Relation of aortic stiffness to left ventricular remodelling in younger adults with type 2 diabetes

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Word count: 1,874

Number of tables and figures: 3 tables and 1 figure.

Abstract

Individuals with type 2 diabetes have a three-to-five-fold increased risk of developing heart failure. Diabetic cardiomyopathy is typified by left ventricular (LV) concentric remodelling, which is a recognised predictor of adverse cardiovascular events. Although the mechanisms underlying LV remodelling 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 magnetic resonance imaging. We prospectively recruited 80 adults (aged 18-65 years) with type 2 diabetes and no cardiovascular disease and 20 age- and sex-matched healthy controls. All subjects underwent comprehensive bio-anthropometric assessment and cardiac magnetic resonance imaging, including measurement of aortic stiffness by aortic distensibility (AD). Type 2 diabetes was associated with increased LV mass, concentric LV remodelling and lower AD compared with controls. On multivariable linear regression, AD was independently associated with concentric LV remodelling in type 2 diabetes. Aortic stiffness may therefore be a potential therapeutic target to prevent the development of heart failure in type 2 diabetes.

Introduction

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 five-fold increased risk of heart failure[3]. Left ventricular (LV) concentric remodelling, 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/American Heart Association regard asymptomatic patients with structural or functional cardiac alterations as having early heart failure[7].

Although the mechanisms underlying concentric LV remodelling 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 ageing. 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 stiffness appears to increase progressively with worsening glycaemic control [13].

Increased arterial stiffness causes alterations in wave reflections, an increase in augmentation pressure, which correspondingly increases LV afterload and contributes to cardiac remodelling[14]. Cardiovascular magnetic resonance imaging is the gold standard technique for the assessment of LV structure and function. Cardiac magnetic resonance imaging 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 remodelling 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 non-diabetic healthy controls were recruited. The study was approved by the local research ethics

committee, 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 HbA1c were measured using standard enzymatic methods on an ADVIA System (Bayer, NY, USA).

CMR image acquisition

CMR was performed using 1.5-T 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 imaging were performed using standard cardiac magnetic resonance imaging techniques as previously described[16]. The complete imaging protocol is summarised in **Supplement 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 (**Supplement 2**). Simultaneous brachial blood pressure (BP) was measured using an automated oscillometric device (Dinamap, GE, USA).

CMR image 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, Alberta, Canada).

Late gadolinium enhancement imaging

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

Aortic distensibility

AD was analysed by a single operator (W.H.H.) using Java Image Manipulation version 6, (Xinapse Software, UK). AD at the ascending and descending aorta was calculated as follows:

$$\mathbf{AD = (A_{max} - A_{min})/A_{min} \times pulse\ pressure}$$

where *A* is the aortic cross-sectional area (**Supplement 2**). Inter- and intra-observer variability for aortic stiffness measurements are shown in **Supplement 3**.

Statistical analysis

Statistical tests were performed using the SPSS v24.0 software (Statistical Package for the Social Sciences, Chicago, IL, USA). Normality was assessed using histograms and the Shapiro-Wilk test. Continuous data were expressed as mean (standard deviation), if normally distributed or median (25-75% interquartile range) if not. Patients and control values were compared by independent *t*-tests or Mann-Whitney tests as appropriate. Categorical variables were compared using Chi-squared test or Fisher's exact test as appropriate.

For correlation analysis, data that were not normally distributed were log-transformed and assessed using Pearson's 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 remodelling: ascending AD, age, systolic BP, gender, body mass index, diabetes duration and HbA1c. 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 controls. Detailed demographics, 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 gender were similar in both groups. Forty two per cent of those with type 2 diabetes had a history of hypertension requiring treatment. Subjects with type 2 diabetes had a higher body mass index and waist:hip ratio than controls. Over half (n=41) of the type 2 diabetes patients were on statins, but high-density lipoprotein cholesterol was lower and cholesterol: high-density lipoprotein ratio and triglycerides were higher than in the controls. There were more smokers in the type 2 diabetes patients than controls.

Cardiac magnetic resonance imaging data

LV volumes and function

Cardiac magnetic resonance imaging data for LV volumes and function are presented in **Table 2**. Type 2 diabetes was associated with reduced LV volumes, increased LV mass and there was a 20% increase in concentric LV remodelling compared with controls (LV mass:volume ratio 0.64±0.13 vs. 0.54±0.12 g/mL, *p*=0.003).

Aortic distensibility

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

Myocardial tissue characterisation

Late gadolinium enhancement images were either unavailable or not analysable in five patients. Of the remaining 75 cases, seven had late enhancement; six of these had mid-wall late enhancement in keeping with nonischaemic fibrosis (**Supplement 4a),** but one patient had subendocardial lateral late enhancement corresponding with a prior silent myocardial infarction **(Supplement 4b).** In one control subject there was mid anterolateral mid-wall late enhancement. Exclusion of this control from final analysis did not alter the results. Overall there was no significant difference in presence or absence of late enhancement between groups. (*P*=0.549).

Univariable and multivariable predictors of LV remodelling.

Both ascending (r= -0.430, p<0.001) (**Figure 1**) and descending AD (r= -0.421, p<0.001) were correlated with LV mass/volume**.** HbA1c was not associated with aortic distensibility (r= -0.133, p=0.25) Other univariable predictors are shown in **Table 3**. On multivariable regression only aortic distenisbility, systolic BP and gender were independently associated with LV mass/volume (**Table 3**).

Discussion

This study is the first to demonstrate that aortic distensibility, an index of aortic stiffness, is independently associated with concentric LV remodelling 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 remodelling, which increases the

risk of subsequent heart failure[4]. Given that both increased LV mass and aortic stiffening are recognised 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 remodelling 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 remodelling.

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 glycaemic spectrum[13], tight blood glucose control could be an alternative therapeutic strategy to lessen aortic stiffness and subsequent cardiac remodelling. Indeed some studies have shown that aortic stiffness is modifiable by diabetes treatments[20]. However in our fairly homogenous group of patients, HbA1c was not associated with aortic distensibility. However, intensive glycaemic control has only modest benefit in major adverse cardiovascular events (hazard ratio 0.91, 95% confidence interval 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 outcomes trials. These may impact on aortic stiffness. Sodium glucose cotransporter-2 inhibitors improve cardiovascular outcomes, including heart failure hospitalisation, in type 2 diabetes patients 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 linking sodium glucose cotransporter-2 inhibitors to lower risk of heart failure and favourable cardiovascular outcomes are unclear, potentially reverse the early signs of and prevent heart failure.

Other lifestyle interventions should also be considered for the reversal of aortic stiffness and cardiac remodelling. 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 remodelling 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 remodelling and prevent subsequent heart failure.

Acknowledgements

Author contributions

G.P.M, T.Y. and E.G.W. and M.J.D conceived the idea for the study and designed the initial study protocol. G.S.G, D.J.S and W.H.H developed study documents, recruited patients and managed the trial. K.S.P. and J.V.W. performed the MRI scanning on study participants. G.S.G., W.H.H., M.P.G-B. and D.J.S. performed the CMR image analysis. F.Y.L performed the statistical analysis. G.S.G. and E.L. wrote the paper, which all authors critically reviewed.

Guarantor statement

G.P.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Funding

This study is part of the research portfolio supported by the NIHR Leicester Biomedical Research Centre. G.P.M. is supported by a NIHR career development fellowship. Funding contributions were also made by Novo Nordisk and the Medical Research Council Interdisciplinary Bridging Award.

References

1. Lascar, N., et al., *Type 2 diabetes in adolescents and young adults.* Lancet Diabetes Endocrinol, 2017.
2. Constantino, M.I., et al., *Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes.* Diabetes Care, 2013. **36**(12): p. 3863-9.
3. Kannel, W.B., M. Hjortland, and W.P. Castelli, *Role of diabetes in congestive heart failure: the Framingham study.* Am J Cardiol, 1974. **34**(1): p. 29-34.
4. Rosen, B.D., et al., *Left ventricular concentric remodeling is associated with decreased global and regional systolic function: the Multi-Ethnic Study of Atherosclerosis.* Circulation, 2005. **112**(7): p. 984-91.
5. Devereux, R.B., et al., *Impact of diabetes on cardiac structure and function: the strong heart study.* Circulation, 2000. **101**(19): p. 2271-6.
6. Cheng, S., et al., *Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the Multi-Ethnic Study of Atherosclerosis.* Circ Cardiovasc Imaging, 2009. **2**(3): p. 191-8.
7. Maisch, B., P. Alter, and S. Pankuweit, *Diabetic cardiomyopathy--fact or fiction?* Herz, 2011. **36**(2): p. 102-15.
8. Ernande, L. and G. Derumeaux, *Diabetic cardiomyopathy: myth or reality?* Arch Cardiovasc Dis, 2012. **105**(4): p. 218-25.
9. van der Meer, R.W., et al., *Magnetic resonance assessment of aortic pulse wave velocity, aortic distensibility, and cardiac function in uncomplicated type 2 diabetes mellitus.* J Cardiovasc Magn Reson, 2007. **9**(4): p. 645-51.
10. Laurent, S., et al., *Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients.* Hypertension, 2001. **37**(5): p. 1236-41.
11. Blacher, J., et al., *Impact of aortic stiffness on survival in end-stage renal disease.* Circulation, 1999. **99**(18): p. 2434-9.
12. Cruickshank, K., et al., *Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function?* Circulation, 2002. **106**(16): p. 2085-90.
13. Webb, D.R., et al., *Impact of metabolic indices on central artery stiffness: independent association of insulin resistance and glucose with aortic pulse wave velocity.* Diabetologia, 2010. **53**(6): p. 1190-8.
14. Antonini-Canterin, F., et al., *Arterial stiffness and ventricular stiffness: a couple of diseases or a coupling disease? A review from the cardiologist's point of view.* Eur J Echocardiogr, 2009. **10**(1): p. 36-43.
15. Khan, J.N., et al., *Subclinical diastolic dysfunction in young adults with Type 2 diabetes mellitus: a multiparametric contrast-enhanced cardiovascular magnetic resonance pilot study assessing potential mechanisms.* Eur Heart J Cardiovasc Imaging, 2014. **15**(11): p. 1263-9.
16. Steadman, C.D., et al., *Determinants and functional significance of myocardial perfusion reserve in severe aortic stenosis.* JACC Cardiovasc Imaging, 2012. **5**(2): p. 182-9.
17. Savage, D.D., et al., *Association of echocardiographic left ventricular mass with body size, blood pressure and physical activity (the Framingham Study).* Am J Cardiol, 1990. **65**(5): p. 371-6.

18. Ripley, D.P., et al., *Aortic remodelling following the treatment and regression of hypertensive left ventricular hypertrophy: a cardiovascular magnetic resonance study.* Clin Exp Hypertens, 2015. **37**(4): p. 308-16.
19. Group, A.S., et al., *Effects of intensive blood-pressure control in type 2 diabetes mellitus.* N Engl J Med, 2010. **362**(17): p. 1575-85.
20. Kiyici, S., et al., *Effect of rosiglitazone, metformin and medical nutrition treatment on arterial stiffness, serum MMP-9 and MCP-1 levels in drug naive type 2 diabetic patients.* Diabetes Res Clin Pract, 2009. **86**(1): p. 44-50.
21. Control, G., et al., *Intensive glucose control and macrovascular outcomes in type 2 diabetes.* Diabetologia, 2009. **52**(11): p. 2288-98.
22. Zinman, B., et al., *Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.* N Engl J Med, 2015. **373**(22): p. 2117-28.
23. Sattar, N., et al., *Novel Diabetes Drugs and the Cardiovascular Specialist.* J Am Coll Cardiol, 2017. **69**(21): p. 2646-2656.
24. Rider, O.J., et al., *Beneficial cardiovascular effects of bariatric surgical and dietary weight loss in obesity.* J Am Coll Cardiol, 2009. **54**(8): p. 718-26.
25. Lean, M.E.J., et al., *Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial.* The Lancet, 2017.

Figure legends

Figure 1. Correlation between ascending aortic distensibility (AD) and LV mass/volume.

Tables

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

	T2D (n=80)	**Controls (n=20)**	**p-value**
Age, years	43.1±9.1	38.8±10.9	0.087
Male sex, n (%)	40 (50)	11 (55)	0.613
History of smoking, n (%)	35 (44)	2 (10)	**0.019**
Hypertension, n (%)	42 (53)	0 (0)	**<0.001**
Hypercholesterolaemia, n (%)	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**
Body mass index, kg/m^2	35.4±6.0	23.0±2.4	**<0.001**
Waist: Hip ratio	0.98±0.1	0.89±0.1	**<0.001**
Glycated haemoglobin, %	7.6±1.7	5.4±0.3	**<0.001**
Glycated haemoglobin, 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: 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, n (%)	72 (90)	0 (0)	
Sulphonylureas, n (%)	14 (17)	0 (0)	

GLP-1 antagonist, n (%)	8 (10)	0 (0)
DPP-4 inhibitor, n (%)	11 (14)	0 (0)
Insulin, n (%)	5 (6)	0 (0)
Diet Control, n (%)	1 (1)	0 (0)
ACE-Inhibitors, n (%)	29 (36)	0 (0)
ARB, n (%)	8 (10)	0 (0)
Beta-Blocker, n (%)	4 (5)	0 (0)
CCB, n (%)	10 (13)	0 (0)
Diuretics, n (%)	5 (6)	0 (0)
Aspirin, n (%)	3 (4)	0 (0)
Statin, n (%)	41 (51)	0 (0)
Fibrate, n (%)	5 (6)	0 (0)

Data are presented as mean±SD. Abbreviations: GLP (glucagon like peptide), DPP (dipeptyl peptidase), ACE (angiotensin converting enzyme), ARB (angiotensin receptor blocker), CCB (calcium channel blocker).

Table 2. CMR data comparison between patients and controls.

	T2D	**Controls**	***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}x10^{-3}	4.85±2.21	6.12±1.78	**0.010**
Descending AD, mmHg^{-1}x10^{-3}	3.87±1.55	4.83±1.46	**0.013**
Mean AD, mmHg^{-1}x10^{-3}	4.36±1.81	5.47±1.56	**0.012**
Tissue characterisation			
LGE present, n (%)	7 (9.3)	1 (5)	0.549

Abbreviations: AD=aortic distensibility, LV=left ventricle, LGE=late gadolinium enhancement.

Table 3. Univariate and multivariate predictors of LV concentric remodelling (LV mass/volume).

	Univariate			**Multivariate**	
	Pearson's correlation coefficient (r)	p-value	Standardised coefficient (β) (R^2=0.333)	95% confidence interval	p-value
Age	0.340	**0.002**	0.008	-0.004 to 0.004	0.953
Gender	-0.355	**0.001**	-0.297	-0.134 to 0.020	**0.009**
T2D 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
HbA1c	-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			

Abbreviations: T2D=type 2 diabetes, BMI=body mass index, BP=blood pressure, AD=aortic distensibility, HDL=high density lipoprotein cholesterol, LDL=low density lipoprotein cholesterol.