Arterial Stiffness Increases With Deteriorating Glucose Tolerance Status

The Hoorn Study

Ronald M.A. Henry, MD; Piet J. Kostense, PhD; Annemieke M.W. Spijkerman, PhD; Jacqueline M. Dekker, PhD; Giel Nijpels, MD, PhD; Robert J. Heine, MD, PhD; Otto Kamp, PhD; Nico Westerhof, PhD; Lex M. Bouter, PhD; Coen D.A. Stehouwer, MD, PhD

Background—Type 2 diabetes (DM-2) and impaired glucose metabolism (IGM) are associated with an increased cardiovascular disease risk. In nondiabetic individuals, increased arterial stiffness is an important cause of cardiovascular disease. Associations between DM-2 and IGM and arterial stiffness have not been systematically investigated.

Methods and Results—In a population-based cohort (n=747; 278 with normal glucose metabolism, 168 with IGM, and 301 with DM-2; mean age, 68.5 years), arterial stiffness was ultrasonically estimated by distensibility and compliance of the carotid, femoral, and brachial arteries and by the carotid elastic modulus. After adjustment for age, sex, and mean arterial pressure, DM-2 was associated with increased carotid, femoral, and brachial stiffness, whereas IGM was associated only with increased femoral and brachial stiffness. Carotid but not femoral or brachial stiffness increased from IGM to DM-2. Standardized βs (95% CI) for IGM and DM-2, compared with normal glucose metabolism, were −0.06 (−0.23 to 0.10) and −0.37 (−0.51 to −0.23) for carotid distensibility; −0.02 (−0.18 to 0.18) and −0.25 (−0.40 to −0.09) for carotid compliance; −0.05 (−0.23 to 0.13) and 0.25 (0.10 to 0.40) for carotid elastic modulus; −0.70 (−0.89 to −0.51) and −0.67 (−0.83 to −0.52) for femoral distensibility; and −0.62 (−0.80 to −0.44) and −0.79 (−0.94 to −0.63) for femoral compliance. The brachial artery followed a pattern similar to that of the femoral artery. Increases in stiffness indices were explained by decreases in distension, increases in pulse pressure, an increase in carotid intima-media thickness, and, for the femoral artery, a decrease in diameter. Hyperglycemia or hyperinsulinemia explained only 30% of the arterial changes associated with glucose tolerance. Adjustment for conventional cardiovascular risk factors did not affect these findings.

Conclusions—IGM and DM-2 are associated with increased arterial stiffness. An important part of the increased stiffness occurs before the onset of DM-2 and is explained neither by conventional cardiovascular risk factors nor by hyperglycemia or hyperinsulinemia. (Circulation. 2003;107:2089-2095.)

Key Words: epidemiology diabetes mellitus glucose remodeling vasculature
Methods

Study Population

For the present investigation, we used data from the 2000 Hoorn Study follow-up examination and, to increase the number of individuals with DM-2, data from a diabetes screening study, both of which were population-based.

The Hoorn Study is a cohort study of glucose metabolism in the general population (n = 2844), which started in 1989. In 2000, a follow-up examination was carried out among all surviving participants who had given their permission to be recontacted. We invited all those who had diabetes, as determined by an oral glucose tolerance test, or who were treated for diabetes at the previous 1996 follow-up (n = 176). Next, we invited random samples of individuals with normal glucose metabolism (NGM) (n = 705) and IGM (n = 193). Of 1074 individuals thus invited, 648 (60%) participated. Additionally, we invited 217 individuals with DM-2 from the Hoorn Screening Study, 188 (87%) of whom participated.

All participants underwent a glucose tolerance test, except those with previously diagnosed diabetes (n = 67). Data on 14 individuals were missing because of logistical problems. Glucose tolerance was defined according to the 1999 WHO criteria. The study population (n = 822) thus consisted of 3 groups: 290 with NGM, 187 with IGM, and 345 with DM-2.

Nonparticipants

Among the 455 nonparticipants (53% women), 13% were complete nonresponders. The remaining nonparticipants gave the following various reasons not to participate: lack of interest (30%), comorbidity (23%), age (7%), unwillingness to travel (6%), participation too time-consuming (6%), and miscellaneous reasons (15%).

Informed Consent

The local ethics committee approved the study. All participants gave their written informed consent.

General Procedures

Blood Pressure Measurements

Brachial systolic and diastolic pressures were assessed in the left upper arm at 5-minute intervals with an oscillometric device (Collin Press-Mate, BP-8800). Brachial pulse pressure was calculated as systolic minus diastolic pressure, and brachial mean arterial pressure (MAP) as (2 diastolic pressure + systolic pressure)/3. Pulse pressure at the carotid and femoral artery was calculated according to the calibration method described by Kelly and Fitchett, with use of aortic pressures from the individual calibration method described by Van Bortel et al. This method assumes a constant difference between MAP and diastolic pressure (PP ref) and a calibration factor (K) at target and reference arteries (K tar and K ref) by the formula:

\[ PP_{tar} = PP_{ref} \cdot K_{tar}/K_{ref}, \]

where \( K \) is defined as (MAP–DP)/PP, and (MAP–DP) can be calculated from the area under the pressure curve divided by time.

As an alternative approximation of carotid pressures, aortic pressures were derived by tonometry with a piezo-resistive pressure transducer (SPT-301, Millar Instruments) connected to a waveform analysis device (SphygmoCor, AtCor Medical). Briefly, after a left brachial pressure reading, the transducer was used to palpate the right radial artery. Pressure waveform data were then obtained during 3 consecutive 12-second periods. A generalized transfer function was then used to obtain the aortic waveform, which enabled calculation of aortic pressures from the individual’s oscillometrically derived pressure.

Arterial Properties

Diameter, Distension, and Intima-Media Thickness

A single observer unaware of the participants’ clinical or glucose tolerance status obtained properties of the right common carotid (10 mm proximal to the carotid bulb), the right common femoral (20 mm proximal to the flow divider), and the right brachial (20 mm proximal to the antecubital fossa) arteries, with the use of an ultrasound scanner equipped with a 7.5-MHz linear probe (350 Series, Pie Medical). The scanner was connected to a PC equipped with vessel wall movement detection software and an acquisition system (Wall Track System, Pie Medical). This setup enables measurements of diameter, distension, and intima-media thickness (IMT). Briefly, after a 15-minute supine rest, the artery was visualized in B-mode. An M-line was then placed at the measurement site. After switching to M-mode, data acquisition in a real-time A-mode presentation on the computer screen was enabled after trackball-assisted identification of the arterial lumen. Data were then obtained during 3 consecutive 4-second measurements, triggered by the R-top of a simultaneously recorded ECG. The first radiofrequency signal was displayed on the screen, enabling the observer to check if the markers, positioned by the Wall Track System, coincided with the anterior and posterior wall reflections in the diastolic phase of the cardiac cycle. The cumulative radiofrequency signals were then digitized and stored. The change in diameter as a function of time (distension) was estimated and presented on the computer screen (distension waveform). Diastolic diameter was calculated as the difference in position between the anterior and posterior wall markers. Additionally, the carotid posterior wall IMT was calculated as the distance from the leading edge interface between lumen and intima to the leading edge interface between media and adventitia. The mean diameter, distension, and IMT of the 3 measurements were used in the analyses.

Arterial Stiffness Distensibility, Compliance, and Young’s Elastic Modulus

Distensibility and compliance coefficients were calculated from diameter, distension, and pulse pressure, as follows:

\[ \text{Distensibility coefficient} = \frac{2D\cdot D + D^2}{\text{pooled mean}} \] in \( \text{mm}^2 \cdot \text{kPa}^{-1} \)

Compliance coefficient = \( \frac{\pi D^3}{2 \cdot D + D^2 \cdot 4 \cdot \Delta P} \) in \( \text{mm}^2 \cdot \text{kPa}^{-1} \), where \( \Delta D \) is distension, \( D \) is diameter, and \( \Delta P \) is pulse pressure.

The distensibility coefficient reflects the arterial elastic properties, whereas the compliance coefficient reflects the arterial buffering capacity. From IMT, diameter, and carotid distensibility, we calculated Young’s elastic modulus \( (E_{\text{mod}}) \), an indicator of the intrinsic elastic wall properties:

\[ E_{\text{mod}} = \text{diameter}/(\text{IMT distensibility coefficient}) \text{ in kPa} \]

Reproducibility

Reproducibility was assessed in 10 individuals (5 men; 58.2 ± 9.5 years) who were examined twice, 2 weeks apart. The intraobserver interseions coefficients of variation [CV = (standard deviation of the mean difference/\( \sqrt{2} \))/pooled mean] were as follows: carotid IMT, 10.9%; diameters, 2.9% (carotid), 2.5% (femoral), and 4.3% (brachial); distension, 5.3% (carotid), 11.6% (femoral), and 12.8% (brachial); distensibility coefficients, 7.0% (carotid), 11.3% (femoral), and 12.8% (brachial); compliance coefficients, 6.3% (carotid), 13.1% (femoral), and 13.9% (brachial); carotid elastic modulus, 11.6%; and aortic pressures, 5.2% (systolic), 3.4% (diastolic), 3.8% (pulse), and 3.2% (mean).

Other Measurements

Health status, medical history, current medication use, and smoking habits were assessed by a questionnaire. Glucose, glycated hemoglobin, serum total, high-density, and low-density-lipoprotein cholesterol, and triglycerides were determined as described elsewhere. Resting electrocardiograms were automatically coded according to the Minnesota Code, and body mass index and the waist-to-hip.
Qualitatively satisfactory examinations were obtained of 747 for technical reasons. In the remaining 796 individuals, examination for logistical reasons; in 8, data collection failed

Of the 822 participants, 18 did not take part in the ultrasound analyzed without adjustments and then with adjustment for potential

Statistical Analysis
All analyses were carried out with SPSS (SPSS). We used multiple linear regression analysis to investigate the associations between glucose tolerance and arterial properties. All associations were first analyzed without adjustments and then with adjustment for potential confounders. Because arterial stiffness is affected by age, sex, and MAP, these variables were considered first in the adjusted models. We used brachial MAP for all adjustments, because MAP is constant throughout the arterial tree and because brachial pressures were determined more precisely (because of the greater number of observations). After we had assessed the main effects, interaction terms were used to investigate whether the association between glucose tolerance and arterial properties differed according to age or gender. P<0.05 was considered statistically significant, except for the interaction analyses, where we used P<0.10.

Results
Ultrasound Examinations
Of the 822 participants, 18 did not take part in the ultrasound examination for logistical reasons; in 8, data collection failed for technical reasons. In the remaining 796 individuals, qualitatively satisfactory examinations were obtained of 747 carotid, 689 brachial, and 665 femoral arteries. The main reason for missing data was poor definition of the arterial wall attributable to obesity (body mass index of those with qualitatively satisfactory examinations versus those without, 26.9±3.3 versus 31.3±5.6 kg/m², P<0.001).

Table 1 shows the characteristics of the study population.

Arterial Properties
With deteriorating glucose tolerance, distension decreased, diameter decreased (only in the femoral artery), pulse pressure increased, and carotid IMT increased. As a result, arterial stiffness, whether expressed as the distensibility coefficient, the compliance coefficient, or as Young’s elastic modulus, increased with deteriorating glucose tolerance (Table 2). Compared with NGM, DM-2 was significantly associated with increased carotid, femoral, and brachial stiffness, whereas IGM was only significantly associated with increased femoral and brachial stiffness (Table 3). In general, these associations were partially explained by MAP with a particularly strong effect for the carotid stiffness indices in IGM (Table 3). When compared with IGM, DM-2 was significantly associated only with an increase of carotid stiffness.

Table 3 shows stiffness indices but does not provide insight into which of the elements of the indices (distension, diameter, pulse pressure, or IMT) drives the changes. Table 4 shows that the association between DM-2 and increased stiffness was driven by a decrease in distension (significantly so in the femoral and brachial arteries), a decrease in diameter (in the femoral artery), an increase in pulse pressure (all arteries), and, for elastic modulus, an increase in carotid IMT. The association between IGM and arterial stiffness was primarily driven by a decrease in

| TABLE 1. Characteristics of the Study Population According to Glucose Tolerance |
|-------------------------------|--------------------|----------------|
| NGM                          | IGM                | DM-2           |
| No. (M/F)                    | 278 (135/143)      | 168 (84/84)    | 301 (156/145) |
| Age, y                       | 68.7±6.1           | 70.3±6.3       | 67.3±8.1      |
| Brachial systolic pressure, mm Hg | 137±20            | 145±17         | 149±20        |
| Brachial diastolic pressure, mm Hg | 75±9              | 78±9           | 80±9          |
| Brachial mean arterial pressure, mm Hg | 95±12             | 100±10         | 103±11        |
| Hypertension, %              | 56.1               | 72.7           | 82.2          |
| Antihypertensive medication, % | 25.6              | 39.0           | 51.1          |
| Total cholesterol, mmol/L    | 5.79±1.03          | 5.80±1.03      | 5.55±1.05     |
| HDL cholesterol, mmol/L      | 1.50±0.42          | 1.43±0.40      | 1.25±0.35     |
| LDL cholesterol, mmol/L      | 3.69±0.90          | 3.69±0.93      | 3.48±0.90     |
| Triglycerides, mmol/L        | 1.2 (0.9 to 1.5)   | 1.4 (1.0 to 1.8)| 1.7 (1.2 to 2.3)|
| Lipid-lowering medication, % | 13.1               | 16.6           | 19.3          |
| Fasting glucose, mmol/L      | 5.43±0.37          | 6.07±0.48      | 7.70±1.75     |
| Post-load glucose, mmol/L    | 5.63±1.15          | 8.01±1.69      | 11.66±2.87    |
| Insulin, pmol/L              | 46.1 (35.2 to 59.7)| 65.4 (48.9 to 88.2)| 84.8 (56.3 to 116.8) |
| Glycated hemoglobin, %       | 5.69±0.41          | 5.88±0.39      | 6.62±0.93     |
| Body mass index, kg/m²       | 26.2±3.3           | 27.9±4.1       | 29.3±5.0      |
| Waist-to-hip ratio           | 0.90±0.09          | 0.94±0.08      | 0.96±0.10     |
| Current smoking, %           | 15.2               | 17.1           | 13.6          |
| (Micro-)albuminuria, %       | 10.3               | 15.0           | 20.5          |
| Prior cardiovascular disease, % | 42.5              | 47.8           | 55.7          |

Data are reported as mean±SD or median (interquartile range).
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Young's elastic modulus
Compliance coefficient

artery, compliance was stronger in men (P < 0.001); however, we found no such interactions, except that the association of deteriorating glucose tolerance with brachial pulse distension (significantly so in the femoral and brachial arteries).

Additional Analyses

Interactions Between Glucose Tolerance and Age and Sex
The impact of deteriorating glucose tolerance on arterial stiffness may be worse in women and with increasing age. Overall, however, we found no such interactions, except that the association of deteriorating glucose tolerance with brachial pulse pressure was stronger in men (P = 0.04) and that, with femoral artery, compliance was stronger in men (P = 0.002) and in younger individuals (P = 0.001; data not shown).

Impact of Glucose and Insulin
To estimate the contribution of hyperglycemia and of hyperinsulinemia to the increase in stiffness associated with IGM and DM-2, we compared the above analyses with those adjusted for HbA1c (or fasting or postload glucose) and for insulin. This showed that at most one third of the arterial changes associated with IGM and DM-2 could be explained by hyperglycemia and hyperinsulinemia (data not shown).

Alternative Estimation of Carotid and Femoral Pulse Pressure
Results were qualitatively similar when we used brachial or tonometry-derived instead of distension-waveform–calibrated distensibility coefficient. Distensibility coefficient 9.12 3.46 6.27 1.82 1.66 4.07 1.82

Table 3. Stiffness Indices According to Glucose Tolerance: Adjusted Analyses

<table>
<thead>
<tr>
<th>Model</th>
<th>IGM</th>
<th>DM-2</th>
<th>IGM</th>
<th>DM-2</th>
<th>IGM</th>
<th>DM-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distensibility coefficient</td>
<td></td>
<td></td>
<td></td>
<td>1: sex+ age</td>
<td>-0.09 (0.00 to 0.10)</td>
<td>-0.27 (0.00 to 0.10)</td>
</tr>
<tr>
<td>2: MAP</td>
<td>-0.02 (0.00 to 0.18)</td>
<td>-0.18 (0.00 to 0.18)</td>
<td></td>
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<tr>
<td>Compliance coefficient</td>
<td></td>
<td></td>
<td></td>
<td>1: sex+ age</td>
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<td>-0.27 (0.00 to 0.10)</td>
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<td></td>
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<tr>
<td>Young's elastic modulus</td>
<td></td>
<td></td>
<td></td>
<td>1: sex+ age</td>
<td>-0.09 (0.00 to 0.10)</td>
<td>-0.27 (0.00 to 0.10)</td>
</tr>
<tr>
<td>2: MAP</td>
<td>-0.05 (0.00 to 0.13)</td>
<td>-0.23 (0.00 to 0.13)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Results are expressed as standardized β and 95% confidence intervals. For absolute values, multiply standardized β by group SD.

| TABLE 2. Arterial Wall Properties According to Glucose Tolerance |
|-----------------|--------|-----------|--------|--------|--------|--------|
|                  | NGM    | IGM       | DM-2   | P (trend) |
| Carotid artery  |        |           |        |         |
| Distension      | 352±103| 346±114   | 338±110| 0.120   |
| Diameter        | 7.80±1.15| 8.04±1.14| 8.09±0.99| 0.001   |
| Pulse pressure  | 59±17   | 62±14     | 68±16  | <0.001  |
| Intima-media thickness | 0.83±0.16 | 0.87±0.16 | 0.88±0.16 | <0.001 |
| Distensibility coefficient | 12.82±4.34 | 11.56±4.55 | 10.44±4.25 | <0.001 |
| Compliance coefficient | 0.59±0.22 | 0.57±0.27 | 0.52±0.21 | <0.001 |
| Young's elastic modulus | 0.87±0.44 | 0.94±0.43 | 1.10±0.65 | <0.001 |
| Femoral artery  |        |           |        |         |
| Distension      | 243±73  | 177±59    | 183±66 | <0.001  |
| Diameter        | 10.17±1.78| 10.30±1.75| 9.78±1.49| 0.007   |
| Pulse pressure  | 68±17   | 70±16     | 74±18  | <0.001  |
| Distensibility coefficient | 5.73±2.25 | 3.97±1.66 | 4.07±1.82 | <0.001 |
| Compliance coefficient | 0.46±0.21 | 0.33±0.15 | 0.30±0.14 | <0.001 |
| Brachial artery  |        |           |        |         |
| Distension      | 160±71  | 138±67    | 131±61 | <0.001  |
| Diameter        | 4.56±0.73| 4.66±0.71| 4.77±0.73| <0.001  |
| Pulse pressure  | 62±16   | 67±14     | 69±15  | <0.001  |
| Distensibility coefficient | 9.12±4.63 | 7.13±3.46 | 6.27±3.13 | <0.001 |
| Compliance coefficient | 0.15±0.07 | 0.12±0.06 | 0.11±0.06 | <0.001 |

Data are reported as mean±SD. Distension is given in μm; diameter and intima-media thickness in mm; pulse pressure in mm Hg; distensibility in 10^-3 kPa^-1; compliance in mm^2 kPa^-1; and Young’s elastic modulus in kPa. Carotid and femoral pulse pressure are those obtained by calibration (see Methods).
pulse pressure. However, compared with distension-waveform–calibrated pulse pressure, brachial pulse pressure overestimated carotid and underestimated femoral stiffness, whereas tonometry-derived pulse pressure overestimated carotid stiffness. For example, the carotid distensibility coefficients in NGM calculated with brachial, calibrated, or tonometric pressures were 11.90, 12.82, and $14.67 \times 10^{-3}$ kPa$^{-1}$ (other data not shown).

**Impact of Additional Adjustments**

Results were similar when additionally adjusted for lipid profile, use of lipid-lowering or antihypertensive medication, body mass index, waist-to-hip ratio, smoking, (micro-) albuminuria, or prior cardiovascular disease (data not shown).

**Discussion**

This population-based study of glucose tolerance and arterial stiffness had 4 main findings. First, after adjustment for age, sex, and MAP, DM-2 was associated with increased arterial stiffness of both elastic (carotid) and muscular (femoral and brachial) arteries, whereas IGM was associated with increased stiffness of the muscular arteries. Second, carotid but not femoral or brachial stiffness increased from IGM to DM-2, suggesting that an important part of the increased stiffness occurs before the onset of DM-2. Third, increases in stiffness indices were explained by decreases in distension, increases in pulse pressure, an increase in carotid IMT, and, for the femoral artery, a decrease in diameter. Fourth, indices of hyperglycemia and hyperinsulinemia explained at most one third of the arterial changes associated with IGM and DM-2.

Our study was comprehensive and had important advantages over previous investigations, which were relatively small, and targeted only 1 type of artery. None of these studies determined how increases in arterial stiffness associated with IGM and DM-2 were driven by changes in distension, diameter, and pulse pressure. Additionally, our study is among the first to estimate local pulse pressure by distension waveform calibration, which is more accurate than brachial pulse pressure. Our data are in agreement with the Atherosclerosis Risk In Communities (ARIC) study, which also showed that DM-2 was associated with increased carotid stiffness.

We showed that both IGM and DM-2 were associated with increased arterial stiffness (both decreased distensibility and compliance) but that an important part of these changes occurred before the onset of DM-2. Arterial stiffness is thought to increase risk of cardiovascular disease through several mechanisms. These findings may thus partially explain why both IGM and DM-2 are associated with an increased cardiovascular disease risk.

Decreased distension and increased pulse pressure contributed importantly to increased arterial stiffness. These changes are thought to be related to quantitative and qualitative alterations in arterial wall elastin and collagen. Our results suggest that such alterations may be caused by factors other than short-term hyperglycemia and hyperinsulinemia, such as carbonyl and oxidative stress, chronic low-grade inflammation, and endothelial dysfunction, including that caused by long-term hyperglycemia and formation of advanced glycation end products. Interestingly, Kass et al recently showed that arterial stiffness in elderly, non-diabetic individuals could be reduced by the use of a novel advanced glycation end product crosslink breaker.

As glucose tolerance deteriorated, femoral diameter decreased but carotid and brachial diameter increased, indicating arterial remodeling, ie, the change of structural arterial properties through time in response to alterations in the arterial environment, in hemodynamics, or in vessel wall material. Arterial remodeling is thought to keep tensile stress and endothelial shear stress within certain limits of operation; it is not clear whether the preservation of arterial compliance despite vessel wall stiffening is also a goal of remodeling. From the viewpoint of arterial remodeling, the increase in brachial and carotid diameter may serve to decrease endothelial shear stress and preserve compliance; the increase in carotid IMT could, at least partially, be viewed...
as a compensatory response to counteract the increased wall stress brought about by the diameter increase (Laplace’s law). The decrease in femoral diameter may represent more advanced atherosclerosis, in which the initial compensatory widening response ultimately fails and finally results in arterial narrowing.39 The mechanisms through which diabetes and IGM affect arterial remodeling are unknown and require additional investigation.40

It is uncertain whether sex and age modify the relationship between glucose tolerance and arterial stiffness.41 In our data, the associations of glucose tolerance with femoral compliance and brachial pulse pressure were stronger in men, whereas associations with carotid stiffness indices were similar between both sexes. In contrast, the ARIC study reported a stronger association of glucose with carotid stiffness in women.4 However, this finding did not hold at a follow-up examination. We found that the association of glucose tolerance and femoral compliance decreased with increasing age but that associations with other stiffness indices were not modified by age. This contrasts somewhat with our earlier finding of a stronger association between age and brachial pulse pressure in diabetic compared with nondiabetic individuals.42 This could potentially be explained by differences in composition of the study population as well as by chance.

Our study had several limitations. First, our findings were obtained in the elderly. Therefore, we may have underestimated the association of arterial stiffness with glucose tolerance because of selective mortality of individuals with diabetes and stiff arteries. Second, we used a novel method to determine carotid IMT based on a single point measurement technique.25 However, this method has shown an excellent correlation with B-mode measurements;42 both are strongly related to age and blood pressure,43 which was also the case in the present study (data not shown). Additionally, we minimized measurement variation related to IMT variability along the artery by clearly defining where the measurements were taken. Finally, data were obtained in a white population, and therefore it remains to be established whether these results can be generalized to other ethnicities. We conclude that both IGM and DM-2 are associated with increased arterial stiffness. An important part of the increased arterial stiffness occurs before the onset of DM-2 and is not explained by indices of hyperglycemia or hyperinsulinemia. These data provide a pathophysiological framework for understanding why glucose tolerance is associated with an increased risk of stiffness-related complications.

Acknowledgments

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References


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