High Serum Lipoprotein(a) Levels in Korean Type 2 Diabetic Patients With Proliferative Diabetic Retinopathy

CHUL-HEE KIM, MD
HYUNG-JOO PARK, MD
JOONG-YEOL PARK, MD
SUNG-KWAN HONG, MD
YOUNG-HEE YOON, MD
KI-UP LEE, MD

OBJECTIVE — To examine the possible association between serum lipoprotein(a) [Lp(a)] concentration and proliferative diabetic retinopathy (PDR) in Korean patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 412 Korean outpatients with type 2 diabetes were examined. Diabetic retinopathy was determined by an ophthalmologist using fundoscopic examination. Serum Lp(a) levels were measured by two-site sandwich enzyme-linked immunosorbent assay.

RESULTS — The patients with PDR had higher serum Lp(a) levels than those with no diabetic retinopathy or with nonproliferative diabetic retinopathy (NPDR). Multiple logistic regression analysis showed that high serum Lp(a) levels and the presence of diabetic nephropathy were independent variables having a statistically significant association with PDR.

CONCLUSIONS — Korean type 2 diabetic patients with PDR had higher serum Lp(a) levels versus those with no diabetic retinopathy or with NPDR. Although these results suggest that Lp(a) might play a role in the occlusion of retinal capillaries leading to PDR, further prospective studies are required to prove the causal relationship.

Diabetes Care 21:2149–2151, 1998

Proliferative diabetic retinopathy (PDR) is the most common cause of acquired blindness in adults. Although a recent study by the Diabetes Control and Complications Trial (DCCT) Research Group (1) clearly demonstrated that intensified insulin therapy could effectively delay the onset and progression of retinopathy in type 1 diabetes, studies performed in type 2 diabetes have suggested that multiple factors along with glycemic control determine the risk of PDR (2–5).

Lipoprotein(a) [Lp(a)] is a plasma complex composed of apolipoprotein(a) [apo(a)] covalently linked to apo B-100 by disulfide bridges (6). Because of the structural similarity of apo(a) to plasminogen, Lp(a) has been suggested to have antifibrinolytic properties (7). High serum Lp(a) levels have thus been shown to be an independent risk factor for atherogenesis and thromboembolic events in both diabetic and nondiabetic subjects.

Capillary occlusion is a frequent finding in diabetic retinopathy and is believed to play an important role in the development of PDR. High serum Lp(a) might play a role in the occlusion of retinal capillaries leading to PDR. However, only a few studies have dealt with this matter, with controversial results (8–11). This study was undertaken to find out whether high serum Lp(a) levels are found in type 2 diabetic patients with PDR.

RESEARCH DESIGN AND METHODS

This study was performed in 412 type 2 diabetic patients attending a university hospital (the Asan Medical Center) in Seoul, Korea. The diagnosis of type 2 diabetes was based on clinical characteristics that included *1*) no episodes of ketoacidosis; 2) diagnosis of diabetes after 30 years of age; and 3) treatment by diet or oral hypoglycemic agents or fasting serum C-peptide values >0.30 nmol/l in patients using insulin. Of the subjects, 25% were using insulin and 61% were using oral hypoglycemic agents.

Arterial blood pressure was measured with a mercury sphygmomanometer in the sitting position after a 10-min rest. Serum glucose, triglycerides, and total cholesterol levels were measured using an autoanalyzer with enzymatic techniques. HDL cholesterol was measured after heparin and manganese chloride precipitation. HbA_1 was measured by affinity chromatography (Isolab, Akron, OH) (normal range 4–8%). Serum C-peptide was measured by radioimmunoassay (Daiichi, Tokyo). Patients collected timed overnight urine samples for the determination of albumin excretion rate (AER) by radioimmunoassay (Diagnostic Products, Los Angeles, CA). Microalbuminuria was defined as AER 20–200 μg/min and overt proteinuria as AER >200 μg/min in at least two of the three measurements. Serum Lp(a) levels were measured by one-step sandwich enzyme-linked immunosorbent assay using monoclonal antibodies (Immuno, Vienna).

Fundoscopic examination was performed by a retinal specialist (Y.-H.Y.) using ophthalmoscope and/or biomicroscope through dilated pupils. The findings were graded as *1*) no signs of diabetic retinopathy, 2) nonproliferative diabetic retinopathy (NPDR), and 3) PDR. Individuals were classified as having PDR if they

From the Departments of Internal Medicine (C.-H.K., H.-J.P., J.-Y.P., S.-K.H., K.-U.L.) and Ophthalmology (Y.-H.Y.), Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

Address correspondence and reprint requests to Ki-Up Lee, MD, Department of Internal Medicine, Asan Medical Center, Song-Pa P.O. Box 145, Seoul 138-600, Korea. E-mail: kulee@www.amc.seoul.kr.

Received for publication 29 May 1998 and accepted in revised form 19 August 1998.

Abbreviations: AER, albumin excretion rate; apo(a), apolipoprotein(a); DCCT, Diabetes Control and Complications Trial; Lp(a), lipoprotein(a); NPDR, nonproliferative diabetic retinopathy; OR, odds ratio; PDR, proliferative diabetic retinopathy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical and laboratory characteristics of the subjects according to retinopathy groups*

	No retinopathy	NPDR	PDR
n	218	143	51
Age (years)	55 ± 0.7	59 ± 0.8	58 ± 1.5
Diabetes duration (years)	5.6 ± 0.3	11.6 ± 0.4*	13.8 ± 0.9*
BMI (kg/m²)	24.8 ± 0.2	23.6 ± 0.2	23.5 ± 0.4
Fasting serum glucose (mmol/l)	9.7 ± 0.2	11.0 ± 0.3*	10.3 ± 0.6
HbA_1 (%)	11.4 ± 0.3	12.3 ± 0.3	11.7 ± 0.4
C-peptide (nmol/l)	0.8 ± 0.03	0.7 ± 0.03	0.6 ± 0.04
Blood pressure (mmHg)			
Systolic	143 ± 1.4	148 ± 1.8	150 ± 2.9
Diastolic	85 ± 0.7	87 ± 1.0	86 ± 2.0
Cholesterol (mmol/l)	5.7 ± 0.07	5.6 ± 0.11	6.0 ± 0.25
Triglycerides (mmol/l)	2.7 ± 0.12	2.3 ± 0.14	2.3 ± 0.22
HDL cholesterol (mmol/l)	1.1 ± 0.02	1.2 ± 0.03	1.2 ± 0.04
AER (μg/min)	23 ± 3.0	64 ± 8.4*	76 ± 15.4*
	(8, 1–237)	(21, 2–517)	(29, 4–525)
Lp(a) (mg/dl)	13.1 ± 1.1	19.3 ± 1.5	32.2 ± 3.3*†
	(6.5, 1.0–75.9)	(13.7, 1.0–80.3)	(27.8, 1.0–97.7)

Data are means ± SEM or means ± SEM (median, range). *$P < 0.05$ vs. no retinopathy; †$P < 0.05$ vs. NPDR group.

had new vessels, vitreous hemorrhage, vitreoretinal traction, or retinal detachment believed to be attributable to diabetic neovascularization.

Statistical analysis

Data are expressed as mean ± SEM or median (range). Variables that showed skewed distribution, such as serum triglyceride levels and AER, were log-transformed before analysis. Comparisons between groups were made by analysis of variance with Duncan's multiple range test or Kruskal-Wallis test where appropriate. Multiple logistic regression analysis was performed to find independent factors associated with the presence of PDR. A P value <0.05 (two-tailed) was considered to be statistically significant.

RESULTS — Among 412 patients, 143 had NPDR and 51 had PDR. Table 1 shows the clinical and laboratory characteristics of the subjects. The patients with retinopathy had longer duration of diabetes, higher fasting serum glucose, and higher AER than patients without retinopathy, but there was no significant difference between the NPDR and PDR groups. Age, BMI, blood pressure, fasting serum C-peptide, total cholesterol, triglycerides, and HDL cholesterol concentrations were similar in the three groups. Subjects with PDR had higher serum Lp(a) levels (32.2 ± 3.3 mg/dl) compared with subjects with no diabetic retinopathy (13.2 ± 1.1 mg/dl) or with NPDR (19.3 ± 1.5 mg/dl, $P < 0.05$).

Because previous studies showed that serum Lp(a) levels are higher in patients with overt proteinuria (12), we subdivided the patients according to urinary AER. As expected, the patients with overt proteinuria showed higher serum Lp(a) levels (27.1 ± 2.7 mg/dl) than those with microalbuminuria (16.5 ± 1.6 mg/dl) and normoalbuminuria (14.2 ± 1.1 mg/dl, $P < 0.05$). Among the patients with overt proteinuria, the patients with PDR showed significantly higher Lp(a) levels (37.7 ± 5.6 mg/dl) than those with NPDR (22.3 ± 3.4 mg/dl) or without retinopathy (18.4 ± 6.0 mg/dl, $P < 0.05$) (Fig. 1).

When factors associated with the presence of PDR were analyzed by multiple logistic regression analysis, the presence of PDR was associated with serum Lp(a) level ($\beta = 0.29$, odds ratio [OR] = 1.34, $P < 0.05$) and the presence of diabetic nephropathy ($\beta = 2.20$, OR = 9.04, $P < 0.01$) (Table 2).

CONCLUSIONS — This cross-sectional study showed that Korean type 2 diabetic patients with PDR had higher serum Lp(a) levels. Conflicting results have been reported about the serum Lp(a) concentrations in patients with diabetic retinopathy. Several studies in Caucasians (10,11,13), mostly done in type 1 diabetes, showed that Lp(a) is not related to retinopathy. On the contrary, other studies in Japan (8,9) reported that serum Lp(a) concentrations were elevated in type 2 diabetic patients with retinopathy. Regarding serum Lp(a)

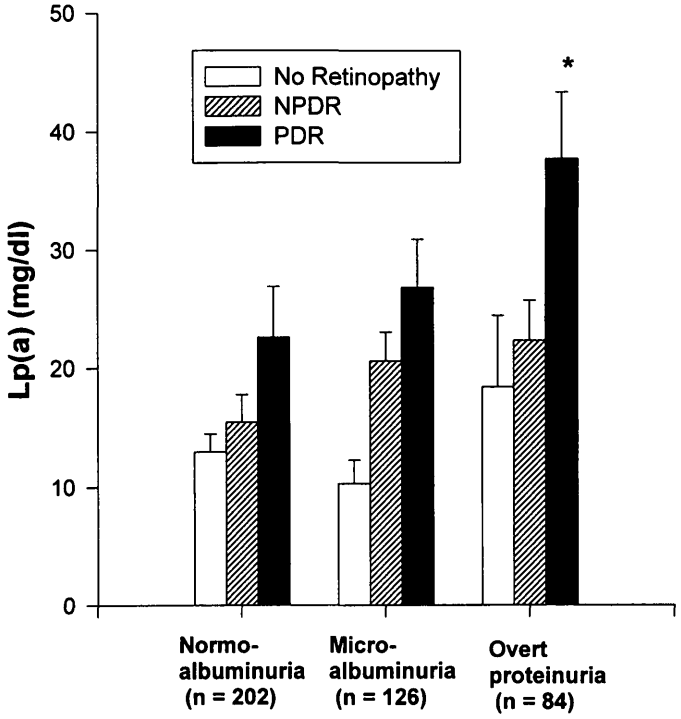

Figure 1—*Serum Lp(a) levels (means ± SEM) according to retinopathy and nephropathy groups (*P < 0.05 vs. no retinopathy and NPDR).*

Table 2—*Multiple logistic regression analysis for PDR*

	OR (95% CI)
Presence of nephropathy	9.04 (2.06–39.8)*
Lp(a) (quartiles)	1.34 (1.01–1.81)†
Age (10 years)	1.27 (0.62–2.59)‡
Diabetes duration (5 years)	1.61 (0.43–6.01)‡
BMI (quartiles)	0.85 (0.45–1.61)‡
Fasting serum glucose (mmol/l)	1.02 (0.92–1.13)‡
Systolic blood pressure (10 mmHg)	1.08 (0.80–1.45)‡

*$P < 0.01$; †$P < 0.05$; ‡NS.

levels in PDR, Maioli et al. (14) reported that serum apo(a) levels were raised in active diabetic retinopathy groups (severe NPDR or PDR) compared with no diabetic retinopathy group. Hessen et al. (15) also reported higher prevalence of preproliferative retinopathy with increasing Lp(a) levels in type 2 diabetic patients. On the other hand, in Japanese studies (8,9), there were no significant differences between the patients with NPDR and those with PDR. The causes for such discrepancies are not clear at present, but differences in types of diabetes, ethnic groups, or classification of retinopathy (all retinopathy or PDR) between the studies may be responsible. In addition, the relatively small number of subjects with PDR in other studies may have attenuated the statistical significance of the differences. Another explanation might be the differences between ethnic groups in allele frequency of apo(a) phenotypes (16,17), known to be a major determinant of serum Lp(a) level.

In agreement with previous studies (12), serum Lp(a) levels were increased in patients with overt proteinuria. But even in the patients with overt proteinuria, Lp(a) levels were further increased in the PDR group than in those with NPDR or no retinopathy. Moreover, serum Lp(a) levels were significantly associated with the presence of PDR after controlling for other factors such as duration of diabetes, degree of glycemia, and nephropathy.

The mechanisms of association between PDR and high Lp(a) levels remain to be elucidated. Lp(a) is believed to have an antifibrinolytic effect (7,18), so it may contribute to the occlusion of small retinal vessels and, therefore, be an independent risk factor for PDR. In line with this possibility, Maioli et al. (14) reported that serum apo(a) levels are raised in active diabetic retinopathy. Konno et al. (19) showed that retinal blood flow progressively decreases from the very early stage of diabetic retinopathy, reflecting increasing resistance to flow through the retinal vascular network. This decrease is followed by a paradoxical increase in retinal blood flow, which was attributed to formation of shunts between arterioles and venules in the areas of capillary occlusion. In our study, serum Lp(a) levels tended to increase with worsening of retinopathy in all three groups of urinary AER, even though the difference between those with NPDR and no retinopathy was not statistically significant. Thus increased serum Lp(a) may contribute to the increased resistance to flow or capillary occlusion in the development or progression of diabetic retinopathy. However, since our study is cross-sectional, it is not clear whether high Lp(a) level is a pathogenic factor or merely a marker of PDR. Prospective studies on large populations are needed to clarify the relationship between PDR and serum Lp(a) levels.

Acknowledgments— This study was supported by a grant (HMP-96-M-2-1009) from the 1996 Good Health R&D Project, Ministry of Health and Welfare, Korea.

References

1. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
2. Hamman FR, Mayer JE, Moo-Yong AG, Hildebrandt W, Marshall AJ, Baxter J: Prevalence and risk factors of diabetic retinopathy in non-Hispanic whites and Hispanics with NIDDM: San Luis Valley Diabetes Study. *Diabetes* 38:1231–1237, 1989
3. Haffner SM, Mitchell BD, Moss SE, Stern MP, Hazuda HP, Patterson J, Van Heuven WA, Klein R: Is there an ethnic difference in the effect of risk factors for diabetic retinopathy? *Ann Epidemiol* 3:2–8, 1993
4. Lee ET, Lee VS, Lu M, Russell D: Development of proliferative retinopathy in NIDDM: a follow-up study of American Indians in Oklahoma. *Diabetes* 41:359–367, 1992
5. Kim H-K, Kim C-H, Kim S-W, Park J-Y, Hong S-K, Yoon Y-H, Lee K-U: Development and progression of diabetic retinopathy in Koreans with NIDDM. *Diabetes Care* 21:134–138, 1998
6. Uterman G: The mysteries of lipoprotein(a). *Science* 246:904–910, 1989
7. Scott J: Thrombogenesis is linked to atherogenesis at last? *Nature* 341:22–23, 1989
8. Onuma T, Kikuchi T, Shimura M, Tsutsui M, Matsui J, Boku A, Takebe K: Lipoprotein(a) as an independent risk factor for diabetic retinopathy in male patients in non-insulin-dependent diabetes mellitus. *Tohoku J Exp Med* 173:209–216, 1994
9. Morisaki N, Yokote K, Tashiro J, Inadera H, Kobayashi J, Kanzaki T, Saito Y, Yoshida S: Lipoprotein(a) is a risk factor for diabetic retinopathy in the elderly. *J Am Geriatr Soc* 42:965–967, 1994
10. Haffner SM, Klein BE, Moss SE, Klein R: Lp(a) is not related to retinopathy in diabetic subjects. *Eur J Ophthalmol* 5:119–123, 1995
11. Maser RE, Usher D, Becker DJ, Drash AL, Kuller LH, Orchard TJ: Lipoprotein(a) concentration shows little relationship to IDDM complications in the Pittsburgh Epidemiology of Diabetes Complications Study cohort. *Diabetes Care* 16:755–758, 1993
12. Kronenberg F, Utermann G, Dieplinger H: Lipoprotein(a) in renal disease. *Am J Kidney Dis* 27:1–25, 1996
13. Willems D, Dorchy H, Dufrasne D: Serum lipoprotein (a) in type 1 diabetic children and adolescents: relationships with HbA_{1c} and subclinical complications. *Eur J Pediatr* 155:175–178, 1996
14. Maioli M, Tonolo G, Pacifico A, Ciccarese M, Brizzi P, Kohner EM, Porta M: Raised serum apolipoprotein (a) in active diabetic retinopathy. *Diabetologia* 36:88–90, 1993
15. Heesen BJ, Wolffenbuttel BH, Leurs PB, Sels JP, Menheere PP, Jackle-Beckers SE, Nieuwenhuijzen-Kruseman AC: Lipoprotein(a) levels in relation to diabetic complications in patients with non–insulin–dependent diabetes. *Eur J Clin Invest* 23:580–584, 1993
16. Abe A, Noma A: Studies on apolipoprotein(a) phenotypes: part 1: phenotype frequencies in a healthy Japanese population. *Atherosclerosis* 96:1–8, 1992
17. Kim JQ, Song JH: High allele frequency of apolipoprotein(a) phenotype LpS4 is associated with low serum Lp(a) concentrations in Koreans. *Clin Biochem* 27:57–62, 1994
18. Hajjar KA, Gavish D, Breslow JL, Nachman RL: Lipoprotein(a) modulation of endothelial cell surface fibrinolysis and its potential role in atherosclerosis. *Nature* 339:303–305, 1989
19. Konno S, Feke GT, Yoshida A, Fujio N, Goger DG, Buzney SM: Retinal blood flow changes in type I diabetes: a long-term, follow-up study. *Invest Ophthalmol Vis Sci* 37:1140–1148, 1996