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Correlation between serum lipoprotein(a) and angiographic coronary artery disease in non-insulin-dependent diabetes mellitus

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Abstract. Çömlekçi A, Biberoğlu S, Kozan Ö, Bahçeci O, Ergene O, Nazli C, Kinay O, Güner G (Dokuz Eylül University, Medical School, İnciraltı, İzmir, Turkey). Correlation between serum lipoprotein(a) and angiographic coronary artery disease in non-insulin-dependent diabetes mellitus. *J Intern Med* 1997; **242**: 449–54.

Objectives. To examine the impact of diabetic state on the concentrations of lipoprotein(a) [Lp(a)] in patients with non-insulin-dependent diabetes mellitus (NIDDM) and the correlation between angiographic coronary artery disease (CAD) and serum Lp(a) concentrations in NIDDM.

Design. In this cross-sectional study of 26 patients with NIDDM and 19 nondiabetic sex- and age-matched patients who underwent coronary angiography, CAD was assessed visually using coronary artery score (CAS), and plasma Lp(a) was measured by an enzyme-linked immunosorbent assay.

Setting. The study was performed in an internal medicine clinic at a university hospital.

Subjects. Twenty-six age- and sex-matched patients with NIDDM and 19 control patients without diabetes.

Results. There was no significant difference between the Lp(a) concentrations of patients with NIDDM and nondiabetic subjects ($P > 0.05$). When patients with NIDDM were stratified by absence or presence of CAD, patients with CAD had higher levels of Lp(a) ($P < 0.05$). However, there was no significant correlation between the concentrations of Lp(a) and CAS ($P > 0.05$).

Conclusions. Diabetic state does not have any impact on Lp(a) concentrations. Lp(a) excess seems to be atherogenic in patients with NIDDM as shown in nondiabetic patients in previous studies. Although diabetic patients with CAD have higher Lp(a) concentrations than the diabetic patients without CAD, Lp(a) levels were not correlated with CAS.

Keywords: coronary angiography, coronary artery disease, lipoprotein(a), NIDDM.

Introduction

Coronary artery disease (CAD) is the most common cause of death in subjects with diabetes mellitus [1]. The increased risk for cardiovascular disease in this group can not totally be attributed to conventional risk factors [2,3]. The nature of the diabetic factor responsible for this increased risk is not clear.

Lipoprotein(a) [Lp(a)] is an atherogenic particle that structurally resembles a low- density lipoprotein (LDL) particle but contains a molecule apolipoprotein(a) attached to apolipoprotein B-100 by a disulphide bond [4]. This particle was originally described by Berg in 1963 [5]. The associations between coronary artery disease and a plasma lipoprotein migrating on agarose gel or cellulose acetate electrophoresis as a distinct pre-β1 band was reported in 1972 [6], which was subsequently shown to be Lp(a) [7].

Lp(a) has been shown to be an independent risk factor for atherosclerotic vascular disease in subjects without diabetes [8–12]. The link between atherosclerosis and Lp(a) may be the striking homology

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found between apoprotein(a) and plasminogen; thus a potential association may exist between the coagulation cascade and atherosclerosis [10,13,14]. The presence of Lp(a) in atherosclerotic plaques is a further evidence of a potential role for this particle in atherogenesis [15,16]. In addition Lp(a)- related plaques are more dangerous after a plaque rupture, as high Lp(a) levels may interfere with fibrinolysis.

Recent studies have indicated that Lp(a) concentrations are elevated in subjects with insulin-dependent diabetes mellitus (IDDM), especially those in poor metabolic control [17,18], and that improved metabolic control results in decreases of Lp(a) [17,19]. More controversial is whether non-insulin-dependent diabetic subjects have higher [20,21], lower [22,23], or similar [24–26] Lp(a) levels compared with nondiabetic subjects. The contribution of Lp(a) to the increased risk of atherosclerosis in subjects with diabetes has not been established clearly.

In this report we examine the following issues: the difference in Lp(a) levels between subjects with NIDDM and control subjects; the relationship between Lp(a) levels and diabetic control as assessed by glycosylated haemoglobin levels in subjects with NIDDM; and the relationship between Lp(a) and CAD as assessed by coronary angiography in terms of CAS in subjects with NIDDM.

Subjects and methods

Subjects

Twenty-six age- and sex-matched patients with NIDDM (10 male, 16 female) and 19 nondiabetic patients (eight male, 11 female), who underwent coronary angiography for chest pain or valvular heart disease, were recruited prospectively without knowledge of CAS. All of the female patients were postmenopausal, and none of them were receiving hormone replacement therapy. Diabetic subjects were defined by National Diabetes Data Group criteria [27]. All of the diabetic patients in this study, except three without CAD and four with CAD, were taking oral antidiabetic agents at the time of the clinic visit. None of the patients were taking antihyperlipidaemic agent. All patients' blood samples were obtained following an overnight fast. The carbohydrate intolerance of control subjects were evaluated by standard oral glucose tolerance test. Patients with impaired glucose tolerance were excluded. Patients in the control group with diabetic nephropathy and proteinuria were excluded.

Methods

Plasma samples were isolated by low-speed centrifugation. Each of the serum was divided into two aliquots. One of them was immediately stored at − 70 °C until the time of Lp(a) measurement. Mean storage time for Lp(a) analysis was three months. The other aliquot was immediately analysed for lipids and apolipoprotein AI and B. Weight and height were measured in light clothing without shoes, and body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Waist hip ratio (WHR) was computed as an index of upper-body versus lower-body adiposity.

Plasma glucose (mmol L^{-1}) was measured using a Biomerieux-glucose enzymatic PAP kit in DACOS autoanalyser. Cholesterol and triglyceride concentrations were assayed enzymatically in plasma samples using DACOS autoanalyser with commercial reagents supplied by Biomerieux Diagnostics. To measure HDL cholesterol, apo B-containing lipoproteins were precipitated from freshly collected plasma by the use of dextran sulphate magnesium chloride. LDL cholesterol was derived by the Friedewald equation, except in patients with triglyceride > 4.0 mmol L^{-1} in whom it was measured after preparative ultracentrifugation [28]. Serum apolipoproteins A-I and B were assayed by immunoturbidimetry using the commercial Beckmann® apolipoprotein A-I and B reagents, respectively (Ireland). Lp(a) was measured using a commercial antiapo(a) polyclonal capture enzyme-linked immunosorbent assay called TintElize®Lp(a) (Biopool AB, Umea, Sweden) according to the instruction sheet of the manufacturer. An intraassay coefficient of variation of 5.8% ($n = 10$) was obtained at 310 mg dL^{-1} level of Lp(a) reference plasma. Glycated haemoglobin levels (HbA1c) were measured spectrophotometrically using a commercial kit produced by BioSystems® (Spain). The intra and interassay of coefficient of variation were 1.5% and 4%, respectively.

Cardiac catheterization and coronary angiography

Cardiac catheterization was performed according to the Judkins technique via femoral approach. Selective coronary arteriography was performed in

patients in the fasting, nonsedated state. The coronary arteries were injected with 3–7 mL of Hexabrix® and examined in anteroposterior, hemiaxial, and right and left oblique views, as described previously [29,30]. Angiograms were assessed by two 'blinded' cardiologists, who recorded the number of occlusions and percentage diameter stenosis of lesions in 10 coronary segments, as described previously [31]. They were graded < 25% = 0, 25–49% = 1, 50–74% = 2, 75–99% = 3, 100% = 4; the sum of which yielded an overall coronary artery score (CAS) [29,30]. The scores were tabulated independently, without knowledge of clinical or laboratory information or the score assessed by the other observer. The mean score from two observers was used in all analyses. Interobserver variability was minimal, as evidenced by a mean difference of five and a Pearson correlation coefficient of 0.91.

Statistical methods

Statistical tests were performed as described in the text using commercial software packages (Statworks™, Cricket Software Inc, Philadelphia, USA and JMP®, SAS Institute Inc, Cary, NC, USA). Comparisons were made by unpaired Student's *t*-test and Mann–Whitney *U*-test. Associations were studied by multivariate correlation and nonparametric rank correlation (Spearman's rho) tests. Because the distribution of Lp(a) was skewed, analyses were done on the transformed variable log [Lp(a) + 1].

Results

Lipoprotein profiles and anthropometric measures in subjects with NIDDM versus control subjects

Lipid and Lp(a) profiles for subjects with NIDDM and control subjects are shown in Table 1. In comparison with control subjects, those with NIDDM had higher triglyceride levels, lower HDL cholesterol and Apo AI levels ($P < 0.05$). There were no significant differences between the Lp(a), total and LDL-cholesterol, Apo B levels and BMI, WHR of subjects with NIDDM and control subjects ($P > 0.05$).

Characteristics of NIDDM groups with and without CAD

The characteristics of the subjects who had NIDDM with and without CAD are shown in Table 2. The subjects with NIDDM with and without CAD were similar relative to age, body mass index and glycaemic control ($P > 0.05$). Abdominal obesity of diabetic patients with CAD was more than the patients' without CAD ($P < 0.05$). Diabetic patients with CAD had higher levels of total cholesterol, LDL-cholesterol and lower levels of Apo AI ($P < 0.05$). Lp(a) levels of diabetic patients with CAD were higher than the Lp(a) levels of patients without CAD ($P < 0.05$). There was no significant difference between the

Table 1 Age, anthropometric measures and lipid data for noninsulin-dependent diabetes mellitus (NIDDM) and control subjects

	NIDDM	Control
	(mean ± SE) ($n = 26$)	(mean ± SE) ($n = 19$)
Age(year)	58.73 ± 1.42	58 ± 2.0
BMI(kg/m^2)	28.13 ± 0.81	27.26 ± 1.03
WHR	0.88 ± 0.015	0.866 ± 0.016
T.cholesterol(mmol L^{-1})	6.65 ± 0.32	6.41 ± 0.32
Triglyceride(mmol L^{-1})	2.74 ± 0.21 *	1.82 ± 0.21*
HDL-cholesterol(mmol L^{-1})	0.95 ± 0.04**	1.16 ± 0.06**
LDL-cholesterol(mmol L^{-1})	4.49 ± 0.26	4.44 ± 0.27
Apo AI (g L^{-1})	1.25 ± 0.07***	1.42 ± 0.06***
Apo B (g L^{-1})	1.59 ± 0.1	1.73 ± 0.1
Lp(a) (mg dL^{-1})[a]	31.25 ± 6.1	35.56 ± 6.54

[a]Data are summarized on natural scale, but analysis was performed on log scale.
[b]SE, Standard error.
*$P = 0.006$, **$P = 0.021$, ***$P = 0.036$ in Student's *t*-test.

Table 2 Characteristics of subjects with noninsulin-dependent diabetes mellitus (NIDDM), stratified by absence or presence of coronary artery disease

	No CAD	CAD
	(mean ± SE) ($n = 10$)	(mean ± SE) ($n = 16$)
Age (year)	57.2 ± 2.3	59.7 ± 1.8
Duration of diabetes (year)	6.82 ± 2.2	9.58 ± 1.95
BMI(kg/m^2)	26.62 ± 1.26	29.07 ± 1.02
WHR	0.836 ± 0.021*	0.906 ± 0.017*
T.cholesterol(mmol L^{-1})	5.62 ± 0.42*	7.30 ± 0.39*
Triglyceride(mmol L^{-1})	2.31 ± 0.40	3.00 ± 0.23
HDL-cholesterol(mmol L^{-1})	1.01 ± 0.07	0.90 ± 0.05
LDL-cholesterol(mmol L^{-1})	3.82 ± 0.34*	4.91 ± 0.33*
Apo AI (g L^{-1})	1.45 ± 0.091*	1.12 ± 0.094*
Apo B (g L^{-1})	1.58 ± 0.15	1.59 ± 0.13
HbA1c (%)	7.43 ± 0.49	7.76 ± 0.44
Lp(a) (mg dL^{-1})[a]	15.72 ± 5.69*	40.95 ± 8.52*

[a]Data are summarized on natural scale, but analysis was performed on log scale.
[b]SE, Standard error.
*$P < 0.05$ Mann–Whitney *U*-test.

Table 3 Correlation of CAS with lipid data and anthropometric measures

CAS	T.chol	TG	HDL-C	LDL-C	Lp(a)	BMI	WHR
Patients with NIDDM	$r = 0.539$ $P = 0.031$	$r = 0.461$ $P = 0.072$	$r = -0.567$ $P = 0.022$	$r = 0.481$ $P = 0.048$	$r = -0.071$ $P = 0.794$	$r = 0.267$ $P = 0.316$	$r = 0.652$ $P = 0.006$
Patients without NIDDM	$r = 0.439$ $P = 0.204$	$r = 0.134$ $P = 0.711$	$r = -0.496$ $P = 0.144$	$r = 0.593$ $P = 0.070$	$r = 0.219$ $P = 0.542$	$r = -0.304$ $P = 0.391$	$r = -0.067$ $P = 0.853$

[a]NIDDM, noninsulin-dependent diabetes mellitus.
[b]Patients with NIDDM: *n*,16; patients without NIDDM: *n*,10.

triglyceride, HDL-cholesterol and Apo B levels of subjects with and without NIDDM ($P > 0.05$).

Lp(a) levels and glycaemic control

Levels of Lp(a) were not significantly correlated with glycosylated haemoglobin amongst the subjects with NIDDM ($r = -0.1151$, $P = 0.5756$). This finding prevailed for both subgroups of subjects with NIDDM (those with and without CAD).

Lipid profile and CAS

The correlations of the lipid data, and the anthropometric measures with CAS are shown in Table 3. In diabetic patients with CAD there was no significant correlation between Lp(a) levels and CAS ($P > 0.05$). In diabetic patients, significant positive correlations were found between CAS, total cholesterol and LDL-cholesterol; significant negative correlation between CAS and HDL-cholesterol ($P < 0.05$). As shown in Table 3, there were no significant correlations between the CAS and triglyceride levels and BMI ($P > 0.05$). In patients without diabetes, none of these parameters were correlated with CAS ($P > 0.05$).

Discussion

Lp(a) is a risk factor for CAD in subjects without diabetes, and is claimed to be related to the severity of CAD as assessed angiographically [32]. The role of Lp(a) in atherogenesis in diabetic patients is not clear. Researchers have postulated that Lp(a) may, in part, explain the increased risk of vascular disease associated with diabetes mellitus that exists after controls have been imposed for conventional risk factors.

It is reported that patients with NIDDM have lower [22,23], higher [20,21], or similar [24–26] Lp(a) levels compared with nondiabetic subjects. Our study confirms the findings of studies in which Lp(a) levels of the patients with NIDDM were similar to the Lp(a) levels of control subjects. We found no significant relationship between Lp(a) levels and glycaemic control in agreement with other reports of subjects with NIDDM [33,34].

Whether Lp(a) excess is a risk factor for CAD in diabetes mellitus is unclear. Haffner and colleagues [35] reported that Lp(a) levels were not higher in subjects with NIDDM who died of CAD than in control survivors. In contrast, Velho and coworkers found increased Lp(a) levels in subjects with diabetes, and a history of myocardial infarction [25]. In our comparison of Lp(a) levels in subjects who had NIDDM with and without CAD, those with CAD had significantly higher Lp(a) levels ($P < 0.05$). However, we didn't find a significant correlation between Lp(a) level and CAS in patients with and without NIDDM. This finding is in contrast with the data of Watts and colleagues [36].

Several possible explanations for these findings can be proposed. First, both our study and that of Watts *et al.*, investigated symptomatic diabetic subjects, who underwent coronary angiography [36]. We don't know the Lp(a) levels of asymptomatic patients with CAD. In sampling bias both of these studies may not represent the real condition. Secondly, although scoring the coronary artery lesions seems to be an objective way of assessing the existence and the severity of CAD, it may not imply that vessels having the score of zero are really normal. Thirdly, one theory is that Lp(a) level has a synergistic role in atherogenesis only in the presence of hypercholesterolaemia [37].

The patients with NIDDM and CAD had higher total cholesterol, triglyceride, and LDL cholesterol levels and lower HDL cholesterol, apo AI levels than those without CAD. This lipid profile implies the

importance of conventional lipid parameters in atherogenesis in diabetic patients.

These data suggest that diabetic state does not imply higher Lp(a) levels. There is no significant association between the level of metabolic control and Lp(a) levels. However, Lp(a) excess seems to be atherogenic in patients with NIDDM as has been shown in nondiabetic patients in previous studies [8–12]. The possibility exists that Lp(a) has a synergistic role in diabetes-related atherogenesis. Further studies are required in diabetic patients to assess the correlation of Lp(a) and CAS using newer techniques such as intravascular ultrasound (IVUS), which can detect atherosclerosis at sites that appear angiographically normal but indeed have occult atherosclerosis [38].

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References

1 Aro A. Macroangiopathy in type II diabetes. *Acta Endocrinol* 1984; **262:** 75–8.
2 Kannel W, McGee D. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham Study. *Diabetes Care* 1979; **2:** 120–26.
3 Kannel W, McGee D. Diabetes and cardiovascular disease: the Framingham Study. *JAMA* 1979; **241:** 2035–8.
4 Gaubatz J, Heideman C, Gotto AJ, Morisett J, Dahlen G. Human plasma lipoprotein (a). Structural properties. *J Biol Chem* 1983; **258:** 4582–9.
5 Berg K. A new serum type system in man — the Lp system. *Acta Pathol Microbiol Scand* 1963; **59:** 369–82.
6 Dahlen G, Ericson C, Furberg C, Lundvist L, Svardsudd K. Angina of effort and an extra pre-beta lipoprotein fraction. *Acta Medica Scand* 1972; **531:** 11–15.
7 Dahlen G, Berg K, Gilnas T, Ericson C. Lp (a) liporotein/pre-beta1-lipoprotein in Swedish middle-aged males and in patients with coronary heart disease. *Clin Genet* 1975; **7:** 334–41.
8 Rhoads GG, Dahlen G, Berg K, Morton NE, Dannenberg AL. Lp (a) lipoprotein as a risk factor for myocardial infarction. *JAMA* 1986; **256:** 2540–44.
9 Sandkamp M, Funke H, Schulte H, Kohler E, Assman G. Lipoprotein (a) is an independent risk factor for myocardial infarction at a young age. *Clin Chem* 1990; **36:** 20–23.
10 Utermann G. The mysteries of Lipoprotein (a). *Science* 1989; **246:** 904–10.
11 Schaefer EJ, Lamon-Fava S, Jenner JL, McNamara JR, Ordovas JM, Davis CE, *et al.* Lipoprotein (a) levels and risk of coronary heart disease in men. The lipid research clinics coronary primary prevention trial. *JAMA* 1994; **271:** 999–1003.
12 Genest JJ, Jenner J, McNamara J, Ordovas JM, Silberman SR, Wilson PW, *et al.* Prevalance of lipoprotein (a) [Lp (a)] excess in coronary artery disease. *Am J Cardiol* 1991; **67:** 1039–45.
13 Scanu AM, Lawn RM, Berg K. Lipoprotein (a) and atherosclerosis. *Ann Intern Med* 1991; **115:** 209–18.
14 Edelberg J, Pizzo S. Why is lipoprotein (a) relevant to thrombosis? *Am J Clin Nutr* 1992; **56:** 791S–2S.
15 Rath M, Niendorf A, Reblin T, Dietel M, Krebber H, Beisiegel U. Detection and quantification of lipoprotein (a) in the arterial wall of 107 coronary bypass patients. *Arteriosclerosis* 1989; **9:** 579–92.
16 Cushing GL, Gaubatz JW, Nava ML, Burdick BJ, Boran TMA, Guyton JR, *et al.* Quantification and localization of apolipoprotein (a) and B in coronary artery bypass vein grafts resected at re-operation. *Arteriosclerosis* 1989; **9:** 593–603.
17 Bruckert E, Davidoff P, Grimaldi A, Truffert J, Giral P, Doumith R, *et al.* Increased serum levels of lipoprotein (a) in diabetes mellitus and their reduction with glycemic control *JAMA* 1990; **263:** 35–6 (letter).
18 Jenkins A, Steele J, Janus E, Best J. Increased plasma apolipoprotein (a) levels in IDDM patients with microalbuminuria. *Diabetes* 1991; **40:** 787–90.
19 Haffner SM, Tuttle KR, Rainwater DL. Decrease of lipoprotein (a) with improved glycemic control in IDDM subjects. *Diabetes Care* 1991; **14:** 302–7.
20 O'Brien T, Nguyen T, Harrison J, Bailey K, Dyck P, Kottke B. Lipids and Lp (a) lipoprotein levels and coronary artery disease in subjects with non-insulin-dependent diabetes mellitus. *Mayo Clin Proc* 1994; **69:** 430–35.
21 Jenkins A, Steele J, Junus E, Santamaria J, Best J. Plasma apolipoprotein (a) is increased in type II (non-insulin-dependent) diabetic patients with microalbuminuria. *Diabetologia* 1992; **35:** 1055–9.
22 Haffner SM, Morales PA, Stern MP, Gruber K. Lp (a) concentrations in NIDDM. *Diabetes* 1992; **41:** 1267–72.
23 Rainwater D, MacCluer JW, Stern M, VandeBerg JL, Haffner S. Effects of NIDDM on lipoprotein (a) concentration and apolipoprotein (a) size. *Diabetes* 1994; **43:** 942–6.
24 Csazar A, Dieplinger H, Sandholzer C, Karadi I, Juhasz E, Drexel H, *et al.* Plasma lipoprotein (a) concentration and phenotypes in diabetes mellitus. *Diabetologia* 1993; **36:** 47–51.
25 Velho G, Erlich D, Tuppin E, Neel D, Cohen D, Froguel P, *et al.* Lipoprotein (a) in diabetic patients and normoglycemic relatives in familial NIDDM. *Diabetes Care* 1993; **16:** 742–7.
26 Joven J, Vilella E. Serum levels of lipoprotein (a) in patients with well controlled non-insulin diabetes mellitus. *JAMA* 1991; **265:** 1113–4 (letter).
27 National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intotelance. *Diabetes* 1979; **28:** 1039–57.
28 Friedewald WT, Levy RI, Frederickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifugation. *Clin Chem* 1972; **18:** 499–502.
29 Watts GF, Lewis B, Brunt JNH, Lewis ES, Coltart DJ, Smith LDR, *et al.* Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas Atherosclerosis Regression Study (STARS). *Lancet* 1992; **339:** 563–9.
30 Austen WG, Edward JE, Frye RI, Gensini GG, Gott VL, Griffith LS, *et al.* AHA committee report. A reporting system

on patients evaluated for coronary artery disease. *Circulation* 1975; **51:** 7–40.

31 Ryan T, Faxon D, Gunnar R. A report of the ACC/AHA task force on assesment of diagnostic and therapeutic cardiovascular procedures. *J Am Coll Cardiol* 1988; **12:** 529–38.

32 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* 1986; **74:** 758–65.

33 Ritter M, Richter W, Lyko K, Schwanelt P. Lp (a) serum concentrations and metabolic control. *Diabetes Care* 1992; **15:** 1441–2 (letter).

34 Haffner S, Tuttle K, Rainwater D. Preliminary report: lack of change of Lp (a) concentrations with improved glycemic control in subjects with type II diabetes. *Metabolism* 1992; **41:** 116–20.

35 Haffner S, Moss S, Klein B, Klein R. Lack of association between Lp (a) concentrations and coronary heart disease mortality in diabetes: the Wisconsin Epidemiologic Survey of Diabetic Retinopathy. *Metabolism* 1992; **41:** 194–7.

36 Watts GF, Gwilym RM, Mazurkiewicz J, Coltart J. Independent correlation between plasma lipoprotein (a) and angiographic coronary artery disease in NIDDM. *Diabetes Care* 1995; **18:** 234–6.

37 Armstrong V, Cremer P, Eberle E, Manke A, Schulze F, Wieland H, *et al.* The association between serum Lp (a) concentrations and angiographically assessed coronary atherosclerosis. Dependence on serum LDL levels. *Atherosclerosis* 1986; **62:** 249–57.

38 Nissen SE, De Frarco AC, Raymond RE, Franco S. Angiographically unrecognized disease at 'normal' reference sites: a risk factor for suboptimal results after coronary interventions. *Circulation* 1993; **88:** 412A.

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