Lipoprotein(a) and Diabetes

An update

STEVEN M. HAFFNER, MD

The risk of cardiovascular disease is increased in both NIDDM (1–3) and IDDM (4–5) compared with nondiabetic subjects. Furthermore, this excess risk is only partially explained by the patients' increased levels of standard risk factors.

Recently, much interest has been focused on Lp(a). Lp(a) is a complex lipoprotein consisting of lipid, carbohydrate, and two large apoproteins, B and a (6,7). Because several excellent reviews have recently appeared (6,7), I will concentrate in this update mainly on Lp(a) in diabetes. The most important determinant of Lp(a) concentration is the genotype at LPA, the locus encoding apo(a), which determines the size polymorphism of apo(a). A large variation in levels occurs among individuals (>1000-fold), but little variation occurs within individuals (8,9). Individuals with higher-molecular-weight apo(a) isoforms tend to have lower Lp(a) concentrations in plasma (8,10). One of the distinctive structural features of apo(a) is triple-looped cysteine-linked amino acid domains called kringles, which have considerable homology to similar domains within plasminogen (11). Thus, Lp(a) may provide a link between the clotting and lipoprotein systems. Lp(a) also has been found in the atheroma of subjects undergoing coronary bypass (12). In many studies of nondiabetic subjects, Lp(a) has been found to be a risk factor for CHD (13–17).

Because Lp(a) levels are mainly genetically determined, environmental modifiers are relatively few. Weight loss has been associated with decreased Lp(a) concentrations (18). Alcohol intake has also been associated with lower Lp(a) concentrations (19). These results, however, need further confirmation.

In nondiabetic subjects, no relation of Lp(a) concentrations to either insulin concentrations (20) or to insulin resistance as determined by the intravenous glucose tolerance test (21) has been found. However, in the latter study, first-phase insulin secretion was associated with lower Lp(a) concentrations (21). Lp(a) levels are not related to age or sex (13,20,22), although they may be increased in postmenopausal women relative to premenopausal women (22).

Early studies on Lp(a) and diabetes

The first report of Lp(a) in diabetes was by Scherthaner et al. (23) in 1983. These investigators suggested that Lp(a) concentrations were similar in diabetic and nondiabetic subjects. However, 14% of diabetic patients had Lp(a) concentrations >20 mg/dl compared with only 5% of control subjects. In this study, no distinction was made between NIDDM and IDDM. Ramirez et al. (24) found elevated Lp(a) levels in a combined group of IDDM and NIDDM subjects relative to nondiabetic subjects. GHb was significantly related to Lp(a) concentrations in IDDM but not in NIDDM subjects.

Bruckert et al. (25) first described the effect of improved metabolic control for 21 days in 10 IDDM subjects. They described a significant reduction in Lp(a) concentrations from 46 to 29 mg/dl ($P < 0.001$), and they found a statistically significant correlation between the degree of improvement in GHb and the amount of decrease in Lp(a) ($r = 0.70$). In April 1991, *Diabetes Care* published the first full-length papers on Lp(a) in IDDM (26,27). Levitsky et al. (26) reported in a cross-sectional study that GHb was associated with Lp(a) concentrations in white but not in black children. Haffner et al. (27) described a significant decline in Lp(a) concentrations in 12 subjects over 21 days from 29 to 21 mg/dl in response to improved metabolic control. The change in Lp(a) concentrations was correlated with the change in GHb ($r = 0.40$), although this correlation was not statistically significant. Finally, IDDM subjects did not have a significantly different distribution of apo(a) isoforms than did normal subjects. Apo(a) isoforms also did not change after improved control. The latter two observations suggested that the elevated Lp(a) concentrations in IDDM patients may not have a genetic basis. Robbins and Howard (28) suggested in an editorial that although glycemic control might have an effect on reducing Lp(a), no data had yet shown that Lp(a) was a risk factor for CHD in diabetes, a particularly farsighted observation.

The rest of this commentary will focus on more recent observations of the

FROM THE DIVISION OF CLINICAL EPIDEMIOLOGY, DEPARTMENT OF MEDICINE, UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO, SAN ANTONIO, TEXAS.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO STEVEN M. HAFFNER, MD, DIVISION OF CLINICAL EPIDEMIOLOGY, DEPARTMENT OF MEDICINE, UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO, 7703 FLOYD CURL DRIVE, SAN ANTONIO, TX 78284–7873.

Lp(a), LIPOPROTEIN(a); NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; CHD, CORONARY HEART DISEASE; HMG-CoA, 3-HYDROXY-3-METHYLGLUTARYL COENZYME A; apo(a), APOPROTEIN(a).

effects of diabetes on Lp(a). Because these effects may differ in IDDM and NIDDM, these entities are discussed separately, as well as the relation of Lp(a) to CHD in diabetic subjects and the effect of renal dysfunction.

Lp(a) in IDDM

Guillauseau et al. (29) have reported, in cross-sectional studies, increased Lp(a) levels in IDDM (n = 36) and NIDDM (n = 90) subjects relative to normoglycemic control subjects (n = 78). These investigators found no relation between GHb and Lp(a) concentrations. Ritter et al. (30) did not find a significant effect of improved metabolic control in 9 IDDM and 9 NIDDM subjects. However, the authors analyzed their IDDM and NIDDM subjects together, and the degree of improvement in glucose control was small. (The fasting glucose fell from 10.2 ± 0.4 to 8.9 ± 0.7 mM after 3 wk.)

Nagashima et al., (this issue, p. 846) have found that Lp(a) levels were elevated in Japanese children with IDDM (n = 31) relative to age- and sex-matched control subjects (n = 17). In IDDM subjects, Lp(a) levels were strongly correlated with HbA_{1c} (r = 0.69, $P < 0.01$). Subjects with continuous microalbuminuria were excluded in this report. In contrast, in a French cross-sectional study (this issue, Heller et al., p. 819–23), Lp(a) levels were similar in normoglycemic individuals (median 9.3 mg/dl); (n = 142) and subjects with IDDM (median 10.0 mg/dl); (n = 66).

Austin et al. (33) found no significant difference in Lp(a) concentrations between Caucasian IDDM subjects (n = 59) and control subjects (n = 18), although the small number of control subjects may have limited the power of the analysis. These authors reported significant correlations between Lp(a) and GHb (r = 0.50, P = 0.01) and between Lp(a) and measures of physical fitness (r = 0.29, P = 0.02). The relation between Lp(a) and physical fitness remained highly correlated with Lp(a) concentrations (r = −0.25, P = 0.05) after adjustment for glycemic control. The authors believed the correlation between Lp(a) and fitness was attributable to improved insulin sensitivity, but this may be unlikely in view of the absence of other studies showing no relation between Lp(a) and insulin resistance or insulin concentrations in nondiabetic subjects (20,21). It is still possible that the association between fitness and Lp(a) might be attributable to changes in GHb, even though the authors controlled for this variable in multivariate analysis.

Maser et al. (this issue, p. 755–58) found only a weak association between Lp(a) levels and GHb in 188 IDDM subjects (aged 13–50 yr) (r = 0.14, P = 0.06). Gall et al. (35) found no increase in Lp(a) concentrations in IDDM subjects (n = 152) relative to control subjects (n = 50). This study included IDDM subjects with both microalbuminuria and mild renal insufficiency.

Cooper et al. (36), in a study of 170 IDDM subjects and 223 control subjects, suggested that Lp(a) concentrations are higher in IDDM subjects only during and after puberty (Tanner stages, 2–5). Interestingly, no effect of puberty on Lp(a) levels was found in normoglycemic subjects. Recently, Haffner et al. (37) found no difference in Lp(a) levels between adolescent Caucasian IDDM subjects (n = 68) and Caucasian normoglycemic subjects (n = 18). In the latter study, adjustment was made for apo(a) phenotype and molecular weight; in addition, subjects with microalbuminuria were excluded. A significant effect of puberty on Lp(a) concentrations was found in IDDM and normoglycemic males. In IDDM females, a trend towards higher Lp(a) levels also was observed (but was not statistically significant). The possible effect of puberty on Lp(a) concentrations is of interest because hormonal interventions have been reported to influence Lp(a) concentrations (38–40).

Lp(a) in NIDDM

Heller et al. (this issue, p. 819–23) showed no difference in Lp(a) concentrations between non-insulin-treated NIDDM subjects (median Lp(a) 8.3 mg/dl) (n = 100) and normoglycemic control subjects (median 9.3 mg/dl) (n = 66). However, these authors did show that insulin-treated NIDDM subjects did have elevated Lp(a) concentrations (19.3 mg/dl). Velho et al. (this issue, p. 742–47) showed no difference in Lp(a) levels between NIDDM subjects and normoglycemic relatives.

Joven et al. (42) have shown no difference in Lp(a) levels between well-controlled NIDDM subjects and normoglycemic subjects. Taskinen et al. (43) have shown that the Lp(a) concentrations in NIDDM subjects on oral antidiabetic agents (n = 116) are slightly lower than in normoglycemic subjects (n = 95) (9.1 vs. 15.2 mg/dl, NS). Furthermore, no significant correlation between Lp(a) and GHb was observed (r = −0.14). These investigators also examined the effect of improved metabolic control with two different tight control groups versus a placebo group (n = 25 in each group for 3 mo). No decrease in Lp(a) concentrations was observed in the tight control groups. This study thus provides strong evidence against an elevation of Lp(a) concentrations in NIDDM and against an effect of glycemic control on Lp(a) concentrations in NIDDM. Haffner et al. (44) found no significant difference in Lp(a) concentrations between diabetic subjects (n = 260) and normoglycemic subjects (n = 336) in the San Antonio Heart Study, a population-based study of diabetes and cardiovascular risk factors (men: NIDDM, 13.6 ± 1.5 vs. normal 16.1 ± 1.4 mg/dl; women: NIDDM 12.6 ± 0.8 vs. 15.9 ± 1.3 mg/dl; P value for NIDDM main effect = 0.361). No difference in Lp(a) levels between NIDDM and normoglycemic subjects was observed even in individuals <45 yr of age, which tends to argue against an elevation in diabetic patients that was

attenuated because of survival bias. No difference in the effect of improved metabolic control for 3 wk on Lp(a) concentrations was observed in NIDDM in two other small studies of NIDDM patients (n = 9 [30] and n = 12 [45]). However, in a 3-mo study of NIDDM subjects (n = 25), a significant decrease in Lp(a) concentrations was seen in NIDDM subjects with improved metabolic control using glipizide and insulin (46). Because this was the only study of improved metabolic control in NIDDM subjects using both insulin and oral agents, perhaps oral agents have an effect on reducing Lp(a) levels.

Lp(a) in coronary heart disease

Relatively few studies have been performed on the relation of Lp(a) to CHD in diabetes (35, this issue, G. Velho et al., p. 742–47, 47–49). These studies have been small and thus tend to lack statistical power. Only one of the studies had a prospective design with CHD mortality as an endpoint (48). The latter point is particularly important because in cross-sectional studies, an elevated Lp(a) concentration could be associated with decreased survival rather than a risk factor for a disease. This association could happen if diabetic subjects with higher Lp(a) levels died before the cross-sectional survey was carried out. An additional problem is that Lp(a) has been mainly documented to be a risk factor for premature CHD (6). Because most subjects develop NIDDM in late-middle or even old age, Lp(a) might not be expected to be a risk factor in this age group. With the preceding caveats considered, three studies found no association between Lp(a) and CHD (IDDM [this issue, R.E. Maser et al., p. 755–58], IDDM and NIDDM [48], NIDDM [49]). Only two studies to date have found that Lp(a) is associated with increased vascular events in NIDDM subjects (this issue, Velho et al., p. 742–47, 47). Caution should be used before assuming that Lp(a) may indicate increased risk for CHD in diabetic subjects. Further studies need to be done in this area.

Lp(a) in renal failure

Several studies suggest that in nondiabetic subjects, Lp(a) concentrations are increased both in subjects on hemodialysis and in those with untreated chronic renal failure (50–52). One study of chronic renal failure included diabetic subjects and found Lp(a) concentrations were increased relative to diabetic subjects without chronic renal failure (52). Takegoshi et al. (53) found a stepwise increase in Lp(a) concentrations from normoglycemic subjects to diabetic subjects with microalbuminuria to diabetic subjects with macroalbuminuria to diabetic subjects with chronic renal failure. However, the type of diabetes was not specified. Jenkins et al. (54) found an increase in Lp(a) concentrations in IDDM subjects with microalbuminuria or clinical proteinuria relative to IDDM subjects without renal disease. However, the levels of Lp(a) were similar in subjects with microalbuminuria and clinical proteinuria. Kapelrud et al. (55) and Wincour et al. (56) also found increases in Lp(a) concentrations in IDDM subjects with microalbuminuria relative to IDDM subjects without renal dysfunction. However, Gall et al. (35) found that IDDM subjects with microalbuminuria or clinical proteinuria did not have increased Lp(a) concentrations relative to IDDM subjects without renal dysfunction. Guillauseau et al. (29) and Maser et al. (this issue, p. 755–58) also found no association between renal disease and Lp(a) concentrations in IDDM subjects.

Much less data exists that examines Lp(a) concentrations in subjects with NIDDM and microalbuminuria. One study found that microalbuminuria was associated with increased Lp(a) concentrations (47), whereas another study found no relation (57).

Treatment of Lp(a) in diabetes

Although little evidence suggests that behavioral interventions may affect Lp(a) concentrations, one study suggested that weight loss in nondiabetic subjects decreased Lp(a) levels (18). Also, one study of IDDM subjects showed an association between physical fitness and Lp(a) concentrations (33). Both of these observations need to be confirmed. Few hypolipidemic drugs affect Lp(a) concentrations. Neomycin and nicotinic acid have been reported to lower Lp(a) concentrations (58), whereas cholestyramine has little effect (59). However, the role of nicotinic acid in diabetic patients is uncertain because it can worsen insulin resistance and glucose control (60). HMG-CoA reductase inhibitors have been reported both to raise (61) and to have little effect (62) on Lp(a) concentrations.

Summary

On the basis of the available data (much of which is contradictory), I suggest that the following might summarize the role of Lp(a) in diabetes currently.

1. Lp(a) in IDDM
   - Concentrations are probably elevated.
   - Concentrations are probably related to metabolic control.
   - Concentrations are increased with microalbuminuria.

2. Lp(a) in NIDDM
   - Concentrations are not elevated.
   - Concentrations do not change with metabolic control.
   - Too few data exist to make an assessment of relation of Lp(a) to microalbuminuria in NIDDM.

3. Lp(a) and CHD in diabetes
   - Little current evidence shows that Lp(a) is a risk factor for CHD in diabetes. More studies—especially prospective studies with larger numbers of subjects—need to be done.

Future directions

I believe it is no longer worthwhile to examine the effect of improved metabolic

control on Lp(a) levels in NIDDM. In subjects with IDDM, larger and longer term studies of improved metabolic control still need to be performed. There is enormous individual variation in Lp(a) concentrations that is genetically determined, and this makes cross-sectional studies, particularly small ones, difficult to intrepret. If cross-sectional studies are to be done, they should also take account of apo(a) isoform structure and molecular weight. The reader should note that the effects of molecular weight or phenotype may not totally take account of genetic structure, so family studies looking at diabetic and nondiabetic siblings of the same phenotype will be much more desirable. In addition, improved metabolic control might affect Lp(a) concentrations only in subjects with certain apo(a) phenotypes or elevated Lp(a) concentrations. Investigators should also take account of microalbuminuria and pubertal status as well.

Much work needs to be done to assess whether Lp(a) concentrations are a risk factor for CHD in diabetic subjects. These studies should be prospective, large scale, and involve younger as well as older subjects. In the absence of firm knowledge, an increased Lp(a) concentration in a diabetic subject should be treated as an additional risk factor much as smoking or increased blood pressure is considered. These subjects should receive particularly aggressive treatment of lipids (e.g., low-density-lipoprotein cholesterol) and blood pressure. Lp(a) need not now be measured routinely in diabetic subjects.

Currently, the most exciting research in the area of Lp(a) and diabetes may be in renal failure. Because Lp(a) may be elevated in IDDM subjects with microalbuminuria, these elevations must either occur early or be a marker (or cause) of early renal disease. This could be studied in the few animal models available for Lp(a) work (European hedgehog or primates) or alternatively examined in prospective human studies. It is exciting to contemplate that Lp(a) may help to explain the vast excess risk of CHD in IDDM subjects with renal failure (4,5).

References

1. Kannel WH, McGee DL: Diabetes and cardiovascular risk factors: the Framingham Study. *Circulation* 59:8–13, 1979
2. Assman G, Schulte H: The Prospective Cardiovascular Münster (PROCAM) Study: prevalence of hyperlipidemia in persons with hypertension and/or diabetes mellitus and the relationship to coronary heart disease. *Am Heart J* 116: 1713–24, 1988
3. Garcia MJ, McNamara PM, Gordon T, Kannel WB: Morbidity and mortality in diabetics in the Framingham population: sixteen-year follow-up study. *Diabetes* 23:105–11, 1974
4. Krolewski AS, Kosinki EI, Warram JH, Bradley RF, Kahn CR, Leland OS, Busick EJ, Asmol AC, Rand LI, Christlieb AR: Magnitude and determinants of coronary artery disease in juvenile onset, insulin dependent diabetes mellitus. *Am J Cardiol* 59:750–56, 1987
5. Jensen T, Stender S, Deckert T: Abnormalities in plasma concentrations of lipoproteins and fibrinogen in type I (insulin-dependent) diabetic patients with increased urinary albumin excretion. *Diabetologia* 31:142–45, 1988
6. Scanu AM, Lawn RM, Berg K: Lipoprotein(a) and atherosclerosis. *Ann Intern Med* 115:209–18, 1991
7. Utermann G: The mysteries of lipoprotein(a). *Science* 246:904–10, 1989
8. 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* 80:458–65, 1987
9. Rainwater DL, Manis GS, Vandeberg JL: Hereditary and dietary effects on apolipoprotein(a) isoforms and Lp(a) in baboons. *J Lipid Res* 30:549–58, 1989
10. Gaubatz JW, Ghanem KI, Guevara J, Nava ML, Patsch W, Morrisett JD: Polymorphic forms of human apolipoprotein(a): inheritance and relationship of their molecular weights to plasma levels of lipoprotein(a). *J Lipid Res* 31:603–13, 1990
11. Eaton DL, Fless GM, Kohr WJ, McLean JW, Xu Q, Miller CG, Lawn RM, Scanu AM: Partially amino acid sequence of apolipoprotein(a) shows that it is homologous to plasminogen. *Proc Natl Acad Sci USA* 84:3224–28, 1987
12. Rath M, Niendorf A, Reblin T, Dietel M, Krebber HJ, Beisiegel U: Detection and quantitation of lipoprotein(a) in the arterial wall of 107 coronary bypass patients. *Arteriosclerosis* 9:579–92, 1989
13. Berg K, Dahlen G, Frick MH: Lp(a) lipoprotein and pre-β lipoprotein in patients with coronary heart disease. *Clin Genet* 6:230–35, 1974
14. Rhoads GG, Dahlen G, Berg K, Morton NE, Dannenberg AL: Lp(a) lipoprotein as a risk factor for myocardial infarction. *JAMA* 256:2540–44, 1986
15. Durrington PN, Ishola M, Arrol S, Bhatgnar D: Apolipoprotein(a), A1 and B and parental history in men with early onset ischemic heart disease. *Lancet* 1:1070–73, 1988
16. Dahlen GH, Guyton JR, Attar M, Farmer JA, Kautz JA, Gotto AM: Association of levels of lipoprotein Lp(a), plasma lipids, and other lipoproteins with coronary artery disease documented by angiography. *Circulation* 74:758–65, 1986
17. Seed M, Hoppichler F, Reavley D, McCarthy S, Thompson GR, Boerwinkle E, Utemann G: Relation of serum lipoprotein(a) concentration and apolipoprotein(a) phenotype to coronary heart disease in patients with familial hypercholesterolemia. *N Engl J Med* 322: 1494–99, 1990
18. Sonnichsen AC, Richler WO, Schwandt P: Reduction of lipoprotein(a) by weight loss. *Int J Obes* 14:487–94, 1990
19. Kervinen K, Savolainen MJ, Kesaniemi YA: A rapid increase in lipoprotein(a) levels after ethanol withdrawal in alcoholic men. *Life Sci* 48:2183–88, 1991
20. Haffner SM, Gruber K, Morales PA, Hazuda HP, Valdez R, Stern MP: Lp(a) concentrations in Mexican Americans and non-Hispanic whites: the San Antonio Heart Study. *Am J Epidemiol* 136:1060–68, 1992
21. Sidhu M, Crook D, Godsland IF, Walton C, Wynn V, Oliver MF: Inverse relationship between serum Lp(a) levels and first

phase insulin secretion. *Diabetes* 41: 1341–45, 1992
22. Guyton JR, Dahlen GH, Patsch W, Kautz JA, Gotto JA: Relationship of plasma lipoprotein Lp(a) levels to race and apolipoprotein (B). *Arteriosclerosis* 5:265–72, 1985
23. Schernthaner G, Kostner GM, Dieplinger H, Prager R, Muhlhauser I: Apolipoproteins (A-I, A-II, B): lipoprotein(a), lipoprotein and lecithin cholesterol acyltransferase activity in diabetes mellitus. *Atherosclerosis* 49:277–93, 1983
24. Ramirez LC, Arauz-Pacheco C, Lackner C, Albright G, Adams BV, Raskin P: Lipoprotein(a) levels in diabetes mellitus: relationship to metabolic control. *Ann Intern Med* 117:42–47, 1992
25. Bruckert E, Davidoff P, Grimaldi A, Truffert J, Giral P, Doumith R, Thervet F, De Gennes JL: Increased serum levels of lipoprotein(a) in diabetes mellitus and their reduction with glycemic control (Letter). *JAMA* 263:35–36, 1990
26. Levitsky L, Scanu A, Gould SH: Lipoprotein(a) levels in black and white children and adolescents with IDDM. *Diabetes Care* 14:283–87, 1991
27. Haffner SM, Tuttle KR, Rainwater DL: Decrease of lipoprotein(a) with improved glycemic control in IDDM subjects. *Diabetes Care* 14:302–307, 1991
28. Robbins DR, Howard BV: Lipoprotein(a) and diabetes (Editorial). *Diabetes Care* 14:347–49, 1991
29. Guillauseau PJ, Peynet J, Chanson P, Legrand A, Altman JJ, Poupon J, N'Guyen M, Rosselet F, Lubetzki J: Lipoprotein(a) in diabetic patients with and without chronic renal failure. *Diabetes Care* 15:976–79, 1992
30. Ritter MM, Richter WO, Lyko K, Schwanelt P: Lp(a) serum concentrations and metabolic control (Letter). *Diabetes Care* 15:1441–42, 1992
33. Austin A, Warty V, Janosky J, Arslanian S: The relationship of physical fitness to lipid and lipoprotein(a) levels in adolescents with IDDM. *Diabetes Care* 16:421–25, 1993
35. Gall MA, Rossing P, Hommel E, Voldsgaard AI, Andersen P, Nielsen FS, Dyerberg J, Parving HH: Apolipoprotein(a) in insulin-dependent diabetic patients with and without nephropathy. *Scand J Clin Lab Invest* 52:513–22, 1992
36. Cooper JJ, Bates DJ, Cocciolone R, Magarey AM, Boulton TJC, Penfold JL, Ryall RG: Association of lipoprotein(a) with puberty in insulin dependent diabetes. *Diabetes Care*. In press
37. Haffner SM, Frangos M, Williamson J, Santiago J, Valdez R, Aldrete G, Mykkänen L, Gruber KK, Rainwater DL: Lp(a) concentrations and phenotypes in subjects with insulin dependent diabetes mellitus. *Chem Phys Lipids*. In press
38. Henriksson P, Angelin B, Berglund L: Hormonal regulation of serum Lp(a) levels: opposite effects after estrogen treatment and orchiectomy in males with prostatic carcinoma. *J Clin Invest* 89: 1166–71, 1992
39. Albers JJ, Taggert HM, Applebaum-Bowden D, Haffner SM, Chestnut CH, Hazzard WR: Reduction of lecithin: cholesterol acyltransferase, apolipoprotein D and the Lp(a) lipoprotein with the anabolic steroid stanozolol. *Biochem Biophys Acta* 795:293–96, 1984
40. Soma MR, Fumagalli R, Paoletti R, Meschia M, Maini MC, Crosignoni P, Ghanem K, Gaubatz J, Morrisett JD: Plasma Lp(a) concentrations after estrogen and progestogen in postmenopausal women (Letter). *Lancet* 337:612, 1991
42. Joven J, Vilella E: Serum levels of lipoprotein(a) in patients with well controlled non-insulin diabetes mellitus (Letter). *JAMA* 265:1113–14, 1991
43. Taskinen MR, Enholm C, Jaubianen M, Kauppinen-Makelin R, Yki-Jarvinen H, FINMIS group: The concentration of Lp(a) is not influenced by the degree of glycemic control in NIDDM (Abstract). In *Proc 9th International Symposium on Atherosclerosis Rosemont, IL, 1991*. p. 196
44. Haffner SM, Morales PA, Stern MP, Gruber MK: Lp(a) concentrations in NIDDM. *Diabetes* 41:1267–72, 1992
45. Haffner SM, Tuttle KR, Rainwater DL: Preliminary report: lack of change of Lp(a) concentrations with improved glycemic control in subjects with type II diabetes. *Metabolism* 41:116–20, 1992
46. Garber AJ, Jones PH, Ghanem KK, Morrisett JD: Response of plasma lipoprotein(a) levels to diabetes control therapy (Abstract). In *Proc 9th International Symposium on Atherosclerosis Rosemont, IL, 1991*. p. 12
47. Jenkins AJ, Steele JS, Junus ED, Santamaria JD, Best JD: Plasma apolipoprotein(a) is increased in type II (non-insulin-dependent) diabetic patients with microalbuminuria. *Diabetologia* 35: 1055–59, 1992
48. Haffner SM, Klein BEK, Moss SE, Klein R: Lack of association between Lp(a) concentrations and coronary heart disease mortality in diabetes: the Wisconsin Epidemiologic Survey of Diabetic Retinopathy. *Metabolism* 41:194–97, 1992
49. Niskanen L, Mykkänen L, Karonen SL, Uusitupa M: Apoprotein(a) levels in relation to coronary heart disease and risk factors in type II (non-insulin-dependent diabetes). *Cardiovasc Risk Factors* 13: 205–10, 1993
50. Cressman MD, Hoff HF, O'Neill J, Heyka RJ, Paganini EP, Koch HM: Lp(a) concentrations are increased during hemodialysis (Abstract). *Circulation* 78 (Suppl. 2):363, 1988
51. Parra HJ, Mezclour H, Cachera C, Pracon M, Tacquert A, Fruchart JC: Lp(a) lipoprotein in patients with chronic renal failure treated by hemodialysis (Letter). *Clin Chem* 33:721, 1987
52. Haffner SM, Gruber K, Aldrete G, Tuttle KTR: Increased Lp(a) concentrations in renal failure. *J Am Soc Nephrol* 3:1156–62, 1992
53. Takegoshi T, Haba T, Hirai JL, Kitoh C, Saga T, Yamazatei Y, Mabuchi H: Alterations of lipoprotein(a) in patients with diabetic nephropathy (Letter). *Atherosclerosis* 83:99–100, 1990
54. Jenkins AJ, Steele JS, Janus ED, Best JD: Increased plasma apolipoprotein(a) levels in IDDM patients with microalbuminuria. *Diabetes* 40:787–90, 1991
55. Kapelrud H, Bangsted HJ, Dahl Jorgensen K, Berg K, Hansen KF: Serum Lp(a) lipoprotein concentrations in insulin-dependent diabetic patients with microalbuminuria. *Br Med J* 303:675–78, 1991
56. Wincour PH, Bhatnagar D, Ishola M, Arrol S, Durrington PN: Lipoprotein(a) and macrovascular disease in type I (insulin-dependent) diabetes. *Diabetic Med* 8:922–27, 1991

57. Haffner SM, Morales PA, Gruber MK, Hazuda HP, Stern MP: Lack of association of lipids, lipoproteins and Lp(a) with microalbuminuria in NIDDM. *Arteriosclerosis* 13:205–10, 1993
58. Gurakar A, Hoeg JM, Kostner G, Papadopoulos NM, Brewer HB: Levels of lipoprotein Lp(a) decline with neomycin and niacin treatment. *Atherosclerosis* 57: 293–301, 1985
59. Vessby B, Kostner G, Lithel H, Thomas J: Diverging effects of cholestyramine on apolipoprotein B and lipoprotein Lp(a): a dose response of the effects of cholestyramine in hypercholesterolemia. *Atherosclerosis* 44:61–71, 1982
60. Garg A, Grundy SM: Nicotinic acid as therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. *JAMA* 264: 723–26, 1990
61. Leren T, Hjermann I, Berg K, Leren P, Foss OP, Viksmoen L: Effects of lovastatin alone and in combination with cholestyramine on serum lipids and apolipoproteins in heterozygotes for familial hypercholesterolemia. *Atherosclerosis* 73: 135–43, 1988
62. Berg K, Leren T: Unchanged serum lipoprotein(a) concentrations with lovastatin (Letter). *Lancet* 2:812, 1989