Decrease of Lipoprotein(a) With Improved Glycemic Control in IDDM Subjects

Steven M. Haffner, MD, MPH
Katherine R. Tuttle, MD
David L. Rainwater, PhD

Objective: Recently, lipoprotein(a) [Lp(a)] has been identified as a major risk factor for coronary heart disease. There are few data available on the influence of metabolic control on plasma Lp(a) concentrations in subjects with insulin-dependent diabetes mellitus (IDDM), a group at high risk for coronary heart disease. Research Design and Methods: We examined the effects of improved metabolic control on plasma lipid and lipoproteins and Lp(a) concentrations in 12 subjects before and after 21 days of tight metabolic control. Results: Glycosylated hemoglobin declined from 8.4 to 6.9% ($P < 0.001$), and Lp(a) declined from 29.7 to 27.1 mg/dl ($P = 0.022$). There were no significant differences in total, low-density lipoprotein, or high-density lipoprotein cholesterol, although the decline in triglyceride concentrations were borderline statistically significant. The distribution of apolipoprotein(a) isoforms in IDDM patients was not unusual, and the apolipoprotein(a) isoform phenotypes did not change with improved metabolic control. Lp(a) concentrations were also significantly higher than in a population-based control group of nondiabetic subjects from the San Antonio Heart Study. Conclusions: Although the number of subjects was small and the degree of improvement in metabolic control was modest, the results suggest that improved metabolic control may decrease the risk of coronary heart disease mediated by Lp(a) in IDDM. *Diabetes Care* 14:302–307, 1991

Subjects with insulin-dependent diabetes mellitus (IDDM) have an increased incidence of coronary heart disease, which is only partially explained by the frequent occurrence of kidney disease in this disorder (1). Although improved metabolic control may decrease very-low-density lipoprotein cholesterol (VLDL-chol) and low-density lipoprotein cholesterol (LDL-chol; 2–4), the magnitude of the differences in these atherogenic lipoproteins is modest.

Recently, a preliminary report (5) has suggested that lipoprotein(a) [Lp(a)], a lipoprotein strongly associated with coronary heart disease (6–10), is decreased with improved metabolic control. This observation is of major interest, because the serum concentration of apolipoprotein(a) [apo(a)], the unique protein of Lp(a), may be genetically controlled to a major degree (11,12). In this study, we examine the effects of improved glycemic control on Lp(a) and other lipoproteins in IDDM subjects. In addition, we examine the distribution of apo(a) isoforms and the effects of improved metabolic control on isoform phenotypes in these subjects.

RESEARCH DESIGN AND METHODS

Subjects with IDDM were recruited from the medical clinics of the University of Texas Health Science Center at San Antonio. All subjects had at least one episode of diabetic ketoacidosis by patient history and medical chart review. Nine subjects were Mexican Americans, two were non-Hispanic whites, and one was black. Plasma for C-peptide determination was obtained in the fasting state and after 3 h of infusion of a balanced amino

From the Divisions of Clinical Epidemiology and Nephrology, Department of Medicine, University of Texas Health Science Center at San Antonio; and the Department of Genetics, Southwest Foundation for Biomedical Research, 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.

Received for publication 6 August 1990 and accepted in revised form 7 November 1990.

acid solution (Travasol 10%), which raised the total plasma amino acid concentration threefold above baseline. In our IDDM subjects, fasting C-peptide concentrations were all <0.3 pmol/ml and remained <0.5 pmol/ml after the amino acid infusion. C-peptide was measured by radioimmunoassay with a commercially available kit (Diagnostic, Los Angeles, CA). The mean duration of IDDM was 6.3 ± 1.4 yr. They had no evidence of clinical nephropathy, as judged by the absence of dipstick-positive proteinuria, normal serum creatinine (≤115 mM), and normal blood pressure (≤140/90 mmHg). Furthermore, none of the subjects had proliferative retinopathy or macrovascular complications. No medications other than insulin were taken during the study. The subjects were recruited in a study of the effect of tight glycemic control on renal hemodynamics and size. At the time of entry into the study, subjects were not in good metabolic control, as indicated by a fasting plasma glucose concentration consistently >10 mM on at least three occasions in the 3 mo before study and a glycosylated hemoglobin value of >7.5% (normal range 4–6%). The protocol was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. All subjects gave written informed consent.

The metabolic studies were performed in the Frederick C. Bartter Clinical Research Unit at the Audie L. Murphy Memorial Veterans' Hospital. On the first study day before normalizing the plasma glucose concentration, subjects were monitored hourly for plasma glucose for 24 h to document the degree of glycemic control. On the second study day, an intravenous insulin infusion designed to normalize plasma glucose was started. Plasma glucose was measured hourly, and the insulin infusion rate was adjusted to maintain the fasting and premeal plasma glucose concentration of <6 mM and the 2-h postprandial values of ≤9 mM. This was continued for 36 h. During the last 24 h of insulin infusion (designated day 1 of improved glycemic control), subjects also had hourly glucose monitoring. On discharge from the clinical research unit, improved metabolic control was accomplished with ultralente twice daily for basal insulinization and regular insulin before each meal with the use of an algorithm developed for each patient in the clinical research unit, which took account of plasma glucose, meal content, and anticipated activity. All subjects were instructed in self-monitoring of blood glucose and received an Ames or Accu-Chek II Glucometer for the duration of the study. Twenty-four-hour glucose monitoring was also repeated during a second admission to the clinical research unit after 21 days of improved metabolic control. Glycosylated hemoglobin was measured at baseline and 21 days. Plasma for lipids, lipoproteins, and Lp(a) were obtained *1*) on the first admission to the clinical research unit in the chronic hyperglycemic state (day 0), *2*) after 36 h of euglycemia achieved by insulin infusion (day 1), and *3*) after 21 days of improved glycemic control. No subject changed their weight by >1 kg during the study. The mean weight was 66.3 ± 3.5 kg at day 0 and 66.8 ± 3.2 kg at day 21.

Plasma glucose was measured by a glucose oxidase technique (Beckman glucose autoanalyzer). Glycosylated hemoglobin was measured by the Bio-Rad HbA_{1c} column test method. Lipid and lipoprotein techniques have been previously described (13). Lp(a) was measured on frozen contingency samples at 70°C. All samples were <8 mo old and had been stored for an average of 4 mo. These samples were not thawed before the performance of the assay. Lp(a) was measured by a monoclonal anti-Lp(a) antibody technique (Terumo, Elkton, MD). Assays were performed in two runs with the kits having the same lot number. All samples for the same subject were run with the same kit. The intra-assay coefficient of variation of this assay was 4%, and the interassay variability was 8% in this laboratory. No cross-reactivity with plasminogen, LDL, VLDL, or high-density lipoprotein (HDL) was observed with this monoclonal anti-Lp(a) antibody technique in a recent study (14). Apo(a) isoform phenotypes were determined in available samples by immunochemical detection in plasma proteins resolved with sodium dodecyl sulfate–polyacrylamide gel electrophoresis, as previously described (12). Proteins in 1 μl of plasma were treated with 2% sodium dodecyl sulfate and 2% 2-mercaptoethanol and subjected to electrophoresis in 3–12% concave gradient gels. After electrophoretic transfer to nitrocellulose paper, apo(a) isoforms were detected immunochemically with antibodies directed against baboon apo(a), which also binds human proteins. The mobility of each isoform was compared with that of an adjacent standard, with apparent molecular weight estimated to be 692,000 (12).

The paired *t* test was used for statistical analysis (15). Lp(a) and triglyceride concentrations were log transformed to improve skewness and kurtosis. Pearson correlations were used to determine the relationship between the change in glycosylated hemoglobin and the change in Lp(a). The χ^2-test was used to compare the distribution in diabetic and nondiabetic populations.

RESULTS

After 3 wk of improved metabolic control, the average glycosylated hemoglobin level decreased from 8.4 ± 0.4% at day 0 to 6.9 ± 0.4% at day 21 ($P < 0.001$). The fasting and mean 24-h plasma glucose concentrations declined from 11.5 ± 0.7 and 12.2 ± 0.8 mM at day 0 to 5.5 ± 0.2 and 6.7 ± 0.3 mM at day 1 and finally to 5.3 ± 0.2 and 6.8 ± 0.3 mM at day 21 ($P < 0.001$). There were no significant differences in total, LDL-, or HDL-chol (Table 1), although there was a borderline significant decline in triglyceride concentrations with improved metabolic control ($P = 0.096$). The Lp(a) concentrations were the same at baseline (29.7 mg/dl) and day 1 (30.1 mg/dl) but had declined significantly at 21 days (21.1 mg/dl; $P = 0.022$). Ten of 12 subjects

TABLE 1
Effect of improved glycemic control on lipoprotein(a) [Lp(a)] and lipid and lipoproteins in insulin-dependent diabetes mellitus

	Age (yr)	Body surface area	M/F	Total cholesterol (mM)	Triglyceride (mM)	HDL-cholesterol (mM)	LDL-cholesterol (mM)	24-h glucose (mM)	HbA_{1c} (%)	Lp(a) (mg/dl)
Day 0	27.6 ± 1.6	1.71 ± 0.04	7/5	4.11 ± 0.34	1.52 (0.85–2.39)	1.22 ± 0.07	2.18 ± 0.26	12.2 ± 0.8	8.4 ± 0.4	29.7 ± 8.0
Day 21				3.85 ± 0.33	1.26 (0.75–2.01)	1.20 ± 0.06	2.08 ± 0.27	6.8 ± 0.13	6.9 ± 0.4	21.1 ± 6.0
P for paired *t* test (0 vs. 21 days)				0.413	0.096	0.654	0.206	<0.001	<0.001	0.022

Values are means ± SE; values in parentheses are 95% confidence intervals. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

showed a decline in their Lp(a) concentrations at 21 days (Fig. 1). The two subjects with a rise in their Lp(a) concentrations also had the smallest decline in glycosylated hemoglobin (from 7.5 to 7.2% and 7.8 to 7.2%). There was a positive correlation between the decline in glycosylated hemoglobin and the decline in Lp(a) concentrations ($r = +0.40$), although this association did not reach statistical significance.

At baseline, 5 of 12 subjects (42%) had Lp(a) concentrations >30 mg/dl, and 2 subjects (17%) had a Lp(a) concentration between 20 and 30 mg/dl. In contrast, nondiabetic subjects ($n = 72$) from the San Antonio Heart Study (a population-based study of diabetes and cardiovascular risk factors in Mexican Americans and non-Hispanic whites; 13) had a median Lp(a) of 15.5 mg/dl; only 15% of subjects had Lp(a) levels >30 mg/dl, and 10% of subjects had Lp(a) levels between 20 and 30 mg/dl. (Even if the 1 black diabetic subject was excluded from the analyses, Lp(a) levels were still significantly higher in diabetic than nondiabetic subjects from the San Antonio Heart Study.) The distribution of Lp(a) concentrations between diabetic and nondiabetic subjects was statistically significant with the χ^2-test ($P < 0.001$). We also examined whether improved metabolic control affected apo(a) isoform phenotypes in samples from eight of the subjects. On the basis of electrophoretic mobilities, at least six different apo(a) isoforms were detected in this group, and no effect of improved metabolic control was observed in numbers or apparent mobilities of the apo(a) isoforms in the eight cases examined (data not shown). The apo(a) isoforms in the diabetic group were not enriched in smaller-sized isoforms compared with samples from a larger population of healthy adults tested for the presence of diabetes (Table 2).

CONCLUSIONS

In subjects with IDDM, we have shown that with improved metabolic control, concentrations of Lp(a) de-

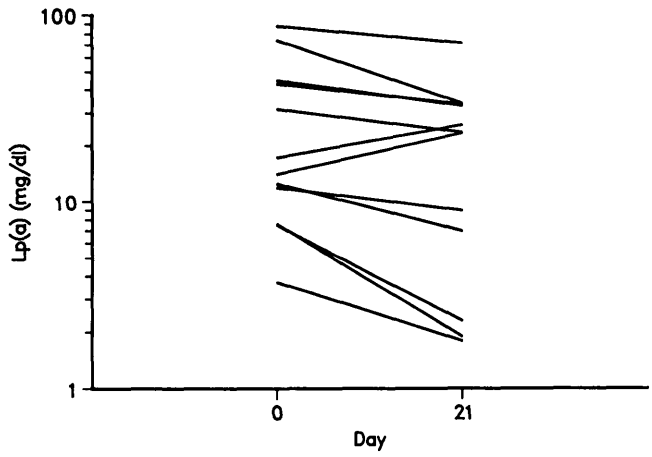

FIG. 1. Change in lipoprotein(a) [Lp(a)] levels (log to base 10) at days 0 and 21.

TABLE 2
Occurrence of apolipoprotein(a) [apo(a)] isoforms in diabetic subjects compared with healthy adult population

	Apo(a) Isoforms	
	Larger	Smaller
Healthy (n = 160)	94	95
Diabetic (n = 11)	8	9

Apo(a) isoforms were dichotomized on basis of mobilities relative to baboon B isoform previously described (apparent molecular weight 692,000; 12). Larger, slower mobility; smaller, mobility equal to or faster than standard.

cline, thereby confirming an earlier preliminary study (5). In addition, subjects with IDDM in this study had higher Lp(a) levels than nondiabetic subjects from a population-based study. In two other studies, Arauz et al. (16) and Levitsky et al. (17) reported in cross-sectional studies that Lp(a) concentrations are positively correlated with HbA_{1c}. Thus, it appears that IDDM subjects may have increased Lp(a) concentrations.

In the previous study by Bruckert et al. (5) on glycemic control in 10 IDDM subjects, the initial severity of the glycemia (glycosylated hemoglobin 10.3%) was more severe than in our study, but the final glycosylated hemoglobin level after improved control (8.5%) was similar to the baseline value in this study (8.4%). Thus, it was of interest that the Lp(a) level declined in the study of Bruckert et al. (5) from 46.1 to 29.3 mg/dl, a value that is nearly identical to the baseline Lp(a) level in this study (29.7 mg/dl). Thus, improved metabolic control may have an effect on Lp(a) concentrations even in subjects who are in fair diabetic control.

HDL- and LDL-chol did not change significantly in this study, although the decline in triglyceride concentrations was borderline statistically significant. Previous studies have suggested declines in triglyceride concentrations (2–4) and in one case a decline in LDL-chol as well (4). The reason for the lack of change in this study is not clear, although it may relate to the low cholesterol levels in our subjects. At baseline, our subjects had mean cholesterol levels of 4.11 mM, triglyceride levels of 1.52 mM, HDL-chol levels of 1.22 mM, and LDL-chol levels of 2.18 mM. In contrast, in the population reported by Dunn et al. (4), the corresponding values were 6.0, 2.20, 0.94, and 4.01 mM. Because the subjects in our study had low-to-normal levels of lipids and lipoproteins at baseline, they may be less likely to decrease after therapy.

The Terumo method for assessing Lp(a) concentrations is new. Although the intra-assay and interassay variations were small in this study and the specificity of the assay appears to be good (15), further validation studies need to be conducted.

We did not detect unusual isoforms of apo(a) in these subjects compared with a healthy population. Furthermore, the frequency of smaller isoforms was similar in both populations. Therefore, the reported inverse relationship between apo(a) size and serum Lp(a) levels does not account for the high Lp(a) levels in our diabetic group (11).

There are several possible explanations why the decline in Lp(a) concentrations was only modest and did not return to the normal range in this study. First, subjects at baseline were only moderately hyperglycemic at baseline, and the period of improved metabolic control (21 days) was brief. The dramatic decline in glycosylated hemoglobin after 3 wk is explained by the extremely tight glycemic control achieved while on intensive insulin therapy; the fasting and mean 24-h plasma glucose concentrations were 11.5 ± 0.7 and 12.2 ± 0.8 mM. These values declined to 5.3 ± 0.2 and 6.8 ± 0.3 mM, respectively, during the period of intensive insulin therapy. Thus, the lack of a significant correlation between change in HbA_{1c} and change in Lp(a) may be due to lack of the full effect of recent changes in glucose control on HbA_{1c} and small sample size. Second, because Lp(a) concentrations are under genetic control (11,12) and because IDDM has a major genetic complement as well (18), it is possible that subjects with IDDM may have a genetic disposition to increased Lp(a) concentrations. If so, then the genetic factor does not appear to be related to apo(a) glycoprotein isoforms that are encoded by the apo(a) structural gene. A third possibility for the lack of decline of Lp(a) concentrations to normal after improved metabolic control may be a differential response to glycemic control among subjects with different isoform structures. Gene-environment interactions have been described in many circumstances. Recently, Bouchard et al. (19) reported that the variability in weight gain and change in body composition within pairs of identical twins in response to a fixed amount of overfeeding was much less than the variability in weight gain and body composition between pairs of identical twins.

The explanation for decreased Lp(a) concentrations after improved metabolic control is unknown. However, Witzum et al. (20) have shown that glycosylation of LDL-apoB in diabetes leads to impaired catabolism of LDL-chol. It is possible that Lp(a) catabolism is impaired or that accumulation of LDL affects catabolism of Lp(a), because subjects heterozygous for familial hypercholesterolemia have higher Lp(a) levels (21). Apo(a) is a heavily glycosylated protein (22), and primary hepatocytes in culture produce apo(a) glycoproteins with mobilities indistinguishable from those of the donors' serum isoforms (23). It is possible that hyperglycemia facilitates the rate of apo(a) biosynthesis at the level of its glycosylation in the liver and that this leads to increased serum Lp(a) levels.

The mechanism of the increase in the risk of coronary heart disease with increased Lp(a) concentrations is not known. Lp(a) has a high degree of homology with plasminogen and thus may provide a link between the lipoprotein system and the hemostasis systems (24). Alterations in fibrinogen have been postulated as a risk factor for coronary heart disease (25). Another possible mechanism is that Lp(a) may prevent the uptake of LDL

by the LDL receptor (26). Furthermore, Lp(a) has been found in the atherosclerotic plaque (27).

Recent data suggest that another environmental modification, i.e., weight loss, may affect Lp(a) levels. After 4 wk of weight loss, Lp(a) declined by 19% in men and 30% in premenopausal women (28). However, no relationship between adiposity at baseline and Lp(a) concentrations was observed in this study.

The importance of the finding of decreased Lp(a) concentrations with improved metabolic control is that alteration of Lp(a) concentrations with lipid-lowering drugs has proved difficult. Neomycin and niacin have been reported to lower Lp(a) concentrations (29), whereas cholestyramine has little effect on Lp(a) concentrations (30). HMG-CoA reductase inhibitors have been reported either to raise (31) or have little effect (32) on Lp(a) concentrations. Thus, alterations in glycemic control, at least in subjects with IDDM, may have a major effect on altering an atherogenic lipoprotein that is predominantly under genetic control. These results need confirmation in large numbers of IDDM subjects after strict glycemic control is achieved for longer periods of time.

ACKNOWLEDGMENTS

This work was supported by grants from the South Texas Research Center (S.M.H.), the National Heart, Lung and Blood Institute (HL-40637; D.L.R. and R-37HL36820; S.M.H.), and the American Heart Association Texas Affiliate (88G-370; K.R.T.).

REFERENCES

1. Krolewski AS, Kosinki EI, Warram JH, Bradley RF, Kahn CR, Leland OS, Busick EJ, Asmal AC, Rand LI, Christlieb AR: Magnitude and determinants of coronary artery disease in juvenile-onset, insulin dependent diabetes mellitus. *Am J Cardiol* 59:750–55, 1987
2. Sosenko JM, Breslow J, Miettinen OS, Gabbay KH: Hyperglycemia and plasma lipid levels: covariations in insulin-dependent diabetes. *Diabetes Care* 5:40–43, 1982
3. Dunn FL, Cleary PH, Schrott HG, Oexman MJ, Castle B, Steffes MW, Lopes-Virella M, Nathan DM: Lipid and lipoprotein levels in patients with insulin-dependent diabetes mellitus: results from the diabetes control and complications trial. In *Proc 8th Int Symp on Atherosclerosis, Rome, 9–13 October 1988*
4. Dunn FL, Pietri A, Raskin P: Plasma lipid and lipoprotein levels with continuous subcutaneous insulin infusion in type I diabetes mellitus. *Ann Intern Med* 95:426–31, 1981
5. Bruckert E, Davidoff P, Grimaldi A, Truffert J, Giral P, Doumith R, Thervet F, DeGennes JL: Increased serum levels of lipoprotein(a) in diabetes mellitus and their reduction with glycemic control. *JAMA* 263:35–36, 1990
6. Berg K, Dahlen G, Frick MG: Lp(a) lipoprotein and prebeta lipoprotein in patients with coronary heart disease. *Clin Genet* 6:230–35, 1974
7. Rhoads GG, Dahlen G, Berg K, Morton NE, Dannenberg HL: Lp(a) lipoprotein as a risk factor for myocardial infarction. *JAMA* 256:2540–44, 1980
8. Durrington PN, Ishola M, Hunt L, Arrol S, Bhatnoaar P: Apolipoproteins (a), AI, and B and parental history in men with early onset ischaemic heart disease. *Lancet* 1:1070–73, 1988
9. Dahlen G, Guyton JR, Attar M, Farmer JA, Kautz JA, Gotto TM: Association of levels of lipoprotein Lp(a), plasma lipids, and other lipoproteins with coronary artery disease documented by angiography. *Circulation* 74:758–65, 1986
10. Seed M, Hoppichler F, Reaveley D, McCarthy S, Thompson GR, Boerwinkle E, Utermann G: Relationship 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
11. Utermann G, Menzel HJ, Kraft HG, Duba HC, Kemmler MG, Seitz C: Lp(a) glycoprotein phenotypes inheritance and relation to Lp(a) concentrations in plasma. *J Clin Invest* 80:458–65, 1987
12. 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
13. Stern MP, Rosenthal M, Haffner SM, Hazuda HP, Franco LJ: Sex difference in the effects of sociocultural status on diabetes and cardiovascular risk factors in Mexican Americans: the San Antonio Heart Study. *Am J Epidemiol* 120:834–51, 1984
14. Silberman SR, Armentrut MA, Saba AL: Macra Lp(a) for quantitation of human lipoprotein (a) by enzyme linked immunoassay (Abstract). *Clin Chem* 36:951, 1990
15. Wilkinson L: *SYSTAT: The System for Statistics*. Evanston, IL, SYSTAT, 1988, p. 457–598
16. Arauz C, Lackner C, Ramirez LC: Lipoprotein (a) levels in diabetic patients and its correlation with the metabolic control (Abstract). *Diabetes* 39 (Suppl. 1):64A, 1990
17. Levitsky L, Scanu A, Gould SH: Lipoprotein(a) protein levels are related to glycemic control in white diabetic children (Abstract). *Pediatr Res* 27:191A, 1990
18. Barnett AH, Eff C, Leslie RD, Pyke DH: Diabetes in identical twins: a study of 200 pairs. *Diabetologia* 20:87–91, 1983
19. Bouchard C, Tremblay A, Despres JP, Lupien PJ, Therault G, Dussault J, Moorjani S, Pinault S, Fournier G: The responses to long term feeding in identical twins. *N Engl J Med* 322:1477–82, 1990
20. Witzum JL, Mahoney EM, Branks MJ, Fisher M, Elam R, Steinberg D: Nonenzymatic glucosylation of low-density lipoprotein alters its biologic activity. *Diabetes* 31:283–91, 1982
21. Utermann G, Hopplicher F, Dieplinger H, Seed M, Thompson G, Boerwinkle E: Defects in the low density lipoprotein receptor gene affect lipoprotein(a) levels: multiplicative interaction of two gene loci associated with premature atherosclerosis. *Proc Natl Acad Sci USA* 86: 4171–74, 1989
22. Gaubatz JW, Cushing GL, Morrisett JD: Quantification, isolation and characterization of human lipoprotein(a). *Methodol Enzymol* 129:167–86, 1986
23. Rainwater DL, Lanford RE: Production of lipoprotein(a) by primary baboon hepatocytes. *Biochim Biophys Acta* 1003:30–35, 1989
24. McLean JW, Tomlinson JE, Kuang WJ: DNA sequence of human apolipoprotein(a) is homologous to plasminogen. *Nature* (Lond) 330:132–37, 1987
25. Stone MC, Thorp JM: Plasma fibrinogen—a major coronary risk factor. *J Royal Coll Gen Pract* 35:565–69, 1985
26. Scanu AM, Fless GM: Lipoprotein(a): heterogeneity and

biological relevance. *J Clin Invest* 85:1709–15, 1990
27. Walton KW, Hitchens J, Magnani HN, Kahn M: A study of methods of identification and estimation of Lp(a) lipoprotein and of its significance in health, hyperlipidemia and atherosclerosis. *Atherosclerosis* 20:323–46, 1974
28. Sonnichsen AC, Richter WO, Schwandt P: Reduction of lipoprotein(a) by weight loss. *Int J Obes* 14:487–94, 1990
29. Guraker 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
30. Vessby B, Kostner G, Lithell H, Thomas J: Diverging effects of cholestyramine on apolipoprotein B and lipoprotein Lp(a). *Atherosclerosis* 44:61–71, 1982
31. 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
32. Berg K, Leren TP: Unchanged serum lipoprotein (a) concentrations with lovastatin (Letter). *Lancet* 2:812, 1989