Left Ventricular Mass Increases With Deteriorating Glucose Tolerance, Especially in Women: Independence of Increased Arterial Stiffness or Decreased Flow-Mediated Dilation

The Hoorn Study

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OBJECTIVE — Type 2 diabetes and impaired glucose metabolism (IGM) are associated with an increased cardiovascular disease (CVD) risk. Increased left ventricular mass (LVM) is thought to increase CVD risk through several unfavorable cardiac changes. Type 2 diabetes and IGM are associated with increased LVM, but the underlying mechanism is unclear. We investigated the association between glucose tolerance status (GTS) and LVM and explored whether any such association could be mediated through increased arterial stiffness, impaired endothelial function, or the presence of atherosclerosis.

RESEARCH DESIGN AND METHODS — We used ultrasound to measure LVM, carotid and femoral stiffness, carotid-femoral transit time, and flow-mediated vasodilation (FMD) and tonometry to estimate compliance and augmentation index. The study population ($n = 780$) consisted of 287 individuals with normal glucose metabolism (NGM), 179 with IGM, and 314 with type 2 diabetes, and the mean age was 68.4 years.

RESULTS — In women, after adjusting for age, height, BMI, and mean arterial pressure, LVM increased significantly with deteriorating GTS (LVM 157 g in NGM, 155 g in IGM, and 169 g in type 2 diabetes; P for trend <0.018). Additional adjustment for arterial stiffness, FMD, or the presence of atherosclerosis did not materially alter the results, even though these variables were significantly associated with both GTS and LVM. Indexes of hyperglycemia/-insulinemia or insulin resistance explained at most 7% of the association between GTS and LVM. In men, no statistically significant associations were observed.

CONCLUSIONS — Our data expand the conceptual view of the pathogenesis of GTS-related changes in LVM because we show that the increase in LVM in women is independent of increased

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Abbreviations: CVD, cardiovascular disease; EDD, end-diastolic diameter; FMD, flow-mediated vasodilation; GTS, glucose tolerance status; IGM, impaired glucose metabolism; IVS, interventricular septum thickness; LVM, left ventricular mass; NGM, normal glucose metabolism; RWT, relative wall thickness.

arterial stiffness, impaired FMD, or the presence of atherosclerosis. In addition, we show that this increase in LVM is only minimally explained by indexes of hyperglycemia/-insulinemia or insulin resistance. Our data may, in part, explain the increased CVD risk seen in women with deteriorating GTS.

Cardiovascular disease (CVD) accounts for most of the morbidity and mortality in type 2 diabetes. An increased CVD risk is already present in individuals with impaired glucose metabolism (IGM), i.e., impaired fasting glucose and/or impaired glucose tolerance (1), and is not accounted for by conventional risk factors.

Increased left ventricular mass (LVM) is thought to increase CVD risk through a series of unfavorable metabolic, functional, and structural cardiac changes (2–4). For example, increased LVM increases the risk of myocardial infarction and heart failure by enhancing myocardial oxygen consumption and by impeding diastolic left ventricular compliance. Several studies have shown that deteriorating glucose tolerance is associated with increased LVM (5–14). The mechanisms responsible for this association remain unclear, but hyperglycemia/-insulinemia and the insulin-resistant state have been implicated in the pathogenesis of increased LVM (14–18).

However, the harmful effects of deteriorating glucose tolerance are not limited to the myocardium, and a variety of both structural and functional maladaptive alterations along the arterial tree have been reported in IGM and type 2 diabetes. We have previously shown that deteriorating glucose tolerance status (GTS) is associ-

ated with increased carotid, femoral, and brachial arterial stiffness (as measured by distensibility, compliance, and elastic modulus) (19) and with impaired endothelial function (as measured by flow-mediated vasodilation [FMD] of the brachial artery) (R.M.A.H., P.J.K., J.M.D., G.N., R.J.H., O.K., L.M.B., C.D.A.S., unpublished observations). Increased arterial stiffness can contribute to increases in LVM by elevating cardiac afterload, where the increase in LVM can be viewed as an adaptive response to keep left ventricular wall stress constant and preserve left ventricular systolic function (20,21). Endothelial dysfunction may contribute to increases in LVM by loss of the inhibitory role of nitric oxide on the synthesis of extracellular matrix components (22) and by shifting the local vasodilator (nitric oxide)/vasoconstrictor (endothelin) balance toward endothelin, a molecule with specific cardiac myocyte growth-promoting properties (23).

In view of these considerations, we hypothesized that increased LVM occurs not only in type 2 diabetes but also in IGM and is mediated, at least in part, by a glucose intolerance–associated increase in arterial stiffness and impairment of endothelial function. We investigated these hypotheses in a population-based cohort.

RESEARCH DESIGN AND
METHODS — For the present investigation, we used data from the 2000 Hoorn Study follow-up examination (19) and the Hoorn Screening Study (24). Briefly, the Hoorn Study is a study of glucose metabolism in the general population ($n = 2,484$) that started in 1989 (25). In 2000, a follow-up examination was carried out among all surviving participants. We invited all those who had diabetes, as determined by an oral glucose tolerance test or who were treated for diabetes at the 1996 follow-up ($n = 176$). We also invited random samples of individuals with normal glucose metabolism (NGM) ($n = 705$) and IGM ($n = 193$). Of 1,074 individuals thus invited, 648 (60%) participated. Additionally, we invited 217 individuals with type 2 diabetes from the Hoorn Screening Study (24), of whom 188 (87%) participated. Data on 14 individuals were missing due to logistical problems. The study population ($n = 822$) thus consisted of three groups: 290 with NGM, 187 with IGM, and 345 with type 2 diabetes. The study was ap-

proved by the local ethics committee. All participants gave their written informed consent.

Among the 455 nonparticipants (53% women), 13% were complete nonresponders. The remaining nonparticipants gave 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%).

Echocardiography
An experienced research technician unaware of the participants' clinical status or GTS obtained an echocardiogram in each participant, according to a standardized protocol, with the use of a single ultrasound scanner (HP SONOS 5500; Hewlett Packard, Andover, MA). M-mode recordings were digitally stored and read according to the guidelines of the American Society of Echocardiography (26).

Left ventricular end-diastolic diameter (EDD), posterior wall thickness (PWT), and interventricular septum thickness (IVS) were measured at end diastole. LVM was calculated as $0.8(1.04)$ $([EDD + IVS + PWT]^3 - EDD^3) + 0.6$ (in grams) and relative wall thickness (RWT) as $(IVS + PWT)/EDD$ (27) Each echocardiogram was inspected afterward by a senior cardiologist blinded to the participants' clinical status or GTS in order to monitor the quality of both recordings and readings. Left ventricular geometric patterns were classified according to Heesen et al. (28).

Arterial stiffness
Carotid and femoral arterial stiffness indexes were determined by ultrasonography, using previously described techniques (19) and calculated as follows. Distensibility coefficient = $(2\Delta D \times D + \Delta D^2)/(\Delta P \times D^2)$ (in $10^{-3} \cdot kPa^{-1}$); compliance coefficient = $\pi (2D \times \Delta D + \Delta D^2)/(4 \times \Delta P)$ (in $mm^2 \cdot kPa^{-1}$); and Young's elastic modulus = $D/(intima-media thickness \times distensibility coefficient)$ (in kPa). ΔD is distension, D is diameter, and ΔP is local pulse pressure. Local pulse pressures were determined with the use of distension waveform calibration (29). The distensibility coefficient reflects the arterial elastic properties, whereas the compliance coefficient reflects the arterial buffering capacity and

Young's elastic modulus indicates the intrinsic elastic wall properties (30).

Systemic arterial compliance (ml/mmHg) was determined according to the exponential decay method (31) and the augmentation index from pressure wave analysis (32), both with the use of tonometry-derived aortic pressure waveforms (Sphygmocor, Moreton-in-Marsh, U.K.), as previously described (33). Systemic arterial compliance and the augmentation index represent the overall buffering capacity of the arterial system and the overall stiffness of the arterial system, respectively, taking into account the contribution of reflected (backward) pulse waves to aortic blood pressure.

The carotid-femoral transit time (in ms) was determined with the use of the ultrasonically recorded carotid and femoral distension wave forms (33) and represents the average stiffness over the aortic segment.

Endothelial function
We measured brachial artery endothelium-dependent vasodilation and the presence of atherosclerosis (both as defined below) as proxies for coronary artery endothelium-dependent vasodilation (34,35).

Brachial artery flow–mediated dilation
All individuals underwent an ultrasound examination according to guidelines of the International Brachial Artery Reactivity Task Force (36). Briefly, baseline arterial diameter and peak flow velocity were determined. A blood pressure cuff was placed on the forearm, inflated, and kept constant at supra-systolic pressure to induce forearm ischemia. After 5 min, the cuff was released, resulting in an increase in arterial blood flow. This increase in blood flow increased shear stress, which served as the stimulus for flow-mediated dilation. After cuff release, maximum peak flow velocity was measured within 15 s and arterial diameter at 45, 90, 180, and 300 s. The maximum diameter in any of these four measurements was used in statistical analysis. After 15 min of rest to reestablish arterial baseline conditions, endothelium-independent, nitroglycerin-mediated dilation was determined as follows: baseline arterial diameter and peak flow velocity were redetermined. Nitroglycerin (400 µg, Nitrolingual Spray; Pohl-Boskamp, Hohenlockstedt, Ger-

many) was then sublingually administered; after 5 min, arterial diameter and peak flow velocity were again determined.

Other measurements

Health status, medical history, medication use, and smoking habits were assessed by a questionnaire (25). Systolic and diastolic pressure; pulse pressure; hypertension; glucose; HbA$_{1c}$; serum total, HDL, and LDL cholesterol; serum triglycerides; BMI; waist-to-hip ratio; microalbuminuria; and ankle-brachial pressure index were determined as described elsewhere (24,25). Insulin resistance was calculated according to the homeostasis model assessment (37). Resting electrocardiograms were coded according to the Minnesota Code. Prior CVD was defined as Minnesota Code 1.1–1.3, 4.1–4.3, 5.1–5.3, or 7.1 on the electrocardiogram, coronary bypass operation or angioplasty, and/or peripheral arterial bypass or amputation. The presence of prior CVD, peripheral arterial disease as defined by an ankle-brachial pressure index <0.9, and/or a carotid intima-media thickness >1.05 mm (i.e., the 90th percentile of the distribution in individuals with NGM) was considered to indicate the presence of atherosclerosis.

Reproducibility

Reproducibility was assessed in 10 individuals (5 men; age 58.2 ± 9.5 years) who were examined twice at 2-week intervals. The intraobserver intersession coefficients of variation ([SD of the difference/$\sqrt{2}$]/pooled mean) were 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%; carotid-femoral transit time 4.4%; aortic augmentation index 3.6%; systemic arterial compliance 8.3%; and endothelium-dependent and -independent dilation, expressed as absolute diameter, 14.7 and 10.3%.

Statistical analysis

All analyses were carried out with SPSS (SPSS, Chicago, IL). We used ANCOVA with linear contrast to investigate trends in left ventricular mean values across the categories of glucose tolerance. All statistically significant trends were tested whether they deviated from linearity. The associations between glucose tolerance

and the measurements of cardiac structure and geometry were examined separately for men and women because, out of five previous population-based studies (5,7,9,11,12), three reported strong sex-specific differences (5,9,11), particularly so for LVM.

We first analyzed the associations without any adjustments (crude model) and then with adjustments for potential confounders (adjusted models). Because left ventricular structure is known to be affected by age, height, BMI, and blood pressure (38), these variables were considered first in the adjusted models. Arterial stiffness indexes, FMD, and the presence of atherosclerosis were then separately added into the models, as were estimates of hyperglycemia-/-insulinemia and insulin resistance.

Individuals with impaired fasting glucose (n = 63) and impaired glucose tolerance (n = 116) did not significantly differ from each other with regard to any of the analyses and were therefore combined. P values <0.05 were considered statistically significant.

RESULTS

Ultrasound examinations

In 42 of the 822 participants, LVM could not be determined due to either a high BMI (n = 33; BMI of those with qualitatively satisfactory examinations versus those without, 27.5 ± 3.8 vs. 37.9 ± 8.9 kg/m^2, P < 0.001) or a poor transthoracic window (n = 9). In the remaining 780 individuals, carotid and femoral stiffness indexes and FMD could be determined in 739, 648, and 636 individuals, respectively. The main reason for missing arterial data was poor definition of the arterial wall due to obesity (BMI of those with qualitatively satisfactory examinations versus those without, 26.9 ± 3.3 vs. 30.5 ± 4.5 kg/m^2, P < 0.001).

Baseline characteristics

Table 1 shows the characteristics of the entire study population. Both IGM and type 2 diabetes were characterized by a worsening cardiovascular risk factor profile compared with NGM.

Glucose tolerance and left ventricular structure: crude associations

In women, LVM increased significantly with deteriorating glucose tolerance (P for

trend <0.001) (Table 2). Similar trends could be observed for EDD, PWT, and IVS. RWT did not show any significant trend (P for trend = 0.358). The proportion of women with a normal geometric pattern decreased significantly with deteriorating glucose tolerance (P for trend ≤0.002), whereas the proportions of women with either eccentric or concentric hypertrophy increased significantly (P for trend = 0.042 and 0.039, respectively). No statistically significant trend was observed for concentric remodeling. In men, neither the measures of left ventricular structure nor the distribution of geometric patterns showed any significant trends with deteriorating glucose tolerance (Table 2).

Glucose tolerance and left ventricular structure: adjusted associations

In women, after adjustment for age, height, BMI and mean arterial pressure, glucose tolerance remained statistically significantly associated with increased LVM (P for trend <0.018) (Table 3, model 2). Additional adjustment for carotid distensibility, FMD, and the presence of atherosclerosis did not materially change the results (P for trend = 0.030, 0.043, and 0.028, respectively, models 3–5), even though carotid distensibility, FMD, and the presence of atherosclerosis were significantly associated with GTS (Table 1) and, after adjustment for age and mean arterial pressure, LVM (data not shown). A similar pattern could be observed for the association between glucose tolerance and end diastolic diameter (models 1–5).

Different effects were observed for PWT, IVS, and RWT. The associations between glucose tolerance and both PWT and IVS were not statistically significant after adjustment for age, height, BMI, and mean arterial pressure (Table 3, models 1 and 2), whereas no significant associations, either crude or adjusted, could be observed between GTS and RWT (RWT, models 1–5). Additional investigations to explore the individual impact of the variables age, height, BMI, and mean arterial pressure revealed that the associations of GTS with PWT and left ventricular wall thickness were rendered insignificant after adjustment for mean arterial pressure, whereas the association with IVS thickness was rendered insignificant after ad-

Table 1—*Characteristics of the study population according to GTS and sex*

	Women				Men			
	NGM	IGM	Type 2 diabetes	P for trend	NGM	IGM	Type 2 diabetes	P for trend
n (M/F)	139	89	165	—	148	90	149	—
Age (years)	68 ± 6	70 ± 6	68 ± 7	0.52	68 ± 5	69 ± 6	65 ± 8	0.59
Heart rate (bpm)	63 ± 11	65 ± 8	66 ± 10	0.008	60 ± 10	61 ± 9	62 ± 10	0.143
Systolic pressure (mmHg)	138 ± 22	148 ± 18	153 ± 20	<0.001	135 ± 17	140 ± 13	144 ± 17	<0.001
Diastolic pressure (mmHg)	73 ± 9	77 ± 9	79 ± 8	<0.001	75 ± 8	78 ± 7	79 ± 9	<0.001
Mean arterial pressure (mmHg)	95 ± 12	101 ± 11	104 ± 11	<0.001	95 ± 10	99 ± 8	101 ± 10	<0.001
Antihypertensive medication	22	44	57	<0.001	28	29	46	0.001
Total cholesterol (mmol/l)	6.2 ± 0.9	6.1 ± 1.0	5.8 ± 1.0	0.004	5.4 ± 0.9	5.6 ± 0.9	5.3 ± 1.0	0.21
HDL cholesterol (mmol/l)	1.6 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	<0.001	1.3 ± 0.4	1.2 ± 0.3	1.1 ± 0.3	<0.001
Triglycerides (mmol/l)	1.0 (0.8–1.5)	1.3 (1.0–1.8)	1.5 (1.2–2.2)	<0.001	1.3 (0.8–1.5)	1.4 (1.0–1.8)	1.5 (1.0–2.0)	<0.001
Lipid-lowering medication	11	17	16	0.24	15	14	22	0.072
Fasting glucose (mmol/l)	5.3 ± 0.3	6.1 ± 0.4	7.5 ± 1.6	<0.001	5.4 ± 0.3	6.0 ± 0.4	7.7 ± 1.8	<0.001
Postload glucose (mmol/l)	5.7 ± 1.1	8.1 ± 1.4	12.1 ± 2.6	<0.001	5.4 ± 1.1	7.9 ± 1.8	11.0 ± 2.7	<0.001
HbA$_{1c}$ (%)	5.7 ± 0.3	5.9 ± 0.3	6.6 ± 0.9	<0.001	5.6 ± 0.4	5.8 ± 0.4	6.5 ± 0.9	<0.001
Insulin (pmol/l)*	45 (34–56)	74 (54–93)	85 (60–107)	<0.001	46 (34–62)	61 (45–77)	82 (52–1.18)	<0.001
HOMA insulin resistance (arbitrary units)*	1.6 ± 0.8	2.8 ± 1.1	4.8 ± 4.6	<0.001	1.7 ± 0.8	2.6 ± 1.4	4.6 ± 3.8	<0.001
Height (cm)	163 ± 6	163 ± 6	163 ± 6	0.89	176 ± 6	175 ± 6	175 ± 6	0.34
BMI (kg/m²)	26.2 ± 3.4	28.7 ± 4.5	29.4 ± 5.2	<0.001	26.2 ± 3.3	27.2 ± 3.1	28.7 ± 3.5	<0.001
Waist-to-hip ratio	0.84 ± 0.07	0.89 ± 0.07	0.92 ± 0.11	<0.001	0.96 ± 0.06	0.99 ± 0.06	1.01 ± 0.06	<0.001
Microalbuminuria	7	14	17	0.012	13	15	23	0.020
Prior CVD	42	47	55	0.031	42	46	51	0.14
Peripheral arterial disease	3	5	7	0.14	6	5	10	0.16
Carotid IMT (mm)†	0.79 ± 0.13	0.86 ± 0.14	0.88 ± 0.14	<0.001	0.86 ± 0.18	0.88 ± 0.17	0.88 ± 0.19	0.37
Carotid distensibility (10⁻³ kPa⁻¹)†	12.5 ± 4.6	10.7 ± 4.3	9.3 ± 3.8	<0.001	13.1 ± 4.0	12.3 ± 4.6	11.4 ± 4.3	0.002
Carotid compliance (mm² kPa⁻¹)†	0.50 ± 0.18	0.45 ± 0.16	0.42 ± 0.15	<0.001	0.67 ± 0.22	0.66 ± 0.30	0.60 ± 0.21	0.012
Carotid Young's elastic modulus (kPa)	0.90 ± 0.52	0.95 ± 0.40	1.17 ± 0.68	<0.001	0.82 ± 0.31	0.92 ± 0.44	1.01 ± 0.59	0.001
Femoral distensibility (10⁻³ kPa⁻¹)‡	5.7 ± 2.3	3.9 ± 1.6	4.1 ± 1.8	<0.001	5.6 ± 2.1	3.9 ± 1.7	4.0 ± 1.7	<0.001
Femoral compliance (mm² kPa⁻¹)‡	0.40 ± 0.19	0.29 ± 0.13	0.27 ± 0.13	<0.001	0.51 ± 0.22	0.35 ± 0.15	0.32 ± 0.13	<0.001
Systemic arterial compliance (ml/mmHg)*	1.00 ± 0.31	0.89 ± 0.24	0.79 ± 0.24	<0.001	1.27 ± 0.33	1.16 ± 0.27	1.06 ± 0.32	<0.001
Augmentation index (%)*	155 ± 18	157 ± 18	158 ± 18	0.33	141 ± 17	145 ± 18	147 ± 20	0.029
Carotid-femoral transit time (ms)§	53 ± 16	51 ± 14	50 ± 14	0.22	57 ± 16	57 ± 15	54 ± 18	0.28
Flow-mediated dilation (mm)‖	0.19 ± 0.13	0.16 ± 0.16	0.13 ± 0.18	0.002	0.19 ± 0.17	0.21 ± 0.18	0.13 ± 0.15	0.009
GTN-mediated dilation (mm)‖	0.44 ± 0.22	0.40 ± 0.20	0.46 ± 0.28	0.72	0.45 ± 0.18	0.46 ± 0.26	0.43 ± 0.21	0.64
Presence of atherosclerosis	44	51	60	0.006	49	53	53	0.49

Data are means ± SD, median (interquartile range), or percent. *$n = 767$, as 13 individuals with type 2 diabetes were on insulin therapy; †$n = 739$ for carotid measurements; ‡$n = 648$ for femoral measurements; §$n = 315$ for carotid-femoral transit time (for technical reasons, not related to participants' characteristics); ‖$n = 636$ for the brachial artery endothelial artery function test and $n = 614$ for augmentation index and systematic arterial compliance measurements. GTN, glyceryl-trinitrate; IMT, intima-media thickness.

Table 2—*Sex-specific characteristics of left ventricular structure according to GTS*

Left ventricular structure	Women				Men			
	NGM	IGM	Type 2 diabetes	*P* for trend	NGM	IGM	Type 2 diabetes	*P* for trend
M-mode measurement								
Mass	147 ± 37	163 ± 48	176 ± 51	<0.001	188 ± 55	187 ± 59	199 ± 66	0.096
EDD	4.78 ± 0.48	4.94 ± 0.56	4.99 ± 0.52	0.001	5.22 ± 0.60	5.17 ± 0.61	5.30 ± 0.58	0.223
Posterior wall thickness	0.85 ± 0.14	0.89 ± 0.15	0.92 ± 0.16	<0.001	0.92 ± 0.14	0.94 ± 0.16	0.93 ± 0.17	0.394
IVS	0.93 ± 0.21	0.96 ± 0.22	1.00 ± 0.26	0.018	1.00 ± 0.23	0.99 ± 0.25	1.02 ± 0.25	0.327
RWT	0.38 ± 0.09	0.38 ± 0.09	0.39 ± 0.09	0.358	0.37 ± 0.09	0.38 ± 0.10	0.37 ± 0.09	0.953
Geometric pattern								
Normal geometry	83.8	77.8	73.2	0.002	76.8	71.9	74.5	0.709
Concentric remodeling	13.5	15.6	14.1	0.931	11.6	16.9	9.7	0.572
Eccentric hypertrophy	1.4	5.6	6.7	0.042	7.2	4.5	7.9	0.791
Concentric hypertrophy	1.4	1.1	6.0	0.039	1.3	6.7	7.9	0.251

All M-mode measurements are given in centimeters (means ± SD), except for mass, which is given in grams. Geometric patterns are expressed as percentages of individuals within the glucose tolerance category. Normal geometry, RWT <0.45 and LVM index <125 g/m^2; concentric remodeling, RWT ≥0.45 and LVM index <125 g/m^2; eccentric hypertrophy, RWT <0.45 and LVM index ≥125 g/m^2; concentric hypertrophy, RWT ≥0.45 and LVM index ≥125 g/m^2.

justment for BMI (detailed data not shown).

In men, neither crude (*P* for trend, all ≥0.096) nor adjusted (*P* for trend, all ≥0.218) analyses showed statistically significant associations between GTS and ventricular structure. Nevertheless, the *P* value for interaction (sex times GTS) was not significant (*P* = 0.11).

Results were similar when BMI was replaced by waist-to-hip ratio and when mean arterial pressure was replaced by systolic, diastolic, or pulse pressure (detailed data not shown). If we replaced IVS or PWT by left ventricular wall thickness, i.e., the sum of both, the crude association with glucose tolerance lost significance after adjustment for the variables of model 2 (detailed data not shown). Results were also similar when carotid distensibility was replaced by other carotid or femoral stiffness indexes or by systemic arterial compliance, augmentation index, or the carotid-femoral transit time (data not shown).

Our study population was too small to further explore any underlying mechanisms between glucose tolerance and ventricular geometry.

Impact of glucose, insulin, and insulin resistance on LVM
To estimate the contribution of hyperglycemia/-insulinemia or insulin resistance to the increase in LVM associated with IGM and type 2 diabetes, we compared the LVM analyses (adjusted for age, height, BMI, and mean arterial pressure)

with those additionally adjusted for HbA$_{1c}$ (or fasting or postload glucose), insulin, and insulin resistance. This showed that in women, at most 7% of the association between glucose tolerance and LVM could be explained by indexes of hyperglycemia/-insulinemia or insulin resistance.

Additional analyses
Additional adjustment for brachial stiffness indexes, heart rate, lipid profile, the use of lipid-lowering or antihypertensive medication including ACE inhibitors, smoking, or (micro-)albuminuria did not materially alter our results (detailed data not shown). Results were also not materially altered if we excluded individuals with left ventricular wall motion abnormalities (*n* = 55) (data not shown). Finally, if we replaced LVM mass (in grams) by LVM index, i.e., LVM divided by body surface area (in grams per meters squared), our results were again not altered (data not shown).

CONCLUSIONS — The present population-based study on the association between glucose tolerance and cardiac structure had three main findings. First, glucose tolerance was independently associated with increased LVM in women, but not clearly so in men. Second, the association between glucose tolerance and LVM in women was not mediated by glucose intolerance–associated increased arterial stiffness and impaired endothelial function. Third, indexes of hyperglyce-

mia/-insulinemia or insulin resistance explained at most 7% of the association between glucose tolerance and LVM.

Our study extends previous population-based investigations (5–7,9,11,12), as we are the first to examine the impact of arterial stiffness and endothelial function on the association between glucose tolerance and cardiac structure. In addition, to be able to sufficiently adjust for potential confounders, we extensively characterized our study population in terms of CVD risk factors, prior CVD, and glucose metabolism.

Our results are in general agreement with previous population-based studies on the association between glucose tolerance and LVM (5,7,9,11,12). However, it is currently unclear whether (5,9,11) or not (7,12) this association is stronger in women than in men. In our investigation, the statistical test for interaction between sex and glucose tolerance on LVM was *P* = 0.11. Therefore, the result of our interaction analysis neither excluded nor proved the existence of a sex-specific association.

We suggest that the independent association we report between glucose tolerance and EDD, as well as the absence of such an association with IVS or PWT, may be explained by the fact that individuals with type 2 diabetes are characterized by an expanded extracellular volume (39), which has been shown to increase left ventricular chamber size relatively more than myocardial wall thickness (40). However, it remains poorly understood

Table 3—*Sex-specific adjusted analyses of left ventricular structure*

Model	Women				Men			
	NGM	IGM	Type 2 diabetes	P for trend	NGM	IGM	Type 2 diabetes	P for trend
Left ventricular mass (g)								
1	147	163*	176†‡	<0.001	188	187	199‡	0.096
2	157	155	169†‡	0.018	195	184	193	0.843
3	156	155	167‡	0.030	194	180	182	0.760
4	154	154	164‡	0.043	191	177	188	0.703
5	157	155	169†‡	0.028	195	184	193	0.756
EDD (cm)								
1	4.78	4.94*	4.99‡	<0.001	5.22	5.17	5.30	0.223
2	4.82	4.90	4.97‡	0.021	5.26	5.17	5.27	0.884
3	4.80	4.86	4.95‡	0.020	5.23	5.11	5.27	0.601
4	4.80	4.85	4.96‡	0.018	5.22	5.09	5.25	0.736
5	4.82	4.90	4.97‡	0.022	5.26	5.17	5.27	0.887
Posterior wall thickness (cm)								
1	0.85	0.89	0.92‡	<0.001	0.92	0.94	0.93	0.394
2	0.88	0.87	0.90	0.300	0.94	0.93	0.92	0.321
3	0.88	0.88	0.89	0.619	0.93	0.92	0.91	0.245
4	0.88	0.88	0.88	0.632	0.93	0.92	0.91	0.440
5	0.88	0.87	0.89	0.386	0.94	0.93	0.92	0.271
IVS (cm)								
1	0.93	0.96	1.00‡	0.18	1.00	0.99	1.02	0.327
2	0.97	0.93	0.97	0.978	1.02	0.98	1.01	0.663
3	0.97	0.94	0.95	0.676	1.02	0.96	0.99	0.274
4	0.96	0.93	0.95	0.625	1.02	0.97	0.99	0.427
5	0.97	0.93	0.97	0.910	1.02	0.98	1.00	0.651
RWT								
1	0.38	0.38	0.39	0.358	0.37	0.38	0.37	0.953
2	0.39	0.37	0.38	0.412	0.38	0.38	0.37	0.447
3	0.39	0.38	0.38	0.219	0.38	0.37	0.36	0.218
4	0.39	0.38	0.37	0.225	0.38	0.38	0.37	0.391
5	0.39	0.38	0.38	0.341	0.38	0.38	0.37	0.436

Model 1, crude; model 2, adjusted for age, height, BMI, and mean arterial pressure; model 3, adjusted for variables of model 2 plus carotid distensibility; model 4, model 2 plus adjusted for endothelial function; model 5, model 2 plus adjusted for the presence of atherosclerosis. *IGM significantly different from NGM; †type 2 diabetes significantly different from IGM; ‡type 2 diabetes significantly different from NGM; all P values < 0.05.

why the left ventricle apparently remodels differentially over its regions (41), although local dispersion of ventricular pressure, ventricular flow patterns (42), and (sex-specific) nonhemodynamic factors are thought to play a role (43,44) in addition to specific, diabetes-associated alterations in cardiac structure (5,7,9,12). Taken together, these (5–7,9,12) and the present data show that the left ventricle is subject to maladaptive alterations with deteriorating glucose tolerance, especially in women. This sex-specific increase in LVM may explain, at least in part, the increased CVD risk in women with type 2 diabetes (45).

Our study showed that increased carotid and femoral arterial stiffness, or any of the other stiffness indexes, influenced the association between glucose tolerance and measurements of cardiac structure only minimally, despite the fact that deteriorating glucose tolerance was associated with increased arterial stiffness (19) and that increased arterial stiffness was associated with increased LVM. The association between glucose tolerance and LVM was also not explained by impairment of endothelial function, as estimated by brachial artery FMD and the presence of atherosclerosis, even though deteriorating glucose tolerance was associated with impaired endothelial function, which in turn was associated with increased LVM. Decreased endothelial synthesis or bioavailibility of nitric oxide may contribute to increases in LVM by loss of its orchestrating role in the synthesis of extracellu-

lar matrix components and by shifting the local myocardial homeostasis toward hypertrophy (22,23,46). Our results therefore suggest that other pathophysiological mechanisms may play a role, such as increased oxidative and carbonyl stress (47), chronic low-grade inflammation (48), and(or) autonomic neuropathy (49). We cannot exclude, however, that the methods we used are insufficiently precise estimates of coronary endothelial function, which, however, is difficult to directly measure in large-scale studies.

Hyperglycemia/-insulinemia and insulin resistance have been implicated in the development of increased LVM (15–18). In our study, the association between GTS and LVM could only be explained to a minor extent (<7%) by any of these

variables. These observations are in line with several previous (population-based) studies (5,50–53) However, conflicting results have been published in relatively small, select, non–population-based investigations (15–18) and one population-based investigation among non-Caucascian individuals (14).

Our study had several limitations. First, it should be kept in mind that the cross-sectional nature of our data does not allow us to make strong causal inferences. Second, our results might have been influenced by the coexistence of CVD affecting left ventricular shape. However, it has been shown that LVM can be estimated accurately from M-mode echocardiography, even in the presence of CVD (27). Nevertheless, to circumvent this possibility, we adjusted for CVD in our analyses. Third, due to the rapid responsiveness of the body to hormonal and metabolic changes, determination of insulin resistance by homeostasis model assessment method is subject to biological variability, which might have weakened its association with LVM. However, recommendations (37) made to diminish this source of variation are not easily applicable in large population-based studies. Finally, our results were obtained in a relatively elderly Caucasian population, and therefore, it remains to be determined whether our results can be generalized to other ages and ethnicities (14).

In conclusion, our data expand the conceptual view of the pathogenesis of glucose tolerance–related changes in LVM, as we show that the increase in LVM in women is independent of increased arterial stiffness, impaired FMD, or the presence of atherosclerosis. In addition, we show that this increase in LVM is only minimally explained by indexes of hyperglycemia/-insulinemia or insulin resistance. Our data may explain, in part, the increased CVD risk seen in women with deteriorating glucose tolerance.

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