Prospective Study of Lipoprotein(a) as a Risk Factor for Deteriorating Renal Function in Type 2 Diabetic Patients With Overt Proteinuria

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OBJECTIVE — The effect of lipoprotein(a) [Lp(a)] on the progression of diabetic nephropathy has not been evaluated yet. The aim of this study was to determine whether Lp(a) is an independent risk factor for deteriorating renal function in type 2 diabetic patients with nephropathy.

RESEARCH DESIGN AND METHODS — We conducted this prospective study in type 2 diabetic patients with overt proteinuria. Patients were divided into two groups according to their baseline serum Lp(a) level. Group 1 had Lp(a) levels ≤ 30 mg/dl ($n = 40$) and group 2 had Lp(a) levels >30 mg/dl ($n = 41$). Patients were followed for 2 years. Progression of diabetic nephropathy was defined as a greater than twofold increase of follow-up serum creatinine concentration from the baseline value.

RESULTS — At baseline and during the follow-up, there was no difference in HbA_{1c} and lipid profile between groups 1 and 2. However, serum creatinine was significantly higher in group 2 than in group 1 after 1 year (148.3 ± 78.0 vs. 108.1 ± 34.9 μmol/l, $P = 0.004$) and after 2 years (216.9 ± 144.5 vs. 131.3 ± 47.3 μmol/l, $P = 0.001$), although baseline serum creatinine did not differ significantly between groups. In all, 13 of 14 patients with progression of diabetic nephropathy (progressors) were from group 2. Baseline Lp(a) levels were higher in the progressors than in the nonprogressors (62.9 ± 26.7 vs. 33.5 ± 27.5 mg/dl, $P < 0.001$). Multiple logistic regression showed that baseline Lp(a) level was a significant and independent predictor of the progression of diabetic nephropathy.

CONCLUSIONS — Our study demonstrated that Lp(a) is an independent risk factor for the progression of diabetic nephropathy in type 2 diabetic patients with overt proteinuria.

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Diabetic nephropathy is characterized by proteinuria, hypertension, progressive loss of renal function, and a high incidence of cardiovascular morbidity and mortality (1). Of patients with type 2 diabetes, 20–40% develop diabetic nephropathy over a period of 15–20 years after the onset of diabetes (2). It is noteworthy that the prevalence of diabetic nephropathy in type 2 diabetes appears to be higher in the Asian population than in the white population, although the underlying mechanisms for this difference are not clear (3,4). Because diabetic nephropathy is the leading cause of end-stage renal disease in many countries including Korea (5,6), it is critical to slow the loss of renal function in diabetic patients at the stage of overt proteinuria or macroalbuminuria (established diabetic nephropathy).

Hyperglycemia, hypertension, hypercholesterolemia, and proteinuria are the most significant risk factors or markers for the development and progression of diabetic nephropathy in type 2 diabetic patients (1,2,7–9). Nevertheless, in type 2 diabetic patients with overt proteinuria, postponing end-stage renal disease remains an elusive goal in the clinical setting. Therefore, it is still important to explore other risk factors with possible therapeutic applications in these patients.

Lipoprotein(a) [Lp(a)] is an LDL-like substance with apolipoprotein(a) bound to apolipoprotein B-100 by a disulfide bond (10). An elevated level of serum Lp(a), primarily genetically determined (11), is a significant risk factor for atherothrombogenesis in both diabetic and nondiabetic subjects (12–17). Renal dysfunction in particular has been associated with elevated Lp(a) levels, which partly explains the increased susceptibility to vascular disease in patients with renal disease, including diabetic nephropathy (18–24). Type 2 diabetic patients with nephropathy may have intrarenal hemodynamic abnormalities (25), and it can be hypothesized that the atherogenic effect of Lp(a) might adversely affect the renal vasculature and aggravate renal function in these patients. However, the effect of Lp(a) on the progression of diabetic nephropathy has not been evaluated yet. Therefore, we performed this prospective study to determine whether Lp(a) is an independent risk factor for deteriorating renal function in type 2 diabetic patients with overt proteinuria.

RESEARCH DESIGN AND
METHODS
— Patients with type 2 diabetes and overt proteinuria who visited the diabetes clinic at St. Vincent Hospital in Suwon, Korea, were recruited between 2001 and 2002. Consecutive patients with dipstick-positive proteinuria were examined by two 24-h urinary protein excretions (UPEs), a urine culture, a urine microscopy, and an ultrasound examination of the kidneys. The inclusion criteria was a UPE >500 mg/day (26) in two consecutive collections and serum creatinine concentration ≤176.8 μmol/l (2.0 mg/dl). Patients with hematuria, pyuria, a positive urine culture, or absence of retinopathy were excluded. In all, 90 patients met these criteria. All patients gave informed consent, and the study was approved by the institutional review board. Each subject provided a diabetes history regarding the diagnosis, treatment, and the occurrence of complications. A blood sample was collected at baseline from each subject for biochemical measurements, including serum Lp(a) level and DNA extraction.

Study subjects were divided into two groups according to their baseline Lp(a) level. Group 1 had Lp(a) levels ≤30 mg/dl ($n = 43$) and group 2 had Lp(a) levels >30 mg/dl ($n = 47$). Subjects were followed for 2 years. The established threshold of Lp(a) level for developing atherosclerosis is 30 mg/dl, and this value was therefore chosen as a cutoff point (27). During the observation period, blood pressure was measured every 2–3 months. The target blood pressure for all patients was a systolic blood pressure <140 mmHg and a diastolic blood pressure <90 mmHg (28). More than 90% of patients were given an ACE inhibitor or an angiotensin II receptor blocker. Diabetes was treated with dietary modification, oral hypoglycemic agents, or insulin as required to achieve glycemic control. A hydroxymethylglutaryl-CoA reductase inhibitor (statin) was given to patients whose serum LDL cholesterol concentration remained >2.6 mmol/l after lifestyle modification alone. During follow-up, serum creatinine and lipid profiles were assessed after 1 and 2 years in each patient. HbA$_{1c}$ (A1C) was measured every 6 months. Progression of diabetic nephropathy was defined as a >2-fold increase of a follow-up serum creatinine from the baseline value.

After an overnight fast, blood samples were obtained for analysis of serum concentrations of creatinine, total cholesterol, triglyceride, and HDL cholesterol. Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula (29) for estimation of creatinine clearance [(140 − age) × body weight in kilograms ÷ serum creatinine (milligrams per deciliter) ÷ 72], multiplying by 0.85 for women. The total cholesterol and triglyceride concentrations were measured enzymatically. The HDL cholesterol concentration was measured enzymatically after precipitation of the other lipoproteins. The A1C level was determined by high-performance liquid chromatography with a reference range of 4.4–6.4%. The serum Lp(a) concentration was measured by a one-step sandwich enzyme-linked immunoassay technique (Biopool AB, Umea, Sweden), as described previously (30).

For insertion/deletion polymorphism of the ACE gene, genomic DNA was extracted from peripheral blood leukocytes. A 287-bp insertion/deletion polymorphism in the intron 16 of the ACE gene was examined by PCR according to a previous method (31). The sequences of the sense and the antisense primers were 5′-CTGGAGACCACTCCCATCCTTTCT-3′ and 5′-GATGTGGCCATCACAT TCGTCAGAT-3′, respectively. PCR was performed in a final volume of 25 μl containing 500 ng of genomic DNA, 500 pmol of each primer, 0.5 mmol/l dNTP, 1.5 mmol/l MgCl$_2$, 0.5 unit Taq DNA polymerase, 50 mmol/l KCl, and 10 mmol/l Tris-HCl. Amplification was carried out for 35 cycles with steps of denaturation at 95°C for 1 min, annealing at 58°C for 1 min, and extension at 72°C for 1 min. The PCR products were subjected to ethidium bromide for visualization.

Statistical analyses were performed using the SPSS statistical package (Chicago, IL). Because Lp(a) concentrations, triglyceride concentrations, and UPE values are not normally distributed, the data were analyzed after logarithmic transformation. The differences in continuous variables between two groups were analyzed by Student's t tests, and χ^2 tests were used to compare frequencies between two groups. The correlation between the fold increase of serum creatinine after 2 years and baseline Lp(a) level in the study subjects was examined by Pearson correlation analysis. Multiple logistic regression was performed to assess the independent predictive effect of the variables on the risk for progression of diabetic nephropathy. Statistical significance was taken at $P < 0.05$.

RESULTS
— Of the initial 90 subjects, nine were lost to follow-up, mainly because they moved to other hospitals. The remaining 81 patients were followed for 2 years. Table 1 compares the clinical characteristics at baseline between patients in groups 1 and 2. The two groups did not differ significantly in age, BMI, the distribution of sex, insulin use, statin use, smoking, DD genotype of the ACE gene, A1C, blood pressure, UPE, calculated GFR, or serum creatinine.

During the follow-up, the two groups did not differ in A1C and lipid profile (total cholesterol, triglyceride, and HDL concentrations). The mean follow-up systolic blood pressure was significantly higher in group 2 than in group 1 (146.3 ± 12.2 vs. 138.9 ± 8.8 mmHg, $P = 0.003$). Serum creatinine was significantly higher in group 2 than in group 1 after 1 year (148.3 ± 78.0 vs. 108.1 ± 34.9 μmol/l, $P = 0.004$) and after 2 years (216.9 ± 144.5 vs. 131.3 ± 47.3 μmol/l, $P = 0.001$). In addition, calculated GFR was significantly lower in group 2 than in group 1 after 1 year (33.6 ± 17.2 vs. 58.4 ± 25.3 ml/min, $P = 0.001$) and after 2 years (17.2 ± 8.8 vs. 49.8 ± 21.3 μmol/l, $P < 0.001$). More importantly, 13 of 14 patients with progression of diabetic nephropathy (progressors) were from group 2. Hemodialysis or peritoneal dialysis was initiated in six of the progressors.

As shown in Fig. 1, the fold increase of serum creatinine after 2 years was found to be positively correlated with baseline Lp(a) level in the whole study subjects ($r = 0.318$, $P = 0.004$).

Table 2 shows the clinical characteristics of the progressors and nonprogressors. Baseline Lp(a) level, serum creatinine, and UPE were higher in the progressors than in the nonprogressors. The mean follow-up blood pressures were higher in the progressors than in the nonprogressors. However, the mean follow-up A1C was lower in the progressors than in the nonprogressors. The frequency of the DD genotype and the follow-up lipid profile did not differ between the progressors and nonprogressors.

Next, we compared the progressors ($n = 13$) and nonprogressors ($n = 28$) in group 2. The progressors had higher

Table 1—Baseline characteristics of study subjects

	Group 1	Group 2	P
n	40	41	
Sex (male/female)	16/24	20/21	0.427
Age (years)	58.7 ± 8.8	59.3 ± 9.6	0.764
BMI (kg/m^2)	25.9 ± 3.7	24.6 ± 3.5	0.096
Duration of diabetes (years)	16.2 ± 7.1	14.9 ± 6.2	0.388
Smoking	6	6	0.963
Insulin use	36	32	0.143
Statin use	14	12	0.581
Systolic blood pressure (mmHg)	138.5 ± 14.1	143.2 ± 21.0	0.245
Diastolic blood pressure (mmHg)	76.8 ± 12.4	81.2 ± 10.7	0.093
A1C (%)	9.1 ± 2.3	9.1 ± 2.2	0.945
Serum total cholesterol (mmol/l)	5.16 ± 1.07	5.73 ± 1.63	0.068
Serum triglyceride (mmol/l)	2.26 ± 1.29	2.03 ± 1.13	0.446
Serum HDL cholesterol (mmol/l)	1.03 ± 0.26	1.04 ± 0.31	0.860
24-h UPE (mg)	2,556.8 ± 2,243.6	2,682.34 ± 1,925.9	0.358
Serum creatinine (μmol/l)	99.4 ± 33.6	102.8 ± 23.2	0.598
Calculated GFR (ml/min)	68.3 ± 33.0	61.1 ± 22.6	0.257
Lp(a) (mg/dl)	16.4 ± 6.8 (16.9 [2.3–29.5])	60.3 ± 26.6 (54.0 [31.2–119.0])	<0.001
DD genotype (DD/ID/II)	5/18/17	7/18/16	0.562*
Proliferative retinopathy	14	12	0.581

Data are n, means ± SD, or means ± SD (median [range]). *Compared frequencies of DD and non-DD genotype (ID or II).

baseline serum creatinine (117.6 ± 20.8 vs. 96.0 ± 21.3 μmol/l, P = 0.004), baseline UPE (4480.5 ± 2044.6 vs. 1847.5 ± 1165.0 mg, P < 0.001), and mean follow-up systolic blood pressures (151.8 ± 9.4 vs. 143.6 ± 12.7 mmHg, P = 0.047) than the nonprogressors. When the progressors were removed from group 2, group 2 did not show significant differences from group 1. Thus, it is conceivable that the progressors in group 2 might have constituted a subgroup of patients particularly sensitive to nephropathy and were responsible for the association of the whole group with reduced renal function.

Multiple logistic regression analysis identified independent predictors of the progression of diabetic nephropathy. Baseline serum creatinine, baseline UPE, baseline Lp(a) level, mean follow-up systolic blood pressure, and mean follow-up A1C were chosen as independent variables in the model. Baseline Lp(a) levels and baseline UPE were significant and independent predictors of the progression of diabetic nephropathy (Table 3). When statin use was added as another variable in the regression model, the result did not change (data not shown).

CONCLUSIONS — This 2-year prospective study provides the first evidence that an elevated Lp(a) level is an independent risk factor for the progression of diabetic nephropathy in type 2 diabetic patients with overt proteinuria. This association was independent of proteinuria, hyperglycemia, or hypertension.

Many studies suggest that dyslipidemias such as hypercholesterolemia contribute to the deterioration of renal function (32–34). A meta-analysis of 13 studies including diabetic patients showed that lipid reduction has beneficial effects on the decline of GFR similar to those of ACE inhibitors (35). An elevated Lp(a) level is another feature of dyslipidemia that can be accompanied by renal dysfunction or increased albuminuria in
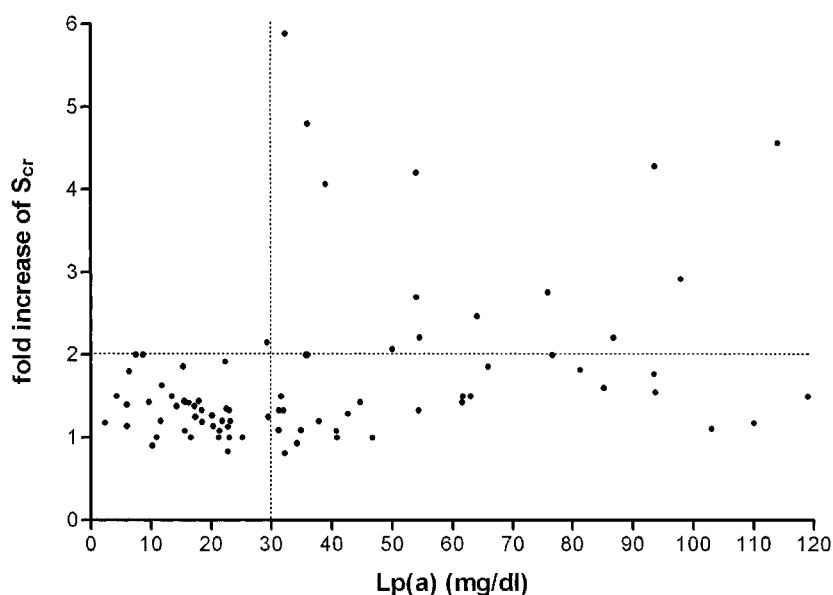

Figure 1—*Relationships between the fold increase of serum creatinine (S$_{Cr}$) after 2 years and baseline Lp(a) level in the whole study subjects. Dotted horizontal and vertical lines indicate a twofold increase of serum creatinine and >30 mg/dl of Lp(a), respectively.*

Table 2—*Clinical characteristics of the progressors and nonprogressors*

	Progressors	Nonprogressors	*P*
n	14	67	
At baseline			
Sex (male/female)	7/7	29/38	0.646
Age (years)	57.1 ± 8.5	59.4 ± 9.3	0.411
BMI (kg/m^2)	24.2 ± 3.9	25.5 ± 3.5	0.231
Duration of diabetes (years)	16.4 ± 6.6	15.4 ± 6.7	0.636
Serum creatinine (μmol/l)	117.5 ± 20.0	97.8 ± 29.2	0.019
Calculated GFR (ml/min)	53.4 ± 16.0	67.0 ± 29.8	0.101
Lp(a) (mg/dl)	62.9 ± 26.7 (54.3)	33.5 ± 27.5 (22.8)	<0.001
24-h UPE (mg)	4,847.8 ± 2,456.6	2,149.2 ± 1,653.8	<0.001
DD genotype (DD/ID/II)	2/5/7	10/31/26	0.951*
During the follow-up			
Mean systolic blood pressure (mmHg)	151.3 ± 9.2	140.8 ± 10.8	0.001
Mean diastolic blood pressure (mmHg)	82.0 ± 5.6	76.8 ± 8.5	0.031
Mean A1C (%)	7.5 ± 1.7	8.5 ± 1.3	0.020
Mean total cholesterol (mmol/l)	5.28 ± 1.00	5.07 ± 1.03	0.500
Mean triglyceride (mmol/l)	1.88 ± 0.47	2.26 ± 1.40	0.613
Mean HDL cholesterol (mmol/l)	0.98 ± 0.17	1.02 ± 0.30	0.631

Data are *n* or means ± SD (median). *Compared frequencies of DD and non-DD genotype (ID or II).

diabetic and nondiabetic patients (18–24). Jerums et al. (20) observed that serum apolipoprotein(a) levels increased with time in 12 of 14 type 2 diabetic patients who had progressively increasing albuminuria over 11 years. Boemi et al. (24) also reported that macroalbuminuria in both type 1 and type 2 diabetic patients is associated with significantly increased plasma concentrations of Lp(a) regardless of kidney dysfunction, as determined by creatinine clearance rates or serum creatinine. In addition, variable alleles at the apolipoprotein(a) gene locus determine to a large extent Lp(a) levels in the general population (11) and in patients with renal failure (23). However, little is known about the effect of Lp(a) on the progression of renal dysfunction.

We demonstrated that patients in group 2, who had elevated Lp(a) levels at baseline, showed more rapid deterioration of renal function as determined by serum creatinine and calculated GFR over the 2-year follow-up. This could not be explained by differences in glycemic control or lipid profile because there was no difference in A1C and lipid profile between the groups at baseline and during the follow-up. However, the mean follow-up systolic blood pressure was significantly higher in group 2, and it is possible that differences in blood pressure control might have affected the result. Alternatively, the worsening blood

pressure in group 2 could have been the outcome of diabetic nephropathy with a decline in GFR. It is often difficult to control blood pressure of patients with progressive renal insufficiency in the clinical setting.

Next, we analyzed the clinical variables of the progressors who had a >2-fold increase of serum creatinine from the baseline value. The progressors had higher baseline Lp(a) level, baseline serum creatinine, baseline UPE, and follow-up blood pressure than the nonprogressors. In addition, 13 of the 14 progressors were from group 2. After adjusting for the variables listed above, baseline Lp(a) level and baseline UPE remained independent predictors for the renal outcome. Taken together, an elevated Lp(a) level was independently related to the deterioration of renal function in our subjects, independent of proteinuria, hyperglycemia, or hypertension. In

addition, our data agree with those of other previous studies (1,36), demonstrating that baseline albuminuria/ proteinuria is a powerful predictor of nephropathy progression in type 2 diabetic patients. On the other hand, we did not find a beneficial effect of better glycemic control on deterioration of renal function, in accordance with other previous studies (37,38).

The reason why elevated Lp(a) levels might adversely affect the progression of diabetic nephropathy is unknown. It can be speculated that the atherogenic effect of Lp(a) leads to renal ischemia because of increased atherosclerotic renal artery stenosis. In addition to vascular injury, Lp(a) might be implicated in glomerular injury. Lp(a) and oxidized Lp(a) have been shown to induce activation of reactive oxygen metabolites in isolated rat glomeruli (39).

The limitations of this study include

Table 3—*Multiple logistic regression analysis of risk factors influencing progression of diabetic nephropathy*

Predictors	Odds ratio	95% CI	*P*
Baseline 24-h UPE (per 1 g)	2.194	1.294–3.710	0.004
Baseline serum Lp(a) (per 10 mg/dl)	1.418	1.040–1.934	0.027
Baseline serum creatinine (per 0.1 mg/dl)	1.364	0.978–1.903	0.068
Mean follow-up systolic blood pressure (per 10 mmHg)	2.526	0.878–7.266	0.086
A1C (per 1%)	0.964	0.512–1.813	0.909

the fact that we did not determine apolipoprotein(a) phenotypes or genotypes; therefore, the association of apolipoprotein(a) isoforms with the progression of diabetic nephropathy remains to be defined. Second, although serum creatinine or calculated GFR was widely used as an indirect estimation of GFR, a more reliable marker of renal function such as ^{51}Cr-EDTA clearance should be used for further investigation. Lastly, we did not measure changes in UPE during the observation period.

In conclusion, these data suggest that an elevated Lp(a) level is an independent risk factor for the progression of diabetic nephropathy in type 2 diabetic patients with overt proteinuria. However, future studies are needed in other ethnic groups.

References

1. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM: Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. *Kidney Int* 65: 2309–2320, 2004
2. Remuzzi G, Schieppati A, Ruggenenti P: Clinical practice: nephropathy in patients with type 2 diabetes. *N Engl J Med* 346: 1145–1151, 2002
3. Sasaki A, Horiuchi N, Hasagawa K, Uehara M: Persistent albuminuria as an index of diabetic nephropathy in type 2 diabetic patients in Osaka, Japan: incidence, risk factors, prognosis and causes of death. *Diabetes Res Clin Pract* 7:299–306, 1989
4. Lee KU, Park JY, Kim SW, Lee MH, Kim GS, Park SK, Park JS: Prevalence and associated features of albuminuria in Koreans with NIDDM. *Diabetes Care* 18:793–799, 1995
5. Ritz E, Orth SR: Nephropathy in patients with type 2 diabetes mellitus. *N Engl J Med* 341:1127–1133, 1999
6. Kim SY, Jin DC, Bang BK: Current status of dialytic therapy in Korea. *Nephrology (Carlton)* 8:S2–S9, 2003
7. Ravid M, Brosh D, Ravid-Safran D, Levy Z, Rachmani R: Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. *Arch Intern Med* 158:998–1004, 1998
8. Song KH, Yoon KH, Kang ML, Cha BY, Lee KW, Son HY, Kang SK: Progression to overt proteinuria in microalbuminuric Koreans with non-insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract* 42: 117–121, 1998
9. Parving HH: Diabetic nephropathy: prevention and treatment. *Kidney Int* 60: 2041–2055, 2001
10. Utermann G: The mysteries of lipoprotein(a). *Science* 246:904–910, 1989
11. Utermann G, Menzel HJ, Kraft HG, Duba HC, Kemmler HG, Seitz C: Lp(a) glycoprotein phenotypes: inheritance and relation to Lp(a)-lipoprotein concentrations in plasma. *J Clin Invest* 80:458–465, 1987
12. Gaubatz JW, Heideman C, Gotto AM Jr, Morrisett JD, Dahlen GH: Human plasma lipoprotein [a]: structural properties. *J Biol Chem* 258:4582–4589, 1983
13. Loscalzo J: Lipoprotein(a): a unique risk factor for atherothrombotic disease. *Arteriosclerosis* 10:672–679, 1990
14. Hiraga T, Kobayashi T, Okubo M, Nakanishi K, Sugimoto T, Ohashi Y, Murase T: Prospective study of lipoprotein(a) as a risk factor for atherosclerotic cardiovascular disease in patients with diabetes. *Diabetes Care* 18:241–244, 1995
15. Gazzaruso C, Garzaniti A, Falcone C, Geroldi D, Finardi G, Fratino P: Association of lipoprotein(a) levels and apolipoprotein(a) phenotypes with coronary artery disease in type 2 diabetic patients and in non-diabetic subjects. *Diabet Med* 18:589–594, 2001
16. Ariyo AA, Thach C, Tracy R: Lp(a) lipoprotein, vascular disease, and mortality in the elderly. *N Engl J Med* 349:2108–2115, 2003
17. Tseng CH: Lipoprotein(a) is an independent risk factor for peripheral arterial disease in Chinese type 2 diabetic patients in Taiwan. *Diabetes Care* 27:517–521, 2004
18. Jenkins AJ, Steele JS, Janus ED, Best JD: Increased plasma apolipoprotein(a) levels in IDDM patients with microalbuminuria. *Diabetes* 40:787–790, 1991
19. Jenkins AJ, Steele JS, Janus ED, Santamaria JD, Best JD: Plasma apolipoprotein(a) is increased in type 2 (non-insulin-dependent) diabetic patients with microalbuminuria. *Diabetologia* 35:1055–1059, 1992
20. Jerums G, Allen TJ, Tsalamandris C, Akdeniz A, Sinha A, Gilbert R, Cooper ME: Relationship of progressively increasing albuminuria to apoprotein(a) and blood pressure in type 2 (non-insulin-dependent) and type 1 (insulin-dependent) diabetic patients. *Diabetologia* 36:1037–1044, 1993
21. Kronenberg F, Konig P, Neyer U, Auinger M, Pribasnig A, Lang U, Reitinger J, Pinter G, Utermann G, Dieplinger H: Multicenter study of lipoprotein(a) and apolipoprotein(a) phenotypes in patients with end-stage renal disease treated by hemodialysis or continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol* 6:110–120, 1995
22. Koch M, Kutkuhn B, Trenkwalder E, Bach D, Grabensee B, Dieplinger H, Kronenberg F: Apolipoprotein B, fibrinogen, HDL cholesterol, and apolipoprotein(a) phenotypes predict coronary artery disease in hemodialysis patients. *J Am Soc Nephrol* 8:1889–1898, 1997
23. Milionis HJ, Elisaf MS, Tselepis A, Bairaktari E, Karabina SA, Siamopoulos KC: Apolipoprotein(a) phenotypes and lipoprotein(a) concentrations in patients with renal failure. *Am J Kidney Dis* 33: 1100–1106, 1999
24. Boemi M, Sirolla C, Fumelli P, James RW: Renal disease as a determinant of increased lipoprotein(a) concentrations in diabetic patients. *Diabetes Care* 22:2033–2036, 1999
25. Ishimura E, Nishizawa Y, Kawagishi T, Okuno Y, Kogawa K, Fukumoto S, Maekawa K, Hosoi M, Inaba M, Emoto M, Morii H: Intrarenal hemodynamic abnormalities in diabetic nephropathy measured by duplex Doppler sonography. *Kidney Int* 51:1920–1927, 1997
26. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861–869, 2001
27. Kostner GM, Avogaro P, Cazzolato G, Marth E, Bittolo-Bon G, Qunici GB: Lipoprotein Lp(a) and the risk for myocardial infarction. *Atherosclerosis* 38:51–61, 1981
28. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345:851–860, 2001
29. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41, 1976
30. Ko SH, Song KH, Ahn YB, Yoo SJ, Son HS, Yoon KH, Cha BY, Lee KW, Son HY, Kang SK: The effect of rosiglitazone on serum lipoprotein(a) levels in Korean patients with type 2 diabetes mellitus. *Metabolism* 52:731–734, 2003
31. Solini A, Giacchetti G, Sfriso A, Fioretto P, Sardu C, Saller A, Tonolo G, Maioli M, Mantero F, Nosadini R: Polymorphisms of angiotensin-converting enzyme and angiotensinogen genes in type 2 diabetic sibships in relation to albumin excretion rate. *Am J Kidney Dis* 34:1002–1009, 1999
32. Keane WF, Kasiske BL, O'Donnell MP, Kim Y: Hypertension, hyperlipidemia, and renal damage. *Am J Kidney Dis* 21:43–50, 1993

33. Krolewski AS, Warram JH, Christlieb AR: Hypercholesterolemia: a determinant of renal function loss and deaths in IDDM patients with nephropathy. *Kidney Int* (Suppl. 45): S125–S131, 1994

34. Ravid M, Neumann L, Lishner M: Plasma lipids and the progression of nephropathy in diabetes mellitus type II: effect of ACE inhibitors. *Kidney Int* 47:907–910, 1995

35. Fried LF, Orchard TJ, Kasiske BL: Effect of lipid reduction on the progression of renal disease: a meta-analysis. *Kidney Int* 59:260–269, 2001

36. Chuahirun T, Khanna A, Kimball K, Wesson DE: Cigarette smoking and increased urine albumin excretion are interrelated predictors of nephropathy progression in type 2 diabetes. *Am J Kidney Dis* 41:13–21, 2003

37. Nosadini R, Velussi M, Brocco E, Bruseghin M, Abaterusso C, Saller A, Dalla Vestra M, Carraro A, Bortoloso E, Sambataro M, Barzon I, Frigato F, Muollo B, Chiesura-Corona M, Pacini G, Baggio B, Piarulli F, Sfriso A, Fioretto P: Course of renal function in type 2 diabetic patients with abnormalities of albumin excretion rate. *Diabetes* 49:476–484, 2000

38. Ueda H, Ishimura E, Shoji T, Emoto M, Morioka T, Matsumoto N, Fukumoto S, Miki T, Inaba M, Nishizawa Y: Factors affecting progression of renal failure in patients with type 2 diabetes. *Diabetes Care* 26:1530–1534, 2003

39. Greiber S, Kreusel M, Pavenstadt H, Schollmeyer P, Wanner C: Lipoprotein(a) induces glomerular superoxide anion production. *Nephrol Dial Transplant* 12:1330–1335, 1997