Relationship Between Lipoprotein Profile and Urinary Albumin Excretion in Type II Diabetic Patients With Stable Metabolic Control

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OBJECTIVE — To assess lipids and lipoprotein composition and the relationship between lipoprotein abnormalities and urinary albumin excretion (UAE) in select type II diabetic patients with stable metabolic control.

RESEARCH DESIGN AND METHODS — Fifty-five type II diabetic patients and 55 healthy control subjects both with a body mass index <30 kg/m^2 were studied. Patients were classified according to their level of UAE as normoalbuminuric (n = 37), microalbuminuric (n = 11), and macroalbuminuric (n = 7). In all cases, serum creatinine and albumin concentrations were in the normal range.

RESULTS — Normoalbuminuric patients showed increased triglyceride (TG) contents in intermediate-density lipoprotein (IDL) ($P < 0.01$), low-density lipoprotein (LDL) ($P < 0.001$), and high-density lipoprotein (HDL) ($P < 0.001$) compared with control subjects. Lipoprotein concentration in microalbuminuric patients did not differ from that of normoalbuminuric patients. On the other hand, patients with macroalbuminuria showed a significant increase in IDL cholesterol ($P < 0.01$) and IDL ($P < 0.01$), LDL ($P < 0.05$), and HDL TGs ($P < 0.01$) compared with the other groups. Diabetic patients with nephropathy, both microalbuminuric and macroalbuminuric, tended to have higher mean lipoprotein(a) (Lp[a]) concentrations than normoalbuminuric patients and control subjects. A strongly positive correlation was observed between UAE and serum TGs (r = 0.56) and very-low-density lipoprotein (r = 0.55), IDL (r = 0.52), LDL (r = 0.54), and HDL TGs (r = 0.52).

CONCLUSIONS — Lipoprotein alterations observed in diabetic patients, specifically IDL abnormalities and a tendency toward high Lp(a) levels, which are more marked in those with increased UAE, may contribute to the excess of cardiovascular disease in type II diabetic patients, particularly those with nephropathy.

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UAE, urinary albumin excretion; TG, triglyceride; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein; BMI, body mass index; BP, blood pressure; sBP, systolic blood pressure; dBP, diastolic blood pressure; apo, apolipoprotein; Lp(a), lipoprotein(a); CVD, cardiovascular disease.

Increased urinary albumin excretion (UAE) (micro- and macroalbuminuria) is associated with an excess of cardiovascular disease (CVD) in type I and type II diabetes (1,2). Although smoking, hypertension, hyperfibrinogenemia, and hypercholesterolemia seem to be more common in diabetic patients with nephropathy (3), the presence of these cardiovascular risk factors probably fails to explain the extremely high incidence of macrovascular disease in patients with diabetic nephropathy (4). Because quantitative and compositional abnormalities in lipoproteins are known to play an important role in the progression of atherosclerosis (5), several studies have been made with the aim of evaluating lipoprotein abnormalities in type I diabetic patients with nephropathy (6–11). However, few studies have assessed the relationship between UAE and lipoproteins in type II diabetes (12–15) and to our knowledge, no data are available on the triglyceride-rich (TG) lipoprotein composition, including intermediate-density lipoprotein (IDL) in this specific group of patients.

In this study, abnormalities in lipoproteins isolated by ultracentrifugation in select type II diabetic patients with stable metabolic control were evaluated. Furthermore, lipoprotein composition in patients with increased UAE was compared with that of normoalbuminuric patients and nondiabetic control subjects.

RESEARCH DESIGN AND METHODS

— During an 8-month period from April to November 1991, 55 of 540 consecutive patients with type II diabetes were recruited from the outpatient clinic of the Endocrinology Section of the Hospital Germans Trias i Pujol in Badalona, Spain. Inclusion criteria were as follows: 1) between 45 and 70 years of age, 2) body mass index (BMI) <30 kg/m^2, 3) normal levels of serum albumin and creatinine, and 4) stable metabolic control for >6 months before entry into

the study (i.e., a variation of HbA_{1c} levels <1% in three separate determinations at a 2-month interval) and in the acceptable range according to the European consensus (16). Patients with associated diseases, drug therapy that could influence lipid metabolism (hypertensive patients were included only if they were treated with calcium antagonists), pregnancy, excessive alcohol consumption, and/or albuminuria >1.2 g/24 h were excluded. According the inclusion criteria, this study was conducted in a very select population (diabetic patients with stable metabolic control, without other associated factors known to cause changes in lipid and lipoprotein profiles) to avoid possible confounding effects. Of 540 patients, 55 were included in the study and 485 were excluded because of additional treatments (24 cases), poor metabolic control (73 cases), BMI ≥ 30 kg/m^2 (143 cases), and because of poor metabolic control, and/or BMI ≥ 30 kg/m^2, and/or additional treatments (245 cases). Patients were classified in three groups according to albuminuria levels (17): *1*) normal UAE (<30 mg/24 h) (n = 37), 2) incipient nephropathy (microalbuminuria) (UAE 30–300 mg/24 h) (n = 11), and 3) overt nephropathy (macro- or clinical albuminuria) (UAE >300 mg/24 h) (n = 7). UAE was determined as the mean of three 24-h urine collections performed at home during normal activity in two monthly separate determinations.

Clinical data, including smoking status, cardiovascular symptoms, examination of pulses, blood presure (BP), oscillometry, resting 12-lead electrocardiography, ocular fundus examination and fluorescein angiography, neurological examination, associated drug therapy, and metabolic control, were obtained from medical records. Each patient received a standard diet with a caloric intake adjusted to age and physical activity, which was moderate in all cases. Food intake and composition were based on American Diabetes Association recommendations (18). Fifty-five healthy subjects with similar age, BMI, and physical activity served as control subjects.

Weight and height were measured with indoor clothing and without shoes, and the BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Blood pressure was measured with a standard sphygomanometer and after 10 min of rest by a sole observer. Two BP measurements were made in the sitting position and the mean recorded. Thereafter, blood samples were collected without stasis while the patient rested in the supine position. The minimum fasting period was 10 h. Urine volume (24 h) was measured and urine aliquots were stored at −40°C for subsequent analysis. Sediment in fresh urine was assayed in each sample and was normal in all cases.

Serum and lipoprotein cholesterol and TG concentrations were assayed by enzymatic methods. Proteins in lipoprotein fractions were measured by a colorimetric method (19). HbA_{1c} (normal range in our laboratory 4.6–7.2%) was measured with a commercial chromatographic method (Biosystem, Barcelona, Spain). Lipoprotein isolation was conducted as follows: Blood was allowed to clot for 1 h at room temperature; serum was removed by centrifugation (1,200 *g*, 20°C, 15 min), supplemented with a preservative solution (20), and stored at 4°C for no more than 4 days before ultracentrifugation. Lipoprotein isolation was conducted by a double ultracentrifugation procedure (21). Briefly, we overlayered serum with NaCl solution (density = 1.006 kg/L) and centrifuged the samples at a fixed-angle 50.38 Ti rotor (Kontron, Milan, Italy) at 150,000 *g* and 10°C for 18 h. Very-low-density lipoprotein (VLDL) fraction was collected by aspiration from the top of the tube. The infranatants were adjusted to a density of 1.25 kg/L with dried KBr and overlayered sequentially with a density of 1.21 kg/L NaCl solution and distilled water. The samples were ultracentrifuged in 41.14 TST rotor (Kontron) at 300,000 *g* for 22 h; and the other lipoproteins, IDL 1.006 < d < 1.019, low-density lipoprotein (LDL) 1.019 < d < 1.063, and high-density lipoprotein (HDL) d > 1.063, were aspirated. The mean intra- and interseries coefficients of variation for the double ultracentrifugation procedure never exceeded 10%. Lipoprotein recovery was verified by comparing the sum of cholesterol and TGs in the fractions with total serum cholesterol and TGs. Apolipoprotein (apo)E polymorphism was studied in all patients and control subjects by isoelectric focusing from delipidated VLDL as described previously by Eto et al. (22). Lipoprotein(a) (Lp[a]) was quantified by enzymoimmunoanalysis (TintElize Lp[a], Biopool, Umeä, Sweden). Urinary albumin concentration was estimated by nephelometry (interassay coefficient of variation was 2.0%).

Statistical analysis

Results were expressed as means ± SD. For the analysis, $\log_{10}$-transformed values of UAE were used. χ^2 tests were used to compare categorical variables among groups. Comparison of continuous variables among groups was performed by analysis of variance followed by Bonferroni tests. The level of statistical significance was set at $P < 0.05$ for a two-tailed distribution. Correlations between variables were tested by simple and multiple regression analysis.

RESULTS — Clinical characteristics of the three groups of type II diabetic patients classified by UAE levels and those of control subjects are shown in Table 1. The groups did not differ except for systolic blood pressure (sBP), diastolic blood pressure (dBP), and the percentage incidence of retinopathy.

Lipids and lipoprotein composition for the groups are shown in Table 2. Normoalbuminuric diabetic patients showed a significant increase in TG contents in IDL ($P < 0.01$), LDL ($P < 0.001$), and HDL ($P < 0.001$) compared with control subjects. No differences were found in lipoprotein concentrations between normoalbuminuric men and

Table 1—*Clinical characteristics of the three groups of type II diabetic patients, classified according to UAE levels, compared with control subjects*

		Diabetic patients		
	Control subjects	Normoalbuminuric <30 mg/24 h)	Microalbuminuric (30–300 mg/24 h)	Macroalbuminuric (>300 mg/24 h)
n	55	37	11	7
Sex (M/F)	35/20	14/23	7/4	5/2
Age (years)	57 ± 9	56 ± 8	59 ± 9	59 ± 9
	(56 ± 10/57 ± 8)	(56 ± 9/57 ± 7)	(59 ± 8/58 ± 9)	(58 ± 10/58 ± 9)
BMI (kg/m^2)	26 ± 3	27 ± 3	27 ± 3	27 ± 2
	(26 ± 3/26 ± 3)	(27 ± 2/26 ± 3)	(27 ± 2/26 ± 3)	(27 ± 1/26 ± 3)
Diabetes duration (years)		9 ± 7	13 ± 7	11 ± 7
		(9 ± 6/10 ± 7)	(14 ± 6/12 ± 5)	(11 ± 8/11 ± 6)
sBP (mmHg)	130 ± 10	132 ± 18	145 ± 18*	157 ± 22*†
	(132 ± 11/128 ± 10)	(125 ± 14/135 ± 20)	(141 ± 15/147 ± 16)	(161 ± 20/150 ± 18)
dBP (mmHg)	70 ± 8	74 ± 9	80 ± 7*	80 ± 10*
	(70 ± 6/71 ± 5)	(72 ± 7/75 ± 4)	(77 ± 8/82 ± 7)	(79 ± 7/82 ± 11)
On insulin (%)		72	63	58
Insulin dose (IU · kg^{-1} · day^{-1})		0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
Creatinine (μM)	90.1 ± 5.2	91.2 ± 4.7	90.3 ± 4.2	92.3 ± 3.5
UAE (mg/24 h) mean (range)			59 (30–239)	644 (344–1200)
HbA_{1c} (%)		7.6 ± 1.1	7.9 ± 0.9	7.3 ± 1.1
		(7.7 ± 1.0/7.6 ± 1.0)	(8.0 ± 1.1/7.7 ± 1.0)	(7.1 ± 1.3/7.4 ± 0.9)
Retinopathy *n* (%)		11 (30)	6 (54)	7 (100)
		(5/6)	(3/3)	(3/4)
Neuropathy *n* (%)		9 (24)	2 (18)	3 (42)
		(4/5)	(2/0)	(2/1)
Macroangiopathy *n* (%)		3 (8)	2 (18)	2 (28)
		(3/0)	(1/1)	(1/1)
Smokers *n* (%)	7 (13)	5 (13)	2 (18)	1 (14)
	(5/2)	(4/1)	(2/0)	(1/0)

Data are means ± SD. Results for age, BMI, diabetes duration, sBP, dBP, and HbA_{1c} of men and women, respectively, indicated in parenthesis.
*$P < 0.05$ compared with control subjects.
†$P < 0.05$ compared with normoalbuminuric patients.

women. On the other hand, no significant differences were observed in cholesterol, TGs, and protein concentrations between normoalbuminuric and microalbuminuric patients. Patients with clinical albuminuria (344–1,200 mg/24 h) showed a significant increase in levels of VLDL ($P < 0.01$), IDL ($P < 0.01$), LDL ($P < 0.05$), and HDL TGs ($P < 0.01$) compared with normoalbuminuric and microalbuminuric patients. In these macroalbuminuric patients, IDL concentration increased significantly. HDL cholesterol was slightly decreased in microalbuminuric patients and, to a greater extent, in macroalbuminuric patients ($P = 0.06$). The most frequent apoE phenotypes in all diabetic patients were distributed as follows: E 3/3 (60%); E 3/2 (12%); and E 4/3 (19%). This distribution did not differ from that of control subjects: E 3/3 (70%); E 3/2 (13%); and E 4/3 (13%). According to the different apoE phenotypes, lipids and lipoprotein concentrations in patients showed the same trends as seen in control subjects. Serum Lp(a) levels did not differ between control subjects and normoalbuminuric patients. However, patients with micro- and macroalbuminuria showed a trend toward increased Lp(a) levels (Table 2).

Using $\log_{10}$ UAE as a continuous variable, multiple regression analysis showed a significant correlation between $\log_{10}$ UAE and serum TGs ($r = 0.56$), VLDL ($r = 0.55$), IDL ($r = 0.52$), LDL ($r = 0.54$), and HDL TGs ($r = 0.52$) but not with HbA_{1c}, cholesterol concentrations, or the other clinical variables. Because the univariate correlation between serum TGs and VLDL, IDL, LDL, and HDL TGs was extremely high ($r > 0.88$), serum TGs were used for the graphic linear regression plot (Fig. 1).

CONCLUSIONS— Compositional abnormalities in lipoprotein classes, in-

Table 2—*Lipoprotein profile in type II diabetic patients, classified according to UAE levels, compared with control subjects*

		Diabetic patients		
	Control subjects	Normoalbuminuric (<30 mg/24 h)	Microalbuminuric (30–300 mg/24 h)	Macroalbuminuric (>300 mg/24 h)
n	55	37	11	7
Serum cholesterol (mM)	5.40 ± 1.21	5.84 ± 1.63	5.65 ± 1.52	6.50 ± 1.71
	(5.31 ± 1.0/5.90 ± 1.4)	(5.75 ± 1.6/5.86 ± 1.6)	(5.64 ± 1.7/5.66 ± 1.3)	(6.40 ± 2.1/6.91 ± 1.2)
Serum TGs (mM)	1.22 ± 0.40	1.37 ± 0.72	1.48 ± 0.29	2.46 ± 1.10*†
	(1.21 ± 0.5/1.22 ± 0.4)	(1.26 ± 0.6/1.41 ± 0.7)	(1.63 ± 0.6/1.44 ± 0.3)	(2.15 ± 1.2/2.58 ± 1.5)
Serum Lp(a) (g/L)	0.12 ± 0.12	0.12 ± 0.11	0.17 ± 0.13	0.23 ± 0.1
	(0.13 ± 0.1/0.12 ± 0.1)	(0.12 ± 0.1/0.12 ± 0.1)	(0.17 ± 0.1/0.16 ± 0.1)	(0.24 ± 0.1/0.22 ± 0.1)
VLDL				
Cholesterol (mM)	0.41 ± 0.40	0.25 ± 0.13‡	0.28 ± 0.19‡	0.61 ± 0.65
	(0.35 ± 0.2/0.52 ± 0.5)	(0.23 ± 0.1/0.26 ± 0.1)	(0.27 ± 0.1/0.28 ± 0.2)	(0.49 ± 0.5/0.80 ± 0.6)
TGs (mM)	0.55 ± 0.34	0.52 ± 0.47	0.58 ± 0.22	1.08 ± 0.65*†
	(0.57 ± 0.3/0.45 ± 0.3)	(0.40 ± 0.3/0.59 ± 0.4)	(0.59 ± 0.2/0.57 ± 0.1)	(0.90 ± 0.5/1.20 ± 0.6)
Proteins (g/L)	0.13 ± 0.11	0.17 ± 0.14	0.23 ± 0.21	0.29 ± 0.12
	(0.10 ± 0.07/0.15 ± 0.12)	(0.11 ± 0.08/0.18 ± 0.15)	(0.23 ± 0.12/0.24 ± 0.12)	(0.21 ± 0.12/0.31 ± 0.19)
IDL				
Cholesterol (mM)	0.19 ± 0.12	0.22 ± 0.15	0.16 ± 0.03	0.39 ± 0.32§†
	(0.19 ± 0.1/0.19 ± 0.1)	(0.21 ± 0.1/0.23 ± 0.1)	(0.16 ± 0.1/0.16 ± 0.1)	(0.30 ± 0.3/0.43 ± 0.3)
TGs (mM)	0.15 ± 0.11	0.23 ± 0.17§	0.22 ± 0.14*	0.49 ± 0.29*†
	(0.13 ± 0.1/0.18 ± 0.1)	(0.19 ± 0.2/0.27 ± 0.1)	(0.23 ± 0.1/0.22 ± 0.1)	(0.42 ± 0.2/0.55 ± 0.4)
Proteins (g/L)	0.06 ± 0.05	0.09 ± 0.09	0.07 ± 0.03	0.14 ± 0.09‡
	(0.05 ± 0.03/0.10 ± 0.07)	(0.10 ± 0.04/0.08 ± 0.05)	(0.07 ± 0.05/0.09 ± 0.07)	(0.14 ± 0.10/0.15 ± 0.09)
LDL				
Cholesterol (mM)	3.26 ± 0.86	3.28 ± 1.34	3.23 ± 1.18	3.63 ± 1.05
	(3.02 ± 0.7/3.80 ± 0.9)	(2.84 ± 1.1/3.42 ± 1.2)	(3.30 ± 1.2/3.19 ± 1.1)	(3.2 ± 0.9/4.0 ± 1.3)
TGs (mM)	0.20 ± 0.08	0.28 ± 0.11*	0.30 ± 0.10*	0.50 ± 0.22*‖
	(0.19 ± 0.1/0.22 ± 0.1)	(0.25 ± 0.1/0.31 ± 0.1)	(0.31 ± 0.1/0.29 ± 0.1)	(0.42 ± 0.2/0.55 ± 0.3)
Proteins (g/L)	0.52 ± 0.15	0.53 ± 0.14	0.59 ± 0.16	0.57 ± 0.16
	(0.50 ± 0.15/0.62 ± 0.17)	(0.50 ± 0.10/0.57 ± 0.11)	(0.58 ± 0.13/0.60 ± 0.19)	(0.54 ± 0.20/0.57 ± 0.15)
HDL				
Cholesterol (mM)	1.18 ± 0.37	1.28 ± 0.44	1.05 ± 0.21	0.97 ± 0.13
	(1.16 ± 0.3/1.27 ± 0.4)	(1.30 ± 0.6/1.24 ± 0.3)	(1.01 ± 0.2/1.10 ± 0.2)	(1.10 ± 0.2/0.90 ± 0.1)
TGs (mM)	0.07 ± 0.06	0.17 ± 0.07*	0.13 ± 0.04*	0.28 ± 0.14*†
	(0.06 ± 0.1/0.10 ± 0.1)	(0.11 ± 0.0/0.20 ± 0.1)	(0.11 ± 0.1/0.15 ± 0.1)	(0.24 ± 0.1/0.30 ± 0.1)
Proteins (g/L)	1.16 ± 0.21	1.22 ± 0.28	1.18 ± 0.11	1.10 ± 0.19
	(1.20 ± 0.11/1.14 ± 0.17)	(1.24 ± 0.20/1.20 ± 0.15)	(1.12 ± 0.23/1.20 ± 0.22)	(1.12 ± 0.22/1.09 ± 0.18)

Data are means ± SD. Results of men and women, respectively, indicated in parenthesis.
*$P < 0.001$ compared with control subjects.
†$P < 0.01$ compared with normoalbuminuric and microalbuminuric patients.
‡$P < 0.05$ compared with control subjects.
§$P < 0.01$ compared with control subjects.
‖$P < 0.05$ compared with normoalbuminuric and microalbuminuric patients.

cluding IDL and Lp(a), were studied in three groups of type II diabetic patients classified according to the evolution of diabetic nephropathy. Despite stable and acceptable metabolic control, normoalbuminuric diabetic patients showed increased TG levels in IDL, LDL, and HDL. This finding concurs with previous observations (23) and suggests impaired conversion from VLDL to LDL. On the other hand, no significant differences were observed in lipoprotein concentration between normoalbuminuric and microalbuminuric patients. Because of the small number of microalbuminuric patients, the power of this negative assertion is relatively low. However, in a previous report by Niskanen et al. (13),

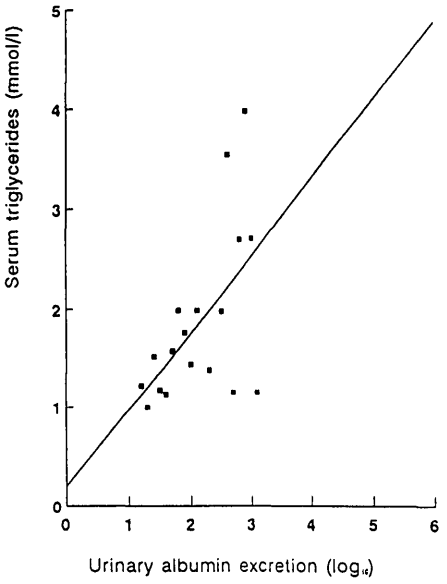

Figure 1—*Correlation between serum TGs and log_{10} UAE in type II diabetic patients with increased UAE (r = 0.56, P = 0.02). The 2.47 (log_{10} 300) on the axis is the threshold between micro- and macroalbuminuria.*

newly diagnosed type II diabetic patients with microalbuminuria showed no lipoprotein differences compared with normoalbuminuric patients. After 5 years of follow-up, patients with persistent albuminuria developed lipoprotein abnormalities such as decreased levels of HDL cholesterol, and TG enrichment in VLDL and LDL. However, the patient group included those with UAE between 35 and 500 mg/dl (i.e., micro- and macroalbuminuric patients), and lipoprotein fractions were not studied extensively (13).

In this study, patients with clinical albuminuria presented interesting lipoprotein alterations, mainly the accumulation of TG content in lipoproteins. Thus, patients with UAE of 344–1,200 mg/24 h showed significantly increased VLDL, IDL, LDL, and HDL TGs. These features suggest that the evolution of diabetic nephropathy aggravates the previously impaired VLDL catabolism. IDL concentration was significantly increased in macroalbuminuric patients, and cholesterol content in the remaining fractions also was slightly increased in these patients. These results emphasize IDL abnormalities in diabetic patients with nephropathy. IDL is an important atherogenic factor for coronary artery disease (24,25), stroke (26), and peripheral vascular disease (27), which are sites of atherosclerosis common in diabetic patients. In this study, HDL-cholesterol concentration was slightly decreased in the microalbuminuric group and in a more remarkable degree in patients with clinical albuminuria. The pathogenesis of this decreased HDL-cholesterol concentration is not well known. Glomerular loss of small-sized particles, such as albumin and HDL, has been postulated as the cause (28), but the well-known inverse correlation between HDL cholesterol and TGs could explain, at least in part, the decreased HDL-cholesterol concentration.

Previous studies (13) suggested that microalbuminuria predicts the appearance of lipid abnormalities in the subsequent evolution of diabetic nephropathy. Furthermore, Mattock et al. (12) found by univariate analysis a significant correlation between serum and VLDL TGs and UAE in type II diabetic patients. In our study, serum TGs and TG content in lipoprotein fractions correlated strongly with log_{10} UAE, even with normal TG levels. This suggests that the more albumin is lost in urine, the greater the TG enrichment in lipoproteins will be. However, it is not clear whether one is the cause of the other or whether both are independent manifestations of a primary event. Hypertension has been suggested (12) as the common factor linking UAE and CVD. Our results concur with this opinion, because BP in the albuminuric patients was significantly raised.

In this study, serum Lp(a) levels did not differ between control subjects and normoalbuminuric diabetic patients. Since Lp(a) levels seem to increase in diabetic patients with poor metabolic control (29), the acceptable and stable metabolic control in our patients may account for the lack of differences. Interestingly, patients with diabetic nephropathy tended to have higher mean Lp(a) concentrations. The lack of statistical significance could be explained by the wide interindividual variation of Lp(a) levels (30). Nevertheless, elevated Lp(a) concentrations in diabetic patients with increased UAE constitute an additional risk factor for atherosclerosis in patients with nephropathy.

We conclude that type II diabetic patients exhibit lipoprotein abnormalities that are more marked in those with diabetic nephropathy and increased UAE and that could play an important role in the excess of CVD in this patient population.

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