OBSERVATIONS

Impaired Vascular Reactivity in Healthy First-Degree Relatives of Subjects With Type 2 Diabetes Is Related to Metabolic Factors

Several studies have suggested that vascular changes precede the development of metabolic disorders in first-degree relatives of subjects with type 2 diabetes, indicating that being a first-degree relative of a subject with type 2 diabetes is a risk per se for vascular dysfunction (1–3). However, these studies have failed to control for relevant metabolic and inflammatory variables that are usually altered in first-degree relatives of subjects with type 2 diabetes and are known to impair vascular reactivity (4).

To investigate the hypothesis that vascular reactivity in first-degree relatives of subjects with type 2 diabetes without metabolic disorders is similar to that in a control group without history of type 2 diabetes, 42 first-degree relatives of subjects with type 2 diabetes (79% women; mean ± SD age 33 ± 9 years) and 45 age- and sex-matched control subjects (78% women; age 34 ± 9 years) were recruited. Vascular reactivity was assessed by reactive hyperemia measured by forearm venous occlusion plethysmography.

Although all values for blood analysis were within normal limits, insulin resistance measured by homeostasis model assessment and plasma glucose levels were higher in the first-degree relatives of subjects with type 2 diabetes than in the control group ($P < 0.05$). Fasting insulin, cholesterol, LDL cholesterol, and leptin showed a trend to be higher in the first-degree relatives of subjects with type 2 diabetes than in the control group. The first-degree relatives of subjects with type 2 diabetes exhibited, at basal conditions, similar forearm blood flow and forearm vascular conductance compared with those in the control group. During reactive hyperemia, forearm blood flow was similar between the groups, but vascular conductance was lower in the first-degree relatives of subjects with type 2 diabetes than in the control group (31.32 ± 8.36 arbitrary units [AU] vs. 34.26 ± 6.72 AU, respectively; $P = 0.037$).

Multiple regression analysis using conductance during reactive hyperemia as the dependent variable yielded only fasting insulin and waist-to-hip ratio as independent predictors (model $r^2 = 0.22$; $P = 0.006$). Because the first-degree relatives of subjects with type 2 diabetes had higher values for several variables known to alter vascular reactivity, the data were reanalyzed using an ANCOVA adjusted for variables that were different between the groups. This analysis yielded no differences between the groups in any of the forearm blood flow measurements ($P = 0.161$). These results were confirmed by another analysis, in which subjects exhibiting insulin resistance and/or inflammation were excluded from both groups in order to match them. This approach revealed no differences for any of the forearm blood flow variables ($P > 0.05$), indicating comparable vascular function between the groups when subjects with metabolic or inflammatory changes are excluded.

In the present study, higher values of metabolic variables were more common in the first-degree relatives of subjects with type 2 diabetes, as found in previous publications (1–3,5), and considering that these factors reduce vascular reactivity (4), it is not surprising that vascular reactivity was diminished in the first-degree relatives of subjects with type 2 diabetes initially studied. The subsequent analysis leads to the main finding of the present study that in the absence of difference of metabolic variables, vascular reactivity in the first-degree relatives of subjects with type 2 diabetes is similar to that in the control group.

Because metabolic disorders are known to impair vascular reactivity and these alterations are an early step in the atherosclerotic process, the present study may have important implications for identifying populations that can derive substantial benefits from early lifestyle modifications. In the absence of metabolic disorders, vascular reactivity in the first-degree relatives of subjects with type 2 diabetes is similar to that in the control group. Therefore, family history of type 2 diabetes seems to be not a risk factor per se for vascular reactivity but, rather, a consequence of metabolic disorders that are more common in these subjects.

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