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Carotid Arterial Remodeling

A Maladaptive Phenomenon in Type 2 Diabetes but Not in Impaired Glucose Metabolism: The Hoorn Study

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Background and Purpose—Deteriorating glucose tolerance is associated with an increased cardiovascular disease (CVD) risk. The underlying mechanisms remain unclear. Arterial remodeling is the change in structural properties through time in response to atherogenic and/or hemodynamic alterations and aims to maintain circumferential wall stress constant (σ_c). Arterial remodeling has not been studied in relation to glucose tolerance.

Methods—The study population consisted of 278 people with normal glucose metabolism, 168 with impaired glucose metabolism, and 301 with type 2 diabetes (DM-2); their mean age was 67.8 years. We assessed carotid intima-media thickness (IMT), interadventitial diameter (IAD), lumen diameter (LD), and σ_c .

Results—After adjustment for age, sex, height, body mass index, and prior CVD, DM-2 was associated with increased IAD, IMT, and σ_c but not LD (regression coefficients: 0.24 mm; 95% confidence interval [CI], 0.07 to 0.41; 0.050 mm; 95% CI, 0.024 to 0.077; 5.00 kPa; 95% CI, 0.92 to 9.08; and 0.13 mm; 95% CI, -0.03 to 0.29, respectively). After additional adjustment for pulse pressure, the association between DM-2 and IAD disappeared, whereas the association with IMT remained. After adjustment, impaired glucose metabolism was not significantly associated with LD (0.12 mm; 95% CI, -0.06 to 0.33), σ_c (0.25 kPa; 95% CI, -4.49 to 4.98), IAD (0.08 mm; 95% CI, -0.11 to 0.27), or IMT (0.029 mm; 95% CI, -0.002 to 0.060). However, the IMT regression coefficient was half that of DM-2.

Conclusions—DM-2 is associated with preserved LD at increased IMT, which, however, does not normalize the increased σ_c . In contrast, impaired glucose metabolism is not associated with changes in LD or IAD, whereas IMT is moderately increased but σ_c remains constant. Carotid remodeling in DM-2 thus appears maladaptive, which may explain the increased CVD risk, especially stroke, in DM-2. (*Stroke*. 2004;35:671-676.)

Key Words: arterial remodeling ■ carotid arteries ■ diabetes mellitus ■ epidemiology

A deteriorating glucose tolerance status is associated with an increased cardiovascular disease (CVD) risk. The mechanisms responsible for this increased risk remain unclear but are likely to involve functional and structural alterations in large arteries.^{1,2}

The process of arterial remodeling, ie, the change in structural arterial properties through time in response to atherogenic and/or hemodynamic alterations within the arterial environment, is thought to be an adaptive phenomenon aimed at maintaining circumferential wall and shear stresses within certain limits of operation and possibly at preserving compliance.^{3,4} Arterial remodeling is characterized by wall thickening (indicated by an increase in intima-media thickness [IMT]) and diameter widening [indicated by an increase in interadventitial diameter [IAD]].^{5,6} At the biochemical level, arterial remodeling is characterized by a complex set of interactions between vasoactive molecules (eg, nitric oxide),

enzymes (eg, matrix metalloproteinases), and inflammatory cells (monocytes/macrophages).^{5,7}

Three different patterns of arterial remodeling have been identified: inward (characterized by a decrease in lumen diameter [LD] resulting from a greater change in IMT than in IAD), outward (characterized by an increase in LD caused by a greater change in IAD than in IMT), and compensatory (characterized by LD preservation despite changes in IMT and IAD) remodeling.^{5,6} Recent studies suggested that inward remodeling and outward remodeling are associated with distinct forms of plaque formation, ie, inward with stable plaque formation and outward with unstable plaque formation.⁵ As such, inward remodeling and outward remodeling have been recognized as markers of CVD risk.⁸ Yet, it is unclear to what extent the process of remodeling is driven by atherogenic factors (ie, the presence of atherosclerosis)^{9,10} compared with hemodynamic factors (ie, increased blood

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pressure).¹¹ This is of particular importance because increased IMT could be the consequence of an unfavorable atherogenic milieu, subsequently leading to increases in IAD (ie, the increase in IMT drives the increase in IAD), whereas alternatively IAD could be the consequence of an unfavorable hemodynamic milieu, which in turn could lead to increases in IMT (ie, the increase in IAD drives the increase in IMT). Alternatively, changes in IMT and IAD may be driven by different processes and thus be unrelated.

With deteriorating glucose tolerance, both IMT^{2,12–14} and IAD² increase. However, previous studies either have targeted selected populations^{12–16} and/or did not consider IMT and IAD in combination and therefore did not address the issue of remodeling. In view of these considerations, we examined in a population-based cohort the associations between glucose tolerance and carotid remodeling. Additionally, we investigated whether any relationship between glucose tolerance and carotid remodeling was mediated through either the presence of atherosclerosis or increased blood pressure.

Methods

Study Population

For the present investigation, we used data from the 2000 Hoorn Study follow-up examination² and the Hoorn Screening Study.¹⁷ Details have been given elsewhere.^{2,17} The study population consisted of 822 individuals: 290 with normal glucose metabolism

(NGM), 187 with impaired glucose metabolism (IGM), and 345 with type 2 diabetes (DM-2).

Carotid Artery Properties

Carotid ultrasonography was performed with previously described techniques.² A single observer obtained structural properties of the right common carotid artery with an ultrasound scanner (350 Series [7.5-MHz linear probe], Pie Medical, the Netherlands). The scanner was connected to a personal computer equipped with wall track software (WTS, Pie Medical, the Netherlands) that enables measurement of IAD and IMT.^{2,18,19}

From IAD and IMT, LD was calculated as $LD = IAD - (2 \cdot IMT)$ in millimeters. Circumferential wall stress (σ_c) was calculated as $\sigma_c = PP(LD/IMT)$ in kilopascals, where PP is carotid pulse pressure (PP) estimated by distension waveform calibration.^{2,20}

Reproducibility

The intraobserver intersession coefficients of variation [CV=(standard deviation of the mean difference divided by the square root of 2) divided by pooled mean] were 2.9% for IAD, 10.9% for IMT, and 12.3% for σ_c .²

Other Measurements

Health status, medical history, medication use, and smoking habits were assessed by questionnaire.^{2,17} We determined systolic and diastolic pressures; mean arterial pressure (MAP); PP; hypertension; glucose; glycohemoglobin; insulin; serum total, high- (HDL), and low-density lipoprotein (LDL) cholesterol; serum triglycerides; body mass index (BMI); waist-to-hip ratio; and ankle-brachial pressure index as described elsewhere.^{2,17,21}

Insulin resistance was calculated according to the HOMA model.²² Prior CVD was defined as described previously.² We considered

TABLE 1. Characteristics of the Study Population According to Glucose Tolerance

	NGM	IGM	DM-2	P (Trend)
MF, n	278 (135/143)	168 (84/84)	301 (156/145)	...
Age, y	69±6	70±6	67±8	0.18
Systolic pressure, mm Hg	137±20	145±17	149±20	<0.001
Diastolic pressure, mm Hg	75±9	78±9	80±9	<0.001
Hypertension, %	56	73	82	<0.001
Antihypertensive medication, %	26	39	51	<0.001
Total cholesterol, mmol/L	5.8±1.0	5.8±1.0	5.6±1.1	0.005
HDL cholesterol, mmol/L	1.5±0.4	1.4±0.4	1.3±0.4	<0.001
LDL cholesterol, mmol/L	3.7±0.9	3.7±0.9	3.5±0.9	0.003
Triglycerides, mmol/L	1.2 (0.9–1.5)	1.4 (1.0–1.8)	1.7 (1.2–2.3)	<0.001
Lipid-lowering medication, %	13	17	19	0.039
Fasting glucose, mmol/L	5.4±0.4	6.1±0.5	7.7±1.8	<0.001
Postload glucose, mmol/L	5.6±1.2	8.0±1.7	11.7±2.9	<0.001
Insulin,* pmol/L	46.1 (35.2–59.7)	65.4 (48.9–88.2)	84.8 (56.3–116.8)	<0.001
Insulin resistance,* AU	1.6 (1.2–2.1)	2.5 (1.9–3.2)	3.6 (2.5–5.4)	<0.001
Glycated hemoglobin, %	5.69±0.41	5.88±0.39	6.62±0.93	<0.001
BMI, kg/m ²	26.2±3.3	27.9±4.1	29.3±5.0	<0.001
Height, cm	169±9	170±9	170±9	0.88
Waist-to-hip ratio	0.90±0.09	0.94±0.08	0.96±0.10	<0.001
Smoking, %	15	17	14	0.54
Creatinine, μmol/L	95±14	95±15	95±20	0.84
(Micro)albuminuria, %	10	15	21	<0.001
Prior CVD, %	43	48	56	<0.001

AU indicates arbitrary units. Data are reported as mean±SD or median (interquartile range).

*n=734 because 13 with DM-2 were on insulin therapy.

TABLE 2. Carotid Artery Properties According to Glucose Tolerance

	NGM	IGM	DM-2	<i>P</i> (Trend)
IAD, mm	7.80±1.15	8.04±1.14	8.09±0.99	0.001
LD, mm	6.13±1.06	6.26±1.04	6.31±0.92	0.030
IMT, mm	0.83±0.17	0.88±0.16	0.88±0.17	<0.001
MAP, mm Hg	95±12	100±10	102±11	<0.001
Carotid PP, mm Hg	59±17	62±14	67±16	<0.001
σ_c , kPa	60±24	60±17	66±23	0.002

Results are expressed as mean±SD.

the presence of prior CVD a reflection of the atherogenic milieu and blood pressure a reflection of the hemodynamic arterial milieu.

Statistical Analysis

All analyses were performed with SPSS (SPSS Inc). We used analysis of covariance to investigate trends in CVD risk factors and arterial properties across categories of glucose tolerance. We used multiple linear regression analyses to investigate the associations between glucose tolerance and IAD, IMT, LD, and σ_c . All associations were analyzed first without adjustments and then with adjustments for potential confounders. Because arterial properties are affected by age, sex, height, and BMI,^{9,23–26} these variables were considered first in the adjusted models. After we assessed the main effects, interaction terms were used to examine whether the association between glucose tolerance and arterial remodeling differed according to the presence or absence of prior CVD or differed with blood pressure. Individuals with impaired fasting glucose (n=61) and impaired glucose tolerance (n=107) did not differ from each other with regard to these analyses and were therefore combined. Values of *P*<0.05 were considered statistically significant, except for the interaction analyses, where we used *P*<0.10.

Results

Ultrasonography

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 arteries. The main reason for missing data was poor definition of the arterial wall attributable to obesity (BMI of those with versus those without qualitatively satisfactory examinations, 26.9±3.3 versus 31.3±5.6 kg/m²; *P*<0.001).

Baseline Characteristics

Table 1 shows the characteristics of the study population according to glucose tolerance. Of the 60 individuals with previously diagnosed DM-2, 13 were treated with insulin and 47 with blood glucose-lowering medication.

Carotid Artery Properties

Table 2 shows that, with deteriorating glucose tolerance, IAD, IMT, LD, brachial MAP, carotid PP, and σ_c increased.

Glucose Tolerance and LD

Table 3 shows that, compared with NGM, the association between DM-2 and LD was not statistically significant after adjustment for age, sex, height, and BMI (model 2). Additional adjustment for prior CVD did not change the regression coefficient (model 3). In contrast, the association between DM-2 and LD completely disappeared after adjustment for MAP and/or PP (models 4 through 6). The association between IGM and LD was not statistically significant (models 1 through 6). The Figure shows adjusted mean values for LD, IAD, IMT, and σ_c according to glucose tolerance.

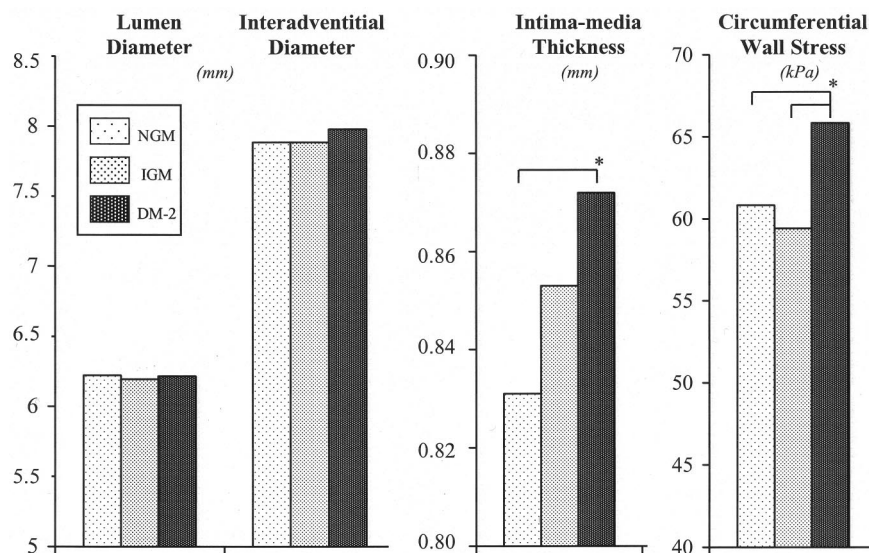
Glucose Tolerance and IAD

Compared with NGM, the association between DM-2 and IAD remained statistically significant after adjustment for age, sex, height, BMI, and prior CVD (Table 3, models 2 and 3). After adjustment for MAP and/or PP, the association between DM-2 and IAD almost completely disappeared (models 4 through 6). The association between IGM and IAD

TABLE 3. Carotid Artery Remodeling According to Glucose Tolerance

Models	Added Variables	LD		IAD		IMT		σ_c	
		IGM	DM-2	IGM	DM-2	IGM	DM-2	IGM	DM-2
1	Crude	0.12 (−0.06 to 0.33)	0.18 (0.02 to 0.35)	0.24 (0.03 to 0.45)	0.30 (0.12 to 0.47)	0.045 (0.012 to 0.077)	0.051 (0.024 to 0.079)	0.25 (−4.49 to 4.98)	6.08 (2.23 to 9.94)
2	Model+Sex+age+height+BMI	0.03 (−0.15 to 0.21)	0.13 (−0.03 to 0.29)	0.10 (−0.09 to 0.28)	0.25 (0.09 to 0.41)	0.027 (−0.003 to 0.058)	0.052 (0.026 to 0.079)	−0.65 (−5.38 to 4.07)	5.77 (1.75 to 9.80)
3	Model 2+prior CVD	0.008 (−0.17 to 0.19)	0.13 (−0.03 to 0.29)	0.08 (−0.11 to 0.27)	0.24 (0.07 to 0.41)	0.029 (−0.002 to 0.060)	0.050 (0.024 to 0.077)	−1.39 (−6.14 to 3.29)	5.00 (0.92 to 9.08)
4	Model 3+MAP	−0.07 (−0.24 to 0.11)	0.00 (−0.16 to 0.16)	0.00 (−0.18 to 0.18)	0.11 (−0.06 to 0.28)	0.026 (−0.005 to 0.057)	0.045 (0.017 to 0.073)
5	Model 3+PP	−0.03 (−0.22 to 0.16)	−0.01 (−0.17 to 0.16)	0.00 (−0.19 to 0.19)	0.09 (−0.08 to 0.26)	0.022 (−0.011 to 0.055)	0.040 (0.011 to 0.070)
6	Model 3+MAP+PP	−0.07 (−0.25 to 0.12)	−0.04 (−0.21 to 0.13)	−0.04 (−0.23 to 0.15)	0.06 (−0.11 to 0.23)	0.023 (−0.010 to 0.056)	0.041 (0.011 to 0.070)
7	Model 5+IAD	0.021 (−0.10 to 0.053)	0.037 (0.009 to 0.065)

Results are expressed as regression coefficients (95% CI).



Adjusted mean values for LD, IAD, IMT, and σ_C according to glucose tolerance. σ_C was adjusted for sex, age, height, BMI, and prior CVD. LD, IAD, and IMT were also adjusted for PP. * $P < 0.05$.

was not statistically significant after adjustment (models 2 through 6).

Glucose Tolerance and IMT

Compared with NGM, the association between DM-2 and IMT remained statistically significant after adjustment for age, sex, height, BMI, and prior CVD (Table 3, models 2 and 3). After adjustment for MAP and/or PP, the association decreased but remained statistically significant (models 4 through 6). Compared with NGM, IGM was not significantly associated with IMT after adjustment for MAP and/or PP (models 4 through 6), but the regression coefficients were about half those of DM-2. The association between DM-2 (and IGM) and IMT was driven to a minor extent by parallel changes in IAD (model 7).

Glucose Tolerance and σ_C

Compared with NGM, the association between DM-2 and σ_C remained statistically significant after adjustment for age, sex, height, BMI, and prior CVD (Table 3, models 2 and 3). The association between IGM and σ_C was not statistically significant (models 1 through 3).

Impact of Hyperglycemia and/or Insulinemia and Insulin Resistance on IMT

To estimate the contribution of hyperglycemia and hyperinsulinemia or insulin resistance to the increase in IMT associated with glucose tolerance, we compared the analyses (adjusted for sex, age, height, BMI, prior CVD, and carotid PP) with those additionally adjusted for indexes of hyperglycemia (either fasting or postload glucose or HbA1c), hyperinsulinemia (fasting insulin), or insulin resistance (HOMA). This showed that the combined contribution of hyperglycemia and/or insulinemia and insulin resistance explained 43% of the association between glucose tolerance and IMT (data not shown).

Additional Analyses

Additional adjustment for heart rate, lipid profile, use of lipid-lowering or antihypertensive medication, smoking, se-

rum creatinine, or (micro)albuminuria did not materially alter the results. If we replaced BMI with waist-to-hip ratio, the results were also not materially altered (data not shown).

No significant interaction terms were observed between glucose tolerance and prior CVD or between glucose tolerance and blood pressure (data not shown).

If we plotted IMT against LD to explore whether LD decreased at high IMT,^{9,25} no such phenomenon was observed (data not shown).

Discussion

The present investigation, the first population-based study on the association between glucose tolerance status and carotid arterial remodeling, had 3 main findings. First, DM-2 is associated with a pattern of compensatory remodeling (ie, preservation of LD at increased IMT), which, however, does not normalize σ_C , which increased. IGM was not associated with a particular pattern of remodeling. Second, in DM-2, the increase in IAD but not IMT was explained by blood pressure. Prior CVD did not explain the increase in IAD nor the increase in IMT. Third, DM-2 and (less so) IGM were associated with an increase in IMT, and 43% of the association between glucose tolerance and IMT was explained by hyperglycemia and/or insulinemia and insulin resistance. Taken together, our results show that DM-2 is associated with compensatory remodeling, whereas IGM is not associated with a particular pattern of remodeling. In DM-2, the alterations in IMT and IAD are unrelated and differentially driven: The increase in IMT is driven mainly by deteriorating glucose tolerance, whereas that in IAD is driven by increased blood pressure.

Our findings support the hypothesis that blood pressure, particularly its pulsatile component, exerts a fatiguing effect on the load-bearing elements of the arterial wall (ie, elastin and collagen), resulting in degenerative changes and fractures and IAD enlargement.¹¹ A methodological advantage of our study was the fact that we were able to quantify local carotid PP.² This is important because of PP amplification,²⁷ which could distort the association between pressure and arterial

geometry if brachial PP is used as an estimate of carotid PP. We also show that the increase in IMT was largely independent of blood pressure and was driven only to a minor extent by the increase in IAD. Therefore, deteriorating glucose tolerance is an independent determinant of increased IMT. This latter finding is supported by the observation that IMT increased before the onset of DM-2 and by the observation that 43% of the relationship between glucose tolerance and IMT could be explained by the combination of hyperglycemia and/or insulinemia and insulin resistance, which may be markers of increased carbonyl and oxidative stress, including the effect of Amadori adducts and advanced glycation end products.²⁸

The relationship between IMT and LD is complex. Previous population-based studies on age-related carotid remodeling^{9,23–26} have not provided consistent results; they have observed LD to increase with increasing IMT,^{24,26} LD to remain constant with increasing IMT,²³ and LD to increase with increasing IMT only up to a certain level of IMT, after which LD markedly decreased.^{9,25} Here, we described glucose tolerance-related carotid remodeling and observed that LD remained constant with increasing IMT. Importantly, our data suggest that, with deteriorating glucose tolerance, changes in IAD and IMT are driven by hemodynamic and metabolic factors, respectively, which may explain why the changes in LD and IMT appear to be uncoordinated.

In apparent contrast to the present results, we have previously observed that the increase in IAD during a 3-year follow-up of individuals with impaired glucose tolerance appeared partly attributable to hyperglycemia.²⁹ However, we may have underestimated the role of PP in our previous investigation²⁹ because there was selective mortality of individuals with high PP,³⁰ which may have caused a relative increase in the importance of the role of hyperglycemia.

Our study had several limitations. First, ultrasound cannot discriminate between the intimal and medial layers of the artery, and this would have given more insight into changes thought to be particularly associated with atherosclerosis (intima) or arteriosclerosis (media).⁵ This limitation will most certainly be eliminated in future studies by the rapid development of ultrasound image processing.³¹ Second, we used a single-point measurement technique^{32,33} to determine IMT. Therefore, our results may have been influenced by variability of IMT along the arterial segment.¹⁹ However, we minimized measurement variability by clearly defining where IMT was determined.² Third, our results were obtained in a white, relatively healthy, elderly population; thus, inferences should be made with care.

In conclusion, DM-2 is associated with preservation of carotid LD at increased IMT (ie, compensatory remodeling), which, however, does not normalize σ_C , which remains increased. In contrast, IGM is not associated with changes in LD or IAD. IMT is moderately increased, but σ_C remains normal. Carotid remodeling in DM-2 thus appears maladaptive, which may explain the increased risk of CVD, especially stroke, in DM-2.

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