

Impaired Fasting Glucose Is Associated with Increased Arterial Stiffness in Elderly People without Diabetes Mellitus: The Rotterdam Study

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OBJECTIVES: To study the association between impaired fasting glucose (IFG) and arterial stiffness in older adults.

DESIGN: Cross-sectional population-based study.

SETTING: The Rotterdam Study, a Dutch population-based cohort study.

PARTICIPANTS: Two thousand nine hundred eighty-seven subjects aged 60 and older.

MEASUREMENTS: Arterial stiffness assessed by measuring common carotid arterial distensibility and glucose status classified into three categories: normal fasting glucose (NFG) (fasting glucose <6.1 mmol/L), IFG (fasting glucose 6.1–6.9 mmol/L), and diabetes mellitus (DM).

RESULTS: In the total cohort, common carotid distensibility decreased with increasing impairment of glucose metabolism. Subjects younger than 75 with IFG were comparable with subjects with NFG with respect to arterial stiffness. Subjects aged 75 and older with IFG had stiffer arteries than subjects with NFG, reaching the same arterial stiffness as subjects with DM. For subjects younger than 75, mean difference in distensibility coefficient between subjects with NFG and with IFG was 0.1 (95% confidence interval (CI) = -0.04–0.05, $P = .88$) and between subjects with NFG and with DM was 1.2 (95% CI = 0.7–1.7, $P < .001$). For subjects aged 75 and older, the mean difference between these groups was 0.7 (95% CI = 0.2–1.2, $P = .007$) and 0.8 (0.3–1.4; $P = .002$), respectively. In the

total cohort, fasting glucose was strongly associated with carotid distensibility (β -coefficient = -0.29, $P < .001$).

CONCLUSION: IFG is related to arterial stiffness in elderly subjects. An advanced stage of arterial stiffness, comparable with that of subjects with DM, is only reached at the age of 75. *J Am Geriatr Soc* 54:397–404, 2006.

Key words: arterial stiffness; glucose metabolism; older adults; population

Stiffening of the arteries is more pronounced in people with diabetes mellitus (DM) than in those without.^{1–5} Furthermore, in subjects with type 2 DM, the presence of insulin resistance is positively associated with arterial stiffness.⁶ Some studies suggest that a positive association between impaired glucose metabolism and arterial stiffness is not confined to subjects with DM,^{6–11} but these studies have been small. Most of these studies have been confined to young or middle-aged subjects.^{6–9} Impairment in glucose metabolism frequently occurs in elderly people without DM.^{12,13} Greater arterial stiffness is associated with greater cardiovascular risk.^{14,15} Therefore, it is important to know whether arterial stiffening accompanies impaired glucose metabolism in elderly people without DM. One study addressed the relationship between impaired glucose metabolism and peripheral arterial stiffness in elderly subjects.¹⁰ Recently, the relationship between impaired glucose metabolism and central arterial stiffness was assessed in the same study population.¹¹ These small studies showed greater femoral and brachial artery stiffness but not greater carotid and central artery stiffness in subjects with impaired glucose metabolism than in subjects with normal metabolism. Because previous studies have not fully clarified the important question of whether impaired glucose metabolism is associated with greater arterial stiffness in elderly people without DM, the aim of the present study was to

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DOI: 10.1111/j.1532-5415.2005.00614.x

examine, in a large population-based cohort, whether arterial stiffness as measured according to common carotid artery distensibility is greater in elderly people without DM with impaired glucose metabolism than in subjects with normal glucose metabolism.

METHODS AND SUBJECTS

The Rotterdam Study

This study was conducted within the Rotterdam Study, a population-based cohort study to assess the occurrence of and risk factors for chronic diseases in older people. The rationale and design of the Rotterdam Study have been described in detail elsewhere.¹⁶ In brief, 7,983 subjects aged 55 and older living in the suburb Ommoord of Rotterdam, the Netherlands, were included in the first (baseline) examination phase, which took place between 1990 and 1993. From 1997 until 1999, in the third examination phase, 5,901 subjects of the original cohort were eligible, of whom 4,148 attended the physical examinations. The protocol used was the same as used at the baseline examinations. The data collection consisted of an extensive home interview and subsequent visits to the study center for clinical examinations. For the present study, the first 3,011 participants who attended the third examination phase and had a measurement of arterial stiffness were eligible. The Medical Ethics Committee of the Erasmus Medical Center approved the study, and written informed consent was obtained from all participants.

Clinical and Laboratory Methods

Cardiovascular Risk Factors

Information on cardiovascular risk factors was collected at the research center. Anthropometric measures were obtained with subjects wearing lightweight clothes and no shoes and included height, weight, and waist and hip circumference. Body mass index ((BMI) weight/height²) and waist-to-hip ratio were calculated. For participants who were not known to have DM, fasting blood samples were obtained using venipuncture with minimal stasis using a 12-gauge butterfly needle. Nonfasting blood samples were obtained from participants with DM. Serum total cholesterol and high-density lipoprotein cholesterol (HDL-C) were determined using an automatic enzymatic procedure (Boehringer Mannheim, Mannheim, Germany). Glucose was enzymatically determined using the Hexokinase method (Boehringer Mannheim). Blood pressure was measured twice at the right upper arm using a random-zero sphygmomanometer with the subject seated. The mean of both readings was used for analyses.

Vascular Disease and Atherosclerosis

History of myocardial infarction (MI) was defined as MI that occurred before the third examination phase. Events before baseline examination were reported by general practitioners and cardiologists and found using electrocardiogram (definite MI) or reported during the home interview (possible MI). General practitioners reported events between baseline and the third examination phase using a computerized system or collected during yearly visits to their office. In addition, discharge reports and letters of medical specialists were obtained for hospitalized patients.

Two independent physicians coded the events according to the *International Classification of Disease, 10th Revision*. In case of disagreement, a medical expert in the field gave the final coding. Hypertension was defined as systolic blood pressure (SBP) of 160 mmHg or greater, diastolic blood pressure (DBP) of 90 mmHg or greater, or the use of blood pressure-lowering medication (diuretics, α -blockers, β -blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, and peripheral vasodilators). Information on the use of medication was collected from the pharmacy.

Peripheral artery disease was defined as an ankle-brachial pressure index less than 0.90 in either leg. Ankle SBP was measured at the left and right posterior tibial artery using an 8-MHz continuous-wave Doppler probe (Huntleigh 500 D, Huntleigh Technology, Bedfordshire, UK) and a random-zero sphygmomanometer with the subject in a supine position. The presence of plaques in the common carotid artery, assessed using on-line evaluation of the ultrasonographic images, was used as an indicator of atherosclerosis in the carotid artery. Ultrasonography of both carotid arteries was performed using a 7.5-MHz linear-array transducer (Ultramark IV, ATL, Bothell, WA). Plaques were defined as a focal widening relative to adjacent segments, with protrusion into the lumen and composed of only calcified deposits or a combination of calcified and noncalcified material. No attempt was made to quantify the size of the lesions. Severity of plaques in the common carotid artery was graded as 0 (no plaques) or 1 (presence of plaques at the far or near wall of the left or right common carotid artery).

Glucose Status

Information on history of DM and use of blood glucose-lowering medication was obtained during a home interview. Additionally, information on prescription of blood glucose-lowering medication was obtained from the pharmacy. Glucose status was classified into three categories: subjects without DM with normal fasting glucose (NFG), subjects without DM with impaired fasting glucose (IFG), and subjects with DM. IFG is a recently defined diagnostic category based on fasting plasma glucose concentration.¹⁷ Analogous to the World Health Organization criteria of impaired glucose tolerance, it represents a metabolic stage intermediate between normal glucose homeostasis and DM and is associated with insulin resistance syndrome.^{17,18} NFG was defined as a fasting glucose level below 6.1 mmol/L, without a history of DM and without the use of blood glucose-lowering medication. IFG was defined as a fasting serum glucose level between 6.1 and 6.9 mmol/L without a history of DM and without the use of blood glucose-lowering medication.¹⁷ Diabetes mellitus was defined as a history of DM, the use of blood glucose-lowering medication, or a fasting serum glucose level of 7.0 mmol/L or greater.¹⁷

Arterial Stiffness

Arterial stiffness was assessed at the research center by measuring common carotid artery distensibility and expressed as the distensibility coefficient. A lower distensibility coefficient indicates greater arterial stiffness. Subjects were instructed to refrain from smoking and from taking coffee, tea, alcohol, or pain medication on the day of measurement and from taking alcohol on the day before. The

vessel wall motion of the right common carotid artery was measured using a Duplex scanner with a operating frequency of 7.5 MHz (ATL Ultramark IV) connected to a vessel wall–movement detector system. The details of this technique have been described elsewhere.^{19,20} Briefly, this system enables the transcutaneous assessment of the displacement of the arterial walls during the cardiac cycle and, hence, the time-dependent changes in arterial diameter relative to its diastolic diameter at the start of the cardiac cycle. Subjects were placed in a supine position, with the head tilted slightly to the contralateral side for the measurements in the common carotid artery. A region 1.5 cm proximal to the origin of the bulb of the carotid artery was identified using B-mode ultrasonography. The displacement of the arterial walls was obtained by processing the radio frequency signals originating from two selected sample volumes positioned over the anterior and posterior walls. The end-diastolic diameter (D), the absolute stroke change in diameter during systole (ΔD), and the relative stroke change in diameter ($\Delta D/D$) were computed as the mean of four cardiac cycles of three successive recordings. Blood pressure was measured twice at the upper arm using a Dinamap automatic blood pressure recorder during the measurement session. The mean was taken as the subject's reading. Pulse pressure (ΔP) was defined as the difference between SBP and DBP. Mean arterial pressure (MAP) was calculated by adding one-third of the pulse pressure to the DBP. The cross-sectional arterial wall distensibility coefficient was calculated according to the following equation:²¹

$$\text{distensibility coefficient} = (2\Delta D/D)/\Delta P(10^{-3}/\text{kPa})$$

With this system, a wall displacement of a few micrometers can be resolved,¹⁹ and D , ΔD , $\Delta D/D$, and the distensibility coefficient can be assessed reliably.²⁰ The arterial wall properties, as determined in this way, are defined as the relative changes in arterial cross-sectional area, expressed in terms of diameter, for a change in pressure. They reflect a combination of passive elastic properties and active components induced by smooth muscle cells. A reproducibility study performed in 47 subjects showed an intraclass correlation coefficient of 0.80 for the distensibility coefficient. In the present study, measurements were restricted to the right side to save time. In previous studies, no differences could be detected between arterial wall properties of the right and left common carotid artery (unpublished results).

Data Analysis

Population for Analysis

Of all participants who attended the follow-up examination, information on common carotid distensibility was available for 77%. The first 3,011 participants with information on common carotid distensibility were eligible for the present study. Twenty-four subjects without a history of DM from whom incorrectly nonfasting blood was drawn were excluded (mainly because these subjects failed to come to the research center in a fasting state), leaving 2,987 subjects to be included in the analyses. An additional analysis adjusted for several possible confounders was performed on a subpopulation with complete information on all variables used in the model ($n = 2,016$). A subanalysis in which possible determinants of reduced arterial distensibility were

evaluated was performed on a subpopulation of 2,816 subjects with complete information on all determinants possibly related to arterial distensibility. In the analysis with fasting glucose as determinant, subjects with DM with nonfasting glucose measurements were excluded ($n = 77$). Information was missing on common carotid distensibility ($n = 903$), determinants ($n = 171$), or one or more confounders ($n = 971$) mainly because of logistic reasons.

Statistical Analysis

Characteristics of subjects with NFG, IFG, and DM were calculated and tested for differences between groups after adjustment for age using one-way analyses of covariance for continuous characteristics and logistic regression analyses for dichotomous characteristics. Before addressing the association between glucose status and arterial distensibility, fasting glucose and other potential determinants were related to common carotid distensibility in the total cohort (subjects without DM with NFG and IFG and subjects with DM) using multiple linear regression analysis. The other potential determinants were age, sex, MAP, total cholesterol, HDL-C, BMI, and waist-to-hip ratio. Analyses were adjusted for age, sex, and MAP, except when one of these variables was the determinant of interest.

The effect of glucose status on arterial distensibility was evaluated using one-way analyses of covariance. Differences in mean distensibility coefficient between subjects with NFG, IFG, and DM were tested, adjusted for age, sex, and MAP. Because arterial stiffening is a slow process, taking years to develop, analyses were performed for the total cohort and within age strata (an a priori arbitrarily chosen cutoff point of 75). Additional analyses were performed in strata of sex and after additional adjustment for the presence of plaques in the common carotid artery to evaluate whether the association between IFG and arterial distensibility persisted independently of atherosclerosis. To exclude residual confounding, an additional analysis was performed with adjustment for several possible confounders (total cholesterol, HDL-C, presence of hypertension or peripheral artery disease, history of MI, use of blood pressure–lowering or lipid-lowering medication). All analyses were performed using the statistical package SPSS 12.0 for Windows XP (SPSS, Inc., Chicago, IL).

RESULTS

Characteristics

The characteristics of subjects with NFG, IFG, and DM are presented in Table 1. Subjects with DM were significantly older than subjects with NFG. After adjustment for age, subjects with IFG and DM tended to have higher levels of cardiovascular risk factors than subjects with NFG, except for total cholesterol, which was lower in subjects with DM than in subjects with NFG and IFG. Subjects with DM had a higher prevalence of plaques in the common carotid artery than subjects with NFG and IFG, adjusted for age.

Determinants of Arterial Stiffness

In the total cohort, age, sex, MAP, fasting glucose, HDL-C, BMI, and waist-to-hip ratio were all significantly associated with the distensibility coefficient after adjustment for age, sex, and MAP where appropriate (Table 2). The

Table 1. Characteristics of the Study Population by Glucose Status: The Rotterdam Study, 1997–1999

Characteristic	Normal Fasting Glucose (n = 2,209)	Impaired Fasting Glucose (n = 422)	Diabetes Mellitus (n = 356)
Age, mean (range)	72 (60–101)	72 (61–93)	74 (61–91)*†
Men, %	41	43	47 [§]
Systolic blood pressure, mmHg, mean ± SD	131 ± 19	137 ± 20 [‡]	140 ± 17 [§]
Diastolic blood pressure, mmHg, mean ± SD	70 ± 10	73 ± 10 [‡]	71 ± 9 [§]
Mean arterial pressure, mmHg, mean ± SD	90 ± 12	94 ± 13 [‡]	94 ± 10 [§]
Total cholesterol, mmol/L, mean ± SD [#]	5.9 ± 1.0	5.9 ± 1.0	5.6 ± 0.9 [§]
High-density lipoprotein cholesterol, mmol/L, mean ± SD [#]	1.44 ± 0.40	1.39 ± 0.45 [‡]	1.24 ± 0.34 [§]
Glucose, mmol/L, mean ± SD [#]	5.3 ± 0.4	6.4 ± 0.2 [‡]	8.8 ± 2.5 [§]
Body mass index, kg/m ² , mean ± SD [#]	26.2 ± 3.8	28.0 ± 4.2 [‡]	28.3 ± 4.3 [§]
Waist-to-hip ratio, mean ± SD [#]	0.91 ± 0.10	0.94 ± 0.10 [‡]	1.0 ± 0.09 [§]
Distension, μm, mean ± SD	324 ± 109	311 ± 111	308 ± 107
Diameter, mm, mean ± SD	7.8 ± 1.0	8.0 ± 1.0 [‡]	8.1 ± 0.9 [§]
Presence of plaques in the common carotid artery, %	14.3	16.1	24.7 [§]
Presence of hypertension, % [¶]	49.9	62.6 [‡]	70.1 [§]
History of myocardial infarction, % [¶]	9.9	9.7	15.5 [§]
Presence of peripheral artery disease, % [¶]	15.7	17.8	24.8 [§]
Use of blood pressure-lowering medication, % [¶]	45.5	57.1 [‡]	64.3 [§]
Use of lipid-lowering drugs, % [¶]	17.0	16.2	20.8 [§]
Distensibility coefficient, 10 ⁻³ /kPa, mean ± SD	10.9 ± 4.4	9.8 ± 4.4 [‡]	8.8 ± 3.6 [§]

* $P < .05$ diabetics versus normal fasting glucose.

† $P < .05$ diabetics versus impaired fasting glucose.

‡ $P < .05$ impaired fasting glucose versus normal fasting glucose, adjusted for age.

§ $P < .05$ diabetics versus normal fasting glucose, adjusted for age.

|| $P < .05$ diabetics versus impaired fasting glucose, adjusted for age.

¶ Data not complete for the total cohort.

SD = standard deviation.

β-coefficient for the association between fasting glucose and distensibility was -0.29 (95% confidence interval (CI) = -0.39 to -0.19). Total cholesterol was not associated with the distensibility coefficient.

Arterial Stiffness and Glucose Status

Figure 1 shows the mean common carotid distensibility coefficient of subjects with NFG, IFG, and DM for the total cohort and in strata of age. All analyses were adjusted for age, sex, and MAP. In the total cohort, adjusted common

carotid distensibility coefficients (10^{-3} /kPa) of subjects with NFG, IFG, and DM were 10.7 (standard error (SE) = 0.07), 10.4 (SE = 0.16), and 9.6 (SE = 0.18), respectively. The difference in distensibility coefficient between subjects with NFG and IFG was not significant (mean difference in distensibility coefficient = 0.3, 95% CI = -0.07 – 0.6 ; $P = .12$). The difference in distensibility coefficient between subjects with NFG and subjects with DM was highly significant (mean difference = 1.1, 95% CI = 0.3 – 1.3 ; $P < .001$). Adjusted common carotid distensibility coefficients (10^{-3} /kPa) of subjects with NFG, IFG,

Table 2. Association Between Various Variables and the Common Carotid Arterial Distensibility Coefficient (10^{-3} /kPa): The Rotterdam Study, 1997–1999 (N = 2,816)

Variable	Beta Coefficient* (95% Confidence Interval)	P-value
Age [†]	-0.28 (-0.30 to -0.26)	$< .001$
Sex [‡]	-0.89 (-1.18 to -0.60)	$< .001$
Mean arterial pressure, mmHg [§]	-0.17 (-0.18 to -0.16)	$< .001$
Fasting glucose, mmol/L	-0.29 (-0.39 to -0.19)	$< .001$
Total cholesterol, mmol/L	-0.06 (-0.19 to 0.07)	.37
High-density lipoprotein cholesterol, mmol/L	0.76 (0.44–1.09)	$< .001$
Body mass index, kg/m ²	-0.09 (-0.12 to -0.06)	$< .001$
Waist-to-hip ratio	-2.58 (-3.99 to -1.17)	$< .001$

* Increase in distensibility coefficient (10^{-3} /kPa) for every unit increase of the independent variable.

† Adjusted for sex.

‡ Adjusted for age.

|| Adjusted for age and sex.

§ Adjusted for age, sex, and mean arterial pressure.

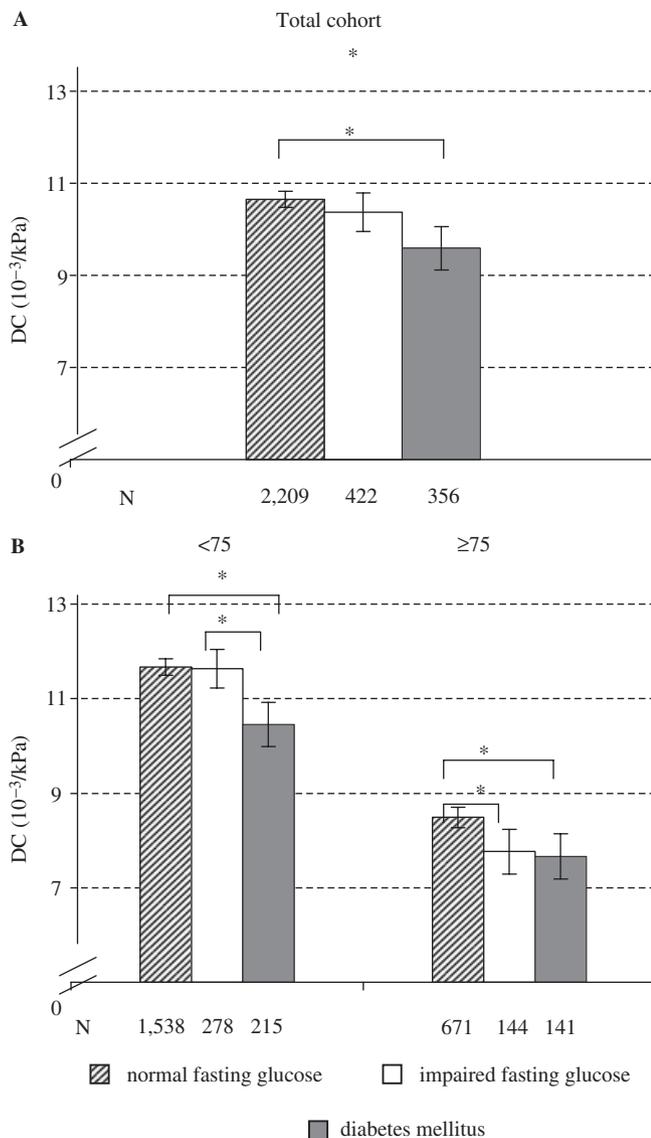


Figure 1. Mean distensibility coefficient (DC) (95% confidence interval) in subjects from the Rotterdam Study with normal fasting glucose, impaired fasting glucose, and diabetes mellitus. A. Total cohort. B. By age, adjusted for age, sex, and mean arterial pressure. The number of subjects within each group is indicated at the lower end of the respective bar. * $P < .01$.

and DM were 11.7 (SE = 0.07), 11.6 (SE = 0.21), and 10.5 (SE = 0.24), respectively, for those younger than 75 and 8.5 (SE = 0.11), 7.8 (SE = 0.24), and 7.7 (SE = 0.25), respectively, for those aged 75 and older. Subjects younger than 75 with IFG were comparable with those with NFG with respect to arterial stiffness (mean difference in distensibility coefficient = 0.01, 95% CI = -0.4–0.5; $P = .88$), whereas subjects with DM younger than 75 had significantly greater arterial stiffness than those with NFG (mean difference = 1.2, 95% CI = 0.7–1.7; $P < .001$). For subjects aged 75 and older, arterial stiffness of those with IFG was on the same order as that of subjects with DM; both had significantly greater arterial stiffness than subjects with NFG (mean difference between subjects with IFG and subjects with NFG = 0.7, 95% CI = 0.2–1.2; $P = .007$ and between subjects with DM and subjects with NFG = 0.8, 95%

CI = 0.3–1.4; $P = .002$). Results were similar for men and women (data not shown). When the analysis was repeated with a different arbitrarily chosen cutoff point (median age of the total cohort: 71.2), results were comparable (data not shown). Results also did not change substantially after additional adjustment for the presence of plaques in the common carotid artery or after adjustment for other possible confounders (Table 3). After adjustments for other possible confounders, arterial stiffness was greater in subjects with IFG than in those with DM aged 75 and older, but the difference was not significant (mean difference = 0.29, 95% CI = -0.51–1.08; $P = .48$).

DISCUSSION

The results of this population-based study in elderly subjects indicate that, in subjects younger than 75, those with IFG are comparable with subjects with NFG with respect to arterial stiffness. Arterial stiffness of subjects aged 75 and older with IFG is similar to that of subjects with DM, and both groups have greater arterial stiffness than subjects with NFG.

Some methodological concerns need to be discussed. First, by calculating the distensibility coefficient, distension of the common carotid artery is adjusted for pulse pressure measured in the brachial artery. It is thereby assumed that pulse pressure measured in the brachial artery is representative of pulse pressure in the carotid arteries. In dogs, it has been demonstrated that pulse pressure in the brachial artery is linearly related to blood pressure in the carotid artery over a wide range of blood pressures,²¹ but the arterial pressure waves undergo transformation in the arterial tree, and therefore pulse pressure is higher in the brachial artery than in more-central vessels like the carotid artery.²² Alternatively, noninvasive cuff-based measurement of blood pressure underestimates pulse pressure.²³ Several groups showed the validity of the use of brachial pressures.^{24–26} Second, in analyses with arterial distensibility, a measure highly dependent on blood pressure, adequate correction for blood pressure is of the utmost importance. The distensibility coefficient is calculated by dividing the relative distension by pulse pressure. Despite this correction, the distensibility coefficient has a strong negative association with MAP. A higher MAP in the artery stretches the elastin and collagen fibers in the arterial wall, making the artery less distensible. Blood pressure is one of the major determinants of arterial stiffness and also part of the insulin-resistance syndrome. Therefore, all analyses were adjusted for MAP. Third, glucose status was classified based on fasting plasma glucose levels; information on oral glucose tolerance was not available. Some individuals with IFG may have undiagnosed DM, which would have been recognized if oral glucose tolerance tests had been conducted, but because fasting glucose levels above 7.0 mmol/L were included in the definition of DM, this misclassification would not have occurred frequently. Fourth, in a large ongoing cohort study such as the Rotterdam Study, missing information due to logistic reasons is likely to occur. It was decided to treat missing information on carotid distensibility or confounders using complete case analyses. Missing information due to logistic reasons is nondifferential with respect to determinant and outcome, and therefore, the relationship

Table 3. Distensibility Coefficient in Subjects with Normal Fasting Glucose, Subjects with Impaired Fasting Glucose, and Diabetic Subjects After Additional Adjustment for Plaques in the Common Carotid Artery or Other Possible Confounders: The Rotterdam Study, 1997-1999

Additional Adjustment	Normal Fasting Glucose		Impaired Fasting Glucose		Mean Difference* (95% CI)		Diabetes Mellitus	P-value	Mean Difference† (95% CI)	P-value
	Fasting Glucose	Distensibility Coefficient (SE)	Fasting Glucose	Distensibility Coefficient (SE)	Distensibility Coefficient (SE)	P-value				
Aged <75										
Plaques in the common carotid artery	11.66 (0.09) (n = 1,538)	11.61 (0.21) (n = 278)	0.05 (-0.40-0.49)		10.55 (0.24) (n = 215)	1.11 (0.61-1.62)	<.001			
Other possible confounders‡	11.44 (0.11) (n = 978)	11.32 (0.25) (n = 196)	0.12 (-0.44-0.66)		10.45 (0.28) (n = 173)	0.99 (0.40-1.58)	<.001			
Aged ≥75										
Plaques in the common carotid artery	8.47 (0.11) (n = 671)	7.79 (0.24) (n = 144)	0.68 (0.17-1.20)		7.72 (0.24) (n = 141)	0.76 (0.24-1.27)	<.004			
Other possible confounders‡	8.41 (0.14) (n = 461)	7.48 (0.28) (n = 108)	0.93 (0.32-1.54)		7.77 (0.29) (n = 100)	0.65 (0.01-1.29)	.047			

Note: All analyses adjusted for age, sex, and mean arterial pressure, with additional adjustment as indicated.

* Mean difference in distensibility coefficient between subjects with normal and impaired fasting glucose.

† Mean difference in distensibility coefficient between subjects with normal fasting glucose and diabetes mellitus.

‡ Other possible confounders were total cholesterol, high-density lipoprotein cholesterol, presence of hypertension, history of myocardial infarction, presence of peripheral artery disease, use of blood pressure-lowering medication, use of lipid-lowering drugs.

CI = confidence interval; SE = standard error.

between determinant and outcome is unlikely to be different in subjects who were examined and subjects who were not. Finally, this study includes survivors of an ongoing cohort of elderly people. When evaluating associations in elderly subjects, it is likely that those most susceptible to the determinants under study had already died; therefore, some survival bias is likely to occur and is inevitable.

The insulin-resistance syndrome consists of insulin resistance, compensatory hyperinsulinemia, obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride or low-HDL type, and hypertension.^{27,28} IFG is a metabolic stage, intermediate between normal glucose homeostasis and DM, and is associated with insulin resistance.^{17,18} Studies concerning insulin resistance and impaired glucose metabolism in relation to arterial stiffness are scarce and mainly confined to subjects with DM or young to middle-aged healthy subjects.^{6,7,9} In subjects with type 2 DM, the presence of insulin resistance, as assessed using the euglycemic hyperinsulinemic clamp technique, is associated with greater arterial stiffness.⁶ Also, in young healthy people without DM, insulin resistance, as assessed using the euglycemic hyperinsulinemic clamp technique, is associated with greater arterial stiffness independent of MAP.⁷ In healthy middle-aged women without DM, variables of the insulin-resistance syndrome were found to be associated with lower arterial distensibility, after adjustment for MAP.⁸ The Atherosclerosis Risk in Community (ARIC) Study examined fasting glucose levels in relation to arterial stiffness in people without DM aged 45 to 64 and reported higher indexes of arterial stiffness when fasting glucose level was above normal.⁹ Recently, impaired glucose metabolism was found to be related to greater femoral and brachial artery stiffness but not to carotid artery stiffness.¹⁰

This is the first large study in which arterial stiffness of elderly subjects with IFG has been compared with that of elderly subjects with NFG and DM. In contrast to the ARIC Study, greater arterial stiffness was only found in subjects without DM with NFG aged 75 and older and not those younger than 75. The fact that the data were adjusted for MAP might explain this discrepancy. When the data were re-analyzed in a similar way to that of the ARIC Study, without adjustment for MAP, similar results were found to those of the ARIC Study in subjects younger than 75; mean age- and sex-adjusted distensibility coefficients ($10^{-3}/\text{kPa}$) of subjects with NFG, IFG, and DM were 11.8 (SE = 0.10), 11.1 (SE = 0.24), and 10.0 (SE = 0.28), respectively. All groups were significantly different from each other, although for reasons explained in a previous paragraph, more value was attached to results adjusted for MAP. In the Hoorn study, no relationship was found between impaired glucose metabolism and central or carotid artery distensibility after correction for MAP in subjects with a mean age of 68.5.^{10,11} In this study population, a subanalysis of the eldest elderly was not performed. The current study is the first to show that people without DM aged 75 and older with IFG reach the same arterial stiffness as subjects with DM. Some studies suggest sex-related differences in the relationship between DM and insulin resistance and arterial stiffness,^{5,7} but data are contradictory. Sex-related differences were not found in the association between IFG and lower arterial distensibility.

Other potential determinants of arterial stiffness were also examined. Several variables evaluated are part of the insulin-resistance syndrome (fasting glucose, HDL-C, BMI, and waist-to-hip ratio). Parameters of the insulin-resistance syndrome were found to be strongly associated with arterial stiffness in elderly subjects, which is in accordance with a previous study in healthy middle-aged women without DM.⁸ Total cholesterol, which is not part of the insulin-resistance syndrome, was not associated with arterial distensibility. The finding of a significant association between fasting glucose as a continuous variable and greater arterial stiffness in the total cohort is in agreement with the trend in increasing arterial stiffness from subjects with NFG to those with IFG to those with DM in the total cohort. Moreover, the analysis with fasting glucose as a continuous variable included subjects with DM who were newly diagnosed in the third examination phase on the basis of their fasting glucose level and had high levels of fasting glucose and high arterial stiffness.

The association between arterial stiffness and atherosclerosis is still subject to debate.^{29–32} The associations between IFG and DM and arterial distensibility were additionally adjusted for the presence of atherosclerosis in the common carotid artery. Additional adjustment did not alter the results. This suggests that the associations between IFG and DM and greater arterial stiffness are in part independent of atherosclerosis. Hyperglycemia leading to greater arterial stiffness via collagen cross-linking due to nonenzymatic glycation may explain the relationship between fasting glucose levels and arterial stiffness independent of atherosclerosis.^{33,34}

Impaired glucose metabolism is a frequent condition in elderly people without DM.^{12,13} In the study population, 13.7% of subjects younger than 75 and 15.1% of subjects aged 75 and older had IFG according to recently developed diagnostic criteria. Arterial stiffness is a process that generally develops slowly, taking years to reach advanced stages. The present study is the first study in which a subanalysis of the eldest elderly has been performed, and the results showed that, at the age of 75, people without DM with impaired glucose metabolism reach the same arterial stiffness as subjects with DM. Greater arterial stiffness is associated with greater cardiovascular risk,^{14,15} and recent evidence suggests that there are opportunities to treat arterial stiffness induced by hyperglycemia in the near future.³⁵ Therefore, it is important to recognize that healthy elderly subjects without DM with high fasting glucose levels reach the same arterial stiffness as subjects with DM at older ages. It was found that, in subjects younger than 75, those with IFG were comparable with those with NFG with respect to arterial stiffness. In this group, early treatment of hyperglycemia may prevent advanced arterial stiffness.

In conclusion, the results of this population-based study show that IFG is related to greater arterial stiffness in elderly men and women without DM.

ACKNOWLEDGMENTS

We are grateful to the participants of the Rotterdam Study. We thank all field workers, computer assistants, and laboratory technicians from the Ommoord research center

especially, Ms. T. Stehmann and Ms. I. T. M. Haumersen, for their enthusiasm and skillful contribution to the data collection.

Financial Disclosure: None of the authors had at the time of submission of their paper any financial arrangements with an organization or company.

Author Contributions: All authors participated in study concept and design, acquisition of subjects and data, analysis and interpretation of data, and preparation of manuscript.

Sponsor's Role: This study was supported by a grant from the Health Research and Development Council, The Hague, the Netherlands (2827210 to Dr. Witteman) and by a grant of the Netherlands Heart Foundation (96.141 to Prof. Dr. Grobbee). The Rotterdam Study is supported in part by the NESTOR program for geriatric research (Ministry of Health and Ministry of Education), the Netherlands Heart Foundation, the Netherlands Organization for Scientific Research, and the Municipality of Rotterdam.

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