol has been calculated by the Friedewald equation (21) or determined by combination of ultracentrifugation at a density of 1.006 g/ml and precipitation (22). Importantly, the “LDL” by both of these methods includes cholesterol of IDL (d = 1.006 to 1.019 g/ml) in addition to cholesterol of LDL (d = 1.019 to 1.063 g/ml). There has been a discussion regarding the atherogenicity of triglyceride-rich lipoproteins, including VLDL and IDL. Several cross-sectional (23–27) and longitudinal studies (28–31) showed that moderately elevated IDL or VLDL remnant levels were closely associated with coronary atherosclerosis and its progression. Recent studies demonstrated that progression of coronary (30) and carotid atherosclerosis (32) was closely associated with IDL, but not with LDL devoid of IDL, in the general population.

In the present study, we have evaluated the independent association of individual lipoproteins with atherosclerosis in hemodialysis patients by measuring aortic pulse wave velocity (PWV). There are two components in atherosclerosis: atherosclerosis (morphologic wall thickening) and sclerosis (functional stiffening) (33). PWV is a noninvasive measure of arterial sclerosis (34) reflecting atherosclerosis as shown in animal (35) and human (36) arteries, and has been used as an early indicator of atherosclerosis (37).
Materials and Methods

Patients

The study comprised 205 patients with chronic renal failure treated with hemodialysis and 184 age- and gender-matched healthy control subjects. They were all Japanese. Clinical characteristics are given in Table 1.

Patients received 3 to 5 h of hemodialysis, 3 times a week, using bicarbonate dialysate. The 182 patients took medication for hypertension, including calcium channel blockers, α- and β-adrenergic antagonists, angiotensin-converting enzyme inhibitors, and combinations of these antihypertensive agents. No patient took lipid-lowering or hypoglycemic drugs. The underlying renal diseases were chronic glomerulonephritis (n = 151), polycystic kidney disease (n = 12), toxemia of pregnancy (n = 10), lupus nephritis (n = 7), hypertensive nephrosclerosis (n = 5), chronic pyelonephritis (n = 4), gout (n = 3), and others (n = 13). Patients with diabetic nephropathy were excluded.

The control subjects were selected from participants of a local health check program. Exclusion criteria were overt proteinuria and liver dysfunction as defined by serum alanine aminotransferase >50 IU and fasting blood glucose >140 mg/dl. Subjects with treated hypertension, treated hyperlipidemia, or treated diabetes mellitus were also excluded. No criteria were made for plasma lipid levels to avoid selection bias.

BP and PWV Measurement

BP and PWV measurements were made with the patient in a supine position after a 5-min bed rest. Arterial BP was measured with a mercury sphygmomanometer and a standard cuff in the arm. The average of two BP measurements was recorded.

Aortic PWV was measured as a noninvasive index of aortic sclerosis (34) by the method of Hasegawa (38), using a PWV meter (model PWV-200, Fukuda Denshi, Tokyo, Japan). Briefly, amorphous sensors were put on the skin at right femoral and left carotid arteries to record pulse waves. Heart sounds S I and S 2 were detected by a microphone set on the right edge of the sternum at the second intercostal space. Electrocardiogram was monitored with electrodes placed on the right and left arms and right leg. The PWV meter measures time intervals between pulse waves at the carotid and femoral sites (T) and between S2 and the notch of carotid pulse wave (Tc). PWV of the aorta was calculated as follows:

\[ PWV [m/s] = 1.3\frac{L}{(T + Tc)} , \]

where \( L \) is the measured distance between the carotid and femoral probes. The actual distance between the aortic orifice and the femoral site was estimated to be 1.3 \( L \) (38). \( T + Tc \) indicates the time for the pulse waves to travel from the aortic orifice to the femoral artery. Because PWV is known to increase as the diastolic pressure increases (39), the PWV meter automatically reports PWV values standardized for the diastolic pressure of 80 mmHg. Thus, PWV by this method gives a pressure-independent elastic property of thoracoabdominal aorta. PWV measurements were done for five consecutive pulses, and the average was used for analysis. Interobservation coefficient of variation of PWV was less than 5%.

Blood Sampling

Blood was drawn the morning after an overnight fast of at least 12 h. For the dialysis patients, it was 68 h after the last hemodialysis session. Blood samples were collected in tubes containing ethylenediaminetetra-acetic acid-2Na and centrifuged at 2000 rpm for 20 min at 4°C to separate plasma.

Plasma Lipids and Lipoproteins

Cholesterol and triglyceride concentrations in each lipoprotein fraction were determined by one-step preparative ultracentrifugation (13). Briefly, three tubes containing 200 μl of plasma were prepared for each subject, and 200 μl of KBr solution having different densities was added to each tube to adjust the density to 1.006, 1.019, or 1.063 g/ml, respectively. Tubes were spun at 100,000 rpm for 3 h at 4°C in a Hitachi Himac 120 CF ultracentrifuge using an RP100 AT2 rotor. Cholesterol and triglyceride concentrations were measured in whole plasma, the \( d < 1.006 \) fraction (VLDL), the \( d < 1.019 \) fraction (VLDL + IDL), the \( d < 1.063 \) fraction (VLDL + IDL + LDL), and the \( d > 1.063 \) fraction (HDL) by enzymatic methods. Lipid content in each lipoprotein fraction was calculated by subtraction. This one-step method has been validated against polyacrylamide gel electrophoresis and against the standard sequential ultracentrifugation (40) as described elsewhere (13). Plasma Lp(a) levels were measured by a latex immunoturbidimetric assay (41).

Statistical Analyses

Data are expressed as mean ± SEM unless otherwise mentioned. Difference of mean values between two groups was assessed by \( t \) test. Independent association between one dependent and more than two independent variables was assessed by multiple regression analysis. Difference of prevalence was evaluated by \( \chi^2 \) test. \( P \) values < 0.05 were considered significant.

Results

Aortic PWV was significantly higher in the hemodialysis patients than in the control subjects (Figure 1). This was true even in age-categorized comparisons.

As shown in Figure 2, plasma total cholesterol was lower (4.36 ± 0.07 versus 5.31 ± 0.05 mmol/L, \( P < 0.0001 \)) and plasma triglyceride was higher (1.34 ± 0.05 versus 1.12 ± 0.05 mmol/L, \( P = 0.0012 \)) in the hemodialysis group than in the control group. The patients showed elevated VLDL (0.87 ± 0.03 versus 0.55 ± 0.02 mmol/L, \( P < 0.0001 \)) and IDL (0.40 ± 0.02 versus 0.18 ± 0.01 mmol/L, \( P < 0.0001 \)) cholesterol levels, and lowered LDL (2.08 ± 0.04 versus 2.77 ± 0.04, \( P < 0.0001 \)) and HDL (1.02 ± 0.02 versus 1.42 ± 0.03 mmol/L, \( P < 0.0001 \)) cholesterol concentrations. Lp(a) levels were not significantly different between the two groups (21.8 ± 1.0 versus 22.2 ± 1.1, \( P = 0.748 \)).
Figure 1. Aortic pulse wave velocity (PWV) in the hemodialysis patients and healthy control subjects. Aortic PWV was measured as described in Materials and Methods. Mean ± SEM. *P < 0.05, **P < 0.01 by t test. The number in each column indicates the subject number in the age category.

Figure 2. Plasma lipoprotein levels in the hemodialysis and control groups. Plasma lipoproteins were fractionated by one-step preparative ultracentrifugation into very low-density lipoprotein (VLDL) (d < 1.006 g/ml), IDL (d = 1.006 to 1.019 g/ml), LDL (d = 1.019 to 1.063 g/ml), and HDL (d > 1.063 g/ml). Plasma lipoprotein (a) (Lp(a)) was measured by a latex immunoturbidimetric assay. TC, total cholesterol; TG, triglycerides. Mean ± SEM. *P < 0.01, **P < 0.001 by t test.

Table 2 gives multiple regression analyses of factors affecting aortic PWV in the healthy control group. In model 1 including age, gender, BP, smoking, and plasma triglycerides as independent variables, age and BP, but not triglycerides, were indicated as significant factors affecting aortic PWV. The association between triglycerides and aortic PWV was again insignificant when HDL cholesterol was included in the analysis (model 2). Model 3, including plasma total cholesterol in place of triglycerides, indicated no significant association between total cholesterol and aortic PWV. Model 4, in which total cholesterol was fractionated into HDL and non-HDL cholesterol (VLDL + IDL + LDL) levels, indicated a significant negative association of HDL cholesterol with aortic PWV, whereas the link between non-HDL cholesterol and aortic PWV was not significant. In model 5, non-HDL cholesterol was further fractionated into VLDL, IDL, and LDL cholesterol levels. However, no significant association was shown between aortic sclerosis and these lipoproteins in the control population. Model 6, in which Lp(a) was included, indicated an independent association of Lp(a) with aortic PWV in the control subjects.

Table 3 shows multiple regression analyses of factors affecting aortic atherosclerosis in the hemodialysis patients. In model 1 including age, gender, BP, smoking, and plasma triglycerides as independent variables, age and triglycerides were indicated as significant factors affecting aortic PWV. The positive association between triglycerides and aortic PWV remained significant even when HDL cholesterol was included in the analysis (model 2). Model 3, in which total cholesterol was entered in place of triglycerides, indicated a significant association between total cholesterol and aortic PWV. Model 4 indicated that non-HDL cholesterol was a significant factor associated with aortic atherosclerosis, whereas HDL cholesterol was not. Among the non-HDL, IDL cholesterol was identified as a significant and independent factor in model 5. Models 6 and 7 showed that Lp(a) and years on hemodialysis...
demonstrated that IDL level was closely and independently factor more closely associated with aortic wall stiffness in the as a significant and independent factor associated with aortic significance (P between uremia and elevated IDL cholesterol. Finally, Lp(a)

interaction (r-value) became smaller, suggesting the interaction between IDL and PWV remained significant when uremia was

in hemodialysis patients. The present study, for the first time, Discussion

coefficients (r-values) of individual lipoprotein levels with aortic

PWV in the total study subjects (model 6). The association

between aortic PWV and triglycerides independent

interaction between uremia and lowered HDL cholesterol. Among non-HDL, IDL was again identified as a significant and independent factor associated with aortic PWV in the total study subjects (model 6). The association between IDL and PWV remained significant when uremia was included in the model (model 7), although its degree of association (β-value) became smaller, suggesting the interaction between uremia and elevated IDL cholesterol. Finally, Lp(a) showed a positive association with aortic PWV at a borderline significance (P = 0.07) in the total subjects (model 8).

Discussion

Recent studies have emphasized the atherogenic role of IDL in the general population (30, 32). Because IDL levels are significantly raised in patients on hemodialysis (13), we examined the relationship between IDL and sclerotic change of aorta in hemodialysis patients. The present study, for the first time, demonstrated that IDL level was closely and independently associated with aortic sclerosis in the uremic population.

Previous epidemiologic studies established “LDL” as an independent risk factor for ischemic heart disease (18). In contrast, our study indicates that IDL, rather than LDL, is a factor more closely associated with aortic wall stiffness in the hemodialysis population. There are several explanations for the lack of significant association between LDL and aortic PWV in the present study. First, it was due simply to mutual correlation among VLDL, IDL, and LDL levels. These apolipoprotein B-containing lipoproteins are in the precursor-product relationship, and their plasma levels correlated with one another, giving correlation coefficients (r values) of 0.315 to 0.577 (P < 0.0001) in this study. However, the results still indicate that IDL is a better correlate with the arterial wall change than LDL.

Second, it came from the differential effects of IDL and LDL on atherosclerosis (42). Hodis et al. (42) reported that triglyceride-rich lipoproteins were more closely associated with progression of coronary atherosclerosis at earlier stages, whereas cholesterol-rich lipoproteins were more closely associated with progression of coronary atherosclerosis at more advanced stages. Because we evaluated subclinical atherosclerosis by aortic PWV, we may have been able to detect the relationship with triglyceride-rich lipoproteins such as IDL more easily than that with LDL.

Third, it was due to the increased proportion of IDL to LDL levels in these patients. As shown by animal (43) and human (44) studies, the proportion of IDL in plasma lipoproteins could affect the accumulation of IDL in the subendothelial space. In our study, the average IDL cholesterol/LDL cholesterol ratio was 3 times greater in the hemodialysis population than in the control subjects (0.198 ± 0.007 versus 0.068 ± 0.003, P < 0.0001).

Finally, the difference in the methods to determine LDL may be critically important. In many previous studies, LDL was determined either by the Friedewald equation (21) or by subtracting HDL cholesterol, determined by a precipitation method (22), from the 1.006 g/ml infranatant fraction cholesterol. In both of these methods, the LDL is the sum of LDL (d = 1.019 to 1.063 g/ml) and IDL (d = 1.006 to 1.019 g/ml). Therefore, the atherogenic effects of IDL and LDL should have been included in the traditionally determined LDL in the previous studies. This issue has gained more attention in recent studies in the nonuremic population (30, 32). Phillips et al. (30) revealed that raised IDL, not LDL, was significantly predictive of both progression of coronary artery stenosis and clinical events in the nonuremic population. Hodis et al. (32) also reported that the progression of carotid arterial wall thickening was closely associated with IDL but not with LDL. Therefore, the risk for atherosclerosis of “LDL” may be attributable to IDL included in the “LDL” at least partly.

The importance of IDL in atherosclerosis in nonuremic individuals has also been investigated by other researchers from Japan (23, 24) and Western countries (25–32). The present study has added the new finding that IDL shows an independent association with aortic sclerosis in hemodialysis patients. Taken together, IDL may take part in the atherogenic process regardless of ethnic groups and underlying diseases such as uremia.

Atherogenicity of hypertriglyceridemia has been a matter of debate in the general population (45). We found a significant association between aortic PWV and triglycerides independent

![Figure 3. Correlation of lipoprotein levels with aortic PWV-adjusted](image-url)

- Healthy control
- Hemodialysis
- Total subjects

**Table 4.** Correlation of lipoprotein levels with aortic PWV-adjusted major nonlipoprotein factors. Bar graphs indicate standard correlation coefficients (r-values) of individual lipoprotein levels with aortic PWV. Adjustment for age, gender, smoking, and BP was made by using multiple regression models, including the four nonlipoprotein variables and the lipoprotein variable in the figure. Those models do not consider the interactions among lipoprotein variables. *P < 0.05; **P < 0.01; ***P < 0.001

- Treatment were not factors affecting aortic sclerosis in the hemodialysis population significantly.

- Similar analyses were performed in the total study subjects (Table 4). Models 1 and 2 showed that plasma triglycerides and HDL cholesterol were both significant and independent factors associated with aortic PWV. Models 3 and 4 indicated that both HDL and non-HDL cholesterol levels were significant factors. In model 5, the statistical impact of HDL cholesterol was no longer significant when uremia was added to the model, indicating the close interaction between uremia and lowered HDL cholesterol. Among non-HDL, IDL was again identified as a significant and independent factor associated with aortic PWV in the total study subjects (model 6). The association between IDL and PWV remained significant when uremia was included in the model (model 7), although its degree of association (β-value) became smaller, suggesting the interaction between uremia and elevated IDL cholesterol. Finally, Lp(a) showed a positive association with aortic PWV at a borderline significance (P = 0.07) in the total subjects (model 8).
Table 2. Multiple regression analysis of factors affecting aortic PWV in the control group

<table>
<thead>
<tr>
<th>Factor</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
<th>Model 6</th>
<th>Model 7</th>
</tr>
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<tbody>
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<td>0.364b</td>
<td>0.383b</td>
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<td>0.363b</td>
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<td>-0.079</td>
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<tr>
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<tr>
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<tr>
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<tr>
<td>HDL cholesterol</td>
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<td>-0.176c</td>
<td>-0.159c</td>
<td>-0.210c</td>
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<tr>
<td>non-HDL cholesterol</td>
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<tr>
<td>LDL cholesterol</td>
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<td>-0.027</td>
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<tr>
<td>Lp(a)</td>
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<td></td>
<td>0.159c</td>
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<td></td>
</tr>
<tr>
<td>$R^2$</td>
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<td>0.216b</td>
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<td>0.217b</td>
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</table>

*Independent association of four nonlipoprotein variables and lipoprotein parameters with aortic PWV was evaluated by multiple regression models. Models 1 and 2 show the impact of plasma triglycerides independent of the nonlipoprotein factors and HDL cholesterol. Model 3 includes total cholesterol in place of triglycerides. In model 4, total cholesterol is fractionated into HDL and non-HDL cholesterol. In model 5, non-HDL cholesterol is further fractionated into VLDL, IDL, and LDL cholesterol. Model 6 includes Lp(a) in addition to the factors in model 5. Standard regression coefficients ($\beta$) are given in the table. $R^2$, multiple coefficient of determination. PWV, pulse wave velocity; Lp(a), lipoprotein (a).

b $P < 0.001.$

c $P < 0.01.$

d $P < 0.05.$

Table 3. Multiple regression analysis of factors affecting aortic PWV in the hemodialysis group

<table>
<thead>
<tr>
<th>Factor</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
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<td>0.103</td>
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<tr>
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<tr>
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<td>0.284b</td>
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<td>0.308b</td>
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</table>

*Independent association of four nonlipoprotein variables and lipoprotein parameters with aortic PWV was evaluated by multiple regression models. Models 1 and 2 show the impact of triglycerides independent of the nonlipoprotein factors and HDL cholesterol. Model 3 includes total cholesterol in place of triglycerides. In model 4, total cholesterol is fractionated into HDL and non-HDL cholesterol. In model 5, non-HDL cholesterol is further fractionated into VLDL, IDL, and LDL cholesterol. Model 6 includes Lp(a) as an independent variable. Model 5 includes years on hemodialysis. Standard regression coefficients ($\beta$) are given in the table. $R^2$, multiple coefficient of determination.

b $P < 0.001.$

c $P < 0.01.$

d $P < 0.05.$
Table 4. Multiple regression analysis of factors affecting aortic PWV in the total study subjectsa

<table>
<thead>
<tr>
<th>Factor</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
<th>Model 6</th>
<th>Model 7</th>
<th>Model 8</th>
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<tbody>
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<td>0.367b</td>
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<td>0.342b</td>
<td>0.335b</td>
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<td>-0.002</td>
<td>0.008</td>
<td>0.012</td>
</tr>
<tr>
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<td>0.190b</td>
<td>0.181b</td>
<td>0.197b</td>
<td>0.182b</td>
<td>0.130d</td>
<td>0.146c</td>
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<tr>
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<td>-0.006</td>
<td>0.112d</td>
<td>0.197b</td>
<td>0.990</td>
<td>0.086</td>
<td>0.074</td>
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<td>non-HDL cholesterol</td>
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<td>VLDL cholesterol</td>
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<td>IDL cholesterol</td>
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<td>Uremia</td>
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<td>Lp(a)</td>
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<td></td>
<td></td>
<td>0.236b</td>
<td>0.188d</td>
<td>0.179d</td>
</tr>
<tr>
<td>R²</td>
<td>0.237b</td>
<td>0.252b</td>
<td>0.193b</td>
<td>0.248b</td>
<td>0.289b</td>
<td>0.296b</td>
<td>0.302b</td>
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a Independent association of four nonlipoprotein variables and lipoprotein parameters with aortic PWV was evaluated by multiple regression models. Models 1 and 2 show the impact of triglycerides independent of the nonlipoprotein factors and HDL cholesterol. Model 3 includes total cholesterol in place of triglycerides. In model 4, total cholesterol is fractionated into HDL and non-HDL cholesterol. In model 5, uremia is added to the independent variables to evaluate the interaction between uremia and HDL cholesterol. In model 6, non-HDL cholesterol is further fractionated into VLDL, IDL, and LDL cholesterol. Model 7 again included uremia as an independent variable to examine the interaction between uremia and levels of non-HDL lipoproteins. Finally, Lp(a) is included in model 8. Standard regression coefficients (β) are given in the table.

b P < 0.001.
c P < 0.01.
d P < 0.05.
e P = 0.07.

of HDL cholesterol in the hemodialysis patients but not in the control subjects. This suggests that the impact of plasma triglycerides on arterial wall may vary among different populations. We have recently demonstrated that a certain concentration of plasma triglycerides reflects markedly different levels of IDL between hemodialysis and healthy populations (13). This finding could explain the closer association between plasma triglycerides and aortic PWV in the hemodialysis patients than in the control subjects.

In the hemodialysis population, the inverse association of HDL with aortic sclerosis was not clearly found, whereas the positive association of IDL with aortic PWV was more impressively demonstrated than in the healthy population. A small variation in HDL cholesterol among the hemodialysis patients would have made it difficult to detect the statistical link between HDL and aortic PWV. This would also be true for the lack of significant association between IDL and PWV in the control group; variation of IDL was smaller in the control subjects. Another explanation would be that modification of lipoproteins in uremic condition could enhance atherogenic nature of non-HDL and reduce antiatherogenic properties of HDL. Uremic lipoproteins can be modified by oxidation (46), carbamylation (47), and glycation (48), although such lipoprotein modifications were out of the scope of the present study.

Elevated plasma Lp(a) has been shown as an independent risk factor for clinical events attributable to atherosclerosis in the general population (49). In hemodialysis patients, Lp(a) was reported as a risk factor for cardiovascular events (50) and for carotid arterial wall thickening (51). On the other hand, we found a significant association between plasma Lp(a) level and aortic PWV only in the healthy control group. The discrepancy between these studies may be explained by the different techniques used to assess atherosclerosis, by the lack of significant Lp(a) elevation in the hemodialysis patients in our study, and by the difference in ethnic groups. In addition, because Lp(a) is believed to play an atherogenic role by suppressing secondary fibrinolysis (52), use of heparin or other anticoagulants for hemodialysis may affect the atherothrombogenic actions of Lp(a).

BP showed an independent association with aortic PWV in the control subjects but not in the hemodialysis group. The control group did not include those with treated hypertension, whereas most of the hemodialysis patients received antihypertensive medications. Such intervention may account for the lack of significant association between BP and aortic PWV in the patients.

Years on hemodialysis treatment had no significant association with aortic sclerosis in this study. It suggests that hemodialysis itself or any parameter occurring during dialysis treatment is not strong enough to influence the progression of aortic sclerosis significantly. On the other hand, an elevated IDL showed a close association with aortic sclerosis. Because high
levels of IDL are found in early and late phases of chronic renal failure (53), this lipoprotein abnormality may promote atherogenesis before and after dialysis treatment is being started.

What is the mechanism for elevated IDL in chronic renal failure? VLDL is degraded into IDL by the action of lipoprotein lipase (54). Hepatic triglyceride lipase (HTGL) then converts IDL into LDL (55). Most of the previous studies reported no change of lipoprotein lipase and remarkable suppression of HTGL in hemodialysis patients (10–12,56). Previously, we showed the markedly reduced levels in both HTGL activity and HTGL mass in postheparin plasma (10). The decline of HTGL was independently associated with increased IDL cholesterol (57). Hypocalcemia and secondary hyperparathyroidism may affect the lowered HTGL level in renal failure (10). We reported previously that carotid and femoral atherosclerosis showed an independent association with impaired calcium homeostasis in hemodialysis patients (3). Taken together, these studies may indicate the sequence of renal failure, impaired calcium homeostasis, suppression of HTGL, raised IDL, and accelerated atherosclerosis.

In conclusion, the present study has demonstrated that raised IDL is the lipoprotein fraction most closely associated with aortic sclerosis in the hemodialysis population. This finding is of importance regarding the atherogenicity of triglyceride-rich lipoproteins, especially of IDL, in end-stage renal disease.

Acknowledgment

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References


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