Clinical Investigations

PREVENTION

Type 2 Diabetes Is Associated With Increased Pulse Wave Velocity Measured at Different Sites of the Arterial System but Not Augmentation Index in a Chinese Population

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ABSTRACT

Background: Patients with type 2 diabetes have increased stiffness of central elastic arteries. However, whether peripheral muscular artery stiffness is equally affected by the disease remains sparsely examined. Moreover, the association between pulse wave velocity (PWV) and augmentation index (AIx) in diabetes is poorly understood.

Hypothesis: Type 2 diabetes is associated with the alterations in arterial stiffness (PWV and AIx) in a community-based population.

Methods: A total of 79 Chinese patients with type 2 diabetes and 79 sex-, age- (±3 years), and body mass index- (±2 kg/m²) matched healthy controls were studied. Carotid-femoral pulse wave velocity (CF-PWV), carotid-radial pulse wave velocity (CR-PWV), and carotid-ankle pulse wave velocity (CA-PWV) were calculated from tonometry waveforms and body surface measurements, whereas AIx was assessed using pulse wave analyses.

Results: In univariate analysis, patients with type 2 diabetes showed increased CF-PWV ($P < 0.001$), CR-PWV ($P = 0.012$), and CA-PWV ($P = 0.016$), and lower AIx ($P = 0.017$) than the control group. In multiple linear regression models adjusting for covariates, type 2 diabetes remained a significant determinant of CF-PWV. Fasting glucose was associated with CR-PWV but was not related to CA-PWV or AIx.

Conclusions: Our findings suggest that patients with type 2 diabetes have increased central and peripheral artery stiffness, but preserved AIx compared to controls. Diabetes was a predictor of central artery stiffness, and glucose was a determinant of peripheral artery stiffness.

Introduction

Type 2 diabetes is associated with a markedly increased risk of cardiovascular morbidity and mortality.[1,2] In nondiabetic individuals, increased arterial stiffness is an important cause of cardiovascular disease.[3–5] Arterial stiffness is not uniform along the arterial tree, and there may be important differences between central elastic (carotid) and peripheral muscular (femoral and brachial) arteries.[6] A previous study showed that different glucose tolerance statuses may have different influences on arterial stiffness of elastic and muscular arteries.[7]

Pulse wave velocity (PWV) is an accepted index of arterial stiffness and is measured at different sites of the arterial tree, such as carotid-femoral pulse wave velocity (CF-PWV), carotid-radial pulse wave velocity (CR-PWV), and carotid-ankle pulse wave velocity (CA-PWV).[6,8,9] CF-PWV is a validated marker of arterial stiffness over the central arteries and has been established as an important predictor of future cardiovascular risk.[4–6] CR-PWV mainly reflects peripheral muscular arterial stiffness (upper limb), whereas CA-PWV is associated with stiffness in both central and peripheral (femoral-ankle) arteries.[6,8] Previous studies have shown that aortic PWV is greater in subjects with diabetes than in controls.[10]

Augmentation index (AIx) has been advocated as an indirect surrogate measure of arterial stiffness,[11,12] but arterial stiffness is only one contributor to the observed AIx, and a number of studies have now demonstrated divergence of AIx and PWV (the current gold-standard assessment of stiffness).[13–16] Previous studies yielded inconsistent results about changes in AIx in patients with type 2 diabetes.[17,18] Moreover, until now, AIx and PWV measured at different

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Table 1. Characteristics of the Study Population

	Controls, n = 79	Type 2 Diabetes, n = 79	*P* Value
Sex (M/F)	39/40	39/40	—
Age (y)	60.1 ± 9.5	60.2 ± 9.6	0.967
Current smoking (%)	43.6	36.2	0.597
Height (cm)	163.9 ± 8.4	162.5 ± 7.5	0.258
Weight (kg)	65.8 ± 10.1	65.3 ± 9.3	0.740
BMI (kg/m^2)	24.4 ± 2.6	24.7 ± 2.6	0.535
Brachial SBP (mm Hg)	119.3 ± 11.0	123.1 ± 11.0	0.032
Brachial DBP (mm Hg)	72.2 ± 8.1	72.9 ± 8.4	0.580
Brachial PP (mm Hg)	47.1 ± 9.3	50.2 ± 9.0	0.037
HR (min^{-1})	73.4 ± 9.0	77.6 ± 9.5	0.006
Glucose (mmol/L)	4.88 (4.37–5.39)	6.97(3.41–10.53)	<0.001
TC (mmol/L)	4.65 ± 0.65	5.05 ± 0.97	0.005
TG (mmol/L)	1.09 (0.57–1.61)	1.51 (0.25–2.77)	<0.001
HDL-C (mmol/L)	1.49 ± 0.34	1.32 ± 0.35	0.003
LDL-C (mmol/L)	2.60 ± 0.53	3.05 ± 0.74	<0.001
Creatinine (μmol/L)	69.1 ± 18.7	61.4 ± 15.9	0.006
UA (mmol/L)	275.0 ± 63.0	276.1 ± 65.6	0.840
eGFR (mL/min)	91.4 ± 26.9	101.8 ± 27.0	0.017

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; F, female; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; M, male; PP, pulse pressure; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UA, uric acid. Data are reported as mean ± standard deviation or median (interquartile range).

Table 2. Indices of Arterial Stiffness in Patients With Type 2 Diabetes and Controls

	Controls, n = 79	Type 2 Diabetes, n = 79	*P* Value[a]	*P* Value[b]	*P* Value[c]
CF-PWV (m/s)	9.95 ± 2.44	11.78 ± 3.04	<0.001	0.002	<0.001
CR-PWV (m/s)	9.14 ± 1.22	9.73 ± 1.65	0.012	0.021	0.046
CA-PWV (m/s)	8.73 ± 1.62	9.36 ± 1.61	0.016	0.036	0.005
AIx (%)	28.1 ± 10.3	24.2 ± 9.8	0.017	0.103	0.023

Abbreviations: AIx, augmentation index; CA-PWV, carotid-ankle pulse wave velocity; CF-PWV, carotid-femoral pulse wave velocity; CR-PWV, carotid-radial pulse wave velocity. Data are reported as mean ± standard deviation. [a]Unadjusted *P* values for nonpaired *t* test. [b]Adjusted *P* values for analysis of covariance (ANCOVA) (adjusting for heart rate and mean arterial pressure). [c]Adjusted *P* values for ANCOVA (adjusting for triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and estimated glomerular filtration rate).

sites have not been evaluated in Chinese patients with type 2 diabetes and well-matched controls. Because the differences in arterial stiffness among different ethnic groups have been previously reported,[19,20] it is necessary to investigate the associations between diabetes and indices of arterial stiffness in Chinese inhabitants.

The aim of the present study was to investigate the relationship between type 2 diabetes and alterations in arterial stiffness in a community-based population in China.

Methods

Study Population

All participants were selected from a population-based investigation study that included 5116 Chinese inhabitants of Haidian or Daxing District, Beijing, China in 2007. The inclusion criteria for type 2 diabetes patients included a fasting plasma glucose ≥7.0 mmol/L, or an oral glucose tolerance test (OGTT) 2-hour postprandial glucose ≥11.1 mmol/L, or a previous diagnosis of type 2 diabetes. Patients with hypertension, coronary heart disease, stroke, and other complications of type 2 diabetes were excluded from the study. The inclusion criteria of normal controls included sex, age (±3 years), and body mass index (BMI) (±2 kg/m^2) that were matched with diabetes patients. The controls were healthy on medical examination. A total of 79 patients with type 2 diabetes (39 males and 40 females; mean age, 60.2 ± 9.6 years) were obtained. Antidiabetic medications among patients included insulin (n = 11) and oral hypoglycemic agents (n = 34). Some patients received no drugs (n = 34), including newly diagnosed patients (n = 15). Seventy-nine matched healthy control subjects were recruited from the same district in Beijing. None of the control subjects were receiving any medications with potential cardiovascular effects. All participants underwent a glucose tolerance test, except 13 previously diagnosed patients who refused to do the test. The local ethics committee approved the study. All participants provided written informed consent.

Brachial Artery Blood Pressure Measurement

Clinical systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained by mercury cuff sphygmomanometer on the right brachial artery in a seated position after 15 minutes of rest. Measurements were repeated at least 2 minutes apart, and the average of the results was recorded. We calculated pulse pressure (PP) using the following equation: PP = SBP − DBP. The mean value was considered representative of brachial blood pressure.

Radial Artery Pulse Wave Analysis

Pulse wave analysis was used to determine aortic AIx. Subjects remained in a seated position, and measurements were taken immediately following determination of brachial blood pressure. The right radial artery pressure waveform was recorded using an instrument designed for such measurements (SphygmoCor, Sydney, Australia). The system software was used to calculate an average radial artery waveform, and the corresponding central aortic pressure waveform was generated using a transfer function of the instrument. AIx was defined as the ratio of augmentation to pulse pressure and was expressed as a

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Table 3. Correlations Between Arterial Stiffness Indices and Study Variables in Patients With Type 2 Diabetes (Univariate Analysis)

	CF-PWV		CR-PWV		CA-PWV		AIx	
	r_p	P	r_p	P	r_p	P	r_p	P
AIx	−0.063	0.605	−0.294	0.014	−0.073	0.549	1.000	1.000
Age	0.491	<0.001	−0.095	0.404	0.354	0.002	0.043	0.722
Height	−0.101	0.376	0.321	0.004	0.013	0.910	−0.518	<0.001
Weight	−0.208	0.067	0.107	0.348	−0.115	0.321	−0.293	0.014
BMI	−0.194	0.087	−0.131	0.250	−0.166	0.148	0.057	0.639
SBP	0.074	0.517	−0.003	0.979	0.218	0.057	0.212	0.078
DBP	−0.260	0.021	0.035	0.757	−0.036	0.756	0.180	0.136
PP	0.331	0.003	−0.036	0.750	0.292	0.010	0.101	0.406
HR	0.148	0.223	0.275	0.021	−0.109	0.368	−0.453	0.001
Glucose	−0.245	0.031	0.065	0.575	−0.219	0.057	−0.191	0.112
TC	−0.112	0.329	−0.089	0.435	0.083	0.477	−0.116	0.339
Triglyceride	−0.118	0.305	0.164	0.153	−0.141	0.225	−0.084	0.487
HDL-C	−0.068	0.555	−0.170	0.136	0.108	0.352	−0.061	0.617
LDL-C	−0.017	0.885	−0.135	0.238	0.087	0.454	0.094	0.439
Creatinine	0.114	0.323	0.245	0.032	0.108	0.355	−0.458	0.001
UA	0.069	0.549	0.018	0.878	0.006	0.956	−0.241	0.044
eGFR	−0.414	0.002	−0.016	0.892	−0.309	0.007	0.135	0.262

Abbreviations: AIx, augmentation index; BMI, body mass index; CA-PWV, carotid-ankle pulse wave velocity; CF-PWV, carotid-femoral pulse wave velocity; CR-PWV, carotid-radial pulse wave velocity; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; PP, pulse pressure; SBP, systolic blood pressure; TC, total cholesterol; UA, uric acid. r_p is Pearson index and P is its significance.

percentage (AIx = (Δ P/PP) × 100). Data from the mean of two central aortic pressure waveforms were taken for each subject. All measurements were made by the same observer.

Measurement of Pulse Wave Velocity

PWVs were calculated from tonometry waveforms and body surface measurements. Subjects were requested to be in a fasted state and to abstain from caffeine, smoking, and alcohol for at least 12 hours before arterial properties assessments were performed. Subjects were studied under supine resting conditions. Measurements were carried out after at least 5 minutes of supine rest. Heart rate was measured by 12-lead electrocardiography in the supine position.

Automatic CF-PWV, CR-PWV, and CA-PWV were measured using the Complior Colson device (Createch Industrie, Massy, France); the technical characteristics of this device have been described previously.[21] PWV along the artery was measured using two strain-gauge transducers (noninvasively, using a TY-306 Fukuda pressure-sensitive transducer [Fukuda Denshi Co., Tokyo, Japan]) fixed transcutaneously over the course of a pair of arteries separated by a known distance; the carotid, femoral, radial, and ankle arteries (dorsalispedis artery), all on the right side, were used. PWVs were calculated from the measurements of the pulse transit time and the distance traveled by the pulse between the two recording sites (measured on the surface of the body in meters), according to the following formula: PWV (m/s) = distance (m)/ transit time (s).

Other Measurements

Anthropometric measurements were recorded. BMI was calculated using the following equation: BMI = weight/height^2 (kg/m^2). Venous blood samples for measurement of glucose, creatinine (Cr), total cholesterol, low-density lipoprotein, and other biochemical parameters were drawn in the morning after an overnight fast on the same days as the AIx and PWV measurements were made. The OGTT was completed with 75 g of glucose after the fasting blood samples were dawn. Glomerular filtration rate (eGFR) was calculated from age, weight, and creatinine using the following Cockcroft-Gault equation[22]:

$$\text{eGFR (ml/min)} = [(140\text{-age}) \times \text{weight (kg)}] \times (\text{female} \times 0.85)/[72 \times \text{Cr (mg/dl)}],$$

where Cr is the plasma concentration of creatinine.

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Table 4. Correlations Between Arterial Stiffness Indices and Study Variables in Nondiabetic Controls (Univariate Analysis)

	CF-PWV		CR-PWV		CA-PWV		AIx	
	r_p	P	r_p	P	r_p	P	r_p	P
AIx	−0.054	0.643	−0.190	0.097	0.060	0.605	1.000	1.000
Age	0.404	<0.001	−0.008	0.945	0.081	0.480	0.031	0.792
Height	0.170	0.132	0.359	0.001	0.075	0.512	−0.487	<0.001
Weight	0.154	0.173	0.253	0.024	0.115	0.314	−0.283	0.012
BMI	0.067	0.553	0.012	0.918	0.094	0.409	0.067	0.561
SBP	0.353	0.001	0.213	0.058	0.277	0.014	−0.048	0.675
DBP	0.046	0.687	0.092	0.418	0.228	0.045	0.094	0.414
PP	0.377	<0.001	0.172	0.128	0.129	0.259	−0.141	0.221
HR	0.112	0.330	−0.013	0.907	−0.007	0.950	−0.141	0.222
Glucose	−0.084	0.460	0.023	0.838	−0.039	0.733	−0.023	0.842
TC	−0.228	0.042	−0.095	0.405	−0.145	0.205	0.236	0.038
Triglyceride	0.037	0.741	−0.145	0.202	−0.160	0.161	0.025	0.829
HDL-C	−0.059	0.605	−0.208	0.066	0.041	0.716	0.186	0.103
LDL-C	−0.199	0.078	−0.025	0.822	−0.186	0.103	0.218	0.056
Creatinine	0.166	0.142	0.204	0.071	0.172	0.130	−0.326	0.003
UA	−0.0001	0.999	−0.056	0.626	0.071	0.539	−0.121	0.294
eGFR	−0.140	0.218	0.060	0.599	−0.040	0.725	0.031	0.785

Abbreviations: AIx, augmentation index; BMI, body mass index; CA-PWV, carotid-ankle pulse wave velocity; CF-PWV, carotid-femoral pulse wave velocity; CR-PWV, carotid-radial pulse wave velocity; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; PP, pulse pressure; SBP, systolic blood pressure; TC, total cholesterol; UA, uric acid. r_p is Pearson index and P is its significance.

Plasma concentrations of glucose, lipids, lipoproteins, and other biochemical parameters were determined by use of an automatic analyzer (Hitachi 7600; Hitachi High-Technologies Corp., Tokyo, Japan).

Statistical Analyses

All analyses were carried out with SPSS 11.5 (SPSS, Inc., Chicago, IL). Normality of data was determined by the Kolmogorov-Smirnov test. All variables were conformed to normal distribution except for fasting glucose and triglyceride. The data distribution of fasting glucose and triglyceride were conformed to normality after being transferred by natural log. The numerical data with normal distribution are expressed as a mean and standard deviation. Variables that did not present normal distribution are expressed as a median (interquartile range). Direct comparisons between data from diabetic patients and controls were made using a non-paired Student t test.

In univariate analysis, the relationship between continuous variables with arterial stiffness measures was described using Pearson correlation coefficients. Analysis of covariance (ANCOVA) was performed to assess the relationship between indices of arterial stiffness and type 2 diabetes after adjusting for heart rate and mean arterial pressure, plasma lipids (triglyceride [TG], total plasma cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and renal function (eGFR). Multiple linear regression analyses were performed to examine whether simple associations were changed after adjustment for potential confounders or intermediaries. The multiple linear regression models were adjusted for the following covariates: age, sex, height, weight, heart rate, TG, TC, HDL-C, LDL-C, current smoking status, mean arterial pressure, and use of antidiabetic medications (insulin, sulfonylureas, α-glucosidase inhibitors, and biguanides).

Statistical significance was inferred at a 2-tailed P value <0.05.

Results

Characteristics

Demographic, clinical, and hemodynamic characteristics of the study participants are shown in Table 1. The two groups were well matched for age, gender, and BMI.

Arterial Stiffness and Type 2 Diabetes

CF-PWV, CA-PWV, and CR-PWV were significantly higher in the diabetic group than the control group. However, compared with the control group, AIx was lower in the

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diabetic group. After adjusting for heart rate and mean arterial pressure in ANCOVA analysis, the differences in PWVs between the diabetic group and control group remained. In addition, indices of arterial stiffness between groups still differed significantly, adjusting for plasma lipids and renal function in ANCOVA analysis (Table 2).

Table 3 and Table 4 show in detail the correlations between arterial stiffness indices and study variables in diabetic patients and nondiabetic controls, respectively. No associations were found between PWVs and AIx. A multiple regression analysis was performed to assess the contribution of study variables in determining the arterial stiffness indices. Data entered into the models included sex, smoking status, type 2 diabetes, and those variables that significantly correlated to arterial stiffness indices in the correlation analysis. Stepwise multiple regression analysis showed that type 2 diabetes was a significant determinant of increased CF-PWV; fasting glucose was a significant determinant of increased CR-PWV, but not CA-PWV and AIx (Table 5).

The impact of antidiabetic medications and the status of blood glucose control on measures of arterial stiffness were also investigated. No differences were found in stiffness indices between patients taking diabetes medications and patients not taking these medications (Supplementary Table 1). In regression analysis, use of medications was not the determinant of any of the stiffness indices (Table 5). In addition, no differences were found in PWVs and AIx in diabetics with better glucose control (fasting glucose <7.0 mmol/L) vs poor glucose control (fasting glucose ≥ 7.0 mmol/L) (Supplementary Table 2).

Table 5. Predictors of Measures of Arterial Stiffness (Results of Multiple-Adjusted Models[a])

Dependent Variables	Variables Entered Into Models	Standardized β	*t*	*P*	R^2
CF-PWV					0.323
	Age	0.423	6.041	<0.001	
	DM	0.241	3.445	0.001	
	SBP	0.205	2.876	0.005	
CR-PWV					0.261
	Sex (M/F)	−0.454	−6.326	<0.001	
	Ln (glucose)	0.219	3.049	0.003	
CA-PWV					0.105
	SBP	0.246	3.152	0.002	
	Age	0.172	2.203	0.029	
AIx					0.359
	HR	−0.348	−5.020	<0.001	
	Height	−0.406	−5.997	<0.001	
	LDL-C	0.201	2.778	0.006	

Abbreviations: AIx, augmentation index; CF-PWV, carotid-femoral pulse wave velocity; CR-PWV, carotid-radial pulse wave velocity; CA-PWV, carotid-ankle pulse wave velocity; DM, diabetes mellitus; F, female; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; M, male; SBP, systolic blood pressure. Stepwise multiple linear regression analysis was performed. Standardized β provides a measure of the relative strength of the association independent of the measurement units. [a]Covariates in the multiple-adjusted models included age, sex, height, weight, heart rate, total plasma cholesterol, high-density lipoprotein cholesterol, LDL-C, current smoking, mean arterial pressure, and use (used = 1; unused = 0) of insulin, sulfonylureas, α-glucosidase inhibitors, and biguanides. Standardized β and *P* value are only shown when $P < 0.05$.

Discussion

This study of arterial stiffness showed that type 2 diabetes was associated with increased arterial stiffness of both central elastic and peripheral muscular arteries in a Chinese population. Our data are in agreement with the Hoorn study,[2] which also showed that type 2 diabetes was associated with increased arterial stiffness of both elastic (carotid) and muscular (femoral and brachial) arteries. In the Hoorn study, arterial stiffness was ultrasonically estimated by distensibility and compliance of the carotid, femoral, and brachial arteries, and by the carotid elastic modulus. By contrast, in our study, arterial stiffness was estimated by PWV, a well-accepted index of arterial stiffness. Multiple regression analysis showed that type 2 diabetes was a significant independent determinant for CF-PWV; fasting glucose was a significant independent determinant for CR-PWV. Neither type 2 diabetes nor fasting glucose was significantly associated with CA-PWV.

Because AIx is a ratio, it can increase either because of an increase in the numerator (augmentation pressure [AG]) or a decrease in the denominator (pulse pressure [PP]). Alternatively, it can decrease either because of an increase in PP or a decrease in AG, or remain little changed because of both the PP and AG increasing or decreasing proportionately. Several other factors are known to affect central aortic AIx. It is confounded by age, gender, and height (as a surrogate for the distance to the principal distal reflecting site).[23] Previous studies also showed that it is inversely related to heart rate.[24] Our data showed an elevated brachial SBP, an elevated PP, and an elevated heart rate in the Chinese diabetics, which were consistent with the study of Lacy et al.[17] In their study of 64 type 2 diabetics, Lacy et al demonstrated that AIx was little changed between the diabetic group and the control group, in spite of a significant elevation in blood pressure in diabetics, even after adjustment for their increased heart rate. By contrast, our study showed that AIx was lower in Chinese diabetic patients compared with controls. The difference no longer existed between the two groups after adjustment for heart rate, which is in line with the study by Lacy et al. Multiple analyses showed that neither type 2 diabetes nor fasting glucose were determents of AIx.

Lacy et al speculate that this might be due to the dissipation of the energy of the incident pressure wave in people with diabetes blunting wave reflections. It is the reduced wave reflections, not the increased outgoing pressure wave, that result in the attenuation of AIx in

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individuals with diabetes. But Khoshdel et al provided a different interpretation of the phenomenon.[25] They reported that AIx is an underestimation for arterial stiffness in diabetics because of their wider PP compared to nondiabetics. In this case, the main determinant of AIx is PP, and not the reflected wave. Therefore, it is not a valid indicator for arterial stiffness in diabetics because of the wide PP, which in turn depends on other factors, such as cardiac contractility and arterial stiffness, and is a strong predictor of cardiovascular mortality.[25] Further studies to investigate this observation are warranted.

Conclusion

Our data suggest that arterial stiffness of both elastic and muscular arteries is increased in Chinese patients with type 2 diabetes as evidenced by increased PWV measured at different sites of the arterial system. Type 2 diabetes was a significant determinant of CF-PWV, whereas fasting glucose was a significant determinant of CR-PWV. No association was found between PWVs and AIx in Chinese patients with type 2 diabetes. The validity of AIx as a useful index of vascular stiffness in Chinese diabetics is questionable.

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