Correlates of Aortic Stiffness Progression in Patients With Type 2 Diabetes: Importance of Glycemic Control

The Rio de Janeiro Type 2 Diabetes Cohort Study

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OBJECTIVE

The correlates of serial changes in aortic stiffness in patients with diabetes have never been investigated. We aimed to examine the importance of glycemic control on progression/regression of carotid-femoral pulse wave velocity (cf-PWV) in type 2 diabetes.

RESEARCH DESIGN AND METHODS

In a prospective study, two cf-PWV measurements were performed with the Complior equipment in 417 patients with type 2 diabetes over a mean follow-up of 4.2 years. Clinical laboratory data were obtained at baseline and throughout follow-up. Multivariable linear/logistic regressions assessed the independent correlates of changes in cf-PWV.

RESULTS

Median cf-PWV increase was 0.11 m/s per year (1.1% per year). Overall, 212 patients (51%) increased/persisted with high cf-PWV, while 205 (49%) reduced/persisted with low cf-PWV. Multivariate linear regression demonstrated direct associations between cf-PWV changes and mean HbA_{1c} during follow-up (partial correlation 0.14, $P = 0.005$). On logistic regression, a mean HbA_{1c} ≥7.5% (58 mmol/mol) was associated with twofold higher odds of having increased/persistently high cf-PWV during follow-up. Furthermore, the rate of HbA_{1c} reduction relative to baseline levels was inversely associated with cf-PWV changes (partial correlation −0.11, $P = 0.011$) and associated with reduced risk of having increased/persistently high aortic stiffness (odds ratio 0.82 [95% CI 0.69–0.96]; $P = 0.017$). Other independent correlates of progression in aortic stiffness were increases in systolic blood pressure and heart rate between the two cf-PWV measurements, older age, female sex, and presence of dyslipidemia and retinopathy.

CONCLUSIONS

Better glycemic control, together with reductions in blood pressure and heart rate, was the most important correlate to attenuate/prevent progression of aortic stiffness in patients with type 2 diabetes.

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There has been over the past decade increasing knowledge on the importance of arterial stiffness for the pathogenesis of age-related cardiovascular diseases (1,2). Central arterial stiffness depends on the structural and geometric properties of the aortic wall and on its distending pressure; and aging and blood pressure are its main determinants (3). The measurement of carotid-femoral pulse wave velocity (cf-PWV) is considered the gold standard method to evaluate aortic stiffness (4). Indeed, several studies (5–7) and a recent meta-analysis (8) have demonstrated its predictive importance for cardiovascular outcomes in various clinical conditions, including in type 2 diabetes (9). Hence, interventions directed toward decreasing aortic stiffness ("de-stiffening") may have beneficial impacts on cardiovascular prognosis (10). However, what determines progression or regression of aortic stiffness over the long-term, which is critical to planning long-lasting interventions to reducing arterial stiffness, remains unsettled. Indeed, most prospective studies evaluated the effects of pharmacological or nonpharmacological interventions in the short-term of few months up to a year (11,12) or only measured cf-PWV once at the end of follow-up (13,14). Few prospective studies evaluated serial changes in cf-PWV and their correlates over the long-term of at least 2–3 years (15–19).

Type 2 diabetic patients have increased arterial stiffness (20–22) and are at particularly augmented risk for cardiovascular morbidity and mortality. This high cardiovascular risk is not completely explained by clustering of traditional risk factors, and increased arterial stiffness may be one pathophysiological mechanism linking diabetes to increased cardiovascular morbidity and mortality (23). We recently demonstrated that increased cf-PWV is a risk marker of worse cardiovascular outcomes, over and beyond classic risk factors, and that it improves cardiovascular risk stratification in patients with type 2 diabetes (9). However, no prospective study with serial cf-PWV measurements has evaluated the factors associated with progression or attenuation of arterial stiffness in patients with diabetes. Therefore, the objective of this prospective study, part of the Rio de Janeiro Type 2 Diabetes Cohort (9,24,25), was to investigate the factors associated with serial changes in aortic stiffness, with particular attention to the importance of glycemic control in promoting aortic de-stiffening, in high-risk patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Patients and Baseline Procedures

This was a prospective study, nested within the Rio de Janeiro Type 2 Diabetes Cohort Study, with 417 patients with type 2 diabetes who performed 1st cf-PWV measurement between 2004 and 2007 and repeated the measurement between 2009 and 2013 in the diabetes outpatient clinic of our tertiary care University Hospital. All participants gave written informed consent, and the local ethics committee had previously approved the study protocol. The characteristics of this cohort, the baseline procedures, and the diagnostic definitions have previously been described (9,24–26). In brief, subjects included were all adults with type 2 diabetes up to 80 years old either with any microvascular (retinopathy, nephropathy, or neuropathy) or macrovascular (coronary, cerebrovascular, or peripheral artery disease) complication or with at least two other modifiable cardiovascular risk factors. Exclusion criteria were morbid obesity (BMI $\geq$40 kg/m^2), advanced renal failure (serum creatinine $>$180 μmol/L or estimated glomerular filtration rate $<$30 mL/min/1.73 m^2), or the presence of any serious concomitant disease limiting life expectancy. All were submitted to a standard baseline protocol that included a complete clinical examination, laboratory evaluation, and cf-PWV measurement. Diagnostic criteria for chronic diabetes complications have previously been described (9,24–26). Specifically for this analysis, patients with aorto-iliac occlusive disease were excluded because of its effect on pulse wave velocity measurement (26). Briefly, coronary heart disease was diagnosed by clinical electrocardiographic criteria or by positive ischemic stress tests. Cerebrovascular disease was diagnosed by history and physical examination and peripheral arterial disease by an ankle-brachial index $<$0.9. Diabetic retinopathy was evaluated by an ophthalmologist. The diagnosis of nephropathy needed at least two albuminuria measurements $\geq$30 mg/24 h or proteinuria measurements $\geq$0.5 g/24 h or confirmed reduction of glomerular filtration rate ($<$60 mL/min/1.73 m^2 or serum creatinine $>$130 μmol/L). Peripheral neuropathy was ascertained by clinical examination (knee and ankle reflex activities, pinprick, and temperature and vibration perception using a 128-Hz tuning fork and 10-g monofilament pressure sensation). Neuropathy was defined as the presence of at least two of the following: symptoms; reduced pinprick, temperature, and vibration perception; insensitivity to monofilament; and absent tendon reflexes. Arterial hypertension was diagnosed in the case of mean systolic blood pressure (SBP) $\geq$130 mmHg or diastolic blood pressure (DBP) $\geq$80 mmHg on a mean of four blood pressure measurements performed on two occasions at study entry or if antihypertensive drugs had been prescribed.

For this analysis, clinic blood pressures were measured three times using a digital oscillometric blood pressure monitor (HEM-907XL; Omron Healthcare, Kyoto, Japan), with a suitably sized cuff, in supine position immediately before cf-PWV measurement. The first measure was discarded; blood pressure considered was the mean between the last two readings. Laboratory evaluation included fasting glycemia, HbA_{1c}, serum creatinine, and lipids. Albuminuria and proteinuria were evaluated in two nonconsecutive sterile 24-h urine collections. The patients were followed up regularly at least three to four times a year until December 2013. All patients had at least two to four annual HbA_{1c} measurements.

cf-PWV Measurement

cf-PWV (aortic) was measured by a single trained independent observer unaware of other patients' data, in all patients within 3 months of study entry, using the foot-to-foot velocity method with the Complior equipment and software (Artech Medical, Paris, France) as previously described (9,26). Patients were in the supine position after a minimum 10-min rest at a comfortable room temperature, and all examinations were carried out in the morning, between 0900 and 1100 h, after patients had taken their morning dose of antihypertensive and hypoglycemic drugs. Briefly, waveforms were obtained transcutaneously by mechanotransducers over the right common carotid artery and the right femoral artery simultaneously

during a minimum period of 10–15 s. The time delay (Δt) was measured between the troughs of the two waveforms, and the distance (D) covered by the waves was measured directly between the femoral and the carotid recording sites. Direct carotid-femoral distance was corrected by a factor of 0.8, as recently recommended (27). The cf-PWV was calculated as D (meters)/Δt (seconds). Three consecutive measurements were performed, and the mean value was used. If any of the three measures differed by more than 1 m/s, a fourth measure was undertaken and the outlier was excluded. Increased aortic stiffness was defined as cf-PWV >10 m/s (27). After a median time interval of 4 years, the same observer repeated the examination under the same protocol; the carotid-femoral distance was kept unchanged in this second examination, but the operator was blinded to the first examination results. In our laboratory, the intraobserver repeatability has an intraclass correlation coefficient >0.90 and a mean relative error <5%; and the Complior equipment and procedures have previously been validated (28). Attending physicians were unaware of cf-PWV results either at baseline or during follow-up.

Statistical Analysis

Continuous data were described as means (SD) or as median (interquartile range). Patients were divided into two subgroups based on having either increased or persisted with high cf-PWV or on having either reduced or persisted with low cf-PWV on the 2nd measurement in relation to the first measurement. To define these two subgroups, we divided the 1st and 2nd cf-PWV measurements into quartiles and classified patients as having either decreased their quartile distribution or persisted within the two lower quartile groups and those who increased their quartile distribution or persisted within the higher quartile groups. Bivariate comparisons between these subgroups were performed by unpaired *t* test (for continuous normal variables), Mann-Whitney test (for continuous asymmetric variables), and χ^2 test (for categorical variables). Annual changes in cf-PWV were evaluated as absolute change, [(2nd measurement − 1st measurement)/time interval between the two measurements] in m/s per year, and as relative change in relation to the 1st measurement, {[(2nd measurement − 1st measurement)/1st measurement] × 100/time interval between the two measurements} in % per year. In the same way, we evaluated changes in SBP and in heart rate measured at the two cf-PWV measurements. Both cf-PWV measurements and their respective changes, as well as SBP and heart rate changes, were normally distributed (Supplementary Figs. 1 and 2). To examine the independent correlates of changes in cf-PWV, we performed two multivariate analyses. In the first analysis, we used a general linear mixed-effects model with the continuous relative cf-PWV change as the dependent variable and the following candidate independent variables: age, sex, baseline BMI and weight change during follow-up, diabetes duration, physical activity, smoking status, dyslipidemia, insulin, statin and aspirin use, arterial hypertension, number of antihypertensive drugs in use, each macro- and microvascular diabetes complication, baseline glomerular filtration rate, SBP and heart rate at 1st cf-PWV measurement and relative changes in SBP and heart rate between 1st and 2nd cf-PWV, and 1st cf-PWV measurement. Importance of glycemic control was evaluated by including separately the baseline HbA_{1c}, the mean HbA_{1c} during the first year of follow-up, and mean HbA_{1c} between the 1st and 2nd cf-PWV measurement. The rate of HbA_{1c} reduction during the first year of follow-up, calculated as [(baseline − mean 1st year)/baseline] × 100, was also evaluated. Collinearity diagnosis was examined by the variance inflation factor (VIF) of each covariate within the model; a VIF larger than three was considered as evidence for collinearity among covariates. In the second analysis, we used a logistic regression modeling with dichotomized change in cf-PWV (reduced/persistently low and increased/persistently high) as the dependent value, and the same candidate covariates, except that HbA_{1c} was categorized at less than versus ≥7.5% (58 mmol/mol). In all multivariate analyses, a stepwise forward selection procedure was adopted, and a *P* value <0.10 was the criterion to enter and to remain into the models. Age, sex, and the 1st cf-PWV, SBP, and heart rate measurements were forced into all models, regardless of their significances, and were further adjusted for the time interval between the two measurements. Results were presented as B coefficients with their SEs and partial correlation coefficients (for general linear regressions) and as odds ratios (ORs) with 95% CI (for logistic regressions). Overall model fitness was evaluated by r^2 (for linear models) and by the area under the receiver operating characteristic curve of the estimated probabilities (for logistic models). All statistics were performed with SPSS statistical package version 19.0 (SPSS, Chicago, IL), and a two-tailed *P* value <0.05 was regarded as significant.

RESULTS

Characteristics According to Changes in Aortic Stiffness During Follow-up

The mean (SD) time interval between the two cf-PWV measurements was 4.2 (0.6) years. Mean 1st cf-PWV measurement was 9.2 (2.0) m/s and increased to 9.6 (2.0) m/s on the 2nd measurement. The mean annual absolute increase in cf-PWV was 0.11 m/s per year (Table 1). Overall, 212 patients (51%) had an increase in aortic stiffness or persisted with high values (at upper quartiles), while 205 (49%) presented a reduction or persisted with low cf-PWV (at lower quartiles). Table 1 outlines the clinical and laboratory characteristics of all patients and of those with reduction in/persistently low and increase in/persistently high cf-PWV values. Patients who increased or persisted with high aortic stiffness were older, had longer diabetes duration, more frequently used insulin, and had greater prevalence of diabetic retinopathy and nephropathy than those who decreased or persisted with low stiffness. Despite using a greater number of antihypertensive medications, particularly diuretics, patients who increased/persisted with high aortic stiffness had higher clinic SBP levels at 1st and 2nd cf-PWV measurement. Notably, patients who attenuated/persisted with low stiffness had an overall decrease in SBP between 1st and 2nd cf-PWV measurements (from 145 to 135 mmHg), whereas patients who increased/persisted with high aortic stiffness presented an increase in SBP levels (from 150 to 153 mmHg). Patients who augmented/persisted with high cf-PWV had higher baseline fasting glycemia and HbA_{1c} and higher mean 1st-year HbA_{1c}

Table 1—Baseline clinical laboratory characteristics of all diabetic patients and grouped according to serial cf-PWV changes (increase or reduction) during follow-up interval

Characteristics	All patients	Patients with reduction in/ persistently low cf-PWV	Patients with increase in/ persistently high cf-PWV
n	417	205	212
Male sex (%)	35.7	37.1	34.4
Age (years)	60.4 (9.5)	58.4 (9.0)	61.6 (8.8)*
Diabetes duration (years)	8 (3–15)	5 (2–13)	10 (5–17)*
BMI (kg/m^2)	29.6 (4.7)	29.8 (4.3)	29.5 (5.0)
Current/past smoking (%)	42.7	43.9	41.5
Physical activity (%)	26.1	27.8	24.5
Dyslipidemia (%)	88.0	85.9	90.1
Statin use	75.8	74.1	77.4
Diabetes treatment (%)			
Metformin	88.5	85.9	91.0
Sulfonylureas	45.3	46.8	43.9
Insulin	45.8	38.0	53.3†
Aspirin	93.2	92.0	94.3
Arterial hypertension (%)	85.9	83.4	88.2
Antihypertensive treatment (%)			
Number of drugs	3 (1–3)	2 (1–3)	3 (1–3)‡
ACE inhibitors/AR blockers	84.1	82.4	85.7
Diuretics	67.2	61.5	72.9 ‡
β-Blockers	48.9	46.3	51.4
Calcium channel blockers	31.1	29.8	32.4
Clinic blood pressures at 1st cf-PWV measurement (mmHg)			
SBP	147 (23)	145 (23)	150 (23)‡
DBP	80 (12)	79 (12)	80 (13)
Clinic blood pressures at 2nd cf-PWV measurement (mmHg)			
SBP	144 (24)	135 (20)	153 (25)*
DBP	76 (14)	72 (12)	79 (15)*
Absolute clinic SBP change (mmHg/year)	−1.2 (−5.3 to 3.9)	−2.6 (−6.5 to 1.8)	0.5 (−3.6 to 5.2)*
Relative clinic SBP change (% per year)	−0.9 (−4.0 to 2.4)	−2.1 (−5.1 to 1.3)	0.3 (−2.7 to 3.1)*
Chronic diabetes complications (%)			
Cerebrovascular disease	7.9	6.3	9.4
Coronary artery disease	15.8	16.6	15.1
Retinopathy	30.0	22.0	37.7*
Nephropathy	26.9	22.4	31.1‡
Peripheral neuropathy	26.4	23.9	28.8
Laboratory variables			
Fasting glucose (mmol/L)	8.60 (3.50)	7.99 (3.11)	9.21 (3.77)*
Baseline HbA_{1c} (%)	7.8 (1.8)	7.6 (1.7)	8.1 (1.9)†
Baseline HbA_{1c} (mmol/mol)	62 (19.7)	60 (18.6)	65 (20.8)
Mean 1st-year HbA_{1c} (%)	7.6 (1.4)	7.2 (1.2)	7.9 (1.5)*
Mean 1st-year HbA_{1c} (mmol/mol)	60 (15.3)	55 (13.1)	63 (16.4)
Mean HbA_{1c} between 1st and 2nd cf-PWV measurements (%)	7.6 (1.3)	7.3 (1.1)	7.9 (1.4)*
Mean HbA_{1c} between 1st and 2nd cf-PWV measurements (mmol/mol)	60 (14.2)	56 (12.0)	63 (15.3)
Triglycerides (mmol/L)	1.63 (1.12–2.48)	1.61 (1.13–2.52)	1.63 (1.10–2.44)
HDL cholesterol (mmol/L)	1.09 (0.28)	1.06 (0.26)	1.11 (0.31)
LDL cholesterol (mmol/L)	3.08 (1.01)	3.03 (0.93)	3.13 (1.06)
Creatinine (μmol/L)	71 (62–88)	71 (62–88)	71 (62–88)
Glomerular filtration rate (mL/min/1.73 m^2)	88 (69–112)	94 (72–117)	83 (67–105)†
Albuminuria (mg/24 h)	13 (7–32)	13 (7–26)	14 (8–46)
Aortic stiffness measurements			
1st cf-PWV measurement (m/s)	9.2 (2.0)	8.7 (1.7)	9.7 (2.0)*
1st cf-PWV >10 m/s (%)	24.7	19.0	30.2†
2nd cf-PWV measurement (m/s)	9.6 (2.0)	8.2 (1.1)	11.0 (1.6)*
2nd cf-PWV >10 m/s (%)	35.0	6.8	62.3*

Continued on p. 901

Table 1—Continued

Characteristics	All patients	Patients with reduction in/ persistently low cf-PWV	Patients with increase in/ persistently high cf-PWV
Time interval between cf-PWV measurements (years)	4.2 (0.6)	4.2 (0.5)	4.3 (0.6)
Absolute cf-PWV change (m/s per year)	0.1 (−0.2 to 0.4)	−0.1 (−0.3 to 0.1)	0.4 (0.2–0.6)*
Relative cf-PWV change (% per year)	1.1 (−1.4 to 4.0)	−0.9 (−2.7 to 1.0)	3.5 (1.2–5.8)*
Heart rate at 1st cf-PWV measurement (bpm)	72 (12)	71 (11)	73 (13)‡
Heart rate at 2nd cf-PWV measurement (bpm)	69 (12)	68 (12)	70 (12)‡
Absolute heart rate change (bpm/year)	−0.7 (−2.5 to 0.8)	−0.7 (−2.3 to 0.9)	−0.7 (−2.6 to 0.7)
Relative heart rate change (% per year)	−0.9 (−3.4 to 1.1)	−0.9 (−3.3 to 1.3)	−0.9 (−3.4 to 1.1)

Data are means (SD) or median (interquartile range), unless otherwise indicated. AR, angiotensin II receptor. *$P < 0.001$, †$P < 0.01$, ‡$P < 0.05$ for bivariate comparisons between patients with reduction in/persistently low and increase in/persistently high aortic stiffness.

and mean Hba_{1c} between the two cf-PWV measurements than patients who had attenuated or persisted with low aortic stiffness. Figure 1 shows serial mean HbA_{1c} during follow-up in the two subgroups. Finally, patients who reduced/persisted with low stiffness had a slightly lower heart rate at both cf-PWV measurements than those who increased/persisted with high aortic stiffness. During follow-up, treatment was equally intensified in both subgroups, including insulin, antihypertensive, and statin use. Also, patients gained a median of 1.2 kg during follow-up, which was equal between those who decreased/persisted with low cf-PWV (1.1 kg) and those who increased/persisted with high cf-PWV (1.4 kg).

Independent Correlates of Serial Changes in Aortic Stiffness

Table 2 shows the results of the multivariate linear regression analysis for the covariates independently associated with relative cf-PWV changes during follow-up. After adjustment for 1st cf-PWV, SBP, and heart rate measurements, which were correlated with cf-PWV changes, relative changes in SBP and heart rate and mean HbA_{1c} between the two cf-PWV measurements were the main correlates of changes in aortic stiffness. Older age, female sex, and presence of diabetic retinopathy and dyslipidemia were the other correlates of progression in arterial stiffness during follow-up. The relative changes in SBP and heart rate between the two cf-PWV measurements explained, respectively, 12% and 4% of the overall cf-PWV change variability, whereas mean HbA_{1c} and age explained 2% of each one. The whole linear model explained 34% of aortic stiffness variability during follow-up. Mean HbA_{1c} during the 1st year of follow-up, entered in the model instead of mean HbA_{1c} during the time interval between the two cf-PWV measurements, was also significantly correlated with relative cf-PWV changes (partial correlation 0.14, $P = 0.004$), whereas baseline HbA_{1c} was not (partial correlation 0.04, $P = 0.39$) (both adjusted for the same covariates of the original analysis). Otherwise, the relative rate of HbA_{1c} reduction during the 1st year of follow-up was inversely correlated with cf-PWV changes (partial correlation −0.11, $P = 0.011$); i.e., the greater reduction of HbA_{1c} during the 1st year of follow-up, the less aortic stiffness progression during follow-up. Using the absolute annual change in cf-PWV as the dependent variable, instead of relative changes, yielded identical results except that the presence of nephropathy substituted for retinopathy in the models (partial correlation 0.10, $P = 0.047$). Simple scatter plot correlations between changes in cf-PWV and the main correlates (mean HbA_{1c} and changes in SBP and heart rate) are shown in Supplementary Figs. 3–6.

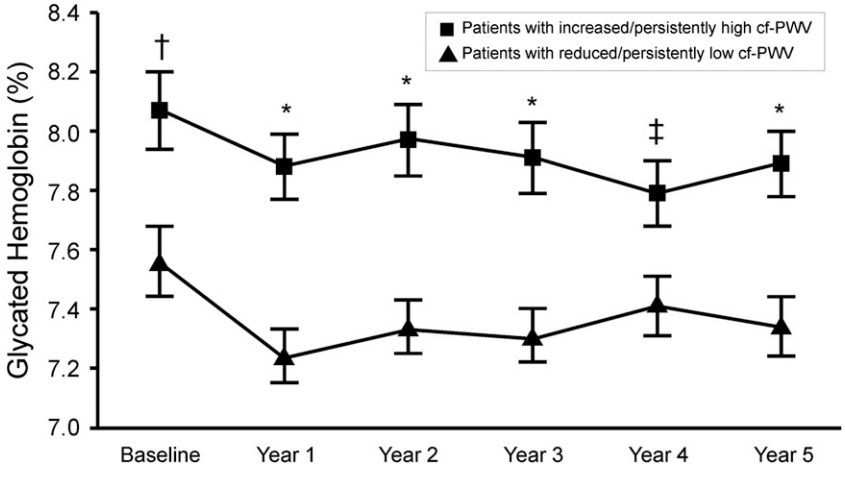

Figure 1—Mean HbA_{1c} levels until the 5th year of follow-up in patients with increased or persistently high cf-PWV (closed squares) and in patients with reduced or persistently low cf-PWV (closed triangles). Bars are SEs. *$P < 0.001$, †$P < 0.01$, and ‡$P < 0.05$ for comparisons between the two subgroups.

Table 3 presents the results of multivariate logistic regression for the independent covariates associated with reduction in/persistently low or increase in/persistently high aortic stiffness during follow-up. Similarly, beyond 1st cf-PWV, SBP, and heart rate measurements, an increase in SBP and heart rate from 1st to 2nd cf-PWV measurements, as well as a higher mean HbA_{1c} between the two measurements, were the main correlates of having either increased or persisted with high aortic stiffness during follow-up. A mean $HbA_{1c} \geq 7.5\%$ (58 mmol/mol) doubled the odds of having increased/persistently high aortic stiffness. The other independent correlates of arterial stiffness progression were older age and presence of diabetic retinopathy, but no influence of sex was demonstrated. A higher mean 1st-year HbA_{1c} (≥7.5%, 58 mmol/mol) was associated with greater

Table 2—Results of multivariate linear regression (general linear mixed-effects model) for the covariates independently associated with relative changes in cf-PWV during follow-up (the dependent variable)

Covariates	B coefficient (SE)	Partial correlation coefficient	*P*	VIF
1st cf-PWV (1-m/s increment)	−0.873 (0.097)	0.41	<0.001	1.77
Relative SBP change between 1st and 2nd cf-PWV (1% per year increment)	0.347 (0.046)	0.35	<0.001	1.47
Relative heart rate change between 1st and 2nd cf-PWV (1% per year increment)	0.188 (0.043)	0.21	<0.001	1.33
Age (1-year increment)	0.065 (0.023)	0.14	0.004	1.54
Mean HbA_{1c} between 1st and 2nd cf-PWV (1% increment)	0.408 (0.143)	0.14	0.005	1.30
Heart rate at 1st cf-PWV (1-bpm increment)	0.043 (0.016)	0.13	0.008	1.42
SBP at 1st cf-PWV (1-mmHg increment)	0.024 (0.009)	0.13	0.011	1.69
Sex (1 = men; 2 = women)	0.756 (0.347)	0.11	0.030	1.03
Retinopathy (0 = absent; 1 = present)	0.780 (0.382)	0.10	0.042	1.14
Dyslipidemia (0 = absent; 1 = present)	1.029 (0.519)	0.10	0.048	1.05

R^2 of the model = 0.34. Linear model was further adjusted for time interval between cf-PWV measurements. Candidate variables to enter the model: age, sex, baseline BMI, change in weight during follow-up, diabetes duration, physical activity, smoking status, dyslipidemia, insulin, statin and aspirin use, arterial hypertension, number of antihypertensive drugs in use, each macro- and microvascular diabetes complication, mean HbA_{1c} between 1st and 2nd cf-PWV, baseline glomerular filtration rate, SBP and heart rate at 1st cf-PWV measurement and relative changes in SBP and heart rate between 1st and 2nd cf-PWV, and 1st cf-PWV measurement.

odds of having increased/persistently high aortic stiffness (OR 2.54 [95% CI 1.55–4.15]; $P < 0.001$), whereas a higher baseline HbA_{1c} was not (OR 1.43 [95% CI 0.90–2.27]; $P = 0.13$). In the same way, the relative rate of HbA_{1c} reduction during the 1st year of follow-up was a protective factor for having increased/persistently high aortic stiffness (OR 0.82 [95% CI 0.69–0.96]; $P = 0.017$ for each 10% relative reduction in HbA_{1c}). No specific medication (antihypertensive, antidiabetic, or statin), used either at baseline or during follow-up, was associated with changes in cf-PWV in linear or logistic regressions or influenced the other correlates of progression/regression in aortic stiffness.

CONCLUSIONS

This prospective study with 4.2 years' mean follow-up of a high-risk middle-aged to elderly type 2 diabetic population has three most important findings. First, it demonstrates, for the first time, that better glycemic control, evaluated either by mean 1st-year or by updated mean HbA_{1c} levels during the whole follow-up, either as continuous or at categorized values, was associated with attenuation in aortic stiffness. Second, it shows that the rate of HbA_{1c} reduction during the 1st year of follow-up was associated with a reduction of risk of having increased/persistently high aortic stiffness, independent of baseline HbA_{1c} levels. Finally, it shows that reductions in blood pressure and heart rate during follow-up were the other most important correlates of attenuating/preventing progression of aortic stiffness in patients with type 2 diabetes. Older age, female sex, and presence of diabetic retinopathy or nephropathy and dyslipidemia were the other correlates of progression in arterial stiffness during follow-up. These findings have important clinical implications: improving glycemic and blood pressure control and reducing heart rate may lead to aortic de-stiffening, which might reduce the burden of morbidity and mortality associated with type 2 diabetes. Whether reducing aortic stiffness will be associated with a better prognosis in patients with type 2 diabetes still needs to be demonstrated in future multiple-intervention prospective investigations.

Some previous cross-sectional studies (29,30) have suggested that aortic stiffness might be associated with HbA_{1c} levels; notably, in this study it was possible to establish temporality, so we can speculate that there is causality between HbA_{1c} levels and aortic stiffness progression/regression, which may be in part mediated by advanced glycation

Table 3—Results of multivariate logistic regression for the covariates independently associated with reduction in/persistently low or increase in/persistently high cf-PWV between first and second measurements (the dependent variable)

Covariates	OR	95% CI	*P*
Relative SBP change between 1st and 2nd cf-PWV (1% per year increment)	1.25	1.17–1.34	<0.001
Relative heart rate change between 1st and 2nd cf-PWV (1% per year increment)	1.11	1.04–1.18	0.001
SBP at 1st cf-PWV (10-mmHg increment)	1.22	1.08–1.39	0.002
Mean HbA_{1c} between 1st and 2nd cf-PWV ≥7.5% (58 mmol/mol)	2.02	1.24–3.30	0.005
1st cf-PWV (1-m/s increment)	1.21	1.06–1.39	0.005
Heart rate at 1st cf-PWV (10-bpm increment)	1.30	1.05–1.62	0.018
Age (10-year increment)	1.43	1.05–1.93	0.022
Retinopathy (0 = absent; 1 = present)	1.68	1.01–2.80	0.046
Sex (1 = men; 2 = women)	1.12	0.71–1.79	0.62

Hosmer-Lemeshow goodness-of-fit test: $P = 0.46$. Area under the receiver operating characteristic curve: 0.79 (95% CI 0.75–0.83). Candidate variables to enter the model were the same as in Table 2, except mean HbA_{1c} between 1st and 2nd cf-PWV that was categorized at ≥7.5% (58 mmol/mol).

end product (AGE) formation. Increased arterial stiffness is thought to be related to quantitative and qualitative alterations in arterial wall elastin and collagen (1,2). Data suggest that such alterations may be caused not only by short-term hyperglycemia but also by carbonyl and oxidative stress, chronic inflammation, and endothelial dysfunction, including that caused by long-term hyperglycemia and formation of AGEs (23). Chronic hyperglycemia increases the reaction between glucose and proteins and facilitates cross-linking of collagen, elastin, and other molecules, so-called AGEs, which have been shown to produce collagen deposition, tissue inflammation, and fibrosis within the vessel wall (29). Chronic hyperglycemia may also affect the arterial wall by promoting proliferation of smooth muscle cells (31). Furthermore, a previous study has shown reduction of arterial stiffness using compounds that affect or break the structure of AGEs, which may represent a future treatment option (32). Supporting that chronic hyperglycemia and higher HbA_{1c} levels may be related to increase in aortic stiffness, a study in hemodialysis patients has shown that pentosidine levels (a well-characterized AGE) was independently associated with progression of aortic stiffness after 1.2 years' mean follow-up (33). Most importantly, we have shown that at least part of the increased aortic stiffness related to poor glycemic control can be reversed by improving HbA_{1c} levels during follow-up, particularly during the 1st year.

Some previous studies (15–19,33–36) evaluated longitudinal changes in cf-PWV in different populations but none in patients with type 2 diabetes. Similar to other reports (13–19,34–36), we observed that aortic stiffness progression was associated with older age and higher blood pressure and heart rate during follow-up. These results are in agreement with the hypothesis that high SBP and heart rate are physiopathological mechanisms that may accelerate fatigue fracture of aortic elastic elements by representing aortic cyclic stress, which multiplied by age is a substitute for cumulative number of cyclic stresses, finally resulting in increased aortic stiffness (37). Moreover, an increased SBP, by increasing aortic distending pressure, augments cf-PWV (1–3). However, the relationship between SBP changes and arterial stiffness progression may be bidirectional, as increased aortic stiffness also makes SBP reduction more difficult to achieve. The effect of sex on aortic stiffness progression is still controversial. As opposed to a previous study (19), which reported higher rates of aortic stiffness progression in men, we found that female sex was associated with aortic stiffness increase during follow-up in linear but not in logistic regression. On the other hand, in most previous cross-sectional studies recently reviewed (27), postmenopausal women had higher cf-PWV than men. The reason for these sex disparities in aortic stiffness are not clear but might be linked to sex differences in patterns of aortic remodeling with aging (38), with women having slower rates of aortic dilatation, which affects aortic stiffness.

We previously reported (26) that the presence at baseline of diabetic microvascular complications, mainly retinopathy and nephropathy, was independently associated with higher aortic stiffness, and additionally, we demonstrate here that their presence is also associated with aortic stiffness progression during follow-up. The physiopathological mechanisms linking diabetic microvascular disease with accelerated aortic stiffness progression are probably bidirectional. Microvascular disease may cause large artery damage by an inward remodeling mechanism (1), where the impaired vasodilatation of small arteries may enhance backward pulse wave reflections and central pulse pressure, which damages the central arterial wall. Otherwise, aortic stiffness progression, because of loss of its normal buffering function, leads to increased transmission of a wider, potentially harmful, forward pulsatile pressure wave to microcirculation, particularly at high-flow organs such as the brain/retina and kidneys (1,2). Alternatively, inflammation within micro- and macrovascular walls might mediate the association between diabetic microvascular disease and worsening of aortic stiffness (39).

We have some limitations to consider. First, the possibility that the "regression to the mean" phenomenon may have affected our findings warrants discussion. Several arguments make it unlikely to have markedly influenced the results, although a minor effect cannot be ruled out. At the study design level, we performed three cf-PWV measurements on each occasion and a fourth one whenever any value differed by >1 m/s. This prevented the chance appearance of spurious extreme cf-PWV values (40). We also adjusted all the multivariable analyses of changes in cf-PWV and in blood pressures and heart rate to their respective baseline values, which is a well-accepted method to decrease the influence of the regression-to-the-mean phenomenon (40). Finally, the correlation coefficient between the 1st and 2nd cf-PWV was high ($r = 0.69$), which also decreases the regression to the mean (40). Second, this study was performed in high-risk middle-aged to elderly patients with type 2 diabetes, so the results may not apply to younger and lower-risk individuals. Third, as previous discussed, an observational cohort study did not allow cause-and-effect or mechanistic inferences or directionality of the associations. Moreover, we also did not measure AGEs, and so we can only speculate on their role in aortic stiffness alterations.

In conclusion, this prospective study provides evidence that better glycemic control, evaluated by HbA_{1c} levels during follow-up; blood pressure; and heart rate reductions were the most important correlated factors to attenuate/prevent progression of aortic stiffness in patients with type 2 diabetes. As to whether such interventions are actually associated with a long-term, sustained regression in aortic stiffness and whether reducing aortic stiffness can improve cardiovascular prognosis, only future well-powered multiple-intervention clinical trials will be able to answer these questions.

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