Increased Arterial Stiffness in Normoglycemic Normotensive Offspring of Type 2 Diabetic Parents

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Abstract—Diabetes is associated with a reduction of arterial distensibility. Limited information exists regarding whether or how early this appears in the course of the disease. We studied 54 normoglycemic, normotensive, healthy offspring of 2 parents with type 2 diabetes mellitus and 55 age- and sex-matched healthy control subjects. Carotid diastolic diameter and systodiastolic change were measured by echo tracking (Wall Track System) and wall thickness by echocolor Doppler (Sonos 5500, Philips). Pulse pressure was measured by a semiautomatic device positioned on the brachial artery and arterial distensibility calculated by Reneman formula. Blood pressure, blood glucose, glycohemoglobin, and insulin sensitivity (homeostasis model assessment index) were normal or only slightly elevated and by and large similar in the 2 groups. Compared with control subjects, offspring of diabetic parents showed similar carotid diameters at diastole and a reduced increase in carotid diameter at systole (−16%), a reduced carotid artery distensibility (−30%), and an increased pulse pressure (+21.8%), all differences being statistically significant (P<0.05) and persisting in subgroups with elevated or normal body mass index values (<25 and ≥25 kg/m²). Carotid artery wall thickness was not different between the 2 groups. Thus, subjects with predisposition to diabetes show carotid artery stiffening even in the absence of blood pressure alterations, as well as substantial alterations of glucose metabolism, body mass index, and changes in carotid wall thickness. This suggests that, in diabetes, alterations in arterial mechanical properties represent an early phenomenon, which may occur in the absence of metabolic and blood pressure alterations.

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Key Words: diabetes mellitus ■ arterial distensibility ■ atherosclerosis ■ blood pressure

Diabetes mellitus is associated with an increase in large artery wall thickness and a reduction in large artery distensibility.1–10 These changes are not late consequences of the disease, because recent studies have shown that arterial distensibility and wall thickness are altered also in subjects with glucose intolerance who do not have but are predisposed to diabetes11,12 and individuals aged <40 years with a type 1 diabetes not accompanied by microvascular or macrovascular complications.13

Except for a small study in which an increase in pulse wave velocity was reported in very young subjects with a familial background for diabetes,14 no information exists on arterial structure and function in normoglycemic subjects with a predisposition to type 2 diabetes. This is of clinical relevance, because arterial stiffening and thickening are independent predictors of an increase in cardiovascular risk.15,16 Furthermore, arterial stiffening has been associated with increased atherogenesis, because its occurrence enhances the traumatic effect of intravascular pressure on the endothelium, triggering the cascade of events that leads to atherosclerosis.17

The present study addressed the impact of a familial diabetic background on large artery function and structure by measuring carotid artery distensibility and wall thickness in a group of normoglycemic healthy offspring of 2 parents with type 2 diabetes mellitus, ie, nondiabetic subjects with a high probability of developing diabetes later in life.18

Materials and Methods

Subjects

We investigated a total of 109 subjects of either sex. Fifty-four subjects (16 males and 38 females; age: 37.8±0.8 years, mean±SE) were selected on a consecutive basis if the following were true: (1) their age was in the 30- to 45-year range; (2) both parents had a type 2 diabetes mellitus under treatment in the outpatient clinic of our hospital; (3) there was no evidence of clinical or subclinical atherosclerotic disease at history, physical examination and laboratory examinations such as a chest x-ray, a standard and an exercise ECG, or an echocardiogram and an echocolor-Doppler of the carotid arteries, the femoral arteries, and the abdominal aorta; (4) fasting blood glucose was <110 mg/dL; (5) there was no history or evidence of major noncardiovascular diseases; (6) blood pressure was <140/90 mm Hg; and (7) serum cholesterol was <200 mg/dL. The remaining 55 subjects (17 males and 38 females) were normotensive healthy individuals without diabetic parents in the age range of 30 to 40 years with a type 1 diabetes mellitus and 55 age- and sex-matched healthy control subjects. Carotid diastolic diameter and systodiastolic change were measured by echo tracking (Wall Track System) and wall thickness by echocolor Doppler (Sonos 5500, Philips). Pulse pressure was measured by a semiautomatic device positioned on the brachial artery and arterial distensibility calculated by Reneman formula. Blood pressure, blood glucose, glycohemoglobin, and insulin sensitivity (homeostasis model assessment index) were normal or only slightly elevated and by and large similar in the 2 groups. Compared with control subjects, offspring of diabetic parents showed similar carotid diameters at diastole and a reduced increase in carotid diameter at systole (−16%), a reduced carotid artery distensibility (−30%), and an increased pulse pressure (+21.8%), all differences being statistically significant (P<0.05) and persisting in subgroups with elevated or normal body mass index values (<25 and ≥25 kg/m²). Carotid artery wall thickness was not different between the 2 groups. Thus, subjects with predisposition to diabetes show carotid artery stiffening even in the absence of blood pressure alterations, as well as substantial alterations of glucose metabolism, body mass index, and changes in carotid wall thickness. This suggests that, in diabetes, alterations in arterial mechanical properties represent an early phenomenon, which may occur in the absence of metabolic and blood pressure alterations.
45 years (mean: 38.2±0.9 years) recruited among the administrative personnel of our hospital and used as control subjects. Five subjects in the group with diabetic parents and 7 subjects in the control group were smokers. Both offspring of diabetic parents and control subjects were further classified according to their body mass index (BMI), ie, <25 kg/m² or ≥25 kg/m². All of the subjects agreed to participate in the study after being informed of its nature and purpose. The ethics committees of the institutions involved approved the protocol of the study.

Carotid Artery Distensibility and Wall Thickness

With the subject supine and the neck in partial extension, the diameter and wall motion of the right common carotid artery (CA) were measured 2 cm below the carotid bifurcation by a B-mode mode echo-tracking device based on Doppler shift (Wall Track System, PIE Medical) and on a transducer operating at a frequency of 7.5 MHz.19,20 The transducer was manually oriented perpendicularly to the longitudinal axis of the vessel under B-mode guidance. After switching to A-mode, the backscattered echoes from the anterior and posterior CA walls were visualized on a screen, and the corresponding radiofrequency signal was tracked by electronic tracers to allow the digitalized signal of the internal diameter variations to be derived at 50 Hz. The spatial resolution was 300 μm.19 Blood pressure was measured from the brachial artery at the same time of the ultrasound evaluation via a semiautomatic device (Dinamap 1846 SX/SXP, Critikon), and CA distensibility was derived according to the following formula19:

\[
\text{Dist} = [(2 \Delta D \times D_d) + \Delta D^2]/\Delta P \times D_d^2
\]

where Dist was distensibility, D_d was the diastolic diameter of the vessel, \(\Delta D\) was the systodiastolic diameter change, and \(\Delta P\) was the corresponding pulse pressure.

CA intima-media wall thickness (IMT) was measured at a posterior wall site located 2 cm below bifurcation through an ultrasonographic device (Philips Sonos 5500). Measurements were obtained by first scanning the artery in B-mode, then freezing the digitized image in M-mode, and finally tracking the inner echoicogenic and the middle anechogenic layers.21

Measurements were made by 2 operators unaware of the subject’s clinical status. The within-operator and interoperator variability of CA diameter measurements at diastole (ie, the coefficient of variation of the mean values of 2 measurements performed at 2 different times) in our laboratory were 2.5% and 3.5%, respectively. The within-operator and interoperator variability for CA wall thickness were 3.0% and 4.0%, respectively.

Additional Measurements

Blood pressure was measured not only by the Dinamap device (see above) but also, with the patient supine, by a mercury sphygmomanometer, taking the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively. Heart rate was obtained by palpatory method over 30 seconds. Abdominal circumference was measured in centimeters with the subject in the standing position, and BMI was derived from the formula: weight (kilograms)/height (meters squared). Blood glucose, total serum cholesterol, high-density lipoprotein (HDL) serum cholesterol, and serum triglycerides were measured from a venous blood sample within the week preceding the study (see below). In both offspring of diabetic parents and in control subjects, glycohemoglobin and homeostasis model assessment (HOMA) index values (derived by the formula: fasting plasma insulin×fasting plasma glucose)22 were also measured. In our laboratory, normal glycohemoglobin and HOMA index values are <6% and <2.5 U, respectively.

Protocol and Data Analysis

Each patient was asked to come to the outpatient clinic of the San Gerardo Hospital in the afternoon, after a 24-hour abstinence from alcohol, caffeine consumption, and cigarette smoking, to undergo the evaluation of CA structure and function. The protocol of the study was as follows: (1) blood pressure was measured 3 times by a mercury sphygmomanometer with the patient in the sitting position; (2) the subject was placed in the supine position and fitted with the semiautomatic blood pressure measuring device on the brachial artery and the probe for CA evaluation on the neck; (3) five 6-second acquisitions of carotid diameter throughout the cardiac cycle were obtained during a 10-minute period together with semiautomatic blood pressure measurements; and (4) carotid IMT was measured by echocolor Doppler.

The 3 sphygmomanometric blood pressure values were averaged. CA diastolic diameter and distensibility were obtained by averaging the data derived from the five 6-second acquisition periods. Carotid IMT was measured on the screen image of the vessel over a 30-second period. Results from individual subjects were averaged. The statistical significance of the differences in mean values was assessed by 2-way ANOVA. The 2-tailed \(t\) test for unpaired observations was used to locate differences between control subjects and subjects with 2 diabetic parents, as well as between groups with higher or lower BMI. The Bonferroni correction was used when multiple comparisons were made. Data were also analyzed by the univariate regression of Spearman. A \(P<0.05\) was taken as the level of statistical significance. Throughout the text the symbol \(±\) refers to the SD (table) or the SE (figure) of the mean.

### Results

As shown in Table 1, abdominal circumference, BMI, and serum triglycerides, while being in the reference range, were significantly greater in subjects with 2 diabetic parents than in control subjects, whereas age, fasting blood glucose, and total and HDL serum cholesterol were similar in the 2 groups. Heart rate and systolic blood pressure also did not show between-group differences, whereas diastolic blood pressure was significantly lower in offspring of diabetic parents than in control subjects. Offspring of diabetic parents also showed normal glycohemoglobin and HOMA index values with no significant differences with respect to control subjects.

As shown in Figure 1, CA diameter at diastole was similar in the 2 groups. Compared with control subjects,
however, in offspring of diabetic parents, the increase in CA diameter with systole (CA distension) was less pronounced, with a reduction in calculated CA distensibility. Pulse pressure was significantly greater in the offspring of diabetic parents compared with control subjects, whereas carotid IMT was somewhat smaller in offspring of diabetic parents, the difference failing to reach statistical significance. There was no significant correlation between BMI and the baseline variables shown in Table 1 ($r$ always $<0.15$; $P$ not significant).

Table 2 shows the baseline values of offspring of diabetic parents and control subjects with a BMI $<$25 kg/m$^2$ and $\geq$25 kg/m$^2$. Most values did not differ significantly between the lower and higher BMI groups except for the abdominal circumference, which was less at the lower BMI both in the offspring of diabetic parents and in control, and the plasma glucose and HOMA index values, which were less at the lower BMI in the offspring of diabetic parents only. As shown in Figure 2, with 1 exception (pulse pressure in offspring of diabetic parents) CA diameter at diastole, CA

Table 2. Baseline, Demographic, Metabolic, and Hemodynamic Values in Offspring of Diabetic Parents and Control Subjects Divided According to a BMI $<$25 kg/m$^2$ or $\geq$25 kg/m$^2$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Offspring of Diabetic Parents</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI $&lt;$25</td>
<td>BMI $\geq$25</td>
</tr>
<tr>
<td>No. (male)</td>
<td>18 (6)</td>
<td>36 (10)</td>
</tr>
<tr>
<td>Age, y</td>
<td>36.5±4.6</td>
<td>40.0±6.0</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>22.0±1.7</td>
<td>28.9±5.8*</td>
</tr>
<tr>
<td>Abdominal circumference, cm</td>
<td>87.0±10.0</td>
<td>96.0±19.2*</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dL</td>
<td>84.3±5.8</td>
<td>93.7±39.0</td>
</tr>
<tr>
<td>Serum total cholesterol, mg/dL</td>
<td>176.5±21.4</td>
<td>185.2±36.4</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>41.4±16.3</td>
<td>39.4±24.6</td>
</tr>
<tr>
<td>Serum triglycerides, mg/dL</td>
<td>122.0±17.2</td>
<td>124.0±23.5†</td>
</tr>
<tr>
<td>Glycated hemoglobin, %</td>
<td>5.10±0.02</td>
<td>5.40±0.03</td>
</tr>
<tr>
<td>HOMA index, U</td>
<td>1.81±0.60</td>
<td>2.2±2.4</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>111.7±11.7</td>
<td>118.2±15.6</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>61.50±0.67</td>
<td>66.5±9.0</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70.7±11.3</td>
<td>70.0±10.8</td>
</tr>
</tbody>
</table>

Data are shown as means±SD. BP indicates blood pressure.

*P$<$0.05 for BMI $<$25 kg/m$^2$ vs $\geq$25 kg/m$^2$.

†P$<$0.05 offspring vs their respective control group.
distension at systole, pulse pressure, calculated CA distensibility, and carotid IMT were not significantly different in the group with a lower and a greater BMI. For all of the above variables, the differences between offspring of diabetic parents and control subjects remained statistically significant regardless of the BMI value.

Discussion
In our normoglycemic healthy offspring of 2 diabetic parents, CA diameter at diastole was similar to that of control individuals, i.e., age-matched healthy subjects with no parental diabetes. However, compared with control subjects, in subjects with 2 diabetic parents, pulse pressure was greater, the ability of the CA to distend in response to an increase in pressure from diastole to systole was less, and the calculated value of arterial distensibility was markedly reduced. This was the case both in subjects with an elevated BMI and in those with a normal BMI, the value of which bore no significant relationship to the CA values. Thus, subjects with a pronounced familial background for and, thus, a high probability of developing diabetes\textsuperscript{18} show arterial stiffening already at a stage in which blood glucose is normal. This has clinical implications, because arterial stiffening is an important cardiovascular risk factor.\textsuperscript{15} That is, its occurrence increases the risk of cardiac and vascular morbidity and fatal events presumably because a reduction in the ability of the arteries to distend when blood pressure increases is associated with an increase in arterial impedance and, thus, in the afterload to the heart, an increase in systolic blood pressure, and endothelial damage because a reduced distensibility enhances the traumatic effect of the intravascular pressure on the vessel wall.\textsuperscript{20}

The mechanisms responsible for the early arterial stiffening of normoglycemic offspring of diabetic parents are not clarified by our study. However, our data allow some considerations to be made. First, the offspring of diabetic parents had greater triglyceride values compared with control subjects, but to date there is no evidence that low triglyceride values exert any substantial modulating role on large artery mechanical properties. Second, because glucose values were normal and similar between the offspring of diabetic parents and control subjects, the arterial stiffening cannot be ascribed to any adverse effect of this substance on the functional characteristics of the vessel wall.\textsuperscript{23,24} Third, although an increase in body weight and/or a state of insulin resistance reduce large artery distensibility (via a sympathetic activation\textsuperscript{25–30} and possibly also via trophic influences that may alter the tissue composition of the vessel wall), it is also unlikely that these factors played a major role. This is because there was no relationship between BMI and carotid distensibility, which, in offspring of diabetic parents, was reduced also when BMI was normal. Furthermore, HOMA index values were within the reference range and slightly and nonsignificantly greater in the offspring of diabetic parents than in control subjects. Finally, taking into account that arterial distensibility decreases as blood pressure increases,\textsuperscript{20}
it is unlikely that a blood pressure factor was involved, because although systolic blood pressure was 5 mm Hg greater in the offspring of diabetic parents than in control subjects (a difference that was not statistically significant), diastolic blood pressure was lower in the former than in the latter group and so was mean blood pressure, although the difference was negligible (81.5 versus 82.7 mm Hg). We may, thus, suggest that the arterial stiffening seen so early in subjects with a strong familial background and predisposition to diabetes depends to only a little degree on initial and inconsistent alterations in glucose metabolism and body weight, does not depend on blood pressure modifications, and that genetic influences operating through other mechanisms may be responsible in the majority. In this context, it is interesting to note that, although diabetes is accompanied by an increased wall thickness even in the absence of microvascular and macrovascular complications, in our normoglycemic offspring of diabetic parents, CA IMT was similar to the value seen in control subjects. This suggests that arterial stiffening may precede arterial thickening and that, if involved, genetic influences do not operate through an increase in the amount of wall tissue.

In the subjects of our study we did not measure pulse pressure at the level of the CA nor did we calculate the central pulse pressure value by subtracting the amplification factor from the peripheral arterial signal. The possibility thus exists that the reduced excursion of CA diameter from diastole to systole seen in the offspring of diabetic parents compared with control subjects was because of a reduced distending stimulus, ie, to the fact that central (and, thus, carotid) pulse pressure was less in the offspring of diabetic parents than in control subjects. Although this possibility cannot be excluded, it seems to be hardly compatible with the opposite phenomenon seen in the periphery, ie, a greater pulse pressure value in the offspring of diabetic parents than in control subjects (50 versus 41.3 mm Hg).

**Perspectives**

In summary, subjects with a pronounced familial background for and, thus, a high probability of developing diabetes show arterial stiffening already at a stage in which blood glucose is normal. In our normoglycemic offspring of diabetic parents, CA IMT was similar to the value seen in control subjects, thus suggesting that arterial stiffening may precede arterial thickening and that, if involved, genetic influences do not operate through an increase in the amount of wall tissue. No relationship between BMI and carotid distensibility was seen, and arterial distensibility in offspring of diabetic parents was reduced also when BMI was normal.

This has clinical implications, because arterial stiffening is an important cardiovascular risk factor. Genetic influences operating through a mechanism different from IMT, BMI, and glucose metabolism may be responsible in the majority.

**Disclosures**

None.

**References**


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