Endothelial Dysfunction Is Correlated With Microalbuminuria in Children With Short-Duration Type 1 Diabetes

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Patients with diabetes have increased risk of developing atherosclerotic diseases (1). In type 1 diabetes, vascular complications are more frequently identified after the 5th year of the disease. Ultrasound assessment of endothelial function is a noninvasive method for detecting early structural and functional atherosclerotic process in the arterial wall. Impaired flow-mediated dilatation (FMD), an early marker of atherosclerosis, has been detected in children with family hypercholesterolemia (2) and diabetes (3). This study assessed the presence of endothelial dysfunction in children with type 1 diabetes and <5 years duration of the disease.

RESEARCH DESIGN AND METHODS

— This cross-sectional study included 18 randomly selected type 1 diabetic patients (13 boys) followed up at a public health assistance center, with disease duration of 2.9 ± 1.2 years (0.7–4.9 years) and without clinical evidence of vascular complications, and 14 healthy control subjects (7 boys) without chronic diseases or hypercholesterolemia, matched by age (±2 years) and BMI. Patients with retinopathy, hypertension, obesity, thyroid disease, and history of smoking were excluded. Laboratory data included fasting blood glucose, plasma lipids, HbA_{1c} (A1C), creatinine, TSH, and microalbuminuria.

After the subjects had been lying in supine position for 10 min in a stable-temperature room, the response to reactive hyperemia (FMD) was evaluated. The diameter of the brachial artery was measured in a longitudinal section (2–15 cm above the elbow) with a high-resolution vascular ultrasound. Reactive hyperemia was induced by occluding arterial blood by using a sphygmomanometer inflated to 100 mmHg above the systolic pressure. After 4 min, the cuff was released. The arterial flow velocity was measured by a pulsed Doppler signal at a 60-degree angle to the vessel during the resting scan and for 15 s after the cuff deflated. The artery was scanned for 30 s before and 90 s after cuff release. An experienced vascular ultrasonographer, blind to the patient's diagnosis, performed and analyzed all images recorded in a high-quality computer. An eletrocardiogram was recorded with the ultrasound images. Diameter changes were derived as percentage changes relative to the first scan. Baseline blood flow was estimated by multiplying the flow velocity integral by heart rate and the square of the radius of the artery. Reactive hyperemia was calculated as the maximum flow measured during the first 15 s after cuff deflation divided by flow during the rest.

Differences in the means were evaluated by Student's *t* test. The Spearman's correlation test was used when indicated. A P value <0.05 defined as statistical significance.

RESULTS

— The mean age was 13.4 ± 3.3 years (7–18 years) and 13.5 ± 3.5 years (6–18 years), respectively, for patients and control subjects ($P = 0.8$). BMI was similar in the two groups (19.1 ± 2.6 vs. 19.4 ± 0.7 kg/m^2, $P = 0.4$). In patients, age at diagnosis was 10.1 ± 3.9 years (2.5–16 years). Mean fasting blood glucose was 213.1 ± 128 mg/dl and A1C was 9.35 ± 2.1%. The lipid profile was within the normal range in both groups. None of the type 1 diabetic children were taking medications other than insulin. There was no significant difference in resting diameters of brachial artery (2.62 ± 0.42 vs. 2.7 ± 0.47 mm, $P = 0.59$) and arterial flow (223 ± 126 vs. 228 ± 88 ml/min, $P = 0.9$) in patients and healthy children, respectively. In the reactive hyperemia stage, no difference was observed between patients and control subjects for FMD (10.9 ± 2.0 vs. 11.2 ± 2.4%, $P = 0.34$) and percentage of increase in maximal blood flow (46.8 ± 39 vs. 47.6 ± 6.8%, $P = 0.9$).

Microalbuminuria was positive (>20 mg/24 h) in 12 of 15 evaluated patients. The percentage of flow increase in reactive hyperemia was inversely correlated with microalbuminuria ($r = -0.5$, $P = 0.049$) and positively with A1C ($r = 0.53$, $P = 0.02$) (Fig. 1). Reactive hyperemia was not correlated with lipid profile, glycemia, and duration of diabetes.

CONCLUSIONS

— The correlation between the timing of endothelial dysfunction and the duration of diabetes is not well established. Studies using ultrasound assessment showed that type 1 diabetic patients, whose diabetes duration varied to a large extent, may develop endothelial dysfunction within the first decade after its onset (3,4). In an animal

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Abbreviations: FMD, flow-mediated dilatation; NOS, nitric oxide synthase.

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

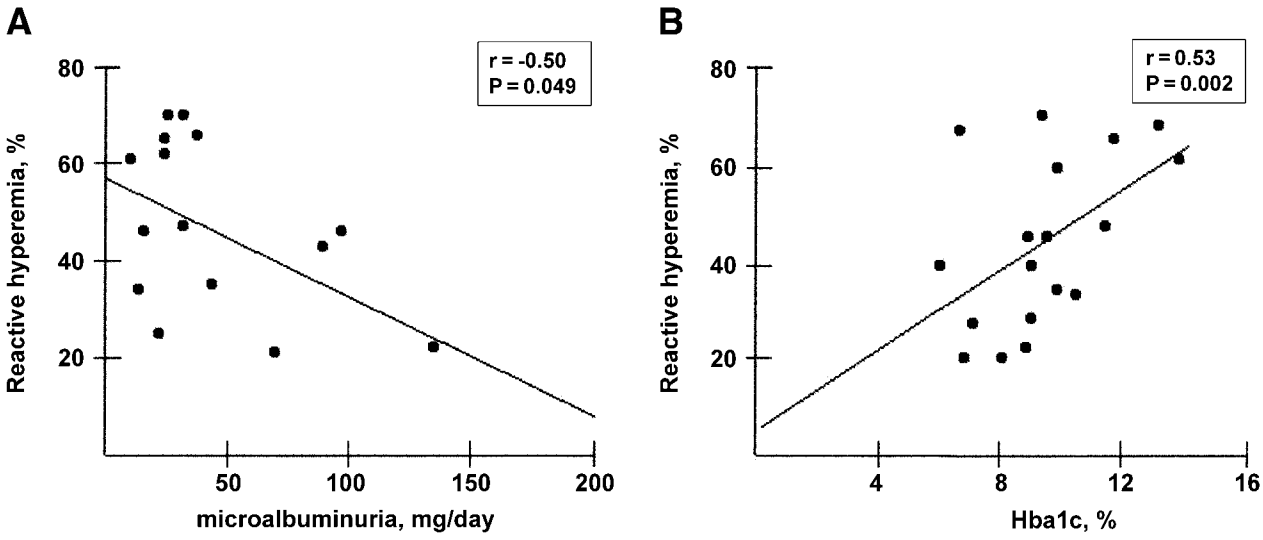

Figure 1—*Correlations between the percentage of flow increase in reactive hyperemia and microalbuminuria* (A)*, and reactive hyperemia and A1C* (B).

model of induced insulin-dependent diabetes, acute endothelium-mediated vasodilatation was not impaired in very short duration of disease (5). This study, including only patients with <5 years after diagnosis of type 1 diabetes and a satisfactory lipid profile, demonstrated no impairment in endothelial function. Thus, the shorter duration of disease and the absence of other risk factors like dyslipidemia may explain our results.

The association between endothelial dysfunction and type 1 diabetes with and without microalbuminuria has been described (6,7). In this study, the microalbuminuria excretion was inversely correlated with the increase in brachial artery flow during reactive hyperemia. Although there was no impaired endothelial function, this finding emphasizes the role of microalbuminuria as a very early marker of vascular disease. Therefore, the close linkage between microalbuminuria and endothelial dysfunction may explain the association between microalbuminuria and the development of extrarenal complications in diabetes (8).

The endothelium-dependent vasodilatation during reactive hyperemia is predominantly modulated by local release of nitric oxide (NO) (4). We found a positive correlation between A1C and the percentage of increase in maximal blood flow during reactive hyperemia ($r = 0.53$, $P = 0.02$). Long-term hyperglycemia increases the activity of NO synthase (NOS) in rat heart (9). Others clearly demonstrated that the synthesis and release of NO are not diminished after exposure to high concentrations of glucose (10). Recently, an experimental study defined a marked perturbation of NOS production and NOS III function in diabetes (11). In healthy subjects, oral glucose loading causes a transient decrease of FMD (12). However, noncomplicated type 1 diabetes is associated with increased microvascular blood flow (13). As A1C represents glycemic control and chronic hyperglycemia may modify the action of endothelial NOS similarly in human vessels, the "apparent normality" of the endothelium-dependent vasodilatation might represent an adaptative phenomenon.

These findings may have implications in the timing of endothelial dysfunction occurrence in type 1 diabetes. At what stage of the disease does endothelial dysfunction become manifest itself? Endothelial function was not found to be altered in young type 1 diabetic patients and short disease duration (<5 years), but the inverse association between the percentage of increase in brachial arterial flow and microalbuminuria may suggest an early alteration in peripheral and renal vascular dynamics.

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