Structural and Functional Cardiac Abnormalities in Adolescent Girls with Poorly Controlled Type 2 Diabetes

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OBJECTIVE — Type 2 diabetes is associated with left ventricular hypertrophy (LVH) and diastolic dysfunction, which may eventually lead to clinical heart failure. We sought to determine the cardiovascular effects of adolescent-onset type 2 diabetes.

RESEARCH DESIGN AND METHODS — We recruited diabetic girls (8 with type 2 and 11 with type 1 diabetes) from a hospital diabetes service and nondiabetic control subjects (9 lean and 11 overweight) from the schools of the diabetic subjects. Echocardiography and measurements were performed by a single observer, blinded to subject group allocation, and included M-mode left ventricular dimensions, two-dimensional left ventricular mass, Doppler diastolic flows, estimation of left ventricular filling pressure, and systolic longitudinal motion. Left ventricular mass was indexed to height and fat-free body mass. ANOVA was used to compare the groups.

RESULTS — The groups were similar in age and height, but significant differences in body composition were observed. Subjects with type 2 diabetes had larger left ventricular dimensions and left ventricular mass, which persisted when indexed to height. Diastolic filling was impaired in both diabetic groups, and systolic longitudinal function was lower in the type 2 diabetic group. Half of the group with type 2 diabetes met the published criteria for LVH and left ventricular dilatation; 25% had evidence of elevated left ventricular filling pressure in association with structural abnormalities.

CONCLUSIONS — This study has demonstrated preclinical abnormalities of cardiac structure and function in adolescent girls with type 2 diabetes, despite the short duration of diabetes and highlights the potential high cardiovascular risk occurring in adolescent type 2 diabetes.

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Adolescent-onset type 2 diabetes is an increasingly prevalent condition occurring in response to childhood obesity (1) and is associated with dyslipidemia, hypertension, and microalbuminuria, all with greater prevalence and rapid progression than in similarly aged patients with type 1 diabetes (2). The main cause of death in adults with type 2 diabetes is cardiovascular disease, irrespective of age at diagnosis (3,4). No data exist regarding the cardiovascular prognosis of adolescent-onset type 2 diabetes, but early-onset type 2 diabetes has been linked to premature clinical atherosclerosis (5).

Adult-onset type 2 diabetes is associated with cardiovascular risk factors, including obesity, hypertension, dyslipidemia, and coronary heart disease but is also associated with deleterious cardiac changes that may lead to clinical heart failure (6), including left ventricular hypertrophy (LVH) (7) and diastolic dysfunction (8). Furthermore, obesity is associated with LVH and diastolic and systolic dysfunction (9), all of which may be reversible with weight loss (10). In children, obesity has been associated with cardiac enlargement (LVH and dilatation) (11) and some measures of diastolic dysfunction (12).

The direct cardiac effects of adolescent type 2 diabetes have not been described previously. Thus, the aim of this study was to determine whether cardiac structural and functional abnormalities occur in adolescent-onset type 2 diabetes. We hypothesize that the obesity-related cardiovascular changes may be further augmented when obese adolescents develop type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Forty adolescent girls (aged 12–18 years) with diabetes (20 with type 1 diabetes and 20 with type 2 diabetes) were identified from our hospital adolescent diabetes database and invited to participate: 11 patients with type 1 and 8 patients with type 2 diabetes agreed to participate. Twenty healthy, nondiabetic girls were recruited from the schools of the diabetic participants and formed two control subject groups: lean and overweight/obese based on age- and sex-specific BMI equivalents (13). No participants had diabetes complications, coexisting cardiovascular disease, or a history of diabetic ketoacidosis in the past 12 months. Participants with type 2 diabetes were not receiving insulin therapy: in all patients, diabetes was treated either by diet alone and/or by metformin. All nondiabetic participants had A1C levels <6% and fasting glucose <5.5 mmol and were pubertal stage 4 or 5 and postmenarchal. All participants had reported low physical fitness (<3 h/week of moderate/intense physical activity). This study was approved by the Auckland Northern Regional Ethics Committee, and all partici-

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Table 1—*Baseline demographics and body composition of the four groups*

	Type 1 diabetes	Type 2 diabetes	Lean control subjects	Overweight control subjects	ANOVA *P* value
n	11	8	9	11	
Age (years)	15.5 ± 1.1	14.9 ± 1.1	14.9 ± 1.182	15.3 ± 1.51	0.62
Height (m)	1.63 ± 0.06	1.67 ± 0.08	1.67 ± 0.07	1.61 ± 0.05	0.13
Weight (kg)	65.0 ± 9.89	107.2 ± 24.06	58.1 ± 7.87	80.6 ± 16.26	<0.0001
BSA (cm^2)	1.69 ± 0.13	2.13 ± 0.24	1.65 ± 0.13	1.84 ± 0.18	<0.0001
Body fat (%)	35.9 ± 7.8	43.9 ± 5.8	28.1 ± 5.7	43.0 ± 3.6	<0.0001
BMI (kg/m^2)	24.5 ± 3.6	38.3 ± 7.4	20.8 ± 2.0	30.9 ± 5.3	<0.0001
FFM (kg)	42.0 ± 4.4	57.4 ± 8.1	42.3 ± 5.1	46.8 ± 9.4	0.0003
Duration of diabetes (months)	66 (13–128)	20 (6–36)	—	—	
Fasting blood glucose (mmol/l)	15.2 ± 6.3	9.4 ± 5.2	4.5 ± 0.34	4.9 ± 0.52	<0.0001
A1C (%)	8.7 ± 1.0	8.2 ± 2.1	5.1 ± 0.21	5.1 ± 0.32	<0.0001

Values are means ± SD or median (interquartile range).

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pants provided written consent before participating; those aged <16 years required parental consent to participate in the study. A fasting venous blood sample was collected for determination of A1C and fasting blood glucose (FBG). During the same visit, body composition and echocardiography were performed.

Measurements of body size and body composition

Height and weight were measured. Body surface area (BSA) was calculated using the DuBois formula; BMI was calculated as weight in kilograms divided by the square of height in meters. Dual-photon X-ray absorptiometry (GE Lunar Prodigy; GE Healthcare, Madison, WI) was performed to determine body composition including fat-free mass (FFM), fat mass, bone mineral content, and total weight using standard analytical software.

Echocardiography

All images were digitally acquired (Philips iE33 or Philips HDI-5000; Phillips Medical Systems, Bothell, WA) according to a standardized protocol by trained research sonographers and measured off-line (DigiView; Digisonics, Houston, TX) without knowledge of the patients' clinical details or group allocation. A comprehensive research echocardiogram was performed, including standard transthoracic views, as well as protocol-specific measurements (below).

Two-dimensional left ventricular mass

Images were obtained in the parasternal short-axis view at the midpapillary muscle level and left ventricular mass was calculated using the area-length method recommended by the American Society of Echocardiography (14). Left ventricular mass was indexed to height and FFM.

Pulsed-wave Doppler and tissue Doppler

Mitral valve inflow pulsed-wave Doppler recordings were made between the leaflet tips, isovolumic relaxation time (IVRT) recordings were made from the left ventricular outflow tract, and tissue Doppler imaging recordings were obtained from the medial and lateral aspects of the mitral annulus in the apical four-chamber view. All Doppler signals were acquired using a 5-mm sample volume, optimized, and recorded at 100 mm/s sweep speed.

Measurements

Measurements were the following: *1*) M-mode measurements: left ventricular end-diastolic dimension and left ventricular end-systolic dimension; *2*) two-dimensional images: left atrial area; *3*) Doppler measurements: mitral valve early filling velocity (E), late-filling velocity (A), mitral E wave deceleration time, and IVRT, and *4*) tissue Doppler measurements (average of lateral and medial): mitral annular E velocity (Ea), mitral annular A velocity (Aa), and mitral annular S velocity (Sa). The following variables were calculated: E-to-A ratio, left ventricular ejection fraction, and E-to-Ea ratio (average).

Statistical analysis

Comparisons between groups for continuous normally distributed variables were performed using Student's *t* test or ANOVA for more than two groups. Tukey's post hoc test was applied to assess pairwise differences within the ANOVA. Nonparametric continuous data were analyzed using Wilcoxon and Kruskall-Wallis tests, where appropriate. Differences between categorical variables were assessed using χ^2 analysis. $P < 0.05$ was accepted as indicating significance.

RESULTS — Thirty-nine girls completed all assessments: 11 with type 1 diabetes, 8 with type 2 diabetes, 9 lean control subjects, and 11 overweight/obese control subjects. Age and height were similar, but significant differences were seen across the groups in weight, BSA, BMI, and percent body fat (Table 1). Weight, BSA, and BMI were highest in the type 2 diabetic group. No significant differences in body size were observed between the type 1 diabetic group and lean control subjects. Percent body fat was highest in the type 2 diabetic group and the overweight control subjects but not different between them. Although the type 1 diabetic group exhibited significantly lower percent body fat, it remained higher than that for the lean control subjects ($P < 0.05$). Duration of diabetes was longer in the type 1 diabetic group ($P = 0.004$). Both FBG and A1C were significantly elevated in the two diabetic groups, with significantly higher FBG in the type 1 diabetic group ($P < 0.05$), but no difference in A1C was seen between the two diabetic groups nor were any echocardiographic measures correlated with A1C.

Cardiac structure

The type 2 diabetic group had the largest hearts (left ventricular diameter, left ventricular mass, and LA area) (Table 2). The largest left ventricular diameters were observed in the type 2 diabetic group: significant differences in end-diastolic left

Table 2—*Echocardiographic measurements of heart size*

	Type 1 diabetes	Type 2 diabetes	Lean control subjects	Overweight control subjects	ANOVA *P* value
n	11	8	9	11	
Echocardiographic structural measurements					
LVEDD (cm)	4.71 ± 0.43	5.42 ± 0.36	4.85 ± 0.49	5.08 ± 0.37	0.006
LVEDD/height (cm/m)	2.89 ± 0.26	3.24 ± 0.23	2.91 ± 0.23	3.15 ± 0.23	0.006
LVESD (cm)	2.87 ± 0.38	3.50 ± 0.42	3.03 ± 0.45	3.13 ± 0.37	0.015
LVESD/height (cm/m)	1.76 ± 0.23	2.09 ± 0.27	1.81 ± 0.24	1.94 ± 0.21	0.021
LV mass (g)	116.8 ± 15.6	170.3 ± 32.9	116.1 ± 33.8	137.2 ± 12.6	0.001
LV mass/height (g/m)	71.6 ± 8.7	102.1 ± 21.0	69.2 ± 17.2	84.9 ± 18.7	0.0007
LV mass/FFM (g/kg)	2.78 ± 0.27	2.97 ± 0.56	2.71 ± 0.48	2.93 ± 0.0.41	0.54
Ejection fraction (%)	69.0 ± 6.8	64.2 ± 5.9	67.4 ± 5.9	68.0 ± 5.5	0.38
Left atrial area (cm^2)	17.1 ± 2.2	19.3 ± 1.5	16.5 ± 2.4	18.5 ± 2.8	0.067
Left atrial area/height (cm^2/m)	10.5 ± 1.2	11.6 ± 1.2	9.9 ± 1.4	11.5 ± 1.8	0.047
Echocardiographic functional measurements					
E velocity (cm/s)	94.5 ± 13.6	100.5 ± 18.4	92.8 ± 11.7	92.7 ± 12.4	0.63
A velocity (cm/s)	60.8 ± 12.6	56.4 ± 12.8	38.1 ± 7.1	45.7 ± 11.4	0.0003
E-to-A ratio	1.61 ± 0.32	1.86 ± 0.45	2.52 ± 0.54	2.21 ± 0.78	0.005
IVRT (ms)	50.3 ± 8.1	50.9 ± 10.1	43.4 ± 6.5	54.9 ± 9.0	0.04
Average Ea (cm/s)	16.04 ± 2.4	12.6 ± 3.5	16.0 ± 1.40	16.2 ± 4.0	0.057
Average E-to-Ea ratio	6.1 ± 1.3	8.4 ± 2.4	5.8 ± 0.9	6.0 ± 1.6	0.005
Average Sa (cm/s)	10.5 ± 2.5	7.2 ± 2.5	9.1 ± 1.2	8.4 ± 1.1	0.008
Proportion with abnormalities					
LV dilatation (referent)	0	5 (63)	1 (11)	3 (27)	
Elevated LV mass (referent)	0	6 (75)	1 (11)	4 (36)	
LA dilatation (referent)	1 (9)	3 (38)	0	3 (27)	
E-to-Ea ratio ≥9 cm/s (referent)	0	4 (50)	0	1 (9)	
E-to-Ea ratio ≥12 cm/s (referent)	0	2 (25)	0	0	
No abnormality	10 (91)	1 (12)	8 (89)	5 (45)	
One abnormality	1 (9)	1 (12)	0	5 (45)	
Two abnormalities	0	3 (38)	1 (11)	0	
Three abnormalities	0	1 (12)	0	1 (9)	
Four abnormalities	0	2 (25)	0	0	

Values are means ± SD or *n* (%). LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension.

ventricular dimension were observed between the type 2 diabetic groups and both the type 1 diabetic group and the lean control subjects (both $P < 0.05$). These differences remained when indexed to height. Left atrial size was also higher in the type 2 diabetic group and overweight control subjects. The highest left ventricular mass occurred in the type 2 diabetic group ($P < 0.001$); this was significantly different from that in both the lean control subjects and type 1 diabetic group (both $P < 0.05$) but similar to that in the overweight control subjects. These relationships persisted when left ventricular mass was indexed to height ($P = 0.02$) but not when left ventricular mass was indexed to FFM ($P = 0.54$) (Fig. 1).

Cardiac function

The type 2 diabetic group demonstrated differences in diastolic filling and systolic function. Specifically, there was a decline in the E-to-A ratio across the groups, with dominant late filling in both diabetic groups, a pattern of diastolic filling usually seen in older individuals. This decline was driven primarily by significant differ-

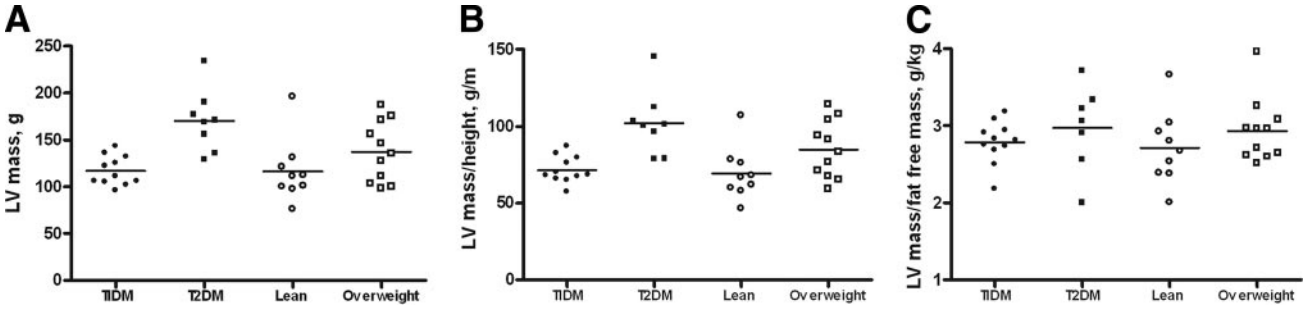

Figure 1—*Left ventricular (LV) mass by group: LV mass* (A)*, LV mass/height* (B)*, and LV mass/FFM* (C)*.T1DM, type 1 diabetes; T2DM, type 2 diabetes.*

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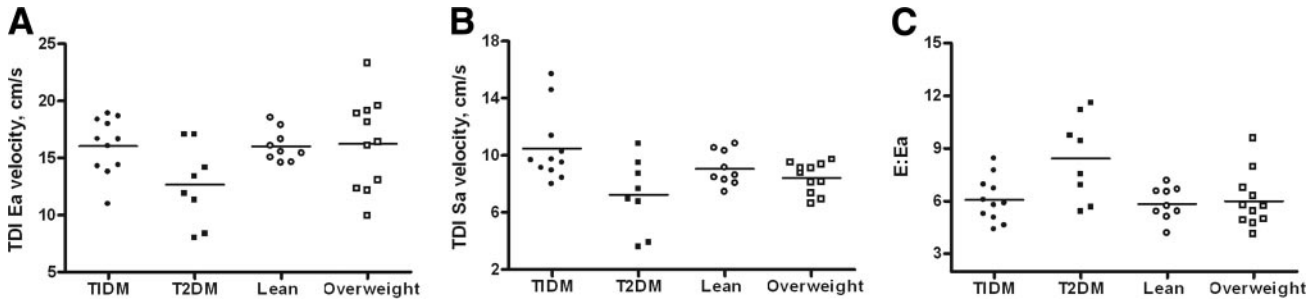

Figure 2—*Pulsed-wave tissue Doppler velocities. Average Ea velocity* (A)*, average Sa* (B)*, and average E:Ea* (C)*. T1DM, type 1 diabetes; T2DM, type 2 diabetes; TDI, tissue Doppler imaging.*

ences in late filling (mitral A velocity) (Table 2). These abnormalities in diastolic function were confirmed by prolonged isovolumic relaxation in all groups, except the lean control subjects ($P = 0.04$), and a trend toward reduced left ventricular longitudinal relaxation (Ea velocity), ($P = 0.057$). Left ventricular filling pressure (estimated from the E-to-Ea ratio) was different across the groups: it was significantly higher in the type 2 diabetic group (all $P < 0.05$).

Longitudinal left ventricular systolic function (measured by longitudinal annular motion [Sa]) was lowest in the type 2 diabetic group, different across the groups, and different between the two diabetic groups ($P < 0.05$). In summary, tissue Doppler velocities indicated lower diastolic and systolic longitudinal myocardial motion and higher left ventricular filling pressure in the type 2 diabetic group (Fig. 2).

Detection of abnormal echo measurements

Compared with published normal values for adult women (14), 63% of the type 2 diabetic group met the criteria for left ventricular dilatation, compared with 11% of the lean control subjects and 27% of the overweight control subjects (Table 2); 75% met the published criteria for LVH, compared with 11% of the lean control subjects and 36% of the overweight control subjects; 38% had larger left atrial areas, compared with 9% of the type 1 diabetic group and 27% of the overweight control subjects; and 50% fell outside the range of normal left ventricular filling pressure (E-to-Ea ratio ≥9 cm/s) (15), of whom three of four subjects had dilated left ventricles and dilated left atria and met the criteria for LVH. Importantly, just one type 2 diabetic subject had no abnormalities detected and one subject had a single abnormality present. The remainder had two or more abnormalities detected. Half of the overweight control subjects had a single abnormality detected, and in all subjects this was LVH. Nearly all of the type 1 diabetic and lean control subjects had no abnormalities detected.

CONCLUSIONS — This study is the first to demonstrate that important cardiac abnormalities occur early in adolescent-onset type 2 diabetes and highlights the potential for higher cardiovascular risk. By comparing type 2 diabetic girls with age-matched girls with type 1 diabetes and lean and overweight control subjects, we found that obesity was associated with increased cardiac dimensions and higher left ventricular mass, both of which were further augmented by the addition of type 2 diabetes. Furthermore, in the type 2 diabetic group there was evidence of impaired diastolic and systolic function, increased left ventricular filling pressure, and larger left atrial volume, a marker of long-standing diastolic disease.

Adolescent-onset type 2 diabetes is a disturbing worldwide epidemic (2). Usually a disease of older patients, type 2 diabetes often coexists with multiple other cardiovascular risk factors, including hyperlipidemia, hypertension, and obesity and is associated with poor cardiovascular outcome (3). LVH, one of the first signs of diabetic cardiomyopathy, may eventually progress to left ventricular dysfunction and clinical heart failure (16) and is an independent risk factor for cardiovascular morbidity and mortality (17). Hypertrophy of cardiac myocytes occurs in response to increased load, leading to increased left ventricular wall thickness and mass. Adolescent obesity has been previously associated with increased left ventricular volumes and mass (11), but obesity is also associated with diastolic dysfunction (18) and may independently lead to heart failure (19).

Although left ventricular mass was similar between the type 2 diabetic group and the overweight control subjects and different from that of the lean and type 1 diabetic control groups, left ventricular dilatation and functional differences were only seen in the type 2 diabetic group, suggesting that obesity may be an important factor contributing to structural changes in the heart and that the presence of diabetes augments these changes. The overweight control subjects in our study displayed important left ventricular structural changes, comparable with those of the type 2 diabetic subjects: both had higher left ventricular mass and this remained true when left ventricular mass was indexed to height. Because left ventricular mass is related to body composition, in particular FFM (20), the higher left ventricular mass in these groups might simply reflect normal physiological growth in response to higher FFM. Although FFM may be the ideal indexing variable for left ventricular mass (20), few data exist regarding the relationship between FFM and LVH in overweight and obese subjects. Indeed, when left ventricular mass was indexed to FFM, no differences were detected among the groups in our study. However, the functional changes observed in the type 2 diabetic group suggest that the higher LV mass observed may be abnormal.

Elevated left ventricular mass leads to alterations in both myocardial relaxation and passive filling of the left ventricle (16), and adults with type 2 diabetes exhibit a high prevalence of diastolic dysfunction (8) as do patients with type 1 diabetes (21). In the current study, a dependence upon active rather than passive diastolic filling was observed in both diabetic groups, despite the shorter duration of diabetes in the type 2 diabetic group.

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We hypothesized that this finding in type 2 diabetic participants reflects a longer exposure to obesity and other cardiovascular risk factors rather than diabetes per se. Obesity is related to hypertension as well as to diabetes, and it is difficult to measure exposure to either in retrospect, perhaps explaining the lack of association between duration of diabetes and cardiac adaptation.

This is the first study to document the direct structural and functional effects of type 2 diabetes on the heart. Obesity in adolescents and young adults has been linked with hypertension (22) and cardiovascular disease (23) in later life and there are some data about the direct cardiovascular effects of obesity: in a study of young women (mean age 30 years), obesity (average duration 12 years) was associated with higher left ventricular mass and diastolic and systolic abnormalities similar to those seen in the type 2 diabetic group in the current study (12). Our subjects were younger with shorter exposure to obesity and yet displayed comparable structural and functional changes.

Adolescent-onset type 2 diabetes is a relatively new disease and increasingly prevalent; thus, long-term data are limited and the prognostic implications of the abnormalities detected in this study are unknown. However, many of these parameters predict cardiovascular outcome in other population cohorts, and these adverse changes may be the precursor of future cardiovascular disease and are unlikely to reverse without significant intervention. In fact, these adolescents may already be progressing toward development of the clinical syndrome of heart failure. Recent American College of Cardiology/American Heart Association heart failure guidelines (24) describe heart failure as a continuum that begins with risk factors, including diabetes and hypertension (stage A), followed by the development of structural heart disease (stage B) and eventually leading to the clinical syndrome of heart failure (stages C and D). Because the diagnosis of type 2 diabetes is a recognized contributor to stage A heart failure, the additional findings of structural and functional abnormalities (LVH and diastolic and systolic dysfunction) suggest that some of these girls could and should be considered to have stage B heart failure already.

LVH is an important and modifiable cardiovascular risk factor. Substantial data exist to support the use of antihypertensive therapy (especially ACE inhibitors and angiotensin receptor blockers) for lowering blood pressure and regressing LVH, but many therapies are not registered for use nor proven in children. Significant weight reduction, such as might be achieved through bariatric surgery or severe caloric restriction, may result in regression of left ventricular mass and reversal of functional (10) and cardiovascular changes (23). Furthermore, physical exercise is recommended by the American Diabetes Association to delay the onset of cardiovascular disease in type 2 diabetes. Thus, a strategy to promote exercise and sustain weight loss may reverse this premature myocardial aging.

Limitations

We found large and clinically significant differences among the groups and a high proportion of subjects with echocardiographic measurements that fell outside of the normal range using adult female normal values. We used adult normal values to ensure that we did not overdiagnose abnormalities by using adolescent normal ranges. If anything, the use of adolescent normal values would have increased the number of subjects with abnormal echocardiographic measurements of left ventricular size and hypertrophy. The diabetic subjects in this study were not matched for duration of diabetes, nor was it possible to match them by A1C, although both groups had elevated A1C. It is possible that the abnormalities detected in this study may be related to both disease duration and glycemic control, as well as to other cardiovascular risk factors; however, it was not possible to determine predictors of these abnormalities. The results of this small study require confirmation in larger cohorts with longitudinal data to determine whether these abnormalities progress.

In summary, to our knowledge this is the first study to report potentially important left ventricular structural and functional changes associated with adolescent-onset type 2 diabetes. Compared with age-matched control subjects, girls with type 2 diabetes exhibited significant LVH and a high prevalence of abnormal echocardiographic measurements. If left unchecked, it is likely that these changes will lead to the development of clinically overt cardiovascular disease.

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No potential conflicts of interest relevant to this article were reported.

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