Increased Central Artery Stiffness in Impaired Glucose Metabolism and Type 2 Diabetes

The Hoorn Study

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Abstract—Impaired glucose metabolism (IGM) and type 2 diabetes (DM-2) are associated with high cardiovascular disease risk. Increases in peripheral and central artery stiffness may represent pathophysiologic pathways through which glucose tolerance status leads to cardiovascular disease. Peripheral artery stiffness increases with deteriorating glucose tolerance status, whereas this trend remains unclear for central artery stiffness. Therefore, we investigated the associations between glucose tolerance status and estimates of central arterial stiffness. We performed a population-based study of 619 individuals (normal glucose metabolism, n=261; IGM, n=170; and DM-2, n=188) and assessed central artery stiffness by measuring total systemic arterial compliance, aortic pressure augmentation index, and carotid-femoral transit time. After adjustment for sex, age, heart rate, height, body mass index, and mean arterial pressure, DM-2 was associated with decreased total systemic arterial compliance, increased aortic augmentation index, and decreased carotid-femoral transit time. IGM was borderline significantly associated with decreased total systemic arterial compliance. Respective regression coefficients (95% confidence intervals) for IGM and DM-2 compared with normal glucose metabolism were −0.05 (−0.11 to 0.01) and −0.13 (−0.19 to −0.07) mL/mm Hg for total systemic arterial compliance; 1.1 (−0.2 to 2.5) and 1.6 (0.2 to 3.0) percentage points for aortic augmentation index; and −0.85 (−5.20 to 3.49) and −4.95 (−9.41 to −0.48) ms for carotid-femoral transit time. IGM and DM-2 are associated with increased central artery stiffness, which is more pronounced in DM-2. Deteriorating glucose tolerance is associated with increased central and peripheral arterial stiffness, which may partly explain why both DM-2 and IGM are associated with increased cardiovascular risk. **(*Hypertension*. 2004;43:176-181.)**

Key Words: diabetes mellitus ■ arteries ■ compliance ■ vascular resistance ■ total peripheral resistance

Both impaired glucose metabolism (IGM) and type 2 diabetes mellitus (DM-2) are associated with a high risk of cardiovascular disease and mortality.[1,2] The mechanisms through which these pathologies increase the risk of cardiovascular disease remain unclear but might involve increased arterial stiffness,[3–6] which leads to increased systolic blood pressure and left ventricular mass and hampers coronary filling during diastole.[7]

Arterial stiffness varies by region and type of artery. It is likely that increased stiffness of both peripheral and central arteries is detrimental. We have previously shown that as compared with individuals with normal glucose metabolism (NGM), stiffness of peripheral arteries is increased in both IGM (femoral and brachial arteries) and DM-2 (femoral, brachial, and carotid arteries). However, it is unknown whether central artery stiffness is increased in IGM and DM-2.

In view of these considerations, we investigated, in a population-based cohort of 619 individuals, the associations of glucose tolerance status with arterial stiffness, expressed as total systemic arterial compliance, which reflects the overall buffering capacity of the arterial system, mainly of the proximal aorta;[8,9] the aortic augmentation index; and the height-adjusted carotid-femoral transit time, a surrogate for carotid-femoral pulse wave velocity,[9] which reflects the stiffness of mainly the descending aorta.[8,9]

Total systemic arterial compliance was estimated by 2 methods, namely, by the time decay of diastolic aortic pressure and by the ratio of stroke volume to aortic pulse pressure. Carotid-femoral transit time estimates the average

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aortic distensibility, or bulk modulus K ($K=PWV^2\times\rho$, where PWV is pulse wave velocity and ρ is blood viscosity).[10] This method assumes a uniform aorta and gives compliance of mainly the descending aorta. However, because most compliance resides in the aorta, this estimate is closely related to total arterial compliance. The aortic augmentation index depends on timing of the reflected waves and thus, on pulse wave velocity, as well as on the magnitude and location of reflection sites,[9] and is therefore a less pure estimate of arterial stiffness.

Methods

Study Population

For the present investigation, we used data from the 2000 Hoorn Study follow-up examination and the Hoorn Screening Study. Details have been described elsewhere.[3,11,12] The local ethics committee approved the study, and written, informed consent was obtained from all participants. The study population consisted of 822 individuals: 290 with NGM, 187 with IGM, and 345 with DM-2.

General Study Procedures

All hemodynamic measurements were obtained by a single observer unaware of the participant's clinical or glucose tolerance status.

Total Systemic Arterial Compliance

Total systemic arterial compliance (mL/mm Hg) was determined according to 2 methods: the exponential-decay method based on the Windkessel model[13,14] and the ratio of stroke volume to aortic pulse pressure.[15] The first method used data obtained by applanation tonometry (vide infra). The second method used the ratio of stroke volume to aortic pulse pressure (in mL/mm Hg) to determine total systemic arterial compliance, for which stroke volume was calculated as cardiac output divided by heart rate, and aortic pulse pressure was calculated by use of a calibration method (vide infra).

Blood Pressure and Aortic Augmentation Index

Brachial artery systolic and diastolic blood pressures were assessed as previously described.[3] Aortic pulse pressure was estimated by 2 methods. The first applied a calibration method, which uses distension waveforms at the brachial and carotid arteries to calibrate the pulse pressure at the carotid artery,[3] and which is subsequently used as an estimate of aortic pulse pressure.[16] The second applies applanation tonometry, which uses pressure registrations at the radial artery to calculate the aortic pulse pressure by use of a generalized transfer function (vide infra).[17] (Numerical values of total systemic arterial compliance differed markedly, depending on the method used. However, associations with glucose tolerance status were comparable, regardless of the method used. We chose to report data obtained with the calibrated aortic pulse pressure because previous studies have suggested that this may be the most accurate estimate of aortic pulse pressure.[3,16,18,19])

Radial applanation tonometry was used to obtain the aortic augmentation index and aortic pulse pressure (vide infra) and was performed with a Millar piezoresistive pressure transducer connected to an arterial waveform analysis device (Sphygmocor).[3] The aortic augmentation index was calculated as augmented pressure divided by (tonometrically derived) central pulse pressure. Because the aortic augmentation index is a ratio of 2 aortic pressure values, the influence of any systematic errors in the estimation of aortic pulse pressure by the transfer function will be minimal.

Carotid-Femoral Transit Time

The carotid-femoral transit time (in ms) is the travel time of a pressure wave from the common carotid to the femoral artery, a measure of the aortic (thoracic-abdominal) compliance. It is closely related to carotid-femoral pulse wave velocity,[9] ie, length of the carotid-femoral arterial segment divided by carotid-femoral transit time. However, because noninvasive measurement of this length might introduce error, especially in obese and older[20] patients, we chose to use carotid-femoral transit time and to adjust for height in the statistical analyses. We determined the carotid-femoral transit time by continuous measurement of the diameter (distension curves) of the right common carotid artery and the right femoral artery diameter.[3] We then determined the average time delay (mean of 3 recordings of 4 seconds per artery) from the electrocardiograph trigger to 10% of the ascending slope of the distension curve of both arteries and subtracted the carotid value from the femoral value to obtain the carotid-femoral transit time.[14] Reproducibilities of the time-decay method, carotid pulse pressure, augmentation index, and carotid-femoral transit time have been reported.[3,14]

Statistical Analyses

All analyses were performed with SPSS 9.0.1 for Windows. We used multiple linear regression analyses to investigate the associations between glucose tolerance status and total systemic arterial compliance, aortic augmentation index, and carotid-femoral transit time. All associations were first analyzed without adjustments and then with adjustment for potential confounders, such as age, sex, heart rate, height, body mass index, and brachial mean arterial pressure. Probability values <0.05 were considered statistically significant.

Results

All analyses presented were performed in 4 groups of patients with the following glucose tolerance status: NGM, impaired fasting glucose[2] (n=89), impaired glucose tolerance[2] (n=108), and DM-2. These analyses showed no significant differences between the impaired fasting glucose and impaired glucose tolerance groups (data not shown), and therefore, we pooled these 2 groups as the IGM group.

Baseline characteristics are shown in Table 1. Of the 822 participants, 18 did not take part in examinations for logistical reasons; in 8, vascular examinations failed for technical reasons. In the remaining 796 individuals, qualitatively satisfactory total systemic arterial compliance measurements for the time-decay method were available for 556 individuals (owing to device availability) and for the ratio of stroke volume to aortic pulse pressure for 511 individuals (owing to technical reasons). The main reason for missing (carotid) ultrasound data was poor definition of the arterial wall attributable to obesity (body mass index of those with versus those without qualitatively satisfactory examinations, 26.9 ± 3.3 versus 31.3 ± 5.6 kg/m^2). Aortic augmentation index was available for 619 individuals (owing to device availability) and carotid-femoral transit time for 319 (again owing to device availability). Device availability was not related to the participant's clinical status.

Total systemic arterial compliance, as determined by the time-decay method, decreased with deteriorating glucose metabolism status, but this was not statistically significant after adjustment, the most important confounder being mean arterial pressure (Table 2). Total systemic arterial compliance, as determined by the ratio of stroke volume to aortic pulse pressure, decreased with deteriorating glucose metabolism status (Table 2). Compared with NGM, both IGM and DM-2 were associated with decreased total systemic arterial compliance. This decrease was significantly more severe in DM-2 than in IGM (Table 2 and Figure 1). Total systemic arterial compliance calculated with aortic pulse pressure, as measured by tonometry, showed similar results, although absolute estimates were higher (adjusted estimated means

TABLE 1. Baseline Characteristics of the Study Population

	NGM (n=261)	IGM (n=170)	DM-2 (n=188)	*P* for Trend
Age, y	68.6±6.0	69.7±6.1	68.0±8.6	0.06
Sex, M/F, n/n	131/130	83/87	102/86	...
Fasting glucose, mmol/L	5.4±0.4	6.1±0.5	7.8±1.9	<0.001
Postload glucose, mmol/L	5.6±1.1	8.0±1.7	11.6±2.9	<0.001
Glycosylated hemoglobin, %	5.7±0.4	5.9±0.4	6.6±0.9	<0.001
Fasting insulin, pmol/L	47 (35–60)	65 (50–87)	80 (56–106)	<0.001
Insulin resistance, arbitrary units (HOMA; n=257, 165, 170)*	1.57 (1.16–2.05)	2.53 (1.87–3.19)	3.55 (2.53–5.37)	<0.001
Brachial blood pressure, mm Hg				
Systolic	137±20	145±17	149±20	<0.001
Diastolic	75±9	78±9	79±9	<0.001
Mean arterial	96±12	100±10	103±12	<0.001
Pulse	63±16	66±14	70±15	<0.001
Heart rate, bpm	62±9	63±9	63±10	0.19
Body mass index, kg/m^2	26.2±3.3	27.8±3.9	28.7±3.7	<0.001
Waist-to-hip ratio	0.90±0.09	0.94±0.08	0.96±0.09	<0.001
Hypertension, %†	38	49	67	<0.001
Use of antihypertensive drugs, %	25	34	50	<0.001
Total cholesterol, mmol/L	5.8±1.0	5.8±1.0	5.6±1.1	0.10
LDL cholesterol, mmol/L	3.7±0.9	3.7±0.9	3.5±0.9	0.08
HDL cholesterol, mmol/L	1.5±0.4	1.5±0.4	1.3±0.3	<0.001
Triglycerides, mmol/L	1.2 (0.9–1.6)	1.3 (1.0–1.8)	1.6 (1.2–2.2)	<0.001
Lipid-lowering medication, %	11	17	19	0.05
Current smoking, %	15	18	11	0.17
Microalbuminuria, %	11	14	19	0.05
Serum creatinine, μmol/L	95±14	95±15	96±22	0.58
Prior cardiovascular disease, %	41	46	53	0.04
Total systemic arterial compliance (time-decay method), mL/mm Hg	0.76±0.32	0.72±0.29	0.69±0.30	0.11
Total systemic arterial compliance (SV/aortic PP), mL/mm Hg	1.13±0.35	1.04±0.29	0.93±0.32	<0.001
Aortic augmentation index, %	31.5±8.9	32.9±8.5	33.0±8.7	0.13
Carotid-femoral transit time, ms	56±17	54±15	53±17	0.34

SV indicates stroke volume; pp, pulse pressure, HOMA, homeostasis model of assessment. Other abbreviations are as defined in text. Data are presented as mean±SD or as median (interquartile range).

*Data on HOMA were missing for n=9 and could not be calculated for 18 DM-2 subjects because of insulin treatment.

†Hypertension was defined as systolic blood pressure ≥140 and/or diastolic pressure ≥90 and/or use of antihypertensive medication.

were 1.27, 1.21, and 1.14 mL/mm Hg [$P<0.001$] in the NGM, IGM, and DM-2 groups, respectively).

The aortic augmentation index increased with deteriorating glucose metabolism status. Compared with NGM, DM-2 was associated with a significantly increased aortic augmentation index, but IGM was not, although values were intermediate between those for NGM and DM-2 (Table 2 and Figure 1). Carotid-femoral transit time decreased with deteriorating glucose metabolism status. Compared with NGM, DM-2 was associated with a significantly decreased carotid-femoral transit time, but IGM was not (Table 2 and Figure 1).

Additional Analyses

Impact of Glucose and Insulin

To estimate the contribution of hyperglycemia and hyperinsulinemia to the increase in central arterial stiffness indices associated with IGM and DM-2, we compared the results of the aforementioned analyses with those additionally adjusted for glycosylated hemoglobin (or fasting or postload glucose levels) and insulin concentrations (or homeostasis model of assessment). This showed that ≈15% to 50% of the decrease in total systemic arterial compliance and ≈10% to 40% of the increase in aortic augmentation index could be explained by these estimates of hyperglycemia, whereas hyperinsulinemia

TABLE 2. Total Systemic Arterial Compliance, Aortic Augmentation Index, and Carotid-Femoral Transit Time According to Glucose Tolerance Status

	IGM		DM-2		
	β	(95% CI)	β	(95% CI)	*P* for Trend
Total systemic arterial compliance (time-decay method), mL/mm Hg					
Unadjusted model	−0.04	(−0.10 to 0.03)	−0.06	(−0.13 to −0.00)*	0.112
Adjusted model	0.01	(−0.04 to 0.06)	−0.03	(−0.08 to 0.02)	0.381
Total systemic arterial compliance (sv/aortic pp), mL/mm Hg					
Unadjusted model	−0.09	(−0.16 to −0.02)*	−0.20	(−0.25 to −0.14)*‡	<0.001
Adjusted model	−0.05	(−0.11 to 0.01)†	−0.13	(−0.19 to −0.07)*‡	<0.001
Aortic augmentation index, % point					
Unadjusted model	1.4	(−0.3 to 3.1)	1.5	(−0.1 to 3.1)†	0.129
Adjusted model	1.1	(−0.2 to 2.5)	1.6	(0.2 to 3.0)*	0.059
Carotid-femoral transit time, ms					
Unadjusted model	−1.26	(−6.04 to 3.53)	−3.08	(−7.22 to 1.06)	0.314
Adjusted model	−0.85	(−5.20 to 3.49)	−4.95	(−9.41 to −0.48)*§	0.079

Results are expressed as regression coefficients (β) and 95% confidence intervals (95%CI). Adjustments were made for sex, age, heart rate, body mass index, and mean arterial pressure. Mean arterial pressure was the main confounder of these associations.

NGM indicates normal glucose metabolism; IGM, impaired glucose metabolism; DM, type 2 diabetes mellitus; sv, stroke volume; pp, pulse pressure.

*$P<0.05$ vs NGM; †$0.05\leq P\geq 0.10$ vs NGM; ‡$P\leq 0.05$ vs IGM; §$0.05\leq P\geq 0.10$ vs IGM.

did not contribute (data not shown). The association of carotid-femoral transit time with DM-2 could not be explained by hyperglycemia or hyperinsulinemia.

Impact of Additional Adjustments

Additional adjustments of the associations of glucose metabolism status with total systemic arterial compliance, aortic augmentation index, and carotid-femoral transit time for the presence of hypertension, use of antihypertensives (including angiotensin-converting enzyme inhibitors), waist-to-hip ratio, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, use of lipid-lowering medication, current smoking, serum creatinine, microalbuminuria, and prior cardiovascular disease did not materially change the results (data not shown).

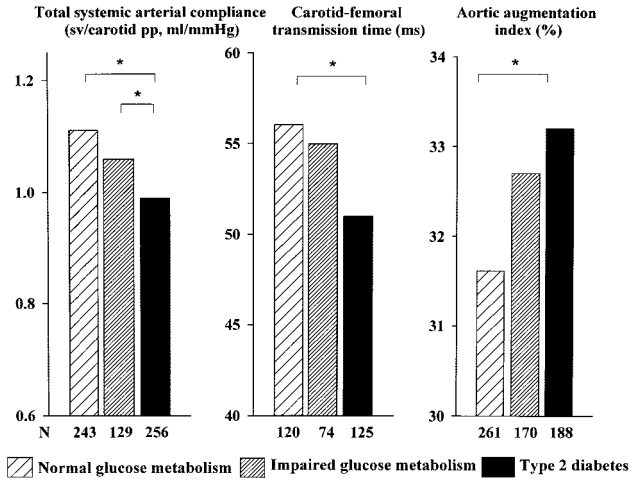

Figure 1. Adjusted estimated means of total systemic arterial compliance, carotid-femoral transit time, and aortic augmentation index according to glucose metabolism status. Values were adjusted for sex, age, heart rate, height, body mass index, and mean arterial pressure. *$P<0.05$; sv indicates stroke volume; pp, pulse pressure.

Discussion

The main outcome of this population-based study is that DM-2 is associated with decreased total systemic arterial compliance, increased aortic augmentation index, and decreased carotid-femoral transit time, independently of age, sex, mean arterial pressure, heart rate, body mass index, and other potential confounders. In IGM, values of central artery stiffness were intermediate between those of the groups with NGM and DM-2 (Figure 1). Part of these associations could be explained by short-term hyperglycemia. Taken together with the data from our previous report on peripheral artery stiffness,[3] these data suggest that central and peripheral arterial stiffness increase in both IGM and DM-2 and that these changes are greater at peripheral than at central sites (Figure 2).

Total systemic arterial compliance was significantly decreased in both IGM and DM-2. Total systemic arterial compliance is an estimate of the buffering capacity of the entire arterial system and is an important determinant of myocardial workload. Changes in total systemic arterial compliance and thus, in properties of the proximal aorta, were less severe in IGM than in DM-2. As have others,[21] we observed differences in the association of glucose metabolism with total systemic arterial compliance, as determined by the time-decay method versus the ratio of stroke volume to aortic pulse pressure. These differences might be due to the fact that total systemic arterial compliance as determined by the time-decay method is computed by combining the results of different measurements, which results in an increase in

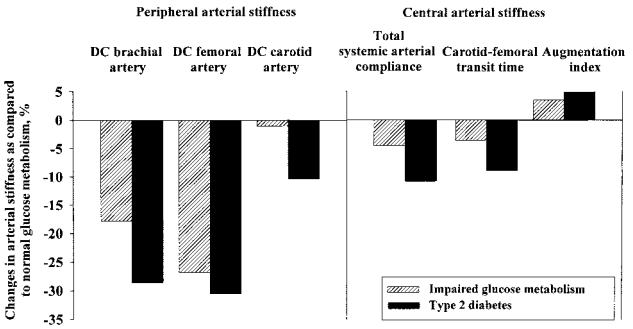

Figure 2. Adjusted percentages of change in peripheral arterial stiffness (local arterial distensibility coefficients [DC] of the brachial, femoral, and carotid artery) and central arterial stiffness (total systemic arterial compliance, carotid-femoral transit time, and aortic augmentation index) in DM-2 and IGM compared with NGM. To facilitate direct comparison of peripheral and central stiffness indices, we expressed these data as percentage change from NGM to IGM and to DM-2. Data were adjusted for sex, age, heart rate, height, body mass index, and mean arterial pressure.

measurement error, as expressed by a relatively large standard deviation of this method.

The aortic augmentation index was increased both in impaired glucose tolerance and more severely so, in DM-2 (Figure 1). The aortic augmentation index depends not only on arterial stiffness but also on the number and location of reflection sites and the amplitude and timing of the reflected wave. Because we cannot discriminate between these determinants of the augmentation index, this might mean that, possibly due to the development of atherosclerotic plaques, reflection sites in IGM are located more centrally than in NGM and that these changes are more pronounced in DM-2. Alternatively or additionally, it might mean that increases in arterial stiffness are responsible for the more pronounced changes in DM-2.

The use of a generalized transfer function to calculate the aortic augmentation index has been criticized on methodological grounds.[22] We acknowledge, therefore that the absolute values we found may be considered questionable. However, if the use of a generalized transfer function introduces errors, then these errors will presumably be similar, regardless of glucose tolerance status. Therefore, our qualitative conclusion that the aortic augmentation index increases with deteriorating glucose tolerance is likely to be valid.

Carotid-femoral transit time was decreased in DM-2 but not clearly so in IGM. The carotid-femoral transit time adjusted for height was used as a surrogate for carotid-femoral pulse wave velocity[9]; it represents the stiffness of mainly the descending aorta and is determined predominantly by the elastic properties of the aortic wall. Because of the relatively small number of observations in IGM, we could not establish with certainty whether the carotid-femoral transit time in this group was normal or decreased, and this issue requires further study. In addition, we may have underestimated the association between carotid-femoral transit time and glucose tolerance status for 2 reasons. First, aging is associated with increases in aortic length, and this is thought to be more pronounced in DM-2. Second, we measured carotid-femoral transit time after 15 minutes of supine rest to reach a steady state with regard to heart rate and blood pressure. During the examination, heart rate and blood pressure did not change. Therefore, it is unlikely that changes in isovolumetric contraction time, for instance, occurred. However, if such changes did occur, it is reasonable to assume that they occurred randomly over the study population (ie, equally in NGM, IGM, and DM-2). These random changes (ie, noise) would then weaken the association between glucose tolerance status and carotid-femoral transit time.

Compared with changes in peripheral artery stiffness,[3] the changes in central artery stiffness with deteriorating glucose tolerance status were relatively small. In peripheral arteries, ie, the brachial, femoral, and carotid, stiffness estimates decreased by 19% to 31% from NGM to DM-2,[3] compared with a 2% to 11% decrease in estimates of central artery stiffness (Figure 2).

Our study extends the findings of other studies, which were relatively small,[23,24] concerned selected populations,[23–26] or targeted only 1 estimate of central artery stiffness.[23,24,26–28] In addition, our study is the first to demonstrate an association between IGM and total systemic arterial compliance and aortic augmentation index.

These data raise the question of whether the increases in central and peripheral artery stiffness with deteriorating glucose tolerance develop in a certain pattern over time. Wittekoek et al[29] have previously suggested that the increase in arterial stiffness starts at peripheral sites and then extends to central arteries. In contrast, Kimoto et al[28] have suggested that increases in arterial pulse wave velocity in DM-2 preferentially occur at central arteries, not at peripheral sites. However, both studies had a cross-sectional setting, whereas longitudinal studies are necessary to investigate these issues.

We show that in contrast to increases in peripheral artery stiffness,[3] increases in central artery stiffness can, to an important extent, be explained by relatively short-term hyperglycemia. This suggests that hyperglycemia causes important quantitative and qualitative changes in arterial wall elastin and collagen of central arteries. As in peripheral arteries, another part of these changes may be attributed to other mechanisms, such as glycation of proteins and the formation of advanced glycation end products,[30] although the mechanisms by which these changes in arterial stiffness occur are not fully understood. Advanced glycation end products can form cross-links in collagen fibers, thereby decreasing the distensibility of the arterial wall. Further evidence for their role in arterial stiffness is provided by studies showing that increases in arterial stiffness are prevented or reduced by treatment with aminoguanidine,[31] which inhibits the formation of advanced glycation end products, or ALT-711,[32] which breaks down cross-links of advanced glycation end products.

Our study had some limitations. First, our study population was relatively old. This might have caused an underestimation of the association of arterial stiffness with glucose metabolism because of selective mortality of individuals with DM-2 and stiff arteries. Second, our data were cross sectional. Therefore, we could not evaluate whether the changes in arterial stiffness develop in a certain pattern over time.

In conclusion, our data show that IGM and DM-2 are associated with decreased total systemic arterial compliance, increased aortic augmentation index, and decreased carotid-femoral transit time, the latter in DM-2 only. These increases in central artery stiffness are more pronounced in DM-2. Taken together with our previous report,[3] we show that changes in arterial stiffness are worse at peripheral than at central arteries in both IGM and DM-2. Deteriorating glucose tolerance, therefore, is associated with a generalized increase in arterial stiffness, which provides a framework for understanding why both DM-2 and IGM are associated with an increased risk for stroke, heart failure, and myocardial infarction.

Perspectives

Our data provide evidence that central artery stiffness is associated with glucose tolerance status. A crucial next step is to investigate whether measures of central artery stiffness have prognostic value in DM-2, as they do in other populations.[33] If so, these measures could be used in clinical practice for risk assessment and to monitor the effects of interventions to decrease arterial stiffness. The method to do this should be reproducible and easy to learn, and the device and software should be robust and not too expensive. Measurement of both carotid-femoral pulse wave velocity by use of the Complior device and aortic augmentation index fulfill these criteria. At present, most prospective data come from measurement of pulse wave velocity.[33]

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