Relation of Aortic Stiffness to Left Ventricular Remodeling in Younger Adults With Type 2 Diabetes

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Individuals with type 2 diabetes have a three- to fivefold increased risk of developing heart failure. Diabetic cardiomyopathy is typified by left ventricular (LV) concentric remodeling, which is a recognized predictor of adverse cardiovascular events. Although the mechanisms underlying LV remodeling in type 2 diabetes are unclear, progressive aortic stiffening may be a key determinant. The aim of this study was to assess the relationship between aortic stiffness and LV geometry in younger adults with type 2 diabetes, using multiparametric cardiovascular MRI. We prospectively recruited 80 adults (aged 18–65 years) with type 2 diabetes and no cardiovascular disease and 20 age- and sex-matched healthy control subjects. All subjects underwent comprehensive bio-anthropometric assessment and cardiac MRI, including measurement of aortic stiffness by aortic distensibility (AD). Type 2 diabetes was associated with increased LV mass, concentric LV remodeling, and lower AD compared with control subjects. On multivariable linear regression, AD was independently associated with concentric LV remodeling in type 2 diabetes. Aortic stiffness may therefore be a potential therapeutic target to prevent the development of heart failure in type 2 diabetes.

The dramatic rise in the levels of obesity and sedentary lifestyles in younger age-groups has resulted in up to a 10-fold increase in the prevalence of type 2 diabetes in younger adults (1). Whereas type 2 diabetes was once a rarity in young people, increasingly the condition is diagnosed in children, adolescents, and adults under the age of 30 years (1). Importantly, the 20-year mortality rate in younger adults with type 2 diabetes is as high as 11%, the majority from cardiovascular disease (2).

One of the most deleterious consequences of developing type 2 diabetes is a three- to fivefold increased risk of heart failure (3). Left ventricular (LV) concentric remodeling, defined as an increase in LV wall thickness disproportionate to the corresponding increase in LV chamber volume, has emerged as a candidate mechanism for increased risk of heart failure in patients with type 2 diabetes (4). This phenomenon is consistently seen in patients with type 2 diabetes and is a strong predictor of adverse cardiovascular events (5), especially in those <65 years of age (6), and is linked to reduced systolic function (4) and diastolic dysfunction (5). The American College of Cardiology and American Heart Association regard asymptomatic patients with structural or functional cardiac alterations as having early heart failure (7).

Although the mechanisms underlying concentric LV remodeling appear to be mutifactorial (8), progressive aortic stiffening may be a key determinant. Aortic stiffening is an increase in the elastic resistance of the aorta to deformation and naturally occurs with aging. However, the process of aortic stiffening is also accelerated by all the traditional cardiovascular risk factors (such as age, diabetes, and hypertension) (9). Increased aortic stiffness is a strong predictor of adverse cardiovascular events in several cohorts (10,11), including type 2 diabetes (12). Importantly, aortic

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stiffness appears to increase progressively with worsening glycemic control (13).

Increased arterial stiffness causes alterations in wave reflections, an increase in augmentation pressure, which correspondingly increases LV afterload and contributes to cardiac remodeling (14). Cardiovascular MRI is the gold standard technique for the assessment of LV structure and function. Cardiac MRI also allows calculation of aortic distensibility (AD), a direct measure of aortic stiffness, and is uniquely suited to investigate ventricular-arterial interaction. In a pilot study of younger adults (aged <40 years) with type 2 diabetes, we demonstrated a correlation between AD and diabetes duration with diastolic function (15).

The aim of this study was to assess whether aortic stiffness was independently related to LV remodeling in younger adults with type 2 diabetes, who have the highest lifetime risk of developing cardiovascular disease.

RESEARCH DESIGN AND METHODS

Study Population

We recruited 80 younger adults (aged 18–65 years) with established type 2 diabetes (diagnosed before age 60 years) and no prior history of cardiovascular disease, from primary and secondary care services. Twenty age- and sex-matched healthy control subjects without diabetes were recruited. The study was approved by the local research ethics committee and conducted according to the Declaration of Helsinki, and all participants provided written informed consent.

Anthropometry and Biochemical Marker Assessment

Participants attended fasted. Height, weight, and waist-to-hip ratio were measured. Serum lipid profile and HbA_{1c} were measured using standard enzymatic methods on an ADVIA System (Bayer, Leverkusen, Germany).

Cardiac MRI Acquisition

Cardiac MRI was performed using a 1.5T scanner (Siemens Avanto or Aera, Erlangen, Germany) with retrospective echocardiographic gating and an 18-channel phased-array cardiac receiver coil. Cardiac volumes and functional imaging and late gadolinium enhancement (LGE) imaging were performed using standard cardiac MRI techniques as previously described (16). The complete imaging protocol is summarized in Supplementary Fig. 1. For measurement of AD, steady-state free precession aortic cine images were acquired in a plane perpendicular to the thoracic aorta at the level of the pulmonary artery bifurcation (Supplementary Fig. 2). Simultaneous brachial blood pressure (BP) was measured using an automated oscillometric device (DINAMAP; GE Healthcare).

Cardiac MRI Analysis

Analysis was performed offline blinded to patient details. LV volumes and function were assessed by two experienced operators (G.S.G. and D.J.S.), using cmr42 version 5 (Circle Cardiovascular Imaging, Calgary, AB, Canada).

LGE Imaging

LGE images were assessed for focal fibrosis, categorized as present or absent, by two experienced observers (E.L. and G.P.M.).

AD

AD was analyzed by a single operator (W.H.H.) using Java Image Manipulation version 6 (Xinapse Software, Essex, U.K.). AD at the ascending and descending aorta was calculated as AD = $(A_{max} - A_{min})/A_{min} \times$ pulse pressure, where A is the aortic cross-sectional area (Supplementary Fig. 2). Inter- and intraobserver variability for aortic stiffness measurements are shown in Supplementary Table 1.

Statistical Analysis

Statistical tests were performed using the SPSS version 24.0 software (Statistical Package for the Social Sciences, Chicago, IL). Normality was assessed using histograms and the Shapiro-Wilk test. Continuous data were expressed as mean (SD) if normally distributed or median (25–75% interquartile range) if not. Patients and control values were compared by independent Student t tests or Mann-Whitney U tests as appropriate. Categorical variables were compared using χ^2 test or Fisher exact test as appropriate.

For correlation analysis, data that were not normally distributed were log transformed and assessed using Pearson correlation coefficient. Multivariable linear regression was performed to identify independent associations of aortic stiffness and LV structure and function in patients with type 2 diabetes. The model contained the following covariables known to be associated with LV remodeling: ascending AD, age, systolic BP, sex, BMI, diabetes duration, and HbA_{1c}. A P value <0.05 was considered statistically significant. Due to the strong correlation between ascending and descending AD, only ascending AD was included in the multivariable model.

RESULTS

Baseline Characteristics

The study group consisted of 80 subjects with type 2 diabetes and 20 age-matched healthy control subjects. Detailed demographic, anthropometric, and biochemical data are presented in Table 1. Consistent with the young age of the cohort, average duration of diabetes was short at just over 5 years. Age and sex were similar in both groups. Forty-two percent of those with type 2 diabetes had a history of hypertension requiring treatment. Subjects with type 2 diabetes had a higher BMI and waist-to-hip ratio than control subjects. Over half (n = 41) of the patients with type 2 diabetes were on statins, but HDL cholesterol was lower and cholesterol-to-HDL ratio and triglycerides were higher than in the control subjects. There were more smokers in the patients with type 2 diabetes than control subjects.

Table 1—Baseline demographic, medication, anthropometric, and biochemical data

	Subjects with type 2 diabetes (n = 80)	Control subjects (n = 20)	P value
Age (years)	43.1 ± 9.1	38.8 ± 10.9	0.087
Male sex	40 (50)	11 (55)	0.613
History of smoking	35 (44)	2 (10)	**0.019**
Hypertension	42 (53)	0 (0)	**<0.001**
Hypercholesterolemia	40 (50)	1 (5)	**<0.001**
Diabetes duration (years)	5.12 ± 3.6	N/A	N/A
Systolic BP (mmHg)	131.4 ± 18.0	126.1 ± 13.7	0.269
Diastolic BP (mmHg)	79.0 ± 12.9	77.0 ± 10.1	0.451
Pulse pressure (mmHg)	52.5 ± 12.9	50.1 ± 10.6	0.449
Heart rate (bpm)	74.6 ± 12.1	61.8 ± 12.8	**<0.001**
Height (cm)	168.0 ± 9.6	169.6 ± 9.6	0.497
Weight (kg)	100.1 ± 19.4	66.4 ± 10.7	**<0.001**
BMI (kg/m^2)	35.4 ± 6.0	23.0 ± 2.4	**<0.001**
Waist-to-hip ratio	0.98 ± 0.1	0.89 ± 0.1	**<0.001**
Glycated hemoglobin (%)	7.6 ± 1.7	5.4 ± 0.3	**<0.001**
Glycated hemoglobin (mmol/mol)	60 ± 7	36 ± 0.9	**<0.001**
Cholesterol (mmol/L)	4.6 ± 1.1	5.1 ± 1.0	0.066
Triglycerides (mmol/L)	2.3 ± 1.5	1.0 ± 0.8	**0.001**
HDL (mmol/L)	1.1 ± 0.3	1.72 ± 0.4	**<0.001**
Cholesterol-to-HDL ratio	4.3 ± 1.3	3.1 ± 0.8	**<0.001**
LDL (mmol/L)	2.5 ± 0.9	3.1 ± 0.9	**0.017**
Medications			
Metformin	72 (90)	0 (0)	
Sulphonylureas	14 (17)	0 (0)	
GLP-1 antagonist	8 (10)	0 (0)	
DPP-4 inhibitor	11 (14)	0 (0)	
Insulin	5 (6)	0 (0)	
Diet control	1 (1)	0 (0)	
ACE inhibitors	29 (36)	0 (0)	
ARB	8 (10)	0 (0)	
β-Blocker	4 (5)	0 (0)	
CCB	10 (13)	0 (0)	
Diuretics	5 (6)	0 (0)	
Aspirin	3 (4)	0 (0)	
Statin	41 (51)	0 (0)	
Fibrate	5 (6)	0 (0)	

Data are presented as mean ± SD or n (%). ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1. Statistically significant data ($P < 0.05$) appear in boldface type.

Cardiac MRI Data

LV Volumes and Function

Cardiac MRI data for LV volumes and function are presented in Table 2. Type 2 diabetes was associated with reduced LV volumes and increased LV mass, and there was a 20% increase in concentric LV remodeling compared with control subjects (LV mass-to-volume ratio 0.64 ± 0.13 vs. 0.54 ± 0.12 g/mL, P = 0.003).

AD

Ascending, descending, and mean AD were lower in subjects with type 2 diabetes compared with control subjects (Table 2).

Myocardial Tissue Characterization

LGE images were either unavailable or not analyzable in five patients. Of the remaining 75 case subjects, 7 had late enhancement (6 of these had midwall late enhancement in keeping with nonischemic fibrosis [Supplementary Fig. 3*A*] and 1 patient had subendocardial lateral late enhancement corresponding with a prior silent myocardial infarction [Supplementary Fig. 3*B*]). In one control subject, there was midanterolateral midwall late enhancement. Exclusion of this control subject from final analysis did not alter the results. Overall there was no significant difference in the presence or absence of late enhancement between groups (P = 0.549).

Table 2—Cardiac MRI data comparison between patients and control subjects

	Subjects with type 2 diabetes	Control subjects	*P* value
LV volumes and function			
Indexed end-diastolic volume (mL/m^2)	73.0 ± 11.6	91.7 ± 16.3	**<0.001**
Indexed end-systolic volume (mL/m^2)	28.6 ± 7.6	38.1 ± 9.4	**<0.001**
Stroke volume (mL)	95.8 ± 20.7	95.5 ± 22.9	0.965
Ejection fraction (%)	61.1 ± 6.5	58.8 ± 5.5	0.156
LV mass (g)	99.5 ± 24.8	89.1 ± 36.9	**0.017**
LV mass index (g/m^2)	40.9 ± 8.2	35.8 ± 12.0	**0.028**
LV mass/volume (g/mL)	0.64 ± 0.13	0.54 ± 0.12	**0.003**
Aortic imaging			
Ascending AD (mmHg^{-1} × 10^{-3})	4.85 ± 2.21	6.12 ± 1.78	**0.010**
Descending AD (mmHg^{-1} × 10^{-3})	3.87 ± 1.55	4.83 ± 1.46	**0.013**
Mean AD (mmHg^{-1} × 10^{-3})	4.36 ± 1.81	5.47 ± 1.56	**0.012**
Tissue characterization			
LGE present, *n* (%)	7 (9.3)	1 (5)	0.549

Data are mean ± SD unless stated otherwise. Statistically significant data ($P < 0.05$) appear in boldface type.

Univariable and Multivariable Predictors of LV Remodeling

Both ascending ($r = -0.430$, $P < 0.001$) (Fig. 1) and descending AD ($r = -0.421$, $P < 0.001$) were correlated with LV mass/volume. HbA_{1c} was not associated with AD ($r = -0.133$, $P = 0.25$). Other univariable predictors are shown in Table 3. On multivariable regression, only AD, systolic BP, and sex were independently associated with LV mass/volume (Table 3).

DISCUSSION

This study is the first to demonstrate that AD, an index of aortic stiffness, is independently associated with concentric LV remodeling in adults with type 2 diabetes. Importantly, this association was independent of BP and supports the reasoning that one mechanism by which aortic stiffening leads to poorer cardiovascular outcomes in type 2 diabetes is through adverse LV remodeling, which increases the risk of subsequent heart failure (4). Given that both increased LV mass and aortic stiffening are recognized predictors of adverse cardiovascular outcomes (17), targeting aortic stiffness (and by proxy LV hypertrophy) could potentially improve survival in subjects with type 2 diabetes. This is especially relevant in younger adults with type 2 diabetes, who have the highest lifetime risk of cardiovascular complications, and in whom aortic stiffening and cardiac remodeling is likely to be reversible. Indeed despite their young age and relatively short duration of diabetes, patients in this study already have evidence of early heart failure with a 20% increase in concentric remodeling.

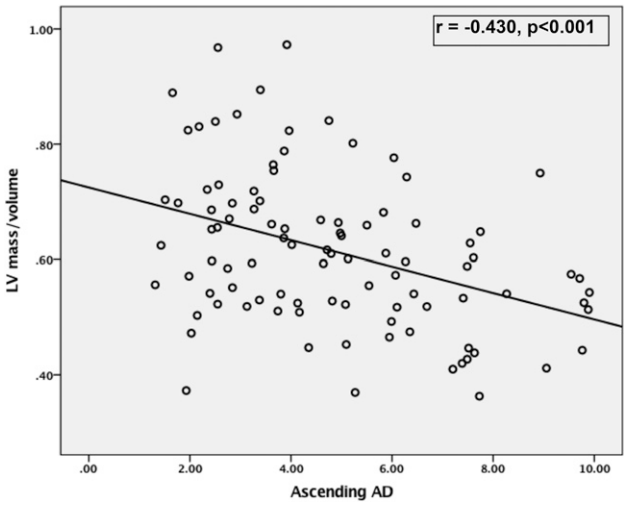

Figure 1—Correlation between ascending AD and LV mass/volume.

In patients with hypertension, aortic stiffness may be improved by intensive BP reduction, regardless of the types of antihypertensive agents used (18). However, the benefit of intensive BP treatment in type 2 diabetes is questionable (19).

Because aortic stiffening has been shown to worsen across the glycemic spectrum (13), tight blood glucose control could be an alternative therapeutic strategy to lessen aortic stiffness and subsequent cardiac remodeling. Indeed some studies have shown that aortic stiffness is modifiable by diabetes treatments (20). In our fairly homogenous group of patients, HbA_{1c} was not associated with AD. However, intensive glycemic control has only modest benefit in major adverse cardiovascular events (hazard ratio 0.91 [95% CI 0.84–0.99]) (21). This was primarily driven by a reduction in myocardial infarction, with no overall benefit on all-cause or cardiovascular death (21).

Newer classes of glucose-lowering drugs, such as sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists, have demonstrated benefit in cardiovascular outcome trials. These may impact aortic stiffness. Sodium–glucose cotransporter 2 inhibitors improve cardiovascular outcomes, including heart failure hospitalization, in patients with type 2 diabetes at high risk or with established cardiovascular disease (22). These agents lower blood glucose levels by promoting urinary glucose excretion. Secondary effects include weight loss, a modest diuretic effect, and BP reduction (23). The precise mechanisms by which sodium–glucose cotransporter 2 inhibitors lead to lower risk of heart failure and favourable cardiovascular outcomes are unclear.

Table 3—Univariate and multivariate predictors of LV concentric remodeling (LV mass/volume)

	Univariate		Multivariate		
	Pearson correlation coefficient (r)	P value	Standardized coefficient (β) (R^2 = 0.333)	95% CI	P value
Age	0.340	**0.002**	0.008	−0.004 to 0.004	0.953
Sex	−0.355	**0.001**	−0.297	−0.134 to 0.020	**0.009**
Type 2 diabetes duration	0.022	0.853	−0.121	−0.012 to 0.003	0.262
BMI	0.034	0.766	0.086	−0.003 to 0.006	0.418
HbA_{1c}	−0.133	0.766	−0.152	−0.027 to 0.004	0.142
Systolic BP	0.001	0.994	−0.268	−0.004 to 0.000	**0.041**
Ascending AD	−0.430	**<0.001**	−0.510	−0.510 to −0.120	**0.002**
Descending AD	−0.421	**<0.001**			
Diastolic BP	−0.131	0.252			
Heart rate	0.077	0.505			
Cholesterol	0.007	0.949			
Triglycerides	0.174	0.127			
HDL	−0.106	0.364			
LDL	−0.051	0.671			

Statistically significant data ($P < 0.05$) appear in boldface type.

One possibility is that they improve aortic stiffness and, given our findings, they may have the potential to reverse the early signs of and prevent heart failure.

Other lifestyle interventions should also be considered for the reversal of aortic stiffness and cardiac remodeling. Dramatic weight loss, either with bariatric surgery or with dieting, can improve both in obesity (24), and this may be particularly relevant with the recent success of low-calorie diet treatments for type 2 diabetes administered in primary care (25).

In conclusion, aortic stiffness is an independent determinant of concentric LV remodeling in younger adults with type 2 diabetes. Further studies are needed to identify whether or not interventions that improve aortic stiffness in type 2 diabetes can reverse cardiac remodeling and prevent subsequent heart failure.

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