Early Microvascular Dysfunction in Healthy Normal-Weight Males With Heredity for Type 2 Diabetes

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The pathogenesis behind diabetic microangiopathy is complex; both genetic (1–3) and metabolic factors (4–6) are clearly of importance. Recently, it has been demonstrated that not only patients with diabetes but also healthy individuals at risk for diabetes have functional vascular disturbances (7). These findings suggest that factors other than hyperglycemia are of importance for microvascular dysfunction. The aim of the present study was to investigate whether genetic factors (heredity for type 2 diabetes) are associated with disturbances in nutritive skin capillary circulation, nonnutritive skin microcirculation, and/or brachial macrocirculation.

RESEARCH DESIGN AND METHODS

— Subjects were from the Stockholm Diabetes Prevention Program, a population-based study (8). Normal-weight men who were free of medication, who were nonsmokers, and who had normal oral glucose tolerance tests and insulin sensitivity as assessed by a hyperinsulinemic-euglycemic clamp (9) were investigated. Ten men with heredity for type 2 diabetes were matched for age and BMI with 10 men without heredity. Heredity for type 2 diabetes was defined as known diabetes in at least two second-degree relatives (grandparent, uncle, or aunt) or in at least one first-degree relative in the generation of the proband (sister or brother) or the parents (8).

The investigations were performed in the morning after an overnight fast. The vascular investigations were performed after 20 min of supine rest at a room temperature of 22–24°C.

Nonnutritive skin microcirculation of the left forearm was studied with laser Doppler perfusion imaging before and after iontophoretic application of acetylcholine (Ach; endothelium dependent) and sodium nitroprusside (SNP; nonendothelium dependent) (10,11). An electrode chamber (Perilont 382; Perimed, Järfälla, Sweden) was filled with a small volume (~250 μl) of either Ach 1% (55 mmol/l) or SNP 1% (33 mmol/l) and attached to the volar side of the forearm. A battery-powered iontophoresis controller (Perimed) provided a direct current (0.2 mA for 60 s) for drug iontophoresis. The changes in skin blood cell flux before and after iontophoresis were studied by laser Doppler perfusion imaging (Lisca PIM II; Lisca Development, Linköping, Sweden). The coefficients of variation (CVs) for peak microcirculatory flux after iontophoresis of Ach and SNP were 21 and 19%, respectively (11).

Nailfold capillaries of the fourth finger of the left hand were visualized (12), and the capillary blood cell velocity (CBV) was determined by a computerized, videophotometric, cross-correlation technique (Capiflow, Stockholm, Sweden). Resting CBV was measured in suitable capillaries with good contrast and visible signals (12–14), and peak CBV (in millimeters per second) and time-to-peak CBV (in seconds) were measured following release of 1-min arterial occlusion of the proximal phalanx of the finger with a cuff pressure of 200 mmHg (13,15–17). For reproducibility see Jörneskog and colleagues (13,15).

Endothelial function of macrocirculation was studied by ultrasound during flow-mediated vasodilatation (FMD) of the brachial artery (18,19). The inner diameter of the brachial artery was determined before and 1 min following forearm ischemia using an 8-MHz transducer. Nonendothelium-dependent dilatation was determined 4 min after administration of sublingual nitroglycerine (0.4 mg). The mean variation of FMD was 1.8 ± 1.0%, and the CV was 26%.

Data are given as means ± SD. The Mann-Whitney *U* test was used to test differences between groups. Microcirculatory variables measured during iontophoresis were evaluated with two-factor repeated-measures ANOVA. A value of $P < 0.05$ was considered statistically significant.

RESULTS

— There were no significant differences in age (with heredity, 53 ± 5.0 vs. without heredity, 51 ± 3.8 years), waist-to-hip ratio (0.86 ± 0.04 vs. 0.85 ±

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Abbreviations: Ach, acetylcholine; CBV, capillary blood cell velocity; FMD, flow-mediated vasodilatation; SNP, sodium nitroprusside.

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

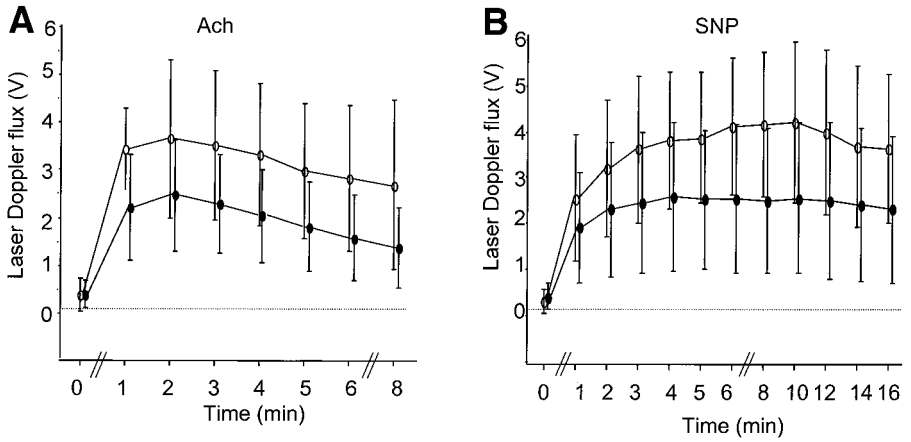

Figure 1—*Responses to Ach* (A) *and SNP* (B) *in nonnutritive skin microcirculation of men with* (●) *and without* (○) *heredity for type 2 diabetes. Values are means ± SD for* n = *10. The overall responses to Ach and SNP, respectively, were lower* (P = *0.03) in subjects with versus without diabetes heredity.*

0.04), BMI (22.2 ± 2.0 vs. 23.0 ± 2.7 kg/m^2), blood pressure, inflammatory variables, or lipid profiles between the groups.

Baseline values of nonnutritive skin microcirculation did not differ (with heredity, 0.35 ± 0.29 vs. without heredity, 0.37 ± 0.35 V). The overall response to Ach was smaller in the group with versus without diabetes heredity ($P < 0.03$) (Fig. 1). The maximal microcirculatory increase (maximal laser doppler flux minus baseline laser doppler flux) after stimulation with Ach was lower ($P < 0.05$) in the group with (2.27 ± 1.06 V) than in the group without (3.91 ± 2.15 V) diabetes heredity. Similarly, the overall vasodilatory response to SNP was lower ($P < 0.03$) in the group with versus without diabetes heredity (Fig. 1), and the maximal microcirculatory increase was reduced ($P = 0.04$) in those with (2.70 ± 1.55 V) versus without diabetes heredity (4.43 ± 1.85 V).

Nutritive skin capillary circulation, as measured by resting CBV, peak CBV, and time-to-peak CBV, did not differ between the groups. No significant differences were found in brachial artery peak flow velocity FMD or nitroglycerine-induced dilatation between the groups.

CONCLUSIONS — The studies of micro- and macrovascular function in healthy normal-weight middle-aged men showed that the subjects with diabetes heredity exhibited impaired microvascular responses to both endothelium- and nonendothelium–dependent stimuli in nonnutritive skin microcirculation whereas no disturbances could be detected in the nutritive capillary circulation or in the macrocirculation (brachial artery). The functional disturbances in nonnutritive skin microcirculation were demonstrated despite normal body dimensions, normal glucose tolerance, and normal insulin sensitivity. Nonnutritive microcirculation includes arterioli and arteriovenous connections, which have different regulation and morphology compared with capillaries and macrocirculation. Alternatively, the small sample size of our study may have precluded detection of disturbances in macrovascular reactivity. In summary, genetic factors may contribute to the early functional microvascular abnormalites in the development of type 2 diabetes and/or cardiovascular disease.

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