Effect of Diabetes on Uremic Dyslipidemia

Eiji Kimoto¹, Tetsuo Shoji¹, Masonori Emoto¹, Takami Miki², Tsutomu Tabata³, Yasuhisa Okuno⁴, Eiji Ishimura⁵, Masaaki Inaba¹, and Yoshiki Nishizawa¹

¹ Department of Metabolism, Endocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan.

² Department of Geriatrics and Neurology, Osaka City University Medical School, Osaka, Japan.

³ Division of Internal Medicine, Inoue Hospital, Osaka, Japan.

⁴ Department of Cardiovascular Medicine, Institute of Geriatrics and Medical Science,

⁵ Department of Nephrology, Osaka City University Graduate School of Medicine, Osaka, Japan.

Elevated intermediate-density lipoprotein (IDL), a remnant lipoprotein, is an independent risk factor for atherosclerosis in patients with end-stage renal disease (ESRD). Since the presence of diabetes mellitus further increases the risk of cardiovascular mortality in ESRD, we examined the effect of diabetes on IDL among ESRD patients. The subjects were 330 healthy control subjects and 287 patients with end-stage renal disease including 80 patients with type 2 diabetes. As compared with the healthy subjects, the nondiabetic ESRD patients had increased plasma triglyceride and IDL cholesterol. Diabetic patients with ESRD showed a further increase in plasma triglyceride and IDL cholesterol compared with the nondiabetic group. However, the difference in IDL levels between the ESRD groups was no longer significant when subjects were stratified by plasma triglyceride. Plasma triglyceride was correlated with IDL cholesterol. Increased hemoglobin A_{1c} was significantly associated with IDL cholesterol in a multiple regression model including age, gender, and the presence of ESRD. Such an association was no longer significant in another model including plasma triglyceride as an additional covariate. Further analysis indicated the positive effects of diabetes and hyperglycemia on plasma triglyceride. These results indicate that increased IDL in ESRD is further deteriorated in the presence of diabetes, and that the adverse effect is accounted for at least partly by hypertriglyceridemia associated with chronic hyperglycemia. *J Atheroscler Thromb*, 2002; 9: 305-313.

Key words: Intermediate density lipoprotein (IDL), Lipoprotein, Triglyceride, End-stage renal disease (ESRD)

Introduction

The risk of cardiovascular mortality is elevated in patients with end-stage renal disease (ESRD) (1-3), and is further increased in those with diabetes mellitus (4-7). We previously showed that the intima-media thickness (IMT)

of the carotid artery was increased in patients with type 2 diabetes (8,9) and in those with ESRD (10,11), and that carotid artery IMT was further increased in patients with both diabetes and ESRD (12). Additional impacts of diabetes and ESRD on atherosclerosis were also found when measuring arterial stiffness (13), and these vascular changes were closely associated with plasma lipoprotein levels. Since lipoprotein abnormalities are known to occur secondary to either diabetes (14) or ESRD (15,16), the particularly increased risk of atherosclerosis in diabetic patients with ESRD may be explained in part by dyslipidemia caused by a combination of the two disease conditions.

Address for correspondence: Tetsuo Shoji, MD, PhD, Department of Metabolism, Endocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka 545-8585, Japan.

E-mail: t-shoji@med.osaka-cu.ac.jp

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Both diabetes (14) and ESRD (15,16) result in potentially atherogenic lipoprotein changes such as increased plasma triglyceride and lowered high-density lipoprotein (HDL) cholesterol. Hypertriglyceridemia is due to the elevation of very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) (14,17,18). Low-density lipoprotein (LDL) cholesterol is not elevated in type 2 diabetes (19,20), and is even decreased in ESRD (21). Among these changes, increased IDL has been shown as an independent risk factor of atherosclerosis. Our previous study (11) revealed that IDL was independently associated with aortic stiffness in patients with ESRD. Also, IDL was an independent factor associated with coronary (22-30) and carotid (31) atherosclerosis in the general population.

So far, only a limited amount of information is available in the literature with regard to changes in IDL in diabetic nephropathy (32-35). Although these studies showed increased IDL in type 1 diabetes patients with microalbuminuria (32), overt proteinuria (34), and dialysis-independent renal failure (33,35), information is lacking about IDL in diabetic patients with ESRD, a group with particularly increased cardiovascular risk.

The purpose of the present study was to examine the possible changes in IDL and other lipoproteins in patients with type 2 diabetes with ESRD patients.

Subjects and Methods

Subjects

This study consisted of 617 adult subjects, including 330 healthy control subjects, 207 ESRD patients without diabetes, and 80 ESRD patients with type 2 diabetes. The

ESRD patients were all stable on maintenance hemodialysis. Informed consent to participate in this study was obtained, and this study was approved by the institute's ethical committee (Inoue Hospital Approval No. 104). The characteristics of the subjects are summarized in Table 1.

The healthy subjects were recruited from participants in a local health check program in Osaka City. We excluded subjects who were treated with medication for renal disease, diabetes mellitus, hypertension and/or hyperlipidemia. We also excluded subjects who had fasting hyperglycemia of 126 mg/dl or higher, overt proteinuria, and/or liver dysfunction as defined by increased serum ALT > 50 IU. No exclusion criteria were established for plasma lipids to avoid selection bias.

The ESRD patients were treated by hemodialysis, 3 times a week, 3-5 hours per session, using bicarbonate dialysate at the Kidney Center, Inoue Hospital, Suita, Japan. Five out of the 80 diabetic ESRD patients (DM/ESRD) used insulin injections for control, whereas other diabetic patients were treated with lifestyle modification only. The diagnosis of diabetes was made according to the World Health Organization criteria (36). We excluded those with type 1 diabetes who were positive for the GAD antibody, who had a past history of ketoacidosis, or who were dependent on insulin therapy for survival. Diabetes associated with specific syndromes and gestational diabetes were carefully ruled out by their history. No patients received lipid-lowering medication. The anti-hypertensive medications were calcium channel blockers (N = 102), loop diuretics (N = 76), angiotensin-converting enzyme inhibitors (N = 55), α -(N = 6), β -(N = 20), and $\alpha\beta$ -blockers (N = 9).

Table 1. Subjects

	Healthy control	NonDM/ESRD	DM/ESRD	P-value
Number of subjects	330	207	80	
Gender (M/F)	148/182	83/124	40/40	0.280 *
Age (years)	55 $\pm$ 1	56 $\pm$ 1	56 $\pm$ 1	0.522
BMI (kg/m ²)	22.8 $\pm$ 0.2	21.1 $\pm$ 0.2 ^a	22.1 $\pm$ 0.3 ^b	< 0.0001
Smoker (%)	36	18	21	< 0.0001 *
Fasting glucose (mg/dl)	96.8 $\pm$ 0.5	76.3 $\pm$ 0.7 ^a	111.4 $\pm$ 5.5 ^{a,b}	< 0.0001
HbA _{1c} (%)	4.85 $\pm$ 0.03	5.34 $\pm$ 0.04 ^a	7.26 $\pm$ 0.15 ^{a,b}	< 0.0001
Creatinine (mg/dl)	—	11.5 $\pm$ 0.1	10.9 $\pm$ 0.3 ^b	0.019
Duration of HD (years)	—	7.2 $\pm$ 0.4	4.3 $\pm$ 0.4 ^b	< 0.0001
Systolic BP (mmHg)	126 $\pm$ 1	149 $\pm$ 2 ^a	162 $\pm$ 3 ^{a,b}	< 0.0001
Diastolic BP (mmHg)	77 $\pm$ 1	84 $\pm$ 1 ^a	85 $\pm$ 2 ^a	< 0.0001
Total cholesterol (mg/dl)	208 $\pm$ 2	169 $\pm$ 3 ^a	176 $\pm$ 5 ^a	< 0.0001
Plasma TG (mg/dl)	102 $\pm$ 3	115 $\pm$ 3 ^a	146 $\pm$ 8 ^{a,b}	< 0.0001

Mean $\pm$ SE.

P-values for continuous variables by one-way analysis of variance (ANOVA) and for prevalence* by chi-square test.

^a p < 0.05 vs. healthy control and ^b p < 0.05 vs. NonDM/ESRD by Scheffe-type multiple comparison.

Abbreviations: BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}; HD, hemodialysis; BP, blood pressure; TG, triglycerides; NonDM/ESRD, nondiabetic patients with end-stage renal disease; DM/ESRD, diabetic patients with end-stage renal disease.

Blood Sampling

Blood was drawn in the morning after an overnight fast of at least 12 hours. In ESRD patients, fasting blood was taken before the morning session of hemodialysis, more than 44 hours after the previous session. Blood was collected in tubes containing EDTA 2Na, chilled in ice, and centrifuged at 2,000 rpm for 15 min at 4°C to separate plasma.

Plasma Lipids and Lipoproteins

Plasma lipoproteins were measured by a one-step micro-ultracentrifugation method as previously described (37). Briefly, 3 tubes containing 0.2 ml of plasma were prepared for each subject, and 0.2 ml of KBr solution with different densities was added to each tube to adjust the density to 1.006, 1.019 and 1.063 g/ml, respectively. Then, the tubes were spun at 100,000 rpm for 3 hours at 4°C in a Hitachi Himac 120CF 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. The lipid content in each lipoprotein fraction was calculated by subtraction. Lipoprotein-lipid values obtained by this method agreed well with those by a standard sequential flotation method (38). No significant cross-contamination was found by polyacrylamide gel electrophoresis.

Other measurements

Hemoglobin A_{1c} (HbA_{1c}) was measured by high performance liquid chromatography, and plasma glucose by a glucose oxidase method. Other measurements were performed by routine laboratory methods.

Statistics

The results were summarized as the mean $\pm$ standard error (SE). The difference between groups was evaluated using one-way analysis of variance (ANOVA), and then a post-hoc test was performed by Scheffe-type multiple comparison. The difference in prevalence was assessed by chi-square test. The correlation between two variables was examined by linear regression analysis. Independent association between the variables was assessed by multiple regression analysis. When the distribution of a variable was skewed, the log-transformed value was used for analysis. P-values less than 0.05 were taken as statistically significant.

Results

Plasma total cholesterol and triglyceride levels in the three groups

As compared with the healthy subjects, the two ESRD groups had lower total cholesterol levels, whereas no sig-

nificant difference was found between the two ESRD groups (Table 1). In contrast, plasma triglyceride was elevated in the two ESRD groups, and the DM/ESRD group had a significantly higher plasma triglyceride than the NonDM/ESRD group.

Comparison of lipoprotein levels among the three groups

As shown in Table 2, VLDL cholesterol was increased in NonDM/ESRD (by 26%), and it was further elevated in DM/ESRD (by 62%) as compared with that of the healthy control subjects. VLDL triglyceride of DM/ESRD patients was significantly higher than the healthy subjects (by 49%) and the NonDM/ESRD patients (by 44%). Both the DM/ESRD and NonDM/ESRD groups had an alteration in the triglyceride/cholesterol ratio of VLDL, showing the relative depletion of triglyceride in VLDL. No difference was found in the VLDL lipid ratio between the two ESRD groups.

IDL cholesterol was increased in NonDM/ESRD (by 84%) and in DM/ESRD (by 126%) as compared with the healthy subjects. IDL triglyceride showed a much greater increase in both NonDM/ESRD (by 122%) and DM/ESRD (by 190%). IDL triglyceride in DM/ESRD was significantly higher than in NonDM/ESRD. The difference in the lipid composition of IDL was not significant among the three groups.

LDL cholesterol was lower than the healthy control level in both NonDM/ESRD (by 28%) and DM/ESRD (by 29%), and there was no significant difference in LDL cholesterol between the two ESRD groups. LDL triglyceride showed a modest increase in the DM/ESRD group (by 18%) as compared with that of the healthy control subjects. The triglyceride to cholesterol ratio of LDL was increased in the NonDM/ESRD and DM/ESRD groups, and the lipid ratio was the highest in DM/ESRD among the three groups.

HDL cholesterol was significantly lower than the healthy control level in both NonDM/ESRD (by 25%) and DM/ESRD (by 32%), whereas it was not statistically different between the two ESRD groups. There was no difference in HDL triglyceride among the three groups. The triglyceride to cholesterol ratio of HDL was increased in NonDM/ESRD (by 32%) and DM/ESRD (by 53%) as compared with that of the healthy subjects, and the lipid ratio was the highest in DM/ESRD among the three groups.

Correlation between plasma triglyceride and lipoprotein parameters

Table 3 summarizes the results of univariate correlation between the plasma triglyceride and lipoprotein parameters. Although plasma triglyceride did not correlate consistently with LDL cholesterol and IDL lipid ratio, it correlated significantly and consistently with other lipoprotein parameters. VLDL cholesterol, VLDL triglyceride, and the triglyceride to cholesterol ratio of VLDL correlated positively with plasma triglyceride. IDL cholesterol

Table 2. Lipoprotein parameters in the three groups

	Healthy control	NonDM/ESRD	DM/ESRD	P-value
VLDL				
C (mg/dl)	25.8 ± 0.8	32.6 ± 0.9 ^a	41.8 ± 2.3 ^{a,b}	< 0.0001
TG (mg/dl)	52.1 ± 2.5	53.9 ± 2.6	77.5 ± 6.8 ^{a,b}	< 0.0001
TG/C ratio	1.92 ± 0.05	1.54 ± 0.04 ^a	1.64 ± 0.07 ^a	< 0.0001
IDL				
C (mg/dl)	7.95 ± 0.23	14.7 ± 0.6 ^a	18.0 ± 0.9 ^{a,b}	< 0.0001
TG (mg/dl)	6.32 ± 0.20	14.1 ± 0.5 ^a	18.3 ± 1.0 ^{a,b}	< 0.0001
TG/C ratio	1.06 ± 0.07	1.02 ± 0.03	1.05 ± 0.04	0.867
LDL				
C (mg/dl)	112.8 ± 1.4	81.6 ± 1.7 ^a	79.7 ± 3.0 ^a	< 0.0001
TG (mg/dl)	29.3 ± 1.0	31.0 ± 0.8	34.4 ± 1.5 ^a	0.026
TG/C ratio	0.267 ± 0.009	0.399 ± 0.010 ^a	0.460 ± 0.023 ^{a,b}	< 0.0001
HDL				
C (mg/dl)	53.5 ± 0.8	40.2 ± 0.8 ^a	36.5 ± 1.2 ^a	< 0.0001
TG (mg/dl)	16.0 ± 0.5	16.1 ± 0.3	16.8 ± 0.5	0.638
TG/C ratio	0.324 ± 0.013	0.427 ± 0.010 ^a	0.495 ± 0.021 ^{a,b}	< 0.0001

Mean ± SE.

P-values by one-way analysis of variance (ANOVA).

^a*p* < 0.05 vs. healthy control and ^b*p* < 0.05 vs. NonDM/ESRD by Scheffe-type multiple comparison.

Abbreviations: VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; C, cholesterol; TG, triglycerides; TG/C ratio, triglyceride to cholesterol ratio; NonDM/ESRD, nondiabetic patients with end-stage renal disease; DM/ESRD, diabetic patients with end-stage renal disease.

Table 3. Univariate correlation between plasma triglyceride and lipoprotein parameters

	Healthy control	NonDM/ESRD	DM/ESRD	Total subjects
VLDL-C	0.892 ^a	0.922 ^a	0.963 ^a	0.915 ^a
VLDL-TG	0.981 ^a	0.934 ^a	0.965 ^a	0.964 ^a
VLDL-TG/C ratio	0.533 ^a	0.682 ^a	0.819 ^a	0.516 ^a
IDL-C	0.328 ^a	0.585 ^a	0.551 ^a	0.485 ^a
IDL-TG	0.497 ^a	0.625 ^a	0.731 ^a	0.569 ^a
IDL-TG/C ratio	-0.017	0.050	0.317 ^b	0.011
LDL-C	-0.053	0.283 ^a	0.108	-0.040
LDL-TG	0.414 ^a	0.661 ^a	0.603 ^a	0.491 ^a
LDL-TG/C ratio	0.545 ^a	0.391 ^a	0.515 ^a	0.527 ^a
HDL-C	-0.493 ^a	-0.349 ^a	-0.506 ^a	-0.480 ^a
HDL-TG	0.326 ^a	0.430 ^a	0.423 ^a	0.333 ^a
HDL-TG/C ratio	0.452 ^a	0.574 ^a	0.722 ^a	0.535 ^a

The numbers in the table indicate correlation coefficients (*r*-values) and the level of significance determined by linear regression analysis between the plasma triglyceride and lipoprotein variables listed in the table.

^a*p* < 0.001, ^b*p* < 0.01.

Abbreviations: VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; C, cholesterol; TG, triglycerides; TG/C ratio, triglyceride to cholesterol ratio; NonDM/ESRD, nondiabetic patients with end-stage renal disease; DM/ESRD, diabetic patients with end-stage renal disease.

and IDL triglyceride correlated positively with plasma triglyceride, whereas the triglyceride to cholesterol ratio of IDL correlated with plasma triglyceride only in the DM/ESRD group. LDL cholesterol correlated positively with plasma triglyceride only in the NonDM/ESRD group. LDL

triglyceride and the triglyceride to cholesterol ratio of LDL correlated positively with plasma triglyceride in all of the three groups. HDL cholesterol correlated inversely, whereas HDL triglyceride and the triglyceride to cholesterol ratio of HDL correlated positively with plasma trig-

lyceride.

Triglyceride-stratified comparison of IDL cholesterol

To reduce the effect of plasma triglyceride, the subjects were stratified by their plasma triglyceride level at intervals of 50 mg/dl, and then IDL levels were compared among the three groups in the same range of plasma triglyceride (Fig. 1). In such comparison, IDL cholesterol was again significantly higher in the two ESRD groups than in the healthy group. However, the difference in IDL cholesterol between the ESRD groups with and without diabetes was no longer significant after stratification by plasma triglyceride level.

Independent association of HbA_{1c} and plasma triglyceride with IDL cholesterol

Table 4 presents the multiple regression analysis to evaluate the independent effects of diabetes, glycemic control and plasma triglyceride on IDL cholesterol in the total subjects. The association between diabetes and IDL was significant and independent of age, gender, and presence of ESRD (model 1). The effect of diabetes was replaced with HbA_{1c} (model 2). However, the association between HbA_{1c} and IDL was no longer significant when plasma triglyceride was included as an additional covariate (model 3), whereas plasma triglyceride was a significant factor. The addition of total cholesterol as another covariate to

the model (model 4) did not affect the significant association between plasma triglyceride and IDL.

Factors independently associated with plasma triglyceride

Table 5 shows the independent association of diabetes or hyperglycemia with plasma triglyceride as evaluated by multiple regression analysis. In model 1, including age, gender, body mass index (BMI), ESRD and diabetes, BMI, ESRD and diabetes were indicated as significant factors associated with plasma triglyceride level. When fasting plasma glucose and HbA_{1c} were entered in place of diabetes (models 2 and 3), these glycemic parameters showed a significant association with plasma triglyceride.

Discussion

Atherosclerosis is advanced in patients with end-stage renal disease (ESRD) (1-3), and the risk of atherosclerosis is further increased in ESRD patients with diabetes (4-7). Uremic dyslipidemia, especially increased IDL, is known as an independent factor associated with atherosclerosis in ESRD (11). Also, increased IDL is an independent risk factor of atherosclerosis in the general population as shown by a number of studies (22-31). Since no previous study has evaluated the possible change in IDL level in diabetes patients with ESRD, it was examined in the present study. The results demonstrated that increased IDL in ESRD was further deteriorated in the presence of type 2 diabetes. Also, the adverse effect of diabetes on IDL was accounted for at least partly by the elevated plasma triglyceride level associated with hyperglycemia. These results indicate that type 2 diabetes adversely affects the raised IDL level of ESRD patients that is potentially atherogenic.

There are only a few studies that examined IDL changes in patients with diabetic nephropathy. Sibley *et al.* (32) showed that IDL was increased in type 1 diabetic patients with early nephropathy, although those with renal failure were not included in their study. Hirano (34) reported an increase in IDL in type 2 diabetic patients with overt proteinuria. Attman *et al.* (33) measured IDL levels in 20 type 1 diabetes patients with renal failure and 20 nondiabetic patients with renal failure, and showed that IDL was higher in the diabetic group. They also reported that IDL correlated positively with plasma triglyceride and HbA_{1c} by univariate analysis. These results were in good agreement with our present observation made in type 2 diabetic patients with ESRD. We (35) recently examined IDL levels in type 2 diabetic patients with various degrees of nephropathy, and found that IDL was higher as the stage of nephropathy advanced. None of these studies examined IDL changes in diabetic patients with ESRD. Therefore, this is the first study to demonstrate the remarkably

Fig. 1. Comparison of IDL levels among the three groups. Cholesterol content in the IDL fraction ($d = 1.006\text{--}1.019$ g/ml) was measured by ultracentrifugation and compared among 330 healthy subjects (open columns), 207 ESRD patients without diabetes (NonDM/ESRD, shaded columns), and 80 ESRD patients with type 2 diabetes (DM/ESRD, solid columns) by one-way analysis of variance followed by Scheffe-type multiple comparison. Also, the comparison was made after stratifying by plasma triglyceride level. (Note that the difference between NonDM/ESRD and DM/ESRD was no longer significant in the plasma triglyceride-stratified comparisons.)

^a $P < 0.05$ vs. healthy control subjects.

^b $P < 0.05$ vs. NonDM/ESRD.

Table 4. Multiple regression analysis to evaluate the effects of diabetes and plasma triglyceride on IDL cholesterol

	Model 1	Model 2	Model 3	Model 4
Age	0.041	-0.023	-0.014	-0.049
Female gender	0.159 ^a	0.229 ^a	0.197 ^a	0.105 ^b
Presence of ESRD	0.447 ^a	0.294 ^a	0.237 ^a	0.427 ^a
Presence of diabetes	0.159 ^a	—	—	—
HbA _{1c}	—	0.137 ^b	0.046	0.028
Log (Plasma TG)	—	—	0.493 ^a	0.353 ^a
Total cholesterol	—	—	—	0.373 ^a
R ²	0.318 ^a	0.201 ^a	0.427 ^a	0.514 ^a

The table gives standard regression coefficients (β -values).

^a $p < 0.001$, ^b $p < 0.01$.

Abbreviations: ESRD, end-stage renal disease; HbA_{1c}, hemoglobin A_{1c}; TG, triglyceride; R², multiple coefficient of determination.

raised IDL in diabetic ESRD patients, a group at particularly increased risk for cardiovascular mortality.

What is the mechanism of the observed remarkable increase in IDL among diabetic ESRD patients? We showed that HbA_{1c} was a significant factor associated with IDL, independent of age, gender and presence of ESRD. The association between HbA_{1c} and IDL was no longer significant when the effect of triglyceride was considered in the multiple regression analysis, suggesting the presence of collinearity between glycemic control and plasma triglyceride. This was confirmed by another set of multiple regression analyses showing that plasma triglyceride was significantly associated with the presence of diabetes, fasting plasma glucose or HbA_{1c}. Hyperglycemia increases the hepatic production of VLDL (39), and VLDL is metabolized to IDL by lipoprotein lipase (40). Therefore, we interpreted these results to indicate that hyperglycemia induced IDL elevation by increasing VLDL concentration.

Another possibility is the suppression of hepatic lipase activity. Raised IDL in renal failure is caused by impaired clearance of this lipoprotein as shown by previous *in vivo* kinetic studies (41). IDL is metabolized by the action of hepatic lipase (40). Hepatic lipase activity (42) and mass (16) are both severely decreased in post-heparin plasma from ESRD patients without diabetes. Lowered hepatic lipase has an independent association with increased IDL in ESRD patients as we have shown (16). Hepatic lipase activity is not reduced in type 2 diabetes patients without renal failure (43). According to Sakurai *et al.* (44), post-heparin plasma hepatic lipase activity is suppressed in type 2 diabetes patients with ESRD, but it was not different from that of nondiabetic patients with ESRD. Therefore, we speculate that the particularly increased IDL in the diabetic ESRD patients was the combined result of overproduction due to diabetes and impaired clearance due to renal failure. Clearly, the mechanism needs to be directly demonstrated by *in vivo* kinetic studies in dia-

Table 5. Multiple regression analysis of factors associated with plasma triglyceride

	Model 1	Model 2	Model 3
Age	0.026	0.018	-0.027
Female gender	-0.022	-0.010	0.048
BMI	0.197 ^a	0.191 ^a	0.223 ^a
Presence of ESRD	0.120 ^b	0.215 ^a	0.126 ^b
Presence of diabetes	0.148 ^a	—	—
Fasting glucose	—	0.160 ^a	—
HbA _{1c}	—	—	0.212 ^a
R ²	0.081 ^a	0.083 ^a	0.124 ^a

The table gives standard regression coefficients (β -values).

^a $p < 0.001$, ^b $p < 0.05$.

Abbreviations: BMI, body mass index; ESRD, end-stage renal disease; HbA_{1c}, hemoglobin A_{1c}; R², multiple coefficient of determination.

betic patients with ESRD.

The atherogenicity of hypertriglyceridemia has been a matter of debate (45). Although plasma triglyceride was significantly correlated with ischemic heart disease, the association was not statistically significant when the effect of HDL cholesterol was considered in the Framingham study (46). Interestingly, epidemiological studies in subjects with diabetes or glucose intolerance (47,48) have indicated plasma triglyceride to be an independent predictor of ischemic heart disease. It may be that hypertriglyceridemia in some groups of subjects represents more atherogenic lipoprotein changes than it does in other populations. We previously showed that plasma triglyceride was significantly associated with aortic stiffness independent of HDL cholesterol in ESRD (11). We also reported that IDL cholesterol was increased as a function of plasma triglyceride in both healthy subjects and ESRD patients and that IDL cholesterol was much higher in ESRD patients than healthy subjects having the same level of plasma triglyceride (37). Furthermore, this study

demonstrated that the plasma triglyceride level had close associations not only with IDL but also with other various lipoprotein parameters. These studies suggest that plasma triglyceride represents multiple and potentially atherogenic lipoprotein abnormalities in ESRD patients including diabetics, and that increased plasma triglyceride levels in ESRD patients suggest the presence of more atherogenic lipoprotein changes than expected in the general population.

In conclusion, this study demonstrated that the increased IDL level in ESRD was further deteriorated in the presence of type 2 diabetes or hyperglycemia. The effect of diabetes on IDL was accounted for at least partly by increased plasma triglyceride associated with poor glycemic control. It is known that glycemic control is an independent predictor of mortality in diabetic ESRD patients (49), and that raised IDL in ESRD is an independent predictor of atherosclerosis. Therefore, there may be a sequence of events of hyperglycemia, hypertriglyceridemia, raised IDL and advanced atherosclerosis in diabetic patients with ESRD. Further studies are needed to examine whether atherosclerosis and the prognosis of ESRD patients is improved by better control of glucose, lipid and lipoprotein levels.

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