

Peripheral Atherosclerosis and Serum Lipoprotein(a) in Diabetes

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OBJECTIVE — Serum lipoprotein(a) [Lp(a)] is strongly associated with atherosclerosis in nondiabetic individuals. To see if atherosclerosis is also associated with serum Lp(a) in both IDDM and NIDDM, we determined the correlation between the toe systolic blood pressure index (TSPI) and serum Lp(a) in tightly controlled diabetic patients without nephropathy.

RESEARCH DESIGN AND METHODS — Cross-sectional study of 57 IDDM and 35 NIDDM patients. All patients had been under strict glycemic control for at least 6 months. The main outcome measure was TSPI of both lower extremities. In addition, we measured serum Lp(a) and other serum lipids, serum uric acid, total plasma homocysteine, plasma C-peptide, HbA_{1c}, albumin excretion rate, glomerular filtration rate, BMI, abdominal fat distribution, left ventricular hypertrophy, probabilities for cardiovascular disease (CVD), and routine clinical parameters.

RESULTS — TSPI was closely and independently related to serum Lp(a) in IDDM patients: $R^2 = 0.2999$, partial $P = 0.0005$, and in NIDDM patients: $R^2 = 0.7326$, partial $P = 0.0030$. TSPI was associated with symptoms of CVD. Median serum Lp(a) concentration was normal in IDDM (45 mg/l [range 10–870]) and NIDDM (72 mg/l [11–803]) patients.

CONCLUSIONS — Systemic atherosclerosis measured as the degree of peripheral occlusive arterial disease is strongly associated with serum Lp(a) in both IDDM and NIDDM patients. Serum Lp(a), however, is normal in both types of diabetic patients. Thus, it is indicated that serum Lp(a) should be measured in diabetic patients when assessing their risk profile for atherosclerosis.

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The serum concentration of lipoprotein(a) [Lp(a)] is genetically determined. Individual serum concentrations of Lp(a) are related inversely to the number of kringle-four moieties in the apolipoprotein(a) [apo(a)] molecule of Lp(a) (1). Therefore, the inherited structure of apo(a) is a major determinant of serum Lp(a) concentrations within the very wide normal range seen in most populations. Serum Lp(a) is strongly associated with coronary artery

occlusion and carotid wall thickness (2–4), and serum Lp(a) is an established risk factor for cardiovascular disease (CVD) (2,5,6) in nondiabetic individuals.

Few pathological conditions affect the genetically determined serum concentration of Lp(a): serum Lp(a) is increased in patients with the nephrotic syndrome and declines as the syndrome resolves (7). Patients with microalbuminuria have a higher median serum Lp(a) concentration

than patients without microalbuminuria (8). Nevertheless, the albumin excretion rate (AER) does not correlate with the serum Lp(a) concentration in either nondiabetic (9) or diabetic patients (8).

In most populations of IDDM (8,10–18) and NIDDM patients (16–19) with normal renal function, the median serum Lp(a) concentration is normal. Exceptions have been found in two studies of NIDDM patients (20,21), in which the median concentrations of Lp(a) were decreased.

In NIDDM patients, as in nondiabetic individuals, atherosclerosis is associated with Lp(a) (22,23), and Lp(a) is a risk factor for CVD in most studies of NIDDM patients (17,24–26), with few exceptions (16,27,28). In contrast, atherosclerosis has not been reported to be related to serum Lp(a) in IDDM, and serum Lp(a) is not a risk factor for CVD in IDDM patients (12,16,27–29). The reason for this difference between NIDDM and IDDM is not known. However, glycemic control has different effects on serum Lp(a) in the two types of diabetes. In IDDM (10,12,30,31), tightened glycemic control lowers serum Lp(a), whereas it does not affect serum Lp(a) in NIDDM patients (16,32–38). Therefore, different levels of glycemic control in populations of IDDM and NIDDM patients might explain the difference.

In view of future possibilities of lowering serum Lp(a) levels genetically, it is essential to know whether the association between atherosclerosis and serum Lp(a) also exists in diabetic patients, as it does in nondiabetic individuals.

We hypothesized that serum Lp(a) in well-controlled IDDM and NIDDM patients is associated with atherosclerosis, as it is in nondiabetic individuals. We related serum Lp(a) to peripheral atherosclerosis, measured quantitatively in IDDM and NIDDM patients with normal renal function and under equally tight glycemic control for 2 years.

RESEARCH DESIGN AND METHODS

Patients

All patients attended the same diabetes referral clinic. They had either IDDM

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Abbreviations: ABI, ankle-brachial index; AER, albumin excretion rate; apo(a), apolipoprotein(a); ARIC, Atherosclerosis Risk in Communities; CV, coefficient of variation; CVD, cardiovascular disease; GFR, glomerular filtration rate; Lp(a), lipoprotein(a); POAD, peripheral occlusive arterial disease; TSPI, toe systolic blood pressure index.

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

Table 1—Clinical characteristics of 92 diabetic patients

Clinical characteristic	IDDM	NIDDM	P value
Sex (M/F)	38/19	26/9	0.4462
Age (years)	50 (46–54)	59 (54–63)	0.0082
Total daily insulin dose (U)	54 (48–60)	65 (51–80)	0.1031
HbA _{1c} (%)	6.3 (6.0–6.6)	6.3 (5.9–6.8)	0.9045
BMI (kg/cm ²)	26 (25–27)	29 (27–30)	0.0053
Abdominal sagittal diameter (cm)	22 (21–23)	25 (24–27)	0.0020
Serum total cholesterol concentration (mmol/l)	5.2 (5.0–5.4)	5.6 (5.2–5.9)	0.0862
Serum HDL cholesterol concentration (mmol/l)	1.5 (1.3–1.6)	1.3 (1.2–1.5)	0.2029
Serum LDL cholesterol concentration (mmol/l)	3.2 (3.1–3.4)	3.5 (3.2–3.8)	0.1408
Ratio of total-to-HDL cholesterol concentration	3.9 (3.6–4.1)	4.7 (4.2–5.3)	0.0020
Serum triglyceride concentration (mmol/l)	1.2 (1.3–1.4)	1.8 (1.5–2.2)	0.0003
Plasma fibrinogen concentration (g/l)	3.4 (3.1–3.6)	4.1 (3.7–4.5)	0.0017
Serum uric acid concentration (μmol/l)	271 (244–298)	330 (287–373)	0.0155
Serum creatinine concentration (μmol/l)	103 (93–113)	98 (88–109)	0.5678
GFR (ml · min ⁻¹ · 1.73 m ⁻²)	100 (92–108)	98 (86–109)	0.7228
Systolic blood pressure (mmHg)	150 (144–156)	150 (144–157)	0.9066
Diastolic blood pressure (mmHg)	82 (79–85)	85 (82–89)	0.1122
Probability for CVD	0.20 (0.15–0.25)	0.34 (0.26–0.41)	0.0022
TSPI	0.79 (0.74–0.84)	0.80 (0.74–0.86)	0.8334

Data are *n* or means (95% CI).

(defined as fasting serum peptide <0.24 nmol/l) or NIDDM with secondary failure (defined as fasting serum C-peptide >0.23 nmol/l and insulin requirements, in addition to continued maximal oral therapy). NIDDM patients in the study, therefore, do not fully represent NIDDM patients in general. Inclusion criteria were the requirements of insulin treatment and willingness to undergo intensive insulin treatment. Patients with overt nephropathy were excluded.

There were 210 patients referred for control of insulin treatment during the 2-year inclusion period, and 136 of these met the inclusion criteria. Of these, 92 patients completed the study (Table 1). Some 9 of 19 women with IDDM were aged <50 years, and 10 were aged >50 years. Two of nine women with NIDDM were aged <50 years, and seven were aged >50 years. None of the patients used estrogen replacement therapy or oral contraceptives. Three IDDM and two NIDDM patients suffered from claudication. Four IDDM and one NIDDM patient had ischemic foot ulcers. No patient had been treated with vascular reconstruction or amputation or was in immediate risk of amputations. Two IDDM patients had suffered stroke. Eight IDDM and six NIDDM patients had verified myocardial infarcts in the past. In summary, 15 IDDM and 12 NIDDM patients had one or more of these clinical signs of CVD.

None of the patients had major intercurrent illnesses requiring hospital contact within 6 months before having blood samples drawn for Lp(a) determinations.

Most of the 44 patients who dropped out did so early in the study because of disappointment with intensified glycemic control, and a selection bias is likely with respect to patient motivation.

Protocol

The insulin treatment schedule for all patients was two daily injections of intermediate-acting insulin in the morning and late afternoon and three daily injections of fast-acting insulin at mealtime. Besides insulin, NIDDM patients were maintained on a combination of maximal doses of glibenclamide and metformin. Metformin was discontinued in two patients because of side effects.

All patients visited the diabetes clinic at least four times yearly. The following laboratory determinations were made at each visit to the clinic: fasting blood glucose, HbA_{1c}, serum total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, uric acid, creatinine, plasma fibrinogen, urinary AER, supine blood pressure, and body weight. Blood samples were drawn in the morning before meals and before insulin administration. The central clinical laboratory of the hospital participates in the Murex Quality Assessment Programmes

(Murex Biotech, Dartford, U.K.). We calculated results as the mean of four different measurements within the last year of the observation period. All other tests were done once or twice during the last year.

Analytical methods

Serum Lp(a) was measured by radioimmunoassay as previously described (39). Serum samples for the assay were stored at -70°C for no longer than 8 months. The coefficient of variation (CV) for samples stored at -70°C for 12 months is <1%. The intra-assay CV was 5.4%. Sensitivity of the assay was 10 mg/l, and the normal range is 10–300 mg/l (mean ± 2 SD). Samples were drawn on two different occasions, 6 months apart, but were all analyzed within the same assay. Results were expressed as the mean of the two samples. Serum samples from 15 female and 35 male blood donors between the ages of 19 and 59 years were normal controls for the Lp(a) assay.

Plasma C-peptide was measured by a modification of the radioimmunoassay described by Heding (40). Sensitivity of the assay is 0.02 nmol/l. Intra-assay CV is 5.8% and interassay CV, 8.1%. The normal range is 0.24–0.64 nmol/l.

Toe systolic blood pressure index (TSPI) was calculated as the systolic blood pressure of the first toe, measured by mercury strain gauge technique, and divided by the systolic blood pressure of the left arm, according to the joined recommendations of the American Diabetes Association and the American Heart Association (41,42). In diabetic patients, TSPI measures peripheral occlusive arterial disease (POAD) of the lower extremities more specifically than the ankle-brachial index (ABI), which is influenced by medial wall stiffness, common in diabetic patients (42,43). Mean TSPI for normal asymptomatic individuals is 0.90, with a normal range of 0.62–1.08 (44–46). All measurements of TSPI were done in one vascular laboratory by the same nurse-technician.

Total plasma homocysteine was measured by an automated high-performance liquid chromatography method (33).

Glomerular filtration rate (GFR) was determined as clearance of intravenous ⁵¹Cr-EDTA over a 4-h period (47). The normal range for GFR in 20-year-old men and women is 85–135 ml · min⁻¹ · 1.73 m⁻² and for 80-year-old men and women is 45–95 ml · min⁻¹ · 1.73 m⁻² (± 2 SD).

Table 2—Median serum Lp(a) concentration (mg/l) in IDDM and NIDDM patients and nondiabetic individuals

	IDDM patients	NIDDM patients	Nondiabetic individuals
<i>n</i>	57	35	50
All	45 (10–870)	72 (11–803)	69 (10–875)
Men	51 (10–846)	46 (10–642)	66 (10–875)
Women	38 (11–870)	115 (49–803)	80 (14–700)

Data are median (range).

Sagittal abdominal diameter was measured on the recumbent patient with a specially constructed gallow.

Left ventricular hypertrophy was estimated electrocardiographically as the sum of S-wave and R-wave amplitudes in leads V1 and V5, respectively.

Cardiovascular risk profiles were calculated according to prediction equations by Anderson et al. (48). The equations are based on data from the original Framingham and Framingham Offspring Cohorts. These cohorts cover an observation period of 12 years and an age span of 30–74 years, and are based on the following continuous cardiovascular risk factors: age, total and HDL cholesterol, systolic and diastolic blood pressures, and the following dichotomous risk factors: electrocardiogram voltage criteria for left ventricular hypertrophy, cigarette smoking, diabetes, coronary heart disease incidence, and sex.

Data analysis

Normality of distribution was tested by the Shapiro and Wilk's *W* statistic. For variables with normal distributions, results were calculated as means with 95% confidence limits. For non-normally distributed variables, results were calculated as medians with interquartile ranges. All *t* tests were two-tailed. A *P* value of <0.05 was defined as significant.

Simple associations between variables were calculated as the Pearson coefficient of correlation *R*. Two explorative multiple regression models were used to identify the combination of variables with the best predictive value: stepwise regression and all possible subsets regression (49). All variables measured in the study were included in the models.

RESULTS

Serum Lp(a)

Women with NIDDM had a median serum Lp(a) concentration of 115 mg/l, which was

higher than the median for normal women, 80 mg/l (*P* = 0.0110), and higher than any other subclass listed in Table 2. However, the number of individuals in this subclass was small. No other differences in median serum Lp(a) concentration between the subclasses of age, sex, IDDM, NIDDM, or normal individuals were significant. The median serum concentration of Lp(a) in women aged <50 years was 52 mg/l and in women aged >50 years, 87 mg/l (*P* = 0.7957).

The coefficient of correlation (*r*) between the two series of Lp(a) samples drawn 6 months apart was 0.9545 (*P* < 0.0001, intercept 2.49 mg/l). Serum Lp(a) was non-normally distributed (Wilk's statistic = 0.6430, *P* < 0.0001).

TSPI

The mean TSPI for IDDM patients was 0.79 (95% CI 0.74–0.84) and for NIDDM patients, 0.80 (0.74–0.86). There were 19 IDDM patients and 9 NIDDM patients who had a TSPI above the mean (0.90) but within the range for asymptomatic normal individuals.

The odds ratio between IDDM and NIDDM patients for having a TSPI <0.90 was 1.69 (0.654–4.42).

Wilk's statistic for TSPI in all patients was 0.9498 (*P* = 0.042).

Clinical characteristics

Clinical characteristics for the 57 IDDM and 35 NIDDM are listed in Table 1.

Glycemic control. The mean HbA_{1c} during the 2-year study period was the same in

the two types of diabetic patients. The mean total daily insulin dose required to maintain this HbA_{1c} was the same in the two groups.

Obesity. Abdominal fat deposition was normal in IDDM patients, but greater in NIDDM patients. The difference in abdominal fat accounted for the difference in BMI between the two types of diabetic patients.

Metabolic abnormalities. Serum LDL cholesterol, serum HDL cholesterol, and homocysteine were the same in the two groups. In contrast, serum total cholesterol, triglyceride, uric acid, and plasma fibrinogen were different in IDDM and NIDDM patients.

Renal function. Median AER was 9 μg/min in IDDM patients (17 patients had an AER >15 μg/min). In NIDDM patients, the median AER was 10 μg/min (10 patients had an AER >15 μg/min). The normal range for AER is 4–15 μg/min. Mean GFR was normal in both types of diabetic patients.

CVD. The median serum concentration of Lp(a) was not different in patients with (130.4 mg/l) and without (147.8 mg/l) signs of CVD (*P* = 0.7168), whereas mean TSPI was lower in patients with signs of CVD (0.69) than in patients without signs of CVD (0.84) (*P* = 0.0005). Except for patients with foot ulcers, patients in all subgroups of CVD (claudication, stroke, and myocardial infarction) had lower mean TSPI than those without CVD, whereas median serum Lp(a) was not different. There were 18 IDDM and 17 NIDDM patients who had a high predicted CVD risk, defined as >25% risk for CVD within 10 years. The odds ratio between IDDM and NIDDM patients was 3.06 (1.26–7.43).

Bivariate relationships

Stratification of mean TSPI by serum Lp(a) is shown for both types of diabetes in Table 3. All 22 diabetic patients with serum Lp(a) <25 mg/l had a mean TSPI of 0.8584 (0.7846–0.9322); 24 patients with serum Lp(a) of 25.0–50.0 mg/l had a mean TSPI

Table 3—TSPI stratified by serum Lp(a) concentration (mg/l)

Serum Lp(a) (mg/l)	IDDM + NIDDM		IDDM		NIDDM	
	<i>n</i>	Mean (95% CI)	<i>n</i>	Mean (95% CI)	<i>n</i>	Mean (95% CI)
<25 mg/l	22	0.86 (0.78–0.93)	17	0.84 (0.75–0.93)	5	0.93 (0.82–1.04)
25–50	24	0.81 (0.74–0.88)	14	0.82 (0.72–0.92)	10	0.81 (0.69–0.92)
50–100	20	0.78 (0.67–0.88)	12	0.77 (0.61–0.93)	8	0.78 (0.63–0.93)
>100	26	0.73 (0.65–0.81)	14	0.72 (0.59–0.84)	12	0.75 (0.62–0.88)

Table 4—Bivariate associations with TSPI in diabetic patients

Independent variables	IDDM + NIDDM		IDDM		NIDDM	
	r	P value	r	P value	r	P value
Serum Lp(a) concentration	-0.2675	0.0099	-0.4454	0.0008	-0.3335	0.0621
Serum uric acid concentration	-0.3059	0.0047	-0.2500	0.0799	-0.3631	0.0422
Age	-0.4032	<0.0001	-0.2379	0.0696	-0.3229	0.0071
Glomerular filtration rate	0.3934	0.0003	0.3356	0.0140	0.4915	0.0068
10-year probability for CVD	-0.3141	0.0027	-0.2578	0.0574	-0.4288	0.0189

of 0.8133 (0.7428–0.8839); 20 patients with serum Lp(a) between 50.0 and 100.0 mg/l had a mean TSPI of 0.7760 (0.6726–0.8794); and 26 patients with serum Lp(a) >100.0 mg/l had a mean TSPI of 0.7313 (0.6486–0.8141).

Serum Lp(a) concentration was strongly associated with the mean TSPI of both feet in IDDM ($P = 0.0008$). The same bivariate association was weaker in NIDDM patients ($P = 0.0621$) (Table 4).

GFR was strongly associated with mean TSPI in both IDDM ($P = 0.0140$) and NIDDM ($P = 0.00068$) patients. Age ($P = 0.0071$), serum uric acid ($P = 0.0422$), and the 10-year probability for CVD were associated with mean TSPI in NIDDM, but not in IDDM, patients (Table 4).

Multivariate relationships

Serum Lp(a) was included in the best possible subsets of variables predicting TSPI in both IDDM and NIDDM patients (Table 5). Serum Lp(a) contributed to both models independently of all variables tested, including age.

For IDDM patients, the model was incompletely specified ($R^2 = 0.2999$) by serum Lp(a) and serum uric acid. No other variables tested in this study contributed to the model. For NIDDM patients, the model was more fully specified ($R^2 = 0.7326$) by serum uric acid, sex, diastolic blood pres-

sure, serum Lp(a), and age, in order of contribution.

For all diabetic patients taken together, the multivariate regression model with TSPI as dependent variable had $R^2 = 0.2928$ and was specified by serum Lp(a) (partial $r = 0.2918$, $P = 0.0086$), serum uric acid (partial $r = 0.3429$, $P = 0.0018$), and age (partial $r = 0.2763$, $P = 0.0131$).

CONCLUSIONS — We found that the TSPI is closely associated with serum Lp(a) in both IDDM and NIDDM patients. The association is independent of all other established risk factors tested in this study, and it is the first demonstration of a relationship between atherosclerosis of the lower extremities and serum Lp(a) in diabetic patients. The serum concentration of Lp(a) is normal in both IDDM and NIDDM patients in tight glycemic control and without overt nephropathy.

The association between atherosclerosis and serum Lp(a) has not been shown before in IDDM patients. However, in NIDDM patients, our results confirm two recent studies: Watts et al. (22) found a strong independent association between the degree of coronary artery occlusion and serum Lp(a) and Yamamoto et al. (23) found an association between carotid wall thickness and serum Lp(a). We conclude that atherosclerosis is associated with

serum Lp(a) in both IDDM and NIDDM patients.

The presence of an association between atherosclerosis and Lp(a) both in diabetic patients with a two- to sixfold increased prevalence of atherosclerosis (50) and in nondiabetic individuals is additional evidence of the relationship between Lp(a) and atherogenesis. Although statistical association between serum Lp(a) and atherosclerosis in humans is no proof of a causal relationship, it is compatible with the causal effect of human Lp(a) on atherosclerosis recently shown by Callow et al. (51) in transgenic mice.

TSPI and ABI are indirect measures of POAD, but they are the only clinically available quantitative methods for measuring the degree of atherosclerosis of the lower extremities. In a study similar to ours, Sutton-Tyrrell et al. (4) recently showed a strong association between serum Lp(a) and the ABI in a population of elderly nondiabetic individuals. Their study is the only other published study of the association between serum Lp(a) and POAD using either ABI or TSPI. POAD is related to systemic atherosclerosis. Thus, Zheng et al. (52) showed POAD to be a strong correlate with carotid wall thickness in the Atherosclerosis Risk in Communities (ARIC) Study, and in 10 large epidemiological studies of nondiabetic individuals, POAD was a strong predictor of cardiovascular (41,53) and cerebrovascular events (41) and all-cause mortality (53). Serum Lp(a) is a risk factor for cardiovascular events in many epidemiological studies of NIDDM patients (17,24–26), although it has never been established as a risk factor for CVD in IDDM patients. In nondiabetic Caucasian individuals, evidence of the association between atherosclerosis and serum Lp(a) has been accumulating over the past 15 years. Dahlen (54) first, and later other large studies, showed an association between

Table 5—Multivariate associations with the TSPI in diabetic patients

Independent variables	IDDM ($R^2 = 0.2999$)			NIDDM ($R^2 = 0.7326$)		
	Partial r^*	P value	Contribution to R^2	Partial r^*	P value	Contribution to R^2
Serum Lp(a) concentration	-0.4952	0.0005	0.2274	-0.5583	0.0030	0.1211
Serum uric acid concentration	-0.3606	0.0138	0.1046	-0.7227	0.00003	0.2924
Age	—	NS†	—	-0.4427	0.0235	0.0652
Diastolic blood pressure	—	NS†	—	-0.5614	0.0028	0.1231
Sex	—	NS†	—	-0.5715	0.0023	0.1297

*Coefficient of correlation with the TSPI after inclusion of all other variables in the model. † $P > 0.05$.

serum Lp(a) and coronary artery disease measured by angiography. Schreiner et al. (55), in the ARIC Study, and Willeit et al. (3), in the Bruneck Study, have shown the close association between serum Lp(a) and carotid artery wall thickness measured by ultrasonography in large populations.

We interpret the association between serum Lp(a) and TSPI in our diabetic patients to show that serum Lp(a) is closely related not only to POAD, but also to the degree of systemic atherosclerosis.

Poor glycemic control may confound the association between atherosclerosis and serum Lp(a) in IDDM patients. Thus, Haffner et al. (10,33) and Ramirez et al. (35) showed that tightened glycemic control lowered the serum Lp(a) concentration in IDDM. Furthermore, Purnell et al. (14) showed in the Diabetic Control and Complication Trial (56) that conventionally treated IDDM patients had a higher median serum Lp(a) than intensively treated IDDM patients and nondiabetic individuals. In NIDDM patients, however, Haffner et al. (33) and O'Brien et al. (32) found tightened glycemic control to be of no effect on serum Lp(a). Nephropathy is another confounder of the association between atherosclerosis and serum Lp(a) in both IDDM and NIDDM patients. Takegoshi et al. (57) first showed that nephropathy increases serum Lp(a) in IDDM patients, a finding that was later confirmed by others (58–61). Haffner et al. (62) and Jenkins et al. (8) showed the same effect of nephropathy on serum Lp(a) in NIDDM patients. Our patients had near-normal glycemic control for 2 years before we measured serum Lp(a), and patients with overt nephropathy were excluded from the study. The association between serum Lp(a) and TSPI was also independent of microalbuminuria. Purnell et al. (14) also found no effect of microalbuminuria on serum Lp(a) in IDDM patients. In addition, adjustments for both HbA_{1c} and the 24-h insulin dose had no effects on the association between TSPI and serum Lp(a). In our study, glycemic control and nephropathy, therefore, did not confound the association in either IDDM or NIDDM patients.

We conclude that peripheral atherosclerosis is closely and independently associated with serum Lp(a) in well-controlled IDDM and NIDDM patients. The association persists in diabetic patients in spite of the combination of a normal serum Lp(a) and a two- to sixfold increased prevalence of atherosclerosis. Thus, it is indicated that serum Lp(a) should be measured as part of

a risk factor assessment for peripheral atherosclerosis in diabetic patients.

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