

Lipoprotein(a) Is an Independent Risk Factor for Coronary Artery Disease in NIDDM Patients in South India

VISWANATHAN MOHAN, MD, PHD, DSC
RAJ DEEPA, MPHIL, PHD
SAI PRASHANTH HARANATH, MBBS
GOPAL PREMALATHA, MBBS, FDIAB

MOHAN REMA, MBBS, DO, PHD
NADIMINTI GANAPATHI SASTRY, MBBS, MDRC
ENAS A. ENAS, MD, FACC

OBJECTIVE — Asian Indians have been reported to have very high prevalence rates of coronary artery disease (CAD) in the absence of traditional risk factors. Recently, elevated levels of lipoprotein(a) [Lp(a)] have been reported to be associated with premature CAD in migrant Asian Indians. However, there are very little data regarding Lp(a) in CAD patients from the Indian subcontinent and virtually none in individuals with NIDDM. The objective of this study was to assess the role of Lp(a) as a marker for CAD in South Indian NIDDM patients.

RESEARCH DESIGN AND METHODS — We estimated serum Lp(a) in 100 control subjects, 100 NIDDM patients without CAD, and 100 NIDDM patients with CAD. Lp(a) values were transformed into natural logarithms. Statistical analysis included Student's *t* test, one-way analysis of variance, and χ^2 test. Multiple logistic regression analysis was used to identify associations with CAD.

RESULTS — Lp(a) levels were significantly higher in NIDDM patients with CAD compared with NIDDM patients without CAD and control subjects (geometric mean 24.6, 15.1, and 19.4 mg/dl, respectively, $P < 0.05$). Results of logistic regression analysis showed that Lp(a), age, and HDL were associated with CAD. In NIDDM patients with CAD, there was no correlation between Lp(a) and serum cholesterol, triglyceride, or HDL cholesterol levels, but there was a weak association with LDL cholesterol and systolic blood pressure.

CONCLUSIONS — The data suggests that serum Lp(a) is an independent risk factor for CAD in NIDDM patients in South India.

Diabetes Care 21:1819–1823, 1998

The prevalence of coronary artery disease (CAD) is known to be very high both among migrant Asian Indians (1–3) and among people within the Indian subcontinent (4–6). Moreover, CAD in Asian Indians occurs prematurely, i.e., at least a decade or two earlier than that seen in Europeans (7,8). It is of further interest that the traditional risk factors for CAD seen among Europeans—namely, hyper-

tension, high cholesterol, smoking, and obesity—do not explain the excess of CAD seen among Asian Indians (1). A host of new risk factors related to the metabolic syndrome (insulin resistance syndrome) have been described in Asian Indians, including an excess of NIDDM (9), increased upper-body obesity with an increase in waist-to-hip ratio (10), elevated plasma insulin levels (hyperinsulinemia)

(11,12), and increased insulin resistance (13,14). A recent prospective study from the U.K. has clearly demonstrated the failure of diabetes to explain the excess cardiac fatality in Asian Indians compared with those of European origin (15). Earlier studies of serum lipids among Asian Indians have not been conclusive because serum cholesterol levels have been reported to be normal or low among Asian Indians (1).

Lipoprotein(a) [Lp(a)] is a modified form of LDL that contains apo B100 linked by a disulfide bridge to a highly polymorphic glycoprotein apolipoprotein [apo(a)] (16,17).

Recent studies have suggested that Lp(a) may be an independent risk factor for CAD (18,19), and it also appears to be related to the severity of CAD as assessed angiographically (20,21). However, some studies have not supported these findings (22).

The significance of Lp(a) in individuals with diabetes is unclear. A recent critical analysis by Haffner (23) concluded that NIDDM per se does not increase plasma levels of Lp(a), although Lp(a) concentrations may be higher in IDDM patients. Studies of the relationship of Lp(a) to CAD in diabetic patients have again yielded conflicting results: some reports found Lp(a) to be an independent risk factor (24), whereas others (25,26) were unable to show a significant relationship between Lp(a) and CAD. O'Brien et al. (27) in the Mayo clinic study found that Lp(a) does not have any association with CAD in subjects with NIDDM. Lp(a) distribution is known to be influenced by ethnic origin (28). It is possible that this may be due to ethnic differences in Lp(a) levels. There are few studies on Lp(a) levels in Asian Indian subjects and virtually none in Asian Indian NIDDM patients. This paper addresses the important role of Lp(a) as a determinant of CAD in NIDDM patients in South India.

RESEARCH DESIGN AND METHODS

The following groups of subjects were studied. Group 1 was composed of 100 consecutive healthy nondiabetic control subjects, selected from an ongoing population-based study at Chennai (Madras) city, aged 33–87 years who satis-

From the Madras Diabetes Research Foundation (V.M., R.D., S.P.H., G.P., M.R., N.G.S.), Gopalapuram, Chennai, India; and the Cadi Research Foundation (E.A.E.), Woodridge, Illinois.

Address correspondence and reprint requests to V. Mohan, MD, MNAMS, PhD, DSc, Madras Diabetes Research Foundation, 35 Conran Smith Rd., Gopalapuram, Chennai-600 086, India. E-mail: dmmohan@02giasmd01.vsnl.net.in.

Received for publication 26 January 1998 and accepted in revised form 21 July 1998.

Abbreviations: apo(a), apolipoprotein(a); CAD, coronary artery disease; Lp(a), lipoprotein(a).

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

Table 1—Clinical characteristics of the study groups

Parameters	Group 1 (control)	Group 2 (NIDDM without CAD)	Group 3 (NIDDM with CAD)
<i>n</i>	100	100	100
Sex ratio (M/W)	72/28	72/28	72/28
Age (years)	55 ± 11	54 ± 8	56 ± 8
BMI (kg/m ²)	22.0 ± 4.4	25.2 ± 4.5*	25.2 ± 3.7*
Duration of diabetes (years)	—	9.3 ± 6.8	11.5 ± 8.4†
Fasting blood glucose (mg/dl)	76 ± 14	152 ± 45*	155 ± 58*
HbA _{1c} (%)	5.3 ± 0.5	9.4 ± 2.2*	8.8 ± 2.2*
Smokers (%)	12.0	11.0	10.0
Hypertension (%)	11.0	15.0	17.0

*Significantly high compared with control group ($P < 0.05$); †significantly high compared with group 2 ($P < 0.05$).

fied the following criteria: normal glucose tolerance tests, absence of angina (according to Rose questionnaire), absence of history of any vascular disease (myocardial infarction, stroke, or intermittent claudication), and normal 12-lead resting electrocardiograms (Minnesota Coded).

Patients with NIDDM (groups 2 and 3) were selected from the M.V. Diabetes Specialities Centre at Chennai. Diagnosis of NIDDM was based on the criteria of the World Health Organization study group on diabetes (29), i.e., fasting plasma glucose ≥ 140 mg/dl, 2-h post-glucose load ≥ 200 mg/dl, or two random plasma glucose values > 200 mg/dl.

Group 2 consisted of 100 NIDDM patients without CAD. All subjects in this group aged 35–80 years denied any history of angina or myocardial infarction. All had normal electrocardiograms and cardiac stress tests (computerized treadmill using Bruce protocol).

Group 3 consisted of 100 NIDDM patients with CAD who were between the ages of 36 and 79 years. CAD was diagnosed if the patients had a documented episode of myocardial infarction ($n = 40$) substantiated by electrocardiographic evidence of Q waves (Minnesota Codes 1-1, 1-2) or symptoms of angina supported by electrocardiographic evidence of ischemia (Minnesota Codes 4-1-1 [ST segment depression], 5-1 [T Wave inversion]; 9-2 [ST segment elevation]). Those with a positive treadmill test (ST depression > 1.5 mm) ($n = 36$) or coronary angiographic evidence of severe ($> 70\%$ diameter) stenosis of one or more coronary vessels ($n = 24$) were also included.

Clinical examination included recording of height and weight with calculation of

BMI and a cardiovascular examination. Blood pressure was recorded in the sitting posture, and systolic blood pressure > 140 and diastolic blood pressure > 90 was considered hypertension (criteria for the fifth report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure) (30).

A fasting blood sample was taken, and serum was separated and stored at -20°C until the assays were performed. Total serum cholesterol, serum triglyceride, and HDL cholesterol (after precipitation of LDL with heparin-manganese) were assayed with a commercial kit (Boehringer Mannheim, Germany) using the Opera Technicon Autoanalyser (Bayer Diagnostics, U.S.). LDL cholesterol was calculated according to the Friedewald equation (31). Lp(a) was estimated by enzyme immunoassay (Macra Lp(a), Strategic Diagnostic, Newark, NJ). Briefly, microtiter plates pre-coated with monoclonal anti-Lp(a) antibodies were incubated with appropriately diluted serum samples (201:1). Bound Lp(a) was revealed by incubation with a polyclonal anti-Lp(a) antibody coupled to

horseradish peroxidase followed by the substrate hydrogen peroxide. A calibration curve was developed using standards (0–80 mg/dl) provided with the kit. Intra- and interassay coefficients of variation were 6.6 and 9.3%, respectively.

Statistical analysis

Lp(a) values were transformed into natural logarithms. One-way analysis of variance with Tukey's honestly significant difference test was used to compare the means of continuous variables in more than two groups. Student's *t* test was used to compare means of continuous variables in two groups. The χ^2 test was used to compare the proportions. Multiple logistic regression analysis was used to identify associations between CAD and the independent parameters. All continuous variables were categorized appropriately. Pearson's correlation coefficient was used to look for association between Lp(a) and other variables. All analyses were performed with the SPSS statistical software package (version 4.0.1, SPSS, Chicago); P values < 0.05 were considered significant.

RESULTS — The clinical characteristics of the study group are shown in Table 1. The study groups were age- and sex-matched. There was no significant difference in the percentage of smokers in the groups. Both diabetic groups had a higher percentage of hypertensive subjects compared with the control group, but this was not statistically significant. In comparison with control subjects, the diabetic patients had higher BMIs ($P < 0.05$). As expected, both diabetic groups had higher blood glucose and HbA_{1c} values compared with control subjects ($P < 0.05$). There were no significant differences in BMI, levels of fasting plasma glucose and glycosylated hemoglobin, or the prevalence of smokers and hypertensive subjects between the two dia-

Table 2—Lipid profile and Lp(a) levels in the study groups

Tests	Group 1 (control)	Group 2 (NIDDM without CAD)	Group 3 (NIDDM with CAD)
<i>n</i>	100	100	100
Serum cholesterol (mg/dl)	182 ± 41	193 ± 51	194 ± 46
Serum triglyceride (mg/dl)	124 ± 63	179 ± 118*	175 ± 121*
HDL cholesterol (mg/dl)	41.0 ± 10	39 ± 9	37 ± 9†
LDL cholesterol (mg/dl)	116 ± 37	118 ± 42	122 ± 36
Lp(a) (mg/dl)	19.4 (2.6)	15.1 (3.3)	24.6 (3.0)‡

Data for Lp(a) are geometric means (SD). *Significantly high compared with control group ($P < 0.05$); †significantly low compared with control group ($P < 0.05$); ‡significantly high compared with group 2 ($P < 0.05$).

Table 3—Multiple logistic regression analysis of determinants of CAD for NIDDM with CAD versus NIDDM without CAD

Variables	B	SEM (B)	Odds ratio (95% CI)	P value
Age	0.35	0.17	1.4 (1.0–2.0)	0.044
HDL	–0.26	0.11	0.77 (0.62–0.95)	0.016
Lp(a)	0.38	0.13	1.5 (1.15–1.87)	0.002

CAD was used as the dependent variable. The following categories were used for continuous variables: age, 10-year intervals; BMI, 3 units; fasting blood glucose, 25 mg/dl; serum cholesterol, 25 mg/dl; serum triglycerides, 25 mg/dl; LDL cholesterol, 25 mg/dl; HDL cholesterol, 5 mg/dl; log Lp(a), 1 unit; duration of diabetes, 5-year intervals; and hypertension, systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg.

betic groups. The diabetic patients with CAD had a longer duration of diabetes than did the diabetic patients without CAD.

Table 2 summarizes the lipid profile and Lp(a) levels of the study groups. Serum triglyceride levels were higher in both groups of NIDDM patients compared with control subjects ($P < 0.05$), but there was no statistically significant difference between the NIDDM patients with and those without CAD. Levels of LDL cholesterol were not significantly different in the study groups. HDL cholesterol levels were lower in the NIDDM patients with CAD compared with control subject but not significantly different from the levels in NIDDM patients without CAD. Lp(a) levels were higher in the NIDDM patients with CAD compared with NIDDM patients without CAD and with control subjects, but the differences reached statistical significance only with control subjects ($P < 0.05$).

The frequency distribution of Lp(a) in all the study groups was skewed, but the NIDDM patients with CAD had higher levels of Lp(a). The risk for CAD appeared to increase progressively beyond a level of 30 mg/dl. With 30 mg/dl being used as the cut-off point, 31% of group 1 subjects, 35% of group 2 subjects, and 51% of group 3 subjects had values above this level. Values above 50 mg/dl were present in 10.0% of group 1 subjects, 15.6% of group 2 subjects, and 49.0% of group 3 subjects. None of the group 1 but 5% of group 2 subjects and 10% of group 3 subjects had values above 80 mg/dl. Group 3 had a significantly higher percentage of subjects above all three cut-off points when compared with group 1 and 2 ($P < 0.05$).

Table 3 shows the results of the multiple logistic regression analysis to look for risk factors for CAD. NIDDM with CAD was taken as the dependent variable, and factors such as age, BMI, hypertension, total serum cholesterol, serum triglyceride, HDL cholesterol, LDL cholesterol, and Lp(a) levels were

considered as independent variables. Lp(a), HDL cholesterol, and age showed an association with CAD in this model.

Table 4 shows the correlation of Lp(a) with other variables in each of the study groups. LDL cholesterol and systolic blood pressure showed a weak association ($P = 0.05$ and $P = 0.03$, respectively) with Lp(a) in the NIDDM with CAD group. Among control subjects, serum triglycerides and BMI correlated with Lp(a); whereas in the NIDDM without CAD group, serum triglycerides and HDL cholesterol showed a correlation with Lp(a).

Figure 1 presents the relative odds ratio for CAD by quartiles of Lp(a) levels determined from the control group. The risk for CAD was significantly high in the fourth quartile of Lp(a) ($P = 0.02$).

CONCLUSIONS — The CAD rate in Asian Indians has been increasing rapidly and has reached alarming levels (1–6). The causes for the high prevalence of CAD among Asian Indians have hitherto remained largely unexplained. The fact that traditional risk factors have failed to explain the excess risk of CAD has raised the possibility of a genetic (ethnic) susceptibility to

CAD among Asian Indians. In this context, studies on Lp(a) levels are significant because Lp(a) is known to be genetically determined (18,19). Moreover, Lp(a) levels have been shown to vary considerably in different ethnic groups that have marked differences in prevalence rates of CAD. For example, Chinese in Singapore have a four-fold lower rate of CAD with correspondingly lower levels of Lp(a) (32,33). Studies from North America have also revealed that South Asians, known for higher rates of premature CAD, also have elevated levels of Lp(a) compared with whites (1,34).

In this study, using multiple logistic regression analysis with age, BMI, cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and Lp(a) as variables, we found Lp(a) levels to be a strong and statistically significant risk factor for CAD ($P = 0.002$). Though HDL cholesterol was also noted to be a risk factor for CAD in the Framingham study (35), the Five City Project Study (36) has shown that the risk for CAD created by Lp(a) level is not modified by different levels of HDL cholesterol. Other reports on CAD subjects suggest that the atherogenicity of Lp(a) is more marked in the presence of a concomitant decrease in HDL cholesterol level (37).

In our study, we observed only a weak correlation of Lp(a) to systolic blood pressure and LDL cholesterol in the NIDDM patients with CAD. The weak correlation to LDL cholesterol can be explained by the small contribution of Lp(a) cholesterol to this variable. Previous studies have also found a correlation between these two parameters (38). Increasing LDL concentrations are also found to markedly increase the risk of CAD in the presence of elevated Lp(a) levels (39).

Lp(a) levels were found to be elevated in earlier studies on migrant Indians with CAD (34,40,41). The present study suggests that

Table 4—Correlation between Lp(a) levels and other variables

Variable	Control	NIDDM without CAD	NIDDM with CAD
Cholesterol	0.040 (0.4)	0.03 (0.40)	0.11 (0.14)
Triglyceride	–0.26 (0.005)*	–0.25 (0.006)*	–0.06 (0.28)
HDL cholesterol	0.10 (0.15)	0.19 (0.03)*	0.05 (0.33)
LDL cholesterol	0.10 (0.16)	0.13 (0.10)	0.16 (0.05)*
Systolic blood pressure	0.08 (0.23)	–0.03 (0.37)	–0.19 (0.03)*
Diastolic blood pressure	–0.03 (0.39)	–0.14 (0.09)	–0.08 (0.22)
Age	0.07 (0.24)	0.09 (0.18)	–0.11 (0.14)
BMI	–0.24 (0.01)*	0.05 (0.31)	0.05 (0.32)
Duration of diabetes	—	–0.06 (0.27)	–0.10 (0.17)

Data are r (P value). *Statistically significant ($P < 0.05$).

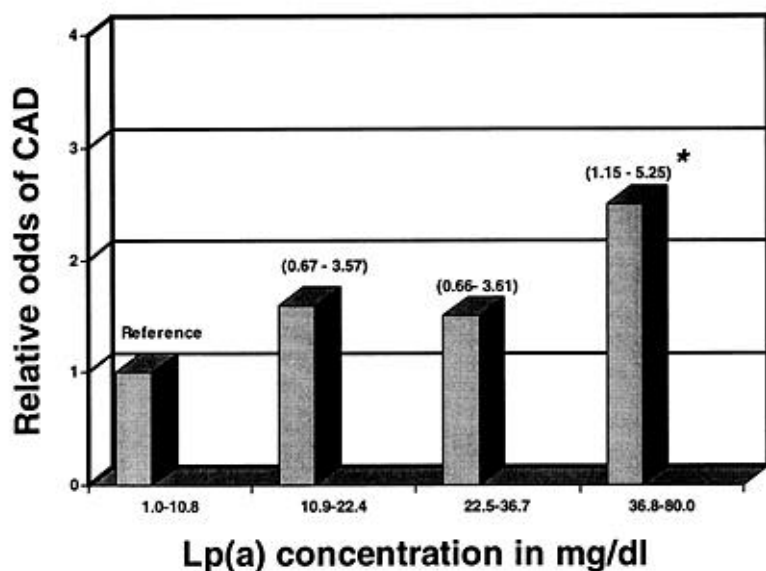


Figure 1—Relative odds ratio for CAD by quartiles of Lp(a) levels. Quartiles of Lp(a) were defined from group I (control group). Figures in parentheses are 95% CIs. *Statistically significant ($P < 0.02$).

Lp(a) is a risk factor for CAD among NIDDM patients in South India. Our study also supports Haffner's view (23) that diabetes per se does not affect Lp(a) levels. Because Lp(a) levels are not influenced by the presence or control of NIDDM, Lp(a) testing can be performed irrespective of the diabetic status or control in Asian Indians, a population known for high rates of diabetes and high morbidity and mortality from premature CAD.

One of the limitations of the study is that the diagnosis of CAD and its absence was based largely on clinical criteria. Because of ethical, logistic, and socioeconomic reasons, coronary angiography could not be performed in all study subjects. Although there is little doubt that those with CAD did indeed have the disease, its absence in the other two groups is not certain. This might explain the presence of elevated Lp(a) in some of the subjects in group 1 and group 2. Furthermore, in these groups, the possible occurrence of CAD in the future cannot be ruled out. One could speculate that the level of significance could have been higher if a more definitive diagnosis of CAD had been used in this study. Finally, we used Lp(a) measurements as a surrogate for apo(a) isoforms because we do not have the facilities to study the latter. Studies of apo(a) isoform size and distribution in Asian Indians with and without CAD appear to be justified.

In conclusion, Lp(a) appears to be a useful marker of CAD in NIDDM patients in

South India, independent of age, sex, BMI, smoking, hypertension, and other lipid parameters. High levels of Lp(a) along with high prevalence of NIDDM and low HDL cholesterol levels may render Asian Indians particularly vulnerable to malignant atherosclerosis at a young age. Further studies on Asian Indians directed at the possible multiplicative effects of these three powerful and prevalent risk factors are urgently needed.

Acknowledgments — We thank K. Karkuzhali for her help in recruiting patients for the study and A.K. Mathai for the statistical analysis.

References

1. Mckeigue PM, Miller GJ, Marmot MG: Coronary artery disease in South Asian overseas: a review. *J Clin Epidemiol* 41:597-598, 1989
2. Balarajan R: Ethnic difference in mortality from ischaemic heart disease in England and Wales. *Br Med J* 302:560-564, 1991
3. Beckles GLA, Miller GJ, Kirkwood BR, Alexis SD, Carson DC, Byam NTA: High total and cardiovascular disease mortality in adults of Indian descent in Trinidad, unexplained by major coronary risk factors. *Lancet* 1:1298-1301, 1986
4. Chadha S, Radhakrishnan S, Ramachandran K, Kaul U, Gopinath N: Epidemiological study of coronary heart disease in urban population of Delhi. *Indian J Med Res* 92:424-430, 1990
5. Raman Kutty V, Balakrishnan KG, Jayasree AK, Thomas J: Prevalence of coronary heart disease in the rural population of Thiru-

- vananthapuram district, Kerala India. *Int J Cardiol* 39:59-70, 1993
6. Gupta R, Prakash H, Majumdar S, Sharma S, Gupta VP: Prevalence of coronary heart disease and coronary risk factors in an urban population of Rajasthan. *Indian Heart J* 47:331-338, 1995
7. Hughes LO, Raval U, Raftery EB: First myocardial infarction in Asian and White men. *Br Med J* 298:1345-1350, 1989
8. Litter WA, Lawrence RE: Acute myocardial infarction in Asians and Whites in Birmingham. *Br Med J* 290:1472, 1985
9. Ramachandran A, Jali MV, Mohan V, Snehalatha C, Viswanathan M: High prevalence of diabetes in an urban population in South India. *Br Med J* 297:587-590, 1988
10. Mckeigue PM, Shah B, Marmot MG: Relation of central obesity insulin resistance with high diabetes prevalence and cardiovascular risk in south Asia. *Lancet* 336:383-386, 1991
11. Mohan V, Sharp PS, Cloke HR, Burrin JM, Schemer B, Kohner EM: Serum immunoreactive insulin responses to a glucose load in Asian Indian and European type 2 (non insulin dependent) diabetic patients and control subjects. *Diabetologia* 29:235-237, 1987
12. Mckeigue PM, Marmot MG, Court YDS, Cottier DE, Rahman S, Riemersman RA: Diabetes, hypertension, and cardiac risk factors in Bangladeshis in East London. *Br Heart J* 60:390-396, 1985
13. Sharp PS, Mohan V, Levy JC, Mather HM, Kohner EM: Insulin resistance in patients of Asian Indian and European origin with non insulin dependent diabetic. *Hum Metab Res* 18:84-85, 1987
14. Laws A, Jeppesen JL, Maheux PC, Schaaf P, Chen YD-I, Reaven GM: Resistance to insulin stimulated glucose uptake and dyslipidemia in Asian Indians. *Arterioscler Thromb* 14:917-922, 1994
15. Forouchi N, McKeigue P: How far can risk factors account for excess coronary mortality in South Asians? (Abstract). *Can J Cardiol* 13:47B, 1997
16. Berg K: Lp(a) Lipoprotein: an overview. In *Lipoprotein (a)*. Scanu AM, Ed. San Diego, CA, Academic, 1990, p. 1-23
17. Utermann G: The mysteries of lipoprotein (a). *Science* 246:904-910, 1989
18. Scanu AM, Lawn RM, Berg K: Lipoprotein (a) and atherosclerosis. *Ann Intern Med* 115:209-218, 1991
19. Hearn JA, DeMaio SJ Jr, Roubin GS, Hammarstrom M, Sgoutas D: Predictive value of lipoprotein (a) and other serum lipoproteins in the angiographic diagnosis of coronary artery disease. *Am J Cardiol* 66:1176-1180, 1990
20. Dahlen GH, Guyton JR, Attar M, Farmer JA, Kautz JA, Gotto AM Jr: Association of levels of lipoprotein Lp(a), plasma lipids and other lipoproteins with coronary artery

- disease documented by angiography. *Circulation* 74:758-765, 1986
21. Frick MH, Dahlen G, Berg K, Valle M, Hekali P: Serum lipids in angiographically assessed coronary atherosclerosis. *Chest* 73:62-65, 1973
 22. Ridker PM, Hennekens CH, Stampfer MJ: A prospective study of lipoprotein (a) and risk of myocardial infarction. *JAMA* 270:2195-2199, 1993
 23. Haffner SM: Lipoprotein (a) and diabetes. *Diabetes Care* 16:835-840, 1993
 24. Jenkins AJ, Steele JS, Junus ED, Santamaria JD, Best JD: Plasma apolipoprotein (a) is increased in type 2 (non insulin dependent) diabetic patient with microalbuminuria. *Diabetologia* 35:1055-1059, 1992
 25. Haffner SM, Moss SEM, Klein BEK, Klein R: Lack of association between Lp(a) concentrations and coronary heart disease mortality in diabetes: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Metabolism* 41:194-197, 1992
 26. Niskanen L, Mykkanen 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 Factor* 3:205-210, 1993
 27. O'Brien T, Nguyen TT, Harrison JM, Bailey KR, Dyck PJ, Kottke BA: Lipids and Lp(a) lipoprotein levels and coronary artery disease in subjects with non insulin dependent diabetes mellitus. *Mayo Clin Proc* 69:430-435, 1994
 28. Guyton JR, Dahlen GH, Patsch M, Kautz JA, Gotto AM Jr: Relationship of plasma lipoprotein Lp(a) levels to race and to apolipoprotein B. *Arteriosclerosis* 5:265-272, 1985
 29. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group* Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
 30. Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure: The fifth report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC-V). *Arch Intern Med* 153:154-183, 1993
 31. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. *Clin Chem* 8:499-502, 1972
 32. Low PS, Heng CK, Saha N, Tay JSH: Racial variation of cord plasma lipoprotein (a) levels in relation to coronary risk level: a study in three ethnic groups in Singapore. *Pediatr Res* 40:718-722, 1996
 33. Hughes K, Aw TC, Kuperan P, Choo M: Central obesity, insulin resistance, syndrome X, lipoprotein (a) and cardiovascular in Indians, Malays and Chinese in Singapore. *J Epidemiol Community Health* 51:394-399, 1997
 34. Anand SS, Enas EA, Pogue J, Haffner S, Pearson T, Yusuf S: Elevated lipoprotein (a) levels in South Asians in North America. *Metabolism* 47:182-184, 1998
 35. Bostom AG, Cupples LA, Jenner JL, Ordovas JM, Seman LJ, Wilson PWF, Schaefer EJ, Castelli WP: Elevated plasma lipoprotein (a) and coronary heart disease in men aged 55 years and younger: a prospective study. *JAMA* 276:544-548, 1996
 36. Wild SH, Fortmann SP, Marcovina SM: A prospective case control study of lipoprotein (a) levels and Apo(a) size and risk of coronary heart disease in Stanford Five-City Project participants. *Arterioscler Thromb & Biol* 17:239-245, 1997
 37. Cobbaert C, Jukema JW, Zwinderman AH, Withagen AJAM, Lindemans J, Brusckhe AVG: Modulation of lipoprotein (a) atherogenicity by high density lipoprotein cholesterol levels in middle-aged men with symptomatic coronary artery disease and normal to moderately elevated serum cholesterol. *Am Coll Cardiol* 30:1491-1499, 1997
 38. Schriewer H, Assmann G, Sandkamp M: The relationship of lipoprotein (a) Lp(a) to risk factors of coronary heart disease: initial results of prospective epidemiological study on company employees in Westfalia. *J Clin Chem Clin Biochem* 2:591-596, 1984
 39. Armstrong VW, Cremer P, Eberle E, Manke A, Schulze F, Wieland H, Kreuzer H, Seidel D: The association between serum Lp(a) concentrations and angiographically assessed coronary atherosclerosis dependence of serum LDL levels. *Atherosclerosis* 62:249-257, 1986
 40. Enas EA, Dhawan J, Petkar S: Coronary artery disease in Asian Indians: lessons learnt and the role of lipoprotein (a). *Indian Heart J* 49:25-34, 1997
 41. Enas EA, Mehta J: Malignant coronary artery disease in young Asian Indians: thoughts on pathogenesis, prevention and therapy. *Clin Cardiol* 18:131-135, 1995