Nondiabetic Glucometabolic Status and Progression of Aortic Stiffness: The Whitehall II Study

Carmel M. McEniery,[1] Ian B. Wilkinson,[1] Nanna B. Johansen,[2,3] Daniel R. Witte,[3,4] Archana Singh-Manoux,[5] Mika Kivimaki,[5] Adam G. Tabak,[5,6] Eric J. Brunner,[5] and Martin J. Shipley[5]

OBJECTIVE

Aortic stiffness is an important predictor of future morbidity and mortality. Diabetes is associated with increased aortic stiffness, but the importance of nondiabetic glucometabolic status for accelerated aortic stiffening is unclear. We tested the hypothesis that adverse glucometabolic status is associated with accelerated aortic stiffening in individuals without diabetes, independently of known risk factors for arterial stiffening.

RESEARCH DESIGN AND METHODS

Glucometabolic status and other cardiovascular risk factors were assessed at baseline in 2008–09, and carotid femoral pulse wave velocity (cfPWV) at baseline and follow-up in 2012–13, in 4,386 participants without diabetes of the Whitehall II Study.

RESULTS

The mean age of the cohort at cfPWV baseline was 60 years, and 74% were male. cfPWV increased from (mean $\pm$ SE) 8.30 ± 0.03 to 8.98 ± 0.04 m/s during 4 years of follow-up. At baseline, cfPWV was associated with fasting and 2-h postload glucose, HbA_{1c}, and HOMA-insulin resistance (HOMA-IR). HbA_{1c} and HOMA-IR were associated with progression of cfPWV after adjusting for physiological confounders and cardiovascular risk factors. A 1 SD higher HbA_{1c} and HOMA-IR were associated with greater increases in cfPWV (0.11 m/s per 5 years [95% CI 0.04, 0.18], $P = 0.003$ and 0.09 m/s per 5 years [0.01, 0.17], $P = 0.03$, respectively). Additional adjustment for BMI weakened the association with HOMA-IR but not with HbA_{1c}.

CONCLUSIONS

HbA_{1c} is independently associated with accelerated progression of aortic stiffness in individuals without diabetes. These findings suggest that long-term glucometabolic status, even in individuals without diabetes, could be an important target for preventative strategies against vascular aging.

[1]Division of Experimental Medicine and Immunotherapeutics, University of Cambridge, Cambridge, U.K.
[2]Steno Diabetes Center A/S, Gentofte, Denmark
[3]Danish Diabetes Academy, Odense, Denmark
[4]Department of Public Health, Aarhus University, Aarhus, Denmark
[5]Research Department of Epidemiology and Public Health, University College London, London, U.K.
[6]1st Department of Medicine, Faculty of Medicine, Semmelweis University, Budapest, Hungary

Corresponding author: Carmel M. McEniery, cmm41@cam.ac.uk.

Aortic stiffness provides important prognostic information on overall cardiovascular risk and mortality (1). In the most recent meta-analysis, carotid femoral pulse wave velocity (cfPWV), the current gold standard measure of aortic stiffness, was an independent predictor of future cardiovascular events and improved risk classification beyond that provided by traditional risk factors (2). This has added to the view that aortic stiffness is a measure of vascular health or vascular age (3,4) and has created considerable interest in aortic stiffness as a novel therapeutic target.

The precise mechanisms underlying aortic stiffening remain poorly understood. The heterogeneity in the rate of stiffening suggests it is not an inevitable consequence of

the aging process (5). A number of risk factors for accelerated aortic stiffening have been described, including elevated blood pressure, renal disease, systemic inflammation, and adiposity (6–10). Diabetes has been linked with increased vascular stiffness in several case-control studies (11–13), and HbA_{1c} level is associated with an accelerated age-related increase in cfPWV in individuals with type 2 diabetes (14). Cross-sectional studies in individuals without diabetes suggest an association between aortic stiffness, glycemia, and indices of insulin resistance (11,15,16). However, a prospective analysis using Whitehall II data are equivocal, finding associations only in men (17). The evidence from longitudinal studies is also conflicting. Only one of seven previous longitudinal studies identified plasma glucose as an independent predictor of the rate of progression of cfPWV after adjusting for confounders, but only in women (18). The remaining longitudinal studies either report no independent association (19–22) or did not examine glucose as a risk factor for stiffening (23,24). None of the studies provide any information concerning HbA_{1c} and aortic stiffening.

We hypothesized that impaired glycemic control is associated with accelerated aortic stiffening in individuals without diabetes and that this would be independent of known risk factors for arterial stiffening. Our aim was to test this hypothesis in the Whitehall II longitudinal study. This cohort study provides data on progression of cfPWV during a 4-year interval, together with repeated assessments of glycemia, insulin resistance, anthropometric parameters, and cardiovascular risk factors. We excluded individuals with clinical or biochemical evidence of diabetes to reduce the confounding effects of treatment and diabetic complications, such as renal disease, which may themselves alter stiffness.

RESEARCH DESIGN AND METHODS

Participants
All participants were drawn from the Whitehall II cohort, a longitudinal observational study of 10,308 civil servants recruited between 1985 and 1988 when aged 35–55 years (25). Participants have been followed up every 4–5 years with detailed clinical examinations and self-administered questionnaires in 1991–94, 1997–99, 2003–04, 2008–09, and 2012–13. Research Ethics

Committee approval was obtained for each examination phase, and participants gave written informed consent.

The cfPWV was assessed in 4,347 of 6,225 participants seen at the screening clinic in 2008–09 and in 4,485 of 5,660 seen in 2012–13. The present analysis was based on participants without diabetes. Diabetes was defined by self-report/doctor diagnosis, the use of antidiabetic medication, fasting glucose ≥7.0, a 2-h glucose ≥11.1 mmol/L during an oral glucose tolerance test, or HbA_{1c} ≥6.5% (48 mmol/mol). Excluded from the analysis were 617 participants who met these criteria at baseline and 582 at follow-up, together with a further 95 participants at baseline and 301 at follow-up who had missing data on covariates. This left 4,386 participants without diabetes who underwent cfPWV assessment during the 2008–09 (n = 3,685) and/or 2012–13 (n = 3,602) examinations who make up the analytic sample. The cfPWF was assessed in 2,901 participants at both time points. The same measurement protocol was used at each examination.

Measurements
PVW
Aortic stiffness was assessed by cfPWV, the current noninvasive gold standard (26). Higher values of cfPWV indicate a faster speed of wave travel between the arterial sites and, hence, a stiffer aorta. Measurements were made after a 15-min supine rest, in duplicate, using the SphygmoCor system (AtCor Medical, Sydney, NSW, Australia), as previously described (27). Briefly, brachial blood pressure was measured and then cfPWV assessed between the carotid and femoral sites. Path length was determined with a tape measure by subtracting the carotid-sternal notch distance from the femoral-sternal notch distance. If the difference between repeated measurements was >0.5 m/s, a third measurement was taken, and the average of the measurements was used in the analysis. Heart rate was derived from the SphygmoCor software, and blood pressure was measured using a validated oscillometric device immediately before cfPWV. Mean arterial pressure (MAP) was calculated as diastolic pressure plus one-third of the pulse pressure.

Vascular Disease, Diabetes, and Antihypertensive Medication
Prevalent vascular disease status (myocardial infarction [MI] and/or stroke) at

the 2008–09 assessment was determined using self-report doctor diagnosis and hospitalization with verification from medical records where available. Prevalent diabetes was determined by oral glucose tolerance test, self-report, doctor diagnosis, and/or medication (28).

Anthropometry and Other Covariates
Anthropometric measures and cardiovascular risk factors were measured in 2003–04 and 2008–09 to provide mean exposure in the 5 years before the baseline cfPWV assessment in 2008–09. Weight, height, and waist and hip circumferences were measured using standard protocols (29). Serum, fluoride plasma, and blood drawn into EDTA tubes was collected after an overnight fast or ≥5 h after a fat-free breakfast for participants presenting in the afternoon. Serum total cholesterol, HDL cholesterol, triglycerides, and plasma glucose were measured.

Glucometabolic Measures
Samples were handled according to standard protocols. Venous blood samples were taken in fasted individuals (≥8 h fasting or ≥5 h for afternoon visits), before a standard 2-h oral glucose tolerance test was administered in all participants (29). Glucose samples were drawn into fluoride Monovette tubes and insulin samples into native tubes that were centrifuged on site within 1 h. Plasma or serum was immediately moved into microtubes and stored at −70°C. Blood glucose was measured using the glucose oxidase method (30) on a YSI model 2300 STAT PLUS analyzer (2003–04 and 2007–09; mean coefficient of variation of 1.4–3.1%) (YSI Corporation, Yellow Springs, OH), and serum insulin with a DAKO insulin ELISA kit (DakoCytomation Ltd., Ely, U.K.) (31) (2003–04, mean coefficient of variation 4.2–9.3%, 2007–09). HOMA insulin sensitivity and HOMA β-cell function were calculated from model-derived estimates (rather than linear approximations) with the HOMA2 version 2.2 calculator (32). HbA_{1c} was measured in whole blood, drawn into EDTA Monovette tubes, using the validated (33) Tosoh G8 high performance liquid chromatography platform (Tosoh Bioscience, Tessenderlo, Belgium).

The exposures and covariates used in the analyses were the mean values of risk factors assessed in 2003–04 and 2008–09 because, compared with a single

measurement in 2008–09, these provide more reliable estimates of exposure in the 5 years before the first cfPWV measurement.

Statistical Analysis

Distributions of glucometabolic indices among people without diabetes were categorized in sex-specific quintiles and also expressed in standardized units. Linear mixed models were used to estimate the relation of glucometabolic indices with cfPWV in 2008–09 and change in cfPWV between 2008–09 and 2012–13. These models used all available cfPWV data, including cases where only one cfPWV measurement was available, which reduced selection bias and allowed better estimates of the associations of potential confounding factors. The models also accounted for correlation between repeated measures within individuals. We fitted the models with a random intercept and slope to account for individual differences in cfPWV at baseline and rate of change during follow-up. From these models, the effect of each glucometabolic index on cfPWV at baseline (2008–09) is estimated by the coefficient for the main effect of the glucometabolic index, and the effect on progression of cfPWV between 2008–09 and 2012–13 is estimated by the interaction of the main effect with time. The longitudinal effects of the glucometabolic indices are expressed as 5-year changes in cfPWV to allow direct comparisons with previous studies (18,20,24). All estimates were initially adjusted for age, sex, ethnic group, heart rate, and MAP at the time of cfPWV measurement. Baseline cfPWV and progression of cfPWV per 5 years were estimated from these models by quintile of each glucometabolic index distribution and per 1 SD increment in each index. This allowed us to examine associations with cfPWV across the distribution of each glucometabolic index and whether the coefficients increased linearly across quintiles. Tests of heterogeneity were conducted using likelihood ratio tests that compared the fit of the models with and without the quintiles of each glucometabolic measure. Two further models cumulatively adjusted for *1*) systolic blood pressure, antihypertensive medication, lipid-lowering medication, smoking status, prevalent MI or stroke, and mean triglyceride and HDL-cholesterol between 2003–04 and 2008–09 and *2*) mean BMI between 2003–04 and 2008–09

and estimated glomerular filtration rate in 2008–09. Sensitivity analysis was conducted to compare characteristics of participants with and without measurements of cfPWV to exclude the possibility of selection bias. Further sensitivity analyses used the glucometabolic measures from baseline (2008–09) or prebaseline (2003–04) rather than averaging the glycemic measures across the two phases.

RESULTS

The cohort at the time of the baseline cfPWV assessment was a mean age of 60 years, 74% male, and predominantly of white ethnic origin. Fewer than 5% had chronic disease, and ~30% were taking antihypertensive medication. A comparison of participants with and without cfPWV assessments across the entire cohort revealed that those individuals who did not have cfPWV measured were more likely to be female and have generally poorer health, in terms of chronic disease and taking antihypertensive or lipid-lowering medication (Supplementary Table 1). Detailed participant characteristics at the time of the two cfPWV examinations are provided in Table 1. Measures of exposure that were averaged across the prebaseline (2003–04) and baseline (2008–09) cfPWV visits are presented separately for each examination phase in Supplementary Table 2.

There was no evidence that the associations of the glucometabolic indices with baseline cfPWV and progression of cfPWV differed between men and women (Supplementary Table 3). Cross-sectional associations between cfPWV and glucometabolic indices are shown by quintile in Table 2, adjusted for age, sex, ethnicity, MAP, and heart rate. Significant positive associations were found with fasting glucose, 2-h glucose, HbA_{1c}, and HOMA-insulin resistance (HOMA-IR). cfPWV increased by between 0.19 and 0.40 m/s when moving from the lowest to highest quintile of each determinant. Additional adjustment for other potential confounders, including drug therapy and cardiovascular risk factors, only modestly attenuated these associations (Supplementary Table 4). When glucometabolic measures were treated as continuous variables, glucose and HOMA-IR were strongly associated and HbA_{1c} was weakly associated with baseline cfPWV (Table 3). These associations were weakened with additional adjustment for potential confounders.

After adjustment for age, sex, ethnicity, MAP, and heart rate, only HbA_{1c} and HOMA-IR were significantly associated with progression of cfPWV. There was a 0.39 m/s greater increase in cfPWV over 5 years in individuals in the top quintile of either parameter compared with those in the lowest quintile (Table 2 and Fig. 1). Adjustment for treatment and other risk factors (Supplementary Table 5) did not significantly attenuate these associations. However, after the addition of BMI to the models, there was no longer an association with HOMA-IR. Analyses using the continuous variables revealed similar findings: a 1 SD higher HbA_{1c} or HOMA-IR at baseline was associated with a ~0.12 m/s greater increase in cfPWV over 5 years (Table 3). In the fully adjusted model, only HbA_{1c} was associated with progression in cfPWV.

Repeating these analyses using glucometabolic measures from baseline (2008–09) or prebaseline (2003–04), rather than averaging across the two phases, did not meaningfully alter the results (Supplementary Tables 6 and 7, respectively). Similarly, excluding the 1.1% of individuals who developed diabetes during follow-up had no influence on the results (data not shown). To exclude the possibility of a selection bias influencing our results because cfPWV was not measured in all participants, a separate analysis using the entire cohort explored the relationship between HbA_{1c} and blood pressure, which is closely related to cfPWV. At baseline and follow-up, HbA_{1c} was ~3% higher in hypertensive individuals than nonhypertensive individuals, in those with and without cfPWV assessment, after adjusting for confounding factors (Supplementary Table 8). This supports our observed association between HbA_{1c} and cfPWV and argues against the possibility that selection bias might be influencing our findings.

CONCLUSIONS

Our main findings are that glucose, HbA_{1c}, and insulin resistance are all cross-sectionally associated with aortic stiffness and that longitudinal analysis shows HbA_{1c} and HOMA-IR are associated with the progression of aortic stiffness during a 4-year period. These associations were independent of other cardiovascular risk factors. The association between HbA_{1c} and aortic stiffening was also independent of BMI.

Table 1—Characteristics of participants without diabetes at baseline

Characteristic	Baseline (2008–09) (N = 3,685)		Follow-up (2012–13) (N = 3,602)	
	Mean (SD)	%	Mean (SD)	%
Age, years	60.1 (5.7)		65.0 (5.6)	
Female		25.6		25.7
Ethnic group				
White		94.0		94.6
South Asian		3.2		2.8
Black		2.1		1.9
Other		0.7		0.7
Diabetes		0.0		1.1
MI or stroke		4.9		4.5
Antihypertensive medication		29.1		36.0
Lipid-lowering medication		26.7		36.6
Former smoker		45.2		48.8
Current smoker		5.2		3.1
BMI, kg/m^2	26.0 (3.7)		26.0 (3.9)	
Systolic blood pressure, mmHg	124.2 (15.3)		126.7 (15.9)	
Diastolic blood pressure, mmHg	70.8 (10.0)		70.8 (9.8)	
Triglyceride, mmol/L	1.16 (0.65)		1.13 (0.57)	
HDL cholesterol, mmol/L	1.63 (0.45)		1.68 (0.47)	
LDL cholesterol, mmol/L	3.14 (0.94)		2.98 (0.94)	
Fasting glucose, mmol/L†	5.05* (0.10)		5.16* (0.10)	
2-h glucose, mmol/L†	6.23* (0.26)		Not done	
HbA$_{1c}$, %†	5.58* (0.07)		5.64* (0.06)	
HbA$_{1c}$, mmol/mol†	37.4* (0.07)		38.4* (0.06)	
HOMA-IR†	1.39* (0.67)		1.68* (0.66)	
Heart rate, bpm	65.8 (11.3)		68.1 (11.6)	
cfPWV, m/s	8.30 (1.93)		8.98 (2.39)	
MAP, mmHg	89.4 (10.5)		93.8 (10.9)	

Characteristics of the participants included in the present analyses at the baseline (2008–09) and follow-up (2012–13) visits. *Geometric mean and SD of logged values. †For glucometabolic indices, the baseline values represent the average of values at the 2003–04 and 2008–09 assessments. The mean for the 4,386 participants included in the analyses is provided in Supplementary Table 2, together with the separate means for 2003–04 and 2008–09.

These observations suggest that factors underlying glucometabolic status may affect aortic stiffening even within the normoglycemic range, which may have important implications for developing antistiffening strategies and exploiting novel therapeutic targets.

Aortic stiffness, and cfPWV in particular, is an important risk factor for future cardiovascular disease independently of other cardiovascular risk factors (2). However, the biological processes underlying aortic stiffening are incompletely understood. Cross-sectional analyses have provided inconsistent results (6) and are limited in their ability to attribute causality. Existing longitudinal data highlight the importance of age and blood pressure, but the importance of other potential risk factors, including indices of glucose homeostasis, is unclear because of lack of replication studies, variable lengths of follow-up, poor availability of data on individual risk factors, and variation in adjustment for confounders. Whitehall II is a large cohort with prospective data on cfPWV and other risk factors, including a variety of glucometabolic indices, making it well suited to examine the relationship between glycemia and aortic stiffening in individuals without diabetes.

As expected, we found significant cross-sectional relationships between indices of glucose homeostasis and insulin resistance with cfPWV. Importantly, this remained after adjustment for physiological confounders of stiffness such as MAP and heart rate (34). Similar results have been reported previously using a variety of study designs, indices of stiffness, and varying levels of adjustment for physiological confounders (11,15,16,35,36). In the current study, adjustment for other potential risk factors for arterial stiffening or cardiovascular disease only modestly reduced the strength of association with glucose measures, but the associations with HOMA-IR and HbA$_{1c}$ were more markedly attenuated, with an approximate halving of the β-values. This contrasts with cross-sectional findings from a cohort of 263 African Americans (16), in whom HbA$_{1c}$ but not fasting or 2-h glucose levels remained independently associated with cfPWV. This disparity possibly reflects ethnic differences in the association between HbA$_{1c}$ and arterial stiffness or may reflect a lack of appropriate statistical power in the African American study. In addition, we a priori excluded individuals with diabetes, which may have removed any association with HbA$_{1c}$ in our data. Alternatively, residual confounding may explain our observed associations with plasma glucose.

In contrast to the cross-sectional observations, fasting and 2-h glucose were not associated with progression of aortic stiffening in the current study, which is consistent with previous observations (19–22). However, HbA$_{1c}$ and HOMA-IR were associated with accelerated progression of cfPWV independently of potential confounders. Previously, one small study reported no association between cfPWV progression and HOMA (19), but HbA$_{1c}$ has been associated with progressive carotid artery stiffening in the Atherosclerosis Risk in Communities (ARIC) Study (37), although, unfortunately, cfPWV was not assessed. In the current study, cfPWV increased by ~0.7 m/s, which is consistent with previous longitudinal studies, which have reported increases of between 0.2 and 0.6 m/s per 5 years in participants aged ~60 years (18,20,24). Moreover, modest differences of 0.07% in HbA$_{1c}$ or 0.67 units in HOMA-IR were associated with an ~0.1 m/s greater increase in cfPWV over 5 years, equating to ~12–14% of the overall change in stiffness. Although the rate of stiffening is strongly dependent on age, our data suggest that even in individuals without diabetes, modest differences in glucometabolic status have a meaningful effect on arterial stiffening, consistent with our hypothesis of accelerated vascular aging.

A strong mechanistic relationship exists between measures of adiposity, insulin resistance, and glycemia. We and others have previously reported that measures

Table 2—The association of glucometabolic indices at baseline with cfPWV measured at baseline and progression of cfPWV during the follow-up period

Glucometabolic measure[a]			cfPWV at baseline			Change in cfPWV (per 5 years)		
	Median	Persons observed (n)	Mean[b]	Difference[c] (95% CI)	P value	Mean[b]	Difference[c] (95% CI)	P value
Fasting glucose, mmol/L		7,287						
Q1-lowest quintile	4.65	1,512	8.30	Ref	—	0.58	Ref	—
Q2	4.93	1,251	8.33	0.04 (−0.13, 0.21)	0.64	0.60	0.02 (−0.21, 0.25)	0.89
Q3	5.10	1,521	8.39	0.11 (−0.05, 0.27)	0.18	0.59	0.01 (−0.20, 0.23)	0.91
Q4	5.35	1,603	8.50	0.22 (0.06, 0.37)	0.007	0.57	0.00 (−0.21, 0.22)	0.99
Q5-highest quintile	5.70	1,400	8.52	0.27 (0.11, 0.43)	0.001	0.59	0.02 (−0.20, 0.24)	0.87
Heterogeneity (P value)				0.005			1.0	
Per 1 SD higher fasting glucose				0.08 (0.03, 0.13)	0.004		0.01 (−0.07, 0.08)	0.89
2-h glucose, mmol/L		7,055						
Q1-lowest quintile	4.65	1,468	8.15	Ref	—	0.53	Ref	—
Q2	5.55	1,488	8.26	0.11 (−0.05, 0.27)	0.18	0.53	0.00 (−0.22, 0.21)	0.97
Q3	6.20	1,379	8.32	0.17 (0.00, 0.33)	0.05	0.52	−0.01 (−0.24, 0.21)	0.90
Q4	6.90	1,409	8.25	0.10 (−0.06, 0.26)	0.22	0.56	0.03 (−0.19, 0.26)	0.76
Q5-highest quintile	8.25	1,311	8.46	0.32 (0.15, 0.48)	<0.001	0.73	0.20 (−0.03, 0.43)	0.09
Heterogeneity (P value)				0.006			0.36	
Per 1 SD higher 2-h glucose				0.11 (0.06, 0.16)	<0.001		0.07 (−0.01, 0.14)	0.07
HbA$_{1c}$, %		7,283						
Q1-lowest quintile	5.0	1,472	8.35	Ref	—	0.44	Ref	—
Q2	5.2	1,197	8.26	−0.08 (−0.25, 0.09)	0.33	0.58	0.14 (−0.09, 0.37)	0.24
Q3	5.4	1,930	8.39	0.04 (−0.11, 0.19)	0.60	0.49	0.05 (−0.15, 0.26)	0.62
Q4	5.6	1,418	8.56	0.21 (0.04, 0.37)	0.01	0.55	0.11 (−0.11, 0.33)	0.34
Q5-highest quintile	5.8	1,266	8.54	0.19 (0.02, 0.36)	0.03	0.83	0.39 (0.15, 0.62)	0.001
Heterogeneity (P value)				0.003			0.01	
Per 1 SD higher HbA$_{1c}$				0.05 (0.00, 0.11)	0.05		0.12 (0.04, 0.19)	0.002
HOMA-IR		7,189						
Q1-lowest quintile	0.73	1,583	8.21	Ref	—	0.41	Ref	—
Q2	1.12	1,480	8.24	0.03 (−0.12, 0.19)	0.67	0.47	0.06 (−0.16, 0.27)	0.61
Q3	1.53	1,474	8.46	0.26 (0.10, 0.41)	0.002	0.60	0.19 (−0.03, 0.40)	0.09
Q4	2.12	1,415	8.55	0.35 (0.19, 0.51)	<0.001	0.62	0.20 (−0.02, 0.42)	0.07
Q5-highest quintile	3.52	1,237	8.61	0.40 (0.23, 0.57)	<0.001	0.80	0.39 (0.15, 0.62)	0.001
Heterogeneity (P value)				<0.001			0.01	
Per 1 SD higher HOMA-IR				0.15 (0.10, 0.21)	<0.001		0.11 (0.04, 0.19)	0.004

[a]Values are the averages of measurements made in 2003–04 and 2008–09. [b]Means are adjusted for age, sex, ethnic group, heart rate, and MAP at the time of the cfPWV measurement and are shown adjusted to white men without diabetes at age 65 with a MAP of 90 mmHg. [c]Differences are adjusted for age, sex, ethnic group, and MAP at the time of the cfPWV measurement.

of adiposity, including BMI, are associated with accelerated aortic stiffening independent of other risk factors (10,18,20,22); therefore, we additionally adjusted for BMI. After this, HbA$_{1c}$ but not HOMA-IR remained predictive of aortic stiffening. These findings suggest that adiposity and insulin resistance share common pathways leading to aortic stiffening but that these pathways may be independent of glycemia, although this hypothesis requires further examination. A number of mechanisms may be responsible, including visceral and perivascular fat accumulation and the vascular effects of insulin. Indeed, fasting insulin concentrations are positively associated with cfPWV in the general population (38). In addition, abdominal and vascular adiposity alter adipokine levels, increase circulating proinflammatory stimuli, and may directly inflame the vasculature (39–41). Low adiponectin levels have previously been associated with obesity and increased cfPWV progression (19), and in the Whitehall II cohort, we have previously shown that a panel of inflammatory markers was associated with increased cfPWV 16 years later (17).

Systemic inflammation is also associated with cfPWV (7,42). Interestingly, the peroxisome proliferator–activated receptor γ agonist, pioglitazone, improves inflammation and glycemic control in obese patients with diabetes (43). Pioglitazone was also effective in preventing strokes (44) and in reducing the progression to diabetes and major cardiovascular events (45) in a high-risk population without diabetes. Peroxisome proliferator–activated receptor γ agonists may thus represent one potential therapeutic strategy to retard aortic stiffening in individuals without diabetes. In addition, formation of advanced glycation end products, which accumulate in tissues over time and with increased plasma glucose levels (46), correlate with aortic stiffness in individuals without diabetes (47,48). Experimental cross-link breakers reduce cfPWV and pulse pressure in animals (49) and humans (50), and our longitudinal finding for HbA$_{1c}$ suggests that advanced glycation end products may represent another novel antistiffening target, even in individuals without diabetes. However, both of these hypotheses need to be tested in well-designed intervention studies.

The current study has a number of limitations. We were restricted to 4-year follow-up data and cannot exclude the

Table 3—The associations of glucometabolic indices with cfPWV and progression of cfPWV after adjustment for confounding factors and other cardiovascular risk factors

Glucometabolic measure[a]	Model adjustments	cfPWV at baseline		Change in cfPWV (per 5 years)	
		Difference[b] (95% CI)	P value	Increase[b] (95% CI)	P value
Fasting glucose	Model 1[c]	0.08 (0.03, 0.13)	0.004	0.01 (−0.07, 0.08)	0.89
	Model 2[d]	0.05 (−0.01, 0.10)	0.08	−0.01 (−0.08, 0.07)	0.87
	Model 3[e]	0.05 (−0.01, 0.10)	0.09	−0.03 (−0.10, 0.04)	0.44
2-h glucose	Model 1[c]	0.11 (0.06, 0.16)	<0.001	0.07 (−0.01, 0.14)	0.07
	Model 2[d]	0.06 (0.01, 0.12)	0.03	0.06 (−0.02, 0.13)	0.12
	Model 3[e]	0.06 (0.00, 0.11)	0.04	0.04 (−0.03, 0.12)	0.24
HbA$_{1c}$	Model 1[c]	0.05 (0.00, 0.11)	0.05	0.12 (0.04, 0.19)	0.002
	Model 2[d]	0.04 (−0.02, 0.09)	0.19	0.11 (0.04, 0.18)	0.003
	Model 3[e]	0.03 (−0.02, 0.09)	0.22	0.10 (0.03, 0.17)	0.008
HOMA-IR	Model 1[c]	0.15 (0.10, 0.21)	<0.001	0.11 (0.04, 0.19)	0.004
	Model 2[d]	0.07 (0.01, 0.13)	0.03	0.09 (0.01, 0.17)	0.03
	Model 3[e]	0.07 (0.00, 0.13)	0.05	0.02 (−0.07, 0.11)	0.63

[a]Values are the averages of measurements made in 2003–04 and 2008–09. [b]Differences and increases in PVW are per 1 SD higher value for each glucometabolic measure. [c]Model 1 is adjusted for age, sex, ethnic group, heart rate, and MAP at the time of the cfPWV measurement. [d]Model 2 is adjusted as for model 1 plus systolic blood pressure, antihypertensive medication, lipid-lowering medication, prevalent MI or stroke, smoking status, and mean triglyceride and HDL-cholesterol between 2003–04 and 2008–09. [e]Model 3 is adjusted as for model 2 plus mean BMI between 2003–04 and 2008–09.

possibility that differences in relative strength of the glucometabolic risk factor effects may be observed with longer follow-up, or indeed, in younger adults. However, our data are consistent with observations made in other cohorts with similar lengths of follow-up. Moreover, we used the gold standard method of cfPWV to assess aortic stiffness and an identical protocol at both examinations. However, use of a 5-h fast for afternoon examinations may have meant that those participants were not truly fasted. We are unable to comment on the effect of diabetes per se because we a priori excluded individuals with diabetes. This allowed us to minimize potential confounding influences, such as therapy. However, we were able to demonstrate meaningful differences in progression of aortic stiffness, even within what is considered a normal range of HbA$_{1c}$. Given that glucometabolic indices determine the development of diabetes up to 15 years in advance (51) and cfPWV predicts future cardiovascular risk (2), we believe that our observations are clinically important and suggest that further mechanistic and intervention studies of arterial stiffening should examine factors related to longer-term glucometabolic status. These could involve lifestyle approaches and/or trials of glucose-lowering therapies in individuals without diabetes, which could ultimately influence public health strategies.

In summary, a higher HbA$_{1c}$ and HOMA-IR are associated with increased aortic stiffening in individuals without diabetes. This was independent of potential confounders or other cardiovascular risk factors and, in the case of HbA$_{1c}$, also independent of BMI. In contrast, point estimates of glucose, either fasting or 2 h after a standard glucose tolerance test, were not associated with progression of aortic stiffness. Our data suggest that higher average glucose levels may be causally related to accelerated vascular aging through long-term mechanisms rather than short-term dynamic changes in the arterial wall. Improving glucometabolic status may thus represent a strategy to improve vascular health.

Figure 1—The association between HbA$_{1c}$ and change in cfPWV. Plotted points show the cfPWV change per 5 years for each quintile of HbA$_{1c}$, plotted at the median of each quintile. The solid line shows the linear association, and the dashed lines show the 95% CI. Values shown are adjusted to white men without diabetes at age 65 with a MAP of 90 mmHg. Test for quadratic (nonlinear) effect gave a P value = 0.48.

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