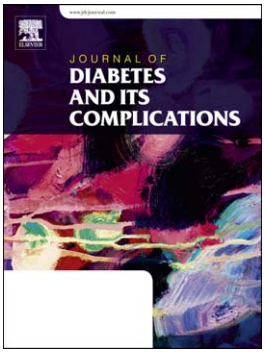

Prevalence, predictors and evolution of echocardiographically defined cardiac abnormalities in adults with type 1 diabetes: an observational cohort study

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Prevalence, predictors and evolution of echocardiographically defined cardiac abnormalities in adults with type 1 diabetes: an observational cohort study

Short title: Cardiac disease and type 1 diabetes

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ABSTRACT

Aims/hypothesis: The aims of this observational study were to determine the prevalence and predictors of an abnormal echocardiogram in adults with type 1 diabetes, and to assess the evolution of changes in a subset of subjects.

Methods: Cardiac function and structure were prospectively investigated by comprehensive transthoracic echocardiographic techniques in asymptomatic adults with type 1 diabetes seen in the ambulatory care setting.

Results: We recruited 136 subjects (mean age 39 years, SD 14 years) with a median diabetes duration of 21 years [25th, 75th interquartile range; 11, 29]. An abnormal echocardiogram was present in 29% of subjects; diastolic dysfunction in 69%, left ventricular hypertrophy in 38% and systolic dysfunction in 10%. The independent predictors of an abnormal echocardiogram were age, with a 9-fold increase in those ≥40 years (OR 9·40 [95% CI 2·68 - 33·04], P <0·0001), and increased body mass index (BMI), with a 17% increase in risk (P=0·04). A second echocardiogram was available in 65 subjects (3·8 ± 1·7 years later). The results showed that one in five with a normal first study had developed an abnormal second study, mainly diastolic dysfunction, with age being the only independent predictor of progression (P=0·006).

Conclusions/interpretation: Subclinical echocardiographic abnormalities are common in asymptomatic type 1 diabetes adults, and changes are progressive. The addition of an echocardiogram to complication surveillance programs in those with type 1 diabetes aged ≥40 years may represent a cost-effective way to screen for, and aggressively treat, occult cardiac disease.

ABBREVIATIONS

ACEi, angiotensin-converting enzyme inhibitors
AER, albumin excretion rate
ARB, angiotensin receptor blockers
ASE, American Society of Echocardiography
BMI, body mass index
CAD, coronary artery disease
CRP, C-reactive protein
CV, cardiovascular
DT, deceleration time
EF, ejection fraction
eGFR, glomerular filtration rate
IVS, inter ventricular septum
LVEDD, left ventricular end-systolic dimension
LVESD, left ventricular end-diastolic dimension
LVH, left ventricular hypertrophy
LVMI, left ventricular mass index
LV, left ventricle
TDI, Tissue Doppler imaging

INTRODUCTION

Cardiovascular (CV) disease is a major cause of death in type 1 diabetes [1, 2], yet non-invasive identification of subclinical cardiac abnormalities, such as left ventricular hypertrophy (LVH) [3], a known and modifiable risk factor, or diastolic dysfunction, a risk factor for the development of heart failure [4], is not part of diabetes complications surveillance programs [5]. Diastolic dysfunction in the absence of coronary artery disease (CAD) or hypertension is the earliest manifestation of diabetic cardiomyopathy in young type 1 diabetes patients [6]. To date, most echocardiographic studies have been in children and adolescents or in younger adults (age <40 years) [6-11], and many excluded anyone with comorbidities and/or diabetes complications, or those on medications other than insulin [12-14].

Given the high relative risk of a CV death in type 1 diabetes, identification and treatment of subclinical cardiac abnormalities such as LVH and diastolic dysfunction, may be one approach to improve CV outcomes. Currently, the prevalence and predictors of cardiac structural and functional abnormalities on echocardiography in 'real-world', asymptomatic adults with type 1 diabetes seen in the ambulatory care setting are unknown. As previous studies have been cross-sectional in nature, it is also unclear whether changes are progressive. We addressed both these issues in a prospective cohort study of 136 asymptomatic adults with type 1 diabetes attending a specialty Diabetes Outpatient Clinic in Melbourne, Australia. The evolution of echocardiographic changes was assessed in 65 subjects with a second echocardiogram to determine the predictors of progression from a normal to an abnormal echocardiogram.

METHODS

Subjects with type 1 diabetes aged ≥18 years were prospectively recruited, after referral for a transthoracic echocardiogram as part of a complications surveillance program at Austin Health, Melbourne. Subjects with a clinically indicated study were not recruited. The study was approved by the Human Research Ethics Committee at Austin Health, Melbourne. All participants provided written informed consent.

Medical history and clinical and biochemical measurements

Subjects had a detailed questionnaire at the time of the echocardiogram, cross-checked by medical record review. Information on diabetes duration, history of hypertension, antihypertensive drug therapy (ACE inhibitors (ACEi), angiotensin receptor blockers (ARB), diuretics, calcium channel blockers, β-blockers) was obtained. Height and weight were measured to determine BMI and body surface area. Blood pressure was measured with a mercury sphygmomanometer and the average of two measurements used for analysis. Urine and plasma electrolytes were measured on a Hitachi 911 automatic analyser (Roche Diagnostics, Mannheim, Germany). Glycated hemoglobin (HbA_{1c}) was measured by automated high-performance liquid chromatography (Biorad Diamat, CA, USA), and fasting lipids by enzymatic colorimetry. Total cholesterol was measured by enzymatic colorimetric methods and LDL cholesterol was calculated using the Friedewald equation. Plasma high-sensitivity C-reactive protein (CRP) levels were measured using the Synchron LX® system on a Beckman Coulter analyser. Urinary albumin excretion was estimated by immunoturbidimetry from a 24-hour urine collection (Dade-Behring, Marburg, Germany).

Echocardiography

Transthoracic echocardiography was performed as previously described by our group [15, 16], using a commercially available ultrasound system (Vivid 7, GE Medical Systems). Echocardiograms were performed in the same centre by experienced sonographers, according to a standardised protocol, and interpreted by a cardiologist, masked to the clinical data. The inter-observer variability of reproducibility was on average 14% and the intra-observer variability was 12%. Measurements were made according to the American Society of Echocardiography (ASE) [17]. Left ventricle (LV) ejection fraction (EF) [18] was calculated using the modified Simpson's rule, and LV mass calculated with the ASE recommended formula. Body surface area was calculated using the Mosteller formula (square root ([height (cm) x weight (kg)]/ 3600)) and LV mass was indexed to the body surface area. LVH was defined as LV mass index (LVMI) >115 g/m^2 in men and >95 g/m^2 in women. Systolic dysfunction was defined by evidence of regional wall motion abnormalities and/or an EF <50%. Tissue Doppler imaging (TDI) was used to evaluate the peak septal mitral annular systolic velocity (S´), which is an early marker of subtle systolic dysfunction [19].

Both conventional and newer parameters of diastolic function were measured. Measurements included mitral inflow Doppler for assessment of peak mitral E and A wave (early and late diastolic peak filling velocities), E/A ratio, mitral E wave deceleration time (DT) and mitral A wave duration, pulmonary vein Doppler for assessment of pulmonary venous atrial reversal maximal velocity and duration of atrial reversal and color M-mode for assessing the flow propagation velocity. TDI was used to obtain the early septal diastolic mitral annular velocity (e´) for the calculation of the E/e´ ratio. Diastolic dysfunction was classified as present if the subjects had abnormal relaxation (mild), pseudonormal (moderate) or a restrictive physiology (severe) pattern. Abnormal relaxation was defined as mitral E/A ratio <0.75 and mitral deceleration time >250 milliseconds. Pseudonormal was defined as mitral E/A ratio >0.75 but <2. For a diagnosis of pseudonormal diastolic dysfunction, evidence of increased LV filling pressures was needed with three out of four of the following criteria being met: E/e´ ratio >10, pulmonary A wave duration longer than mitral A wave duration, pulmonary venous atrial reversal maximal velocity >35 cm/s, and a positive Valsalva manoeuvre. A positive Valsalva was designated if there was E/A reversal and DT prolongation with Valsalva manoeuvre. Restrictive physiology pattern was defined as mitral E/A ratio ≥2 and mitral deceleration time <150 milliseconds.

Definitions

An abnormal echocardiogram was present if LVH, diastolic dysfunction and/or systolic dysfunction were present. Hypertension was defined as present if subjects were on anti-hypertensive medication, gave a history of hypertension and/or have evidence of hypertension (blood pressure ≥140/80 mmHg) [5]. The estimated glomerular filtration rate (eGFR) was calculated using the four component abbreviated MDRD equation [20]. Retinopathy was assessed after examination of a dilated fundus by an ophthalmologist. Microvascular disease was present if one or more of the following were present, an eGFR <60 ml/min/1·73m^2, microalbuminuria (urinary albumin excretion rate (AER) ≥20 μg/min and ≤200 μg/min) or macroalbuminuria (AER >200 μg/min) in 2 of 3 consecutive urine samples, retinopathy or peripheral neuropathy. The latter was determined after using tests of pin-prick sensation, vibration perception, monofilament pressure sensation, and assessment of ankle reflexes. Macrovascular disease was defined by the presence of myocardial infarction, previous angioplasty and/or cardiac bypass surgery, stroke, transient ischemic attack (TIA) or peripheral vascular disease (PVD).

Statistical analyses

Analyses were performed using SPSS version 19 (IBM Corp, USA). Continuous variables are presented as mean ± SD and variables not normally distributed are presented as medians [25th, 75th quartile]. Differences between clinical and echocardiographic characteristics in subjects with a normal and abnormal echocardiogram, and subjects with a second echocardiogram, were compared using the independent samples T-test for continuous variables and the Mann-Whitney U test for non-parametric variables. Differences between categorical variables were assessed using Fishers Exact Test. For comparison of subjects with repeat echocardiograms, differences between echocardiogram assessments at examination 1 (echo 1) and 2 (echo 2) were compared using the paired t-test and categorical variables were compared using the McNemar test. Non-parametric variables were compared using the Wilcoxon Signed Rank test. Statistically independent risk factors that predicted the presence of an abnormal echocardiogram were entered into a multivariate logistic regression model to estimate odds ratios and 95% confidence intervals (CI). Two-tailed P-values <0·05 were considered significant.

RESULTS

We recruited 141 subjects with a single echocardiogram, and excluded five due to moderate/severe valvular dysfunction (n=1) or an indeterminate echocardiogram (n=4). Of the 136 subjects in Study 1, 65 had been referred for a second echocardiogram (Study 2).

Study 1: Prevalence and predictors of an abnormal echocardiogram

The cohort included 81 men and 55 women, mean age 39 ± 14 years, median duration of diabetes 21 years and mean age of onset of diabetes 19.8 years (minimum - maximum, 2·0 - 34·8 years). Hypertension was common (59%), and 45% of subjects had microvascular complications (retinopathy, 34% and albuminuria, 22%), and 10% had macrovascular disease.

An abnormal echocardiogram was present in 39/136 subjects (29%). Only four subjects aged less than 40 years had an abnormal study (P<0·001), with 90% occurring in those aged ≥40 years (Figure 1). The characteristics according to the echocardiographic result are shown in Table 1. On univariate analysis, those with an abnormal echocardiogram were ~ 20 years older, with a longer duration of diabetes, and a higher BMI (all P<0·001). Systolic blood pressure was higher (P<0·001), despite the use of more antihypertensive agents (P<0·001), and 69% were taking ACEi/ARBs. Microvascular complications were more common (P<0·001) in those with an abnormal echocardiogram, but there was no difference in glycaemic control or systemic inflammation (as measured by CRP) between the groups. The abnormal echocardiogram group had more macrovascular complications (P<0·001), but serum lipids were similar, despite the increased use of statins.

The major abnormality on the echocardiogram, diastolic dysfunction was present in 69% of subjects, whilst 38% had LVH and 10% had systolic dysfunction. Those with LVH were 10 years older, and the 27 subjects with diastolic dysfunction alone were 20 years older than those with a normal study. The four subjects with systolic dysfunction were 30 years older, all had established macrovascular disease, all were on ACEi/ARBs, and most had microvascular disease.

An abnormal echocardiogram (Table 2) was associated with increased LV mass index and LVH, lower E/A ratio and increased E/e´ ratio (all P <0·001). The specific abnormalities on

echocardiography included LVH in 15 subjects either alone (n=8) or in combination with cardiac dysfunction. By definition, LVH was associated with increased LV mass index (P<0·001) and increased left atrial area (P<0·01) compared to those with a normal echocardiogram. Diastolic dysfunction was present in 27 subjects and associated with increased E/e´ ratio, and was further classified into mild (abnormal relaxation pattern) (n=7, 26%) or moderate diastolic dysfunction (pseudonormal pattern) (n=20, 74%). No subject had restrictive physiology. Ejection fraction was normal (~70%) in those with LVH and/or diastolic dysfunction, but reduced (~36%) in the four subjects with systolic dysfunction, who also had reduced peak septal mitral annular systolic velocity (S´).

On multivariate logistic regression analysis, age was the strongest predictor of an abnormal echocardiogram (Table 3), with a 9-fold increase in risk in those ≥40 years (P <0·0001). Each unit increase in BMI (1 kg/m^2) predicted a 17% increased risk of an abnormal echocardiogram (P=0·04). Neither renal function nor systolic blood pressure predicted an abnormal echocardiogram. On multivariate analysis, there was no independent association between the presence of micro- and macrovascular complications. The overall model fit was good (Hosmer and Lemeshow test, 11·39; P=0·18) and explained between 37% and 54% of the variance in subjects with an abnormal echocardiogram.

Study 2: Evolution of echocardiographic changes

There was a second echocardiogram (echo 2) in 65/136 subjects (48%), with a mean time between echocardiograms of 3·8 ± 1·7 years (range, 1 to 7 years). Comparison of clinical characteristics between those with and without a second echocardiogram revealed no differences in age, gender, BMI, diabetes duration, glycaemic control, lipid levels, blood pressure, micro- and macrovascular disease or medications. However, the proportion of those with an abnormal first echocardiogram was less than in the total cohort (20% vs. 29%). Those with a second echocardiogram had significantly better diastolic function, and no evidence of systolic dysfunction, compared to subjects without a second echocardiogram.

In those with two echocardiograms (Table 4), a priori, age was increased (P<0·001), but both the smoking rate (P=0·004) and HDL (P<0·001) dropped, and use of statins (P<0·001) and ACEi/ARBs (P=0·002) increased. BMI, glycaemic control, eGFR, blood pressure, prevalence of hypertension, or microvascular and macrovascular complications did not change between the two studies, but the proportion of subjects with an abnormal echocardiogram increased from 20% (n=13) to 32% (n=21). Interestingly, and perhaps related to increased use of ACEi/ARBs, LV mass index was significantly lower at the second echocardiogram (P=0·006), although the proportion of those with LVH was not different. Ejection fraction was unchanged and remained in the normal range, but S´ medial, an early marker of systolic dysfunction was reduced with time (P<0·001). Diastolic function worsened over time with a significant decrease in e´ leading to an increase in the E/e´ ratio from a normal to an abnormal value (7·4 vs. 9·6, P<0·001).

In those with a *normal* first echocardiogram (n=52, 80%), nine subjects (17%) developed an abnormal echocardiogram (P=0·021), with the majority (n=8) developing diastolic dysfunction (abnormal relaxation in 3, pseudonormal pattern in 5). In those with an *abnormal* first echocardiogram (n=13, 20%), four subjects had LVH, and nine had diastolic dysfunction. Three of the four subjects with LVH at baseline progressed to diastolic dysfunction (two with a pseudonormal pattern) and one subject improved from LVH to a normal echocardiogram. All subjects with diastolic dysfunction at the first study had diastolic dysfunction at the second. Two out of three progressed from an abnormal relaxation pattern

to a pseudonormal pattern. The majority of subjects (n=6) with diastolic dysfunction at baseline had a pseudonormal pattern, and five subjects remained as pseudonormal.

On multivariate logistic regression analysis, age was the only predictor of developing an abnormal echocardiogram (Table 5), with a 46% increase in the risk of an abnormal echocardiogram with each year of increased age. The overall model fit was good (Hosmer and Lemeshow test, 4·54; P=0·82) and explained between 57% and 81% of the variance in subjects with an abnormal echocardiogram.

DISCUSSION

Subclinical cardiac abnormalities of structure and function, detectable using myocardial TDI and conventional echocardiographic imaging were common in this prospective study of adults with type 1 diabetes. Nearly 30% of asymptomatic adults had an abnormal study, with diastolic dysfunction in 69%, LVH in 38% and systolic dysfunction in 10%. Whilst systolic dysfunction could be predicted from the past history of CAD, diastolic dysfunction would not have been diagnosed without rigorous echocardiographic assessment. The strongest independent predictor of an abnormal echocardiogram in this study was age, with a 9-fold risk in those aged ≥40 years. Neither glycaemic control, blood pressure nor renal function predicted an abnormal echocardiogram, and although micro- and macrovascular complications were common, there were no independent associations between an abnormal echocardiogram and complications. Age was the only predictor of developing an abnormal echocardiogram with time.

The main cardiac abnormalities detected were diastolic dysfunction and LVH, both of which are associated with increased morbidity and mortality in the non-diabetic population. The prevalence of LVH at 11%, was two-fold higher than in the general population [3]. LVH is a modifiable risk factor in the non-diabetic population, and can be reduced with renin angiotensin system blockade, an effect that may be independent of blood pressure reduction [21]. However regression of LVH was not a useful surrogate in hypertensive type 2 diabetes [22], suggesting a more complex interrelation between cardiac structural abnormalities and CV outcomes in diabetes. In our study, 69% of subjects with an abnormal echocardiogram were already on ACEi/ARBs, suggesting other approaches may be needed. Intensive glycaemic control had no effect to reduce LV mass in a recent report from DCCT/EDIC [23]. Our previous work in an experimental model of type 1 diabetic heart disease suggested a role for advanced glycation end products in the pathogenesis of LVH, as therapy with the cross-link breaker, alagebrium had beneficial cardiac effects to regress LVH [24]. Interestingly, in a small study in non-diabetic patients with diastolic heart failure, alagebrium also resulted in a decrease in left ventricular mass and improvements in left ventricular diastolic filling [25]. To date, the use of alagebrium on cardiac parameters in subjects diabetes has not been investigated.

The prevalence of diastolic dysfunction (20%) in this cohort of adults with type 1 diabetes with a mean age of 39 years, was similar to that in community studies of non-diabetic subjects in their sixth decade [4]. Diastolic dysfunction is now recognised as being associated with increased mortality and the development of heart failure [4, 26]. In a retrospective study in people with diabetes (unknown type) and a clinically indicated echocardiogram, diastolic dysfunction was commonly associated with the development of heart failure as well as increased mortality [26].

The optimal treatment of diastolic dysfunction is unknown, but improved blood pressure control can improve diastolic parameters in hypertensive subjects [27]. Although hypertension was more common in those with an abnormal echocardiogram, it was not an independent risk factor. Each unit increase (1 kg/m^2) in BMI was associated with a 17% increase in risk of an abnormal echocardiogram, which is of interest as a recent study in adults with type 1 diabetes reported that there was a 5% increase in hospitalisation with heart failure per 1 kg/m^2 increase in BMI, and a 30% increase with each 1% increase in HbA_{1c} [28]. Our cohort has lower smoking rates (8% vs. 22%) and increased ACEi/ARB use (69% vs. 13%) compared to Swedish subjects of similar age and glycaemic control, but it is not yet known if this will translate to a reduced incidence of heart failure in the future.

With regard to the evolution of diastolic dysfunction, a population-based cohort with a clinically indicated echocardiogram reported that the prevalence of diastolic dysfunction increased, and was associated with development of heart failure during 6 years of follow-up [29]. This is the first study to assess the evolution of echocardiographically detectable cardiac disease in type 1 diabetes. Not all subjects were referred for a second study, but those that were had less cardiac abnormalities on the first echocardiogram, and thus it is likely that the results can be extrapolated to the whole cohort. Over a mean period of 3·8y, 17% of subjects with a normal first echocardiogram developed diastolic dysfunction. Although there was a significant increase in ACEi/ARB use over time, only 54% of those with an abnormal baseline echocardiogram were on ACEi/ARBs, and only 57% were on ACEi/ARBs at follow up. One could speculate that further increased use may result in improved blood pressure control and cardiac parameters.

Clinical perspectives

Non-invasive and early identification of patients with diabetes at increased cardiovascular risk is needed. Since the only exclusion in this prospective study was a clinically indicated echocardiogram, the cohort represents "real-world" adults with type 1 diabetes being seen in the ambulatory care setting with comorbidities, diabetes complications, and on multiple medications including insulin.

Nearly 30% of asymptomatic adults with type 1 diabetes had an abnormal echocardiogram, mainly diastolic dysfunction, which progressed over time. In this relatively young cohort, age was the major independent predictor of both an abnormal echocardiogram and the risk of progression to an abnormal study. Our results lead us to suggest that an echocardiogram be incorporated into type 1 diabetes complication screening programs for those aged over 40 years to identify, at an earlier stage, those at increased CV risk, due to LVH and diastolic dysfunction, and to aggressively treat risk factors. Whilst long term follow up is needed to confirm that diastolic dysfunction predicts heart failure in type 1 diabetes, it is now quite clear that it has adverse prognostic implications in non-diabetic population.

Author contributions

B.W. and S.P. collected the data, performed the statistical analyses and wrote and edited the manuscript. M.O. assisted with the questionnaires and reviewed the manuscript. L.B. conceived the study, and contributed to writing and editing the manuscript. P.S., R.M. and G.J. contributed to collecting and interpreting the data, and reviewed and edited the manuscript.

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Duality of interest
The authors have no conflicts of interest.

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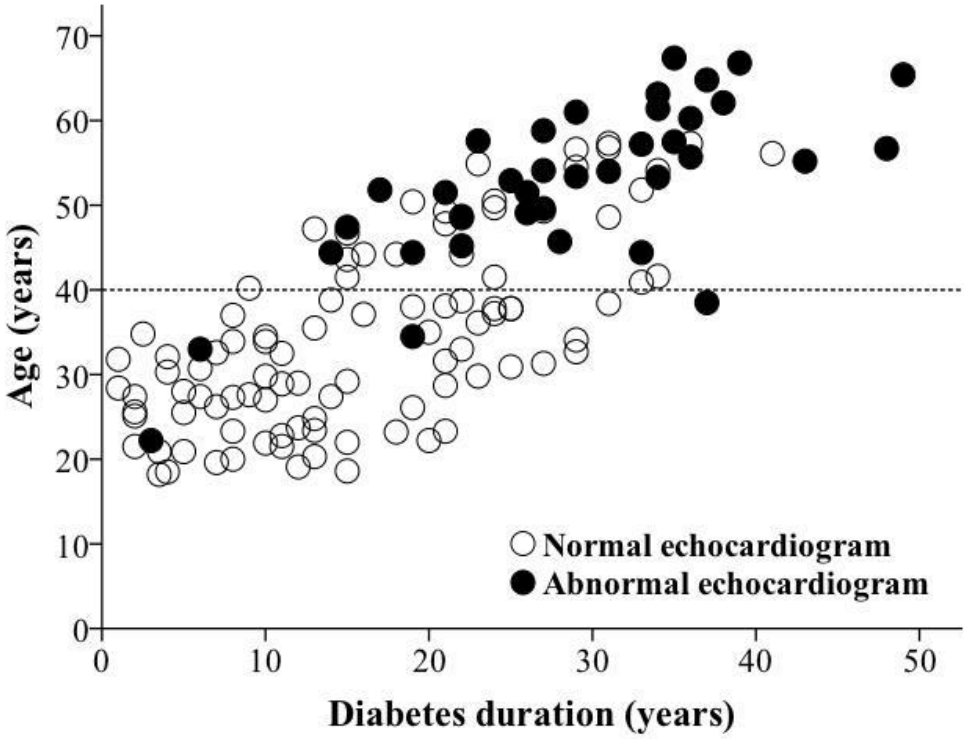

Figure 1: The presence of cardiac abnormalities on an echocardiogram according to age and diabetes duration. Subjects with a normal echocardiogram are shown with an open circle and those with an abnormal echocardiogram are shown with a solid black circle. Mean age of onset of type 1 diabetes was 19·8 y (minimum - maximum, 2·0 - 34·8 y).

Table 1: Clinical characteristics according to abnormalities on echocardiogram

	Echocardiogram		Abnormal echocardiogram with		
	Normal	**Abnormal**	**LVH alone**	**Diastolic dysfunction**	**Systolic dysfunction‡**
n	97	39	8	27	4
Age (years)	34·4 ± 10·8	52·9 ± 10·3***	44·6 ± 11·5*	53·5 ± 8·1***	66·1 ± 6·2
Male sex, % (n)	60 (62%)	21 (54%)	4 (50%)	16 (59%)	1 (25%)
Diabetes duration (years)†	16 [10, 24]	30 [10, 24]***	23 [15, 31]	31 [23, 39]***	37 [11, 29]
BMI (kg/m^2)	25·7 ± 3·6	28·9 ± 4·6***	25·6 ± 4·3	29·9 ± 4·3***	28·9 ± 4·9
HbA_{1c} (%)	8·2 ± 1·6	8·2 ± 1·0	8·3 ± 1·8	8·2 ± 0·7	8·0 ± 0·5
Fasting cholesterol (mmol/l)	4·7 ± 0·8	4·6 ± 1·0	4·3 ± 0·9	4·8 ± 0·9	4·0 ± 1·3
HDL-cholesterol (mmol/l)	1·5 ± 0·4	1·4 ± 0·5	1·3 ± 0·2	1·5 ± 0·6	1·7 ± 0·3
LDL-cholesterol (mmol/l)	2·8 ± 0·7	2·6 ± 0·9	2·5 ± 0·8	2·7 ± 0·8	1·9 ± 0·9
Triglycerides (mmol/l)†	0·9 [0·6, 1·2]	1·0 [0·6, 1·2]	1·1 [0·6, 1·8]	1·1 [0·7, 1·9]	0·9 [0·9, 1·0]
CRP (mg/l) †	1·9 [0·7, 5·0]	3·6 [1·4, 8·5]	4·2 [1·1, 10·1]	3·4 [1·7, 8·2]	5.1 [1.4, 9.4]
eGFR (ml/min/1·73m^2)	91 ± 23	70 ± 29***	83 ± 31	67 ± 30***	61 ± 16
24hr albumin excretion (μg/min) †	8·3 [5·6, 15·7]	12·7 [7·6, 24·2]	10·2 [7·4, 14·2]	15·1 [6·5, 33·1]	13.4 [9.6, 17.1]
Systolic BP (mmHg)	126 ± 16	138 ± 22***	136 ± 18	138 ± 24***	135 ± 8
Diastolic BP (mmHg)	73 ± 12	74 ± 10	71 ± 4	75 ± 11	74 ± 11
Hypertension	52 (54%)	32 (82%)**	5 (63%)	23 (85%)**	4 (100%)
Current smoker	15 (16%)	3 (8%)	1 (13%)	2 (7%)	0
Microvascular disease	33 (34%)	28 (72%)***	4 (50%)	21 (78%)***	3 (75%)
Reduced eGFR (<60 ml/min/1·73m^2)	3 (3%)	9 (23%)***	1 (13%)	6 (22%)**	2 (50%)
Albuminuria (AER ≥20 μg/min)	17 (18%)	7 (18%)	1 (13%)	6 (22%)	0
Retinopathy	23 (24%)	23 (59%)***	3 (38%)	17 (63%)***	3 (75%)
Peripheral neuropathy	11 (11%)	17 (44%)***	3 (38%)	10 (37%)**	4 (100%)
Macrovascular disease	3 (3%)	10 (26%)***	0	6 (22%)**	4 (100%)
Myocardial infarction	0	5 (13%)**	0	2 (7%)**	3 (75%)
Coronary artery bypass graft	1 (1%)	1 (3%)	0	1 (4%)*	0
Percutaneous revascularisation	0	6 (15%)***	0	4 (15%)**	2 (50%)
Other macrovascular disease§	2 (2%)	6 (15%)**	0	2 (7%)	4 (100%)
Medications					
Statins	10 (10%)	14 (36%)**	0	12 (44%)***	2 (50%)
Aspirin	5 (5%)	11 (28%)***	1 (13%)	7 (26%)**	3 (75%)
Beta blockers	1 (1%)	7 (18%)***	1 (13%)	4 (15%)**	2 (50%)

ACEi/ ARBs	13 (13%)	27 (69%)***	4 (50%)*	19 (70%)***	4 (100%)
Diuretics	3 (3%)	9 (23%)**	3 (38%)**	5 (19%)*	1 (25%)
Calcium channel blockers	4 (4%)	6 (15%)*	0	5 (19%)*	1 (25%)

Values are as mean ± SD. [†]Median [interquartile range, 25th, 75th quartile]. [§]Other macrovascular disease includes transient ischaemic attack, stroke and peripheral vascular disease. Proportions are presented as n (%). BMI - body mass index; HDL - high-density lipoprotein; LDL - low density lipoprotein; CRP - C-reactive protein; AER – albumin excretion rate; ACEi - angiotensin converting enzyme inhibitors; ARBs - angiotensin receptor blockers. Results are shown for subjects with a normal and abnormal echocardiogram, along with subjects with an abnormal echocardiogram subdivided according to the presence of LVH alone, diastolic dysfunction or systolic dysfunction. [‡]Statistical differences between the normal echocardiogram and systolic dysfunction group are not provided, as data was available in only 4 subjects. All comparisons are to the normal echocardiogram group. P values: *** <0·001, ** <0·01, *<0·05.

Table 2: Echocardiographic characteristics

	Echocardiogram		Abnormal echocardiogram with		
Echocardiographic parameters	**Normal**	**Abnormal**	**LVH alone**	**Diastolic dysfunction**	**Systolic dysfunction‡**
n	97	39	8	27	4
Structural					
LV mass index (g/m^2)	78 ± 15	95 ± 23***	113 ± 12***	89 ± 24*	99 ± 23
LVH (%)	0	15 (38%) ***	8 (100%) ***	5 (19%) ***	2 (50%)
Left atrial area (cm^2)	18·4 ± 4·1	20·5 ± 2·9**	20·8 ± 3·0	20·2 ± 2·8*	22·1 ± 4·3
IVS (cm)	0·88 ± 0·12	0·99 ± 0·13***	1·09 ± 0·09***	0·98 ± 0·14	0·91 ± 0·13
LVESD (cm)	3·0 ± 0·5	3·2 ± 0·7*	2·9 ± 0·3	3·0 ± 0·4	4·8 ± 0·5
LVEDD (cm)	4·9 ± 0·5	5·1 ± 0·5*	5·2 ± 0·4	4·9 ± 0·5	5·9 ± 0·5
Functional					
LV ejection fraction (%)	66·6 ± 8·1	65·1 ± 12·6	73·1 ± 6·5*	67·3 ± 7·9	36·0 ± 4·9
S´ (cm/s)	9·5 ± 2·5	8·6 ± 2·5	10·1 ± 2·6	8·6 ± 2·1	5·4 ± 3·1
E (m/s)	0·86 ± 0·19	0·86 ± 0·20	0·94 ± 0·20	0·83 ± 0·21	0·98 ± 0·22
A (m/s)	0·61 ± 0·14	0·82 ± 0·20***	0·70 ± 0·24	0·87 ± 0·18***	0·76 ± 0·22
E/A ratio	1·48 ± 0·45	1·13 ± 0·56***	1·61 ± 0·37	0·97 ± 0·24***	1·31 ± 0·20
Deceleration time (ms)	186 ± 34	207 ± 47**	196 ± 23	213 ± 48**	184 ± 75
e´ (cm/s)	11·8 ± 3·9	8·7 ± 3·3***	13·2 ± 5·2	8·0 ± 2·8***	6·4 ± 3·6
E/e´ ratio†	8·0 [6·5, 9·9]	10·8 [7·7, 14·7]***	7·6 [6·8, 10·0]	11·2 [7·5, 14·6]***	15·4 [10·4, 24·0]

Values are as mean ± SD. LVH presented % (n). †Median [interquartile range, 25th, 75th quartile]. Proportions are presented as n (%).
LV - left ventricular; LVH - left ventricular hypertrophy; LVESD - left ventricular end-diastolic dimension; LVEDD - left ventricular end-systolic dimension; IVS - inter ventricular septum. Results are shown for subjects with a normal and abnormal echocardiogram, along with subjects with an abnormal echocardiogram subdivided according to the presence of LVH alone, diastolic dysfunction alone, and systolic dysfunction. All those with systolic dysfunction also had diastolic dysfunction. ‡ Statistical differences between the normal echocardiogram and systolic dysfunction group are not provided, as only 4 subjects in the latter group). All comparisons are to the normal echocardiogram group. P values: *** <0·001, ** <0·01, *<0·05.

Table 3: Independent predictors of an abnormal echocardiogram in type 1 diabetes

Variable	Odds ratio (95% CI)	P value
Age ≥40 years	9·40 (2·68 – 33·04)	<0·0001
BMI (kg/m^2) †	1·17 (1·01 – 1·36)	0·04
Systolic blood pressure (mmHg) †	1·02 (0·99 – 1·06)	0·25
eGFR (ml/min/1·73m^2) †	0·99 (0·96 – 1·01)	0·19
Microvascular disease	2·89 (0·92 – 9·12)	0·07
Macrovascular disease	2·28 (0·43 – 12·16)	0·33

†The odds ratios for risk of an abnormal echocardiogram are given per each unit increase in BMI (1 kg/m^2), systolic blood pressure (1 mmHg) and eGFR (1 ml/min/1·73m^2). eGFR - estimated glomerular filtration rate.

Table 4: Clinical and echocardiographic characteristics of subjects at first and second echocardiogram

	Echo 1	Echo 2	P values
n	65	65	
Age (year)	39·8 ± 12·9	43·7 ± 13·3	<0·0001
BMI (kg/m^2)	26·1 ± 3·6	26·4 ± 3·7	0·13
HbA_{1c} (%)	8·0 ± 1·2	7·8 ± 1·2	0·31
Fasting cholesterol (mmol/l)	4·7 ± 0·8	4·4 ± 0·9	0·02
HDL-cholesterol (mmol/l)	1·5 ± 0·4	1·3 ± 0·4	<0·0001
LDL-cholesterol (mmol/l)	2·7 ± 0·7	2·7 ± 0·7	0·69
Triglycerides (mmol/l)†	0·8 [0·6, 1·2]	0·8 [0·6, 1·1]	0·04
CRP (mg/l) †	2·4 [0·5, 4·8]	2·0 [1·0, 3·7]	0.10
eGFR (ml/min/1.73m^2)	88 ± 19	90 ± 22	0·39
24hr albumin excretion (µg/min) †	9·2 [6·0, 15·0]	4·7 [3·3, 15·0]	0·24
Systolic BP (mmHg)	128 ± 18	131 ± 16	0·17
Diastolic BP (mmHg)	73 ± 11	72 ± 10	0·67
Hypertension	33 (55%)	40 (62%)	0·50
Current smoker	14 (22%)	5 (8%)	0·004
Microvascular disease	23 (35%)	27 (41%)	0·48
Reduced eGFR (<60 ml/min/1·73m^2)	1 (2%)	4 (6%)	0.25
Albuminuria (AER ≥20 µg/min)	9 (14%)	9 (14%)	1.00
Retinopathy	13 (20%)	18 (28%)	0.27
Peripheral neuropathy	7 (11%)	10 (15%)	0.25
Macrovascular disease	3 (5%)	6 (9%)	0·25
Myocardial infarction	1 (2%)	2 (3%)	1.00
Coronary artery bypass graft	2 (3%)	3 (5%)	1.00
Percutaneous revascularisation	2 (3%)	2 (3%)	1.00
Other macrovascular disease§	1 (2%)	2 (3%)	1.00
Medications			
Statins	7 (11%)	23 (35%)	<0·0001
Aspirin	4 (6%)	7 (11%)	0·453
Beta blockers	2 (3%)	3 (5%)	1·000
ACEi/ ARBs	13 (20%)	23 (35%)	0·002
Diuretics	3 (5%)	7 (11%)	0·13
Calcium channel blockers	5 (8%)	5 (8%)	1·00
Echocardiographic parameters			
Normal echocardiogram	52 (80%)	43 (68%)	0.02
Abnormal echocardiogram	13 (20%)	21 (32%)	
Structural			
LV mass index (g/m^2)	83 ± 16	76 ± 17	0·006
LVH (%)	5 (8%)	2 (3%)	0·45
Left atrium area (cm^2)	18·7 ± 3·9	19·0 ± 3·5	0·34
IVS (cm)	0·92 ± 0·14	0·89 ± 0·14	0·09
LVESD (cm)	3·0 ± 0·5	3·1 ± 0·4	0·50
LVEDD (cm)	4·9 ± 0·5	4·8 ± 0·5	0·13
Functional			
LV ejection fraction (%)	66·1 ± 8·6	64·5 ± 6·7	0·18
S´ (cm/s)	9·7 ± 2·5	7·8 ± 1·4	<0·0001
E (m/s)	0·85 ± 0·19	0·86 ± 0·20	0·46
A (m/s)	0·64 ± 0·17	0·68 ± 0·20	0·04
E/A ratio	1·41 ± 0·54	1·38 ± 0·54	0·53
Deceleration time (ms)	195 ± 40	215 ± 50	0·002
e´ (cm/s)	11·8 ± 3·9	8·8 ± 2·5	<0·0001
E/e´ ratio†	7·4 [5·9, 9·2]	9·6 [8·3, 12·0]	<0·0001

Values are mean ± SD. [†]Median [interquartile range, 25th, 75th quartile]. [§]Other macrovascular disease includes transient ischaemic attack, stroke and peripheral vascular disease. Proportions are presented as n (%). HDL - high-density lipoprotein; LDL - low density lipoprotein; CRP - C-reactive protein; AER – albumin excretion rate; ACEi - angiotensin converting enzyme inhibitors; ARBs - angiotensin receptor blockers; LV - left ventricular; LVH, left ventricular hypertrophy; LVESD - left ventricular end-diastolic dimension; LVEDD - left ventricular end-systolic dimension; IVS - inter ventricular septum.

Table 5: Independent predictors of developing an abnormal echocardiogram

Variable	Odds ratio (95% CI)	P value
Age (years)	1·46 (1·12 – 1·92)	0·006
BMI (kg/m^2)	1·28 (0·94 – 1·75)	0·12
Systolic blood pressure (mmHg)	1·02 (0·94 – 1·09)	0·70
eGFR (ml/min/1·73m^2) †	0·97 (0·90 – 1·03)	0·31
Microvascular disease	1·49 (0·09 – 25·9)	0·79

†The odds ratios for risk of an abnormal echocardiogram are given per each unit increase in BMI (1 kg/m^2), systolic blood pressure (1 mmHg) and eGFR (1 ml/min/1·73m^2). eGFR - estimated glomerular filtration rate.

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