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Raised serum apolipoprotein (a) in active diabetic retinopathy

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Summary. Progressive capillary occlusion often leads to severe retinopathy within 15–20 years of the onset of Type 1 (insulin-dependent) diabetes mellitus. Lipoprotein (a), a complex formed by apolipoprotein (a), apo B-100 and lipids, is considered an independent, genetically determined, predictor of cardiovascular disease. It may have antifibrinolytic properties in view of its similarity to plasminogen. To test the hypothesis that circulating lipoprotein (a) is associated with the process that leads to clinically active diabetic retinopathy, we measured the circulating levels of apolipoprotein (a) (which are strictly correlated with those of lipoprotein (a)) in two groups of patients with Type 1 diabetes of at least 15 years duration: 25 with active retinopathy and 27 without clinically detectable retinal lesions. Thirty-eight healthy subjects of the same age and sex served as controls. Serum apolipoprotein (a) was higher in the patients with active retinopathy (36(2–193) U/dl, geometric mean and range) than in those without clinically detectable retinal lesion (17(1–160)) and the control subjects (14(0–115)), $p < 0.01$ in both cases. The distribution of apolipoprotein (a) levels was skewed to the left, as expected, in the patients without clinically evident retinal lesions and the control groups, but there was a bimodal trend of distribution among those with active retinopathy. The levels of glycated haemoglobin were similar in the two groups of diabetic patients, and no significant differences were found for total and HDL cholesterol, triglycerides or apolipoproteins A1 and B between them and the control subjects. These preliminary results suggest that serum apolipoprotein (a) is elevated in patients with active retinopathy. The role of this lipoprotein as a predictor or a pathogenic effector of diabetic retinopathy, or both deserves further investigation.

Key words: Lipoprotein (a), Type 1 (insulin-dependent) diabetes mellitus, diabetic retinopathy.

The prevalence of retinopathy of any severity is above 90% within 15 years of the onset of Type 1 (insulin-dependent) diabetes mellitus and proliferative retinopathy, the commonest cause of blindiness in Type 1 diabetes, increases from 0% during the first 5 years after diagnosis to 25% after 15 years and 56% after 20 years of diabetes duration [1]. Severe retinopathy is the consequence of progressive capillary occlusion, leading to large areas of retinal ischaemia which may stimulate new vessel formation [2]. The causes of such capillary occlusions have not been identified. No clear relationship has been established between metabolic control and the development of severe retinopathy. Endothelial damage due to metabolic disturbance or increased blood flow, or both may result in reduced fibrinolytic and antithrombin activity of the vessel wall [2]. Genetic factors may also be involved, as suggested by the clinical observation that some patients do not develop retinopathy even after many years of diabetes [3].

Lipoprotein (a) (Lp(a)) is a plasma complex composed of apolipoprotein (a) (apo(a)) covalently linked to apo B-100 by disulphide bridges [4]. Its plasma levels are genetically determined but can be modified to a minor extent by environmental factors, including metabolic control in Type 1 diabetic patients [5]. High plasma Lp(a) has been shown to be an independent risk factor for atherogenesis and thromboembolytic events [6]. Due to its structural similarity to plasminogen, Lp(a) has been suggested to have anti-fibrinolytic properties because it may compete for the binding sites of plasminogen activator [6].

High plasma Lp(a) might play a role in the capillary occlusions leading to severe retinopathy. This work was aimed at verifying whether subjects with Type 1 diabetes of at least 15 years duration and no retinopathy (NR) differ in their levels of apo(a) (which are strictly correlated with circulating Lp(a)) from patients of similar age and duration of diabetes who suffer from clinically active retinopathy (AR).

Table 1. Clinical data, plasma apolipoprotein (a), lipids and apolipoproteins A1 and B of the two groups of Type 1 diabetic patients and the control subjects

	AR	NR	C
Number of subjects	25	27	38
Gender (male/female)	11/14	13/14	18/20
Age [years and (range)]	38 ± 2(21–58)	35 ± 2(21–56)	35 ± 2(21–58)
Diabetes duration [years (range)]	23 ± 4(15–47)	21 ± 1(15–28)	–
Insulin requirement (IU/day)	44 ± 12	37 ± 14	–
HbA_{1c} (%)	9.0 ± 0.5[a]	7.9 ± 0.3[a]	4.5 ± 0.4
Urea (mmol/l)	5.9 ± 0.3	5.7 ± 0.2	5.8 ± 2.5
Creatinine (μmol/l)	82 ± 7	80 ± 5	75 ± 3
SBP/DBP (mm Hg)	119 ± 2/82 ± 2	114 ± 1/78 ± 2	116 ± 2/79 ± 2
Microalbuminuria (mg/24 h)	46 ± 15(2–200)[a]	29 ± 9(5–120)[a]	5 ± 6(0–20)
Macroalbumuria (n)	4	–	–
apo(a) (U/dl)	36(2–193)[b]	17(1–160)	14(0–115)
Cholesterol (mmol/l)	4.5 ± 0.2	4.6 ± 0.2	4.5 ± 0.2
CHOL-HDL (mmol/l)	1.2 ± 0.1	1.4 ± 0.08	1.4 ± 0.08
Triglycerides (mmol/l)	0.98 ± 0.1	0.77 ± 0.1	0.81 ± 0.1
Apo A1 (mmol/l)	$4.8 \times 10^{-2} \pm 3 \times 10^{-3}$	$4.5 \times 10^{-2} \pm 2 \times 10^{-3}$	$5 \times 10^{-2} \pm 2 \times 10^{-3}$
Apo B (mmol/l)	$2 \times 10^{-3} \pm 1.8 \times 10^{-4}$	$1.5 \times 10^{-3} \pm 7 \times 10^{-5}$	$1.8 \times 10^{-3} \pm 1.1 \times 10^{-4}$

Data are means ± SEM, apart from Lp(a) which is expressed as geometric mean and (range). [a] $p < 0.01$ vs C, [b] $p < 0.01$ vs NR and C. AR, Active retinopathy; NR, no clinical detectable retinal lesion; C, control subjects. SBP/DBP, systolic/diastolic blood pressure

Patients and methods

Twenty-five patients with Type 1 diabetes and AR, 27 Type 1 diabetic patients with NR and 38 non-diabetic control subjects were studied. Their clinical details are reported in Table 1. Subjects gave their informed consent to the study protocol, previously approved by the local ethical committee. AR was defined as either the recent appearance of new vessels or more than one of the following: multiple haemorrhages, multiple cotton-wool spots, venous irregularities, widespread capillary closure with leakage of dye on fluorescein angiography [2]. NR was determined by ophthalmoscopy, 7-field stereo colour photography with or without fluorescein angiography. All the patients had developed diabetes before the age of 30 years and had been continuously on insulin therapy for at least 15 years, with the possible exception of the first year of diabetes. They all had normal serum urea and creatinine, were normotensive and had similar age, sex and glycated haemoglobin (Table 1). None was receiving any medication which may have altered serum lipids, apart from insulin. A control group of 38 non-diabetic healthy individuals (C) of the same age and sex distribution was studied. These were either hospital staff, medical students, or patients' spouses. After overnight fasting, blood samples for blood glucose, glycated haemoglobin, plasma lipids and apo(a) were obtained. Plasma total and HDL-cholesterol, triglycerides, apolipoproteins A_1 and B were measured by established techniques [7]. Apo(a) was determined by radioimmunoassay using a commercial kit (Pharmacia, Uppsala, Sweden). The intra- and interassay coefficients of variation of the method were 6% and 8% respectively. Glycated haemoglobin (HbA_{1c}) was measured by HPLC (Daiichi, Kyoto, Japan) with automatic exclusion of anomalous haemoglobins. Microalbuminuria was determined on three different occasions (on 24-h urine collections) by radioimmunoassay (Pharmacia).

Statistical analysis

Data are expressed as means ± SEM or geometric means and ranges for data not normally distributed. Statistical analysis was carried out using non-parametrical tests (Wilcoxon's signed rank sum test).

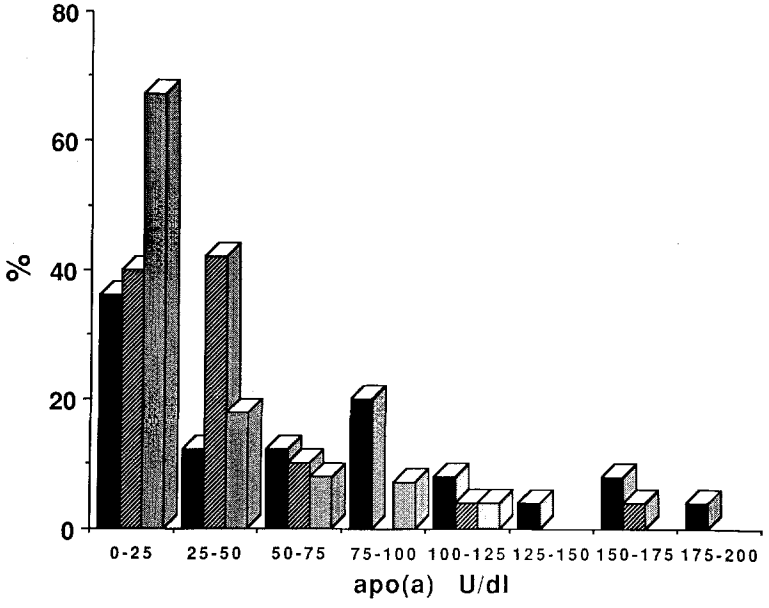

Fig. 1. Frequency distribution of circulating apolipoprotein (a) (apo(a)) in Type 1 (insulin-dependent) diabetic patients with active retinopathy ($n = 25$, ■), without active retinopathy ($n = 27$, ▨) and in the control subjects ($n = 38$, ▩)

Results

The results are summarized in Table 1 and Figure 1. HbA_{1c} was higher in the patients than in the control subjects, but did not differ between the AR and NR groups. Plasma lipids were similar in the three groups, with only apo(a) significantly higher in the AR group than in the NR group and C group ($p < 0.01$ in both cases). Figure 1 shows the frequency distributions of plasma apo(a) in the three groups: this was skewed to the left in the control subjects and NR patients, but appeared to have a bimodal distribution pattern within the AR group. No significant correlation was found between HbA_{1c} and apo(a) within the groups.

Macroalbuminuria was present in four patients in the AR group; in these patients the circulating levels of apo(a) were (in U/dl) 159, 93, 40, and 17, respectively. No macroalbuminuria was evident in any other patient or control subject. There were no significant differences for microalbuminuria between the AR and NR groups, both being significantly different from the control group (Table 1). No significant correlation between apo(a) and microalbuminuria was present among the patients with either AR or NR (data not shown).

Discussion

These results suggest that patients with Type 1 diabetes who develop retinopathy of sufficient severity to require laser treatment have higher circulating levels of apo(a) than other patients with similar duration of diabetes, metabolic control and serum lipids, but no clinically detectable retinal lesions. The latter group did not differ from a control population of the same age and sex distribution. Figure 1 shows that the frequency distribution of apo(a) levels is skewed to the left in the control and NR groups, which is in accordance with all previous reports in the literature [4], but apparently bimodal among the AR. This suggests that the latter may include two subpopulations, one with normal and the other with elevated plasma apo(a). Since the levels of this apolipoprotein are genetically determined, normal values do not exclude the risk of developing severe retinopathy, but high levels may be a predictor. Indeed, high apo(a) is an independent risk factor for cardiovascular disease [6], which in turn is increased among patients with proliferative retinopathy [2].

Increased circulating levels of apo(a) were reported by some authors in patients with micro- and macroalbuminuria [8], which is also a risk factor for large vessel disease in Type 1 diabetes [9]. However, that study [8] indicated that Type 1 diabetic patients with AR who needed laser treatment had higher levels of Lp(a) than those who did not. In a previous work carried out in this laboratory, we were unable to find any significant difference in circulating apo(a) between Type 1 diabetic patients with and without microalbuminuria, when patients with diabetic retinopathy of any grade were carefully excluded [10]. In that paper we expressed circulating Lp(a) as arithmetic instead of geometric means, so that the values of the control subjects were only apparently higher than in those described here.

High plasma levels of apo(a) may facilitate small vessel occlusion, due to the alleged antifibrinolytic properties of this circulating complex [6]. Capillary occlusion, on the other hand, is a feature of diabetic retinopathy but not nephropathy, at least at the stage of microalbuminuria [2]. Although the two complications may often co-exist, it is tempting to speculate that high circulating levels of Lp(a) may favour occlusion of the retinal small vessels.

In conclusion, these preliminary results suggest that apo(a), and consequently Lp(a), may play a role in the development of severe retinopathy but further prospective studies of larger populations are warranted to define its significance as a predictor and/or an effector of this complication of diabetes.

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