ORIGINAL RESEARCH

Cardiopulmonary Dysfunction and Adiponectin in Adolescents With Type 2 Diabetes

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***Background*—**Myocardial mechanics are altered in adults with obesity and type 2 diabetes (T2D); insulin resistance and adipokines have been implicated as important risk factors for cardiovascular disease, but these relationships are poorly described in adolescents. We hypothesized that obese adolescents and adolescents with T2D would have abnormal cardiac function compared to lean adolescents. In addition, we hypothesized that insulin sensitivity (IS), adiposity, and adipokines would be associated with altered cardiac strain and cardiopulmonary fitness in adolescents with T2D.

***Methods and Results*—**Adolescents (15±2 years) with T2D (n=37), obesity without diabetes (n=41), and lean controls (n=31) of similar age and pubertal stage underwent echocardiography with speckle tracking, assessment of IS by hyperinsulinemic–euglycemic clamp, body composition by dual-energy x-ray absorptiometry, peak oxygen consumption (VO_2peak) by cycle ergometry, adiponectin, and leptin. Compared to lean and to obese controls, adolescents with T2D had significantly lower cardiac circumferential strain (CS) (−18.9±4.6 [T2D] versus −21.5±3.5 [obese] versus −22.0±4.2% [lean], P=0.04) and VO_2peak (37.6±7.5 [T2D] versus 43.4±8.2 [obese] versus 47.6±8.6 mL/lean kg/min [lean], P<0.0001). In T2D youth, VO_2peak was associated with CS, and the association remained significant after adjusting for age, sex, and IS (β±SE: −0.73±0.26, P=0.02). Among adolescents with T2D, CS was also associated with adiponectin, longitudinal strain with leptin, and VO_2peak with adiponectin and IS.

***Conclusions*—**Adolescents with T2D had abnormal CS and reduced VO_2peak compared to obese and lean controls, which may represent the earliest evidence of cardiac functional impairment in T2D. Low adiponectin, rather than conventional risk factors and IS, correlated with CS, while both adiponectin and IS related to cardiopulmonary fitness. **(*J Am Heart Assoc*. 2016;5:e002804 doi: 10.1161/JAHA.115.002804)**

Key Words: diabetic cardiomyopathy • left ventricular strain • myocardial mechanics • type 2 diabetes

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in type 2 diabetes (T2D).[1–3] While exercise abnormalities have been reported in adolescents and adults with T2D, it remains unknown whether the underlying mechanisms are cardiac and/or peripheral in origin. Myocardial mechanics are altered in adults with T2D, with decreased longitudinal strain (LS) from subendocardial fibrosis reportedly occurring early in the disease process, and abnormalities in circumferential strain (CS), suggesting midwall fiber damage, thought to be a later finding.[4–6] The limited data available on adolescents with T2D suggest that cardiac target organ damage can be detected early on in the course of the disease.[1,7–9] We previously reported evidence of left ventricular hypertrophy in a small group of adolescents with T2D, along with reduced cardiopulmonary fitness.[8] However, studies have not yet examined the relationship between myocardial strain and cardiopulmonary fitness in youth with T2D, or the relationships between CVD risk factors and cardiac structure, function, and strain.

Insulin resistance, adiposity, and adipokines have been implicated in the development of abnormal myocardial mechanics in adults with obesity and T2D, but limited data exist for adolescents. New echocardiographic techniques have been developed to identify early changes in myocardial function that may antedate overt diabetic cardiomyopathy. Accordingly, we first sought to examine cardiac structure and

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Received October 24, 2015; accepted January 22, 2016.

function, including strain measurements, in concert with cardiopulmonary fitness among obese adolescents with T2D compared to obese and lean controls without diabetes. Second, we sought to examine the relationships between insulin resistance, body composition, adipokines (leptin and adiponectin), and measures of myocardial function, including strain, and cardiopulmonary fitness in adolescents with T2D. Adiponectin and leptin have both been reported to impact myocardial function; adiponectin is thought to be protective in cardiac myocyte cell cultures and abnormal leptin signaling to be deleterious in animal models.[10,11] In this study, we hypothesized that (1) adolescents with T2D and obese adolescents would have abnormal cardiac structure and function compared to their lean counterparts; and (2) insulin resistance, adiposity, and adipokines would be associated with measures of cardiac function and cardiopulmonary fitness in adolescents with T2D.

Methods

Participants

A total of 111 pubertal adolescents between the ages of 12 and 19 years were recruited from University of Colorado obesity and diabetes clinics as well as advertisement in the community for a study of diabetes and insulin resistance in youth, and had insulin sensitivity assessed by hyperinsulinemic–euglycemic clamp, cardiac structure and function examined by echocardiography, and cardiopulmonary fitness assessed by cycle ergometry, as well as data on adipokines (adiponectin and leptin) and conventional risk factors. Of the 111 adolescents, 37 were diagnosed with obesity (body mass index [BMI] >95th percentile) and T2D, 41 with obesity but no diabetes, and 33 were normal-weight youth without diabetes (BMI >5th percentile and <85th percentile). Family history of diabetes was similar in obese and T2D participants, and normal-weight participants had no reported family history of diabetes. Obese participants were chosen to have similar BMI *z*-score and fat mass as participants with T2D. Participants were not matched, but all 3 subject groups were chosen to be of similar age, Tanner stage, level of habitual physical activity, and sex distribution. The study was approved by the University of Colorado Anschutz institutional review board, and appropriate consent and assent were obtained.

Height and weight were measured for determination of BMI. BMI *z*-score was calculated using BMI, sex, and age by the Lamda Mu-Sigma method[12] with 2000 Center for Disease Control and Prevention Growth Charts (ages 0 to <20 years) as a reference.[13] Absence of diabetes was confirmed in the nondiabetic groups by a 2-hour, 75-g oral glucose tolerance test. Type 2 diabetes was defined by American Diabetes Association's criteria and the absence of glutamic acid decarboxylase, islet cell or insulin autoantibodies, or secondary causes of diabetes. Pubertal development was assessed by pediatric endocrinologists using the criteria established by Tanner and Marshall for pubic hair and breast development. Testicular volume was measured using an orchidometer. Inclusion criteria included pubertal status (Tanner stage >1), and sedentary status (<3 hours of exercise per week) to minimize training effects. Exclusions included body weight greater than 300 pounds, blood pressure greater than 140/90 mm Hg at rest or greater than 190/100 mm Hg during exercise, hemoglobin less than 9 mg/dL, serum creatinine greater than 1.5 mg/dL, smoking, antihypertensive drugs, pregnancy, breastfeeding, 3 or more hours of physical activity per week, or plans to alter exercise or diet during the study. For participants with T2D, additional exclusion criteria included hemoglobin A1c ≥12%, medications known to affect insulin sensitivity other than metformin (oral or inhaled steroids, thiazolidinediones, atypical antipsychotics), and other antidiabetic drugs except insulin. For nondiabetic participants, additional exclusions included medications known to affect insulin sensitivity (metformin, oral or inhaled steroids, thiazolidinediones, atypical antipsychotics), other antidiabetic drugs, and insulin.

Because carbohydrate and fat intake can acutely impact cardiovascular function and insulin sensitivity, all tests were performed in the morning following a 12-hour fast, preceded by 3 days of a fixed-macronutrient, weight-maintenance diet (55% carbohydrates, 30% fat, and 15% protein provided by the Clinical and Translational Research Center (CTRC)). As acute exercise also impacts cardiac and exercise function and insulin sensitivity, the visit was also preceded by 3 days without vigorous physical activity.

Laboratory Measures

Leptin and adiponectin were measured on a morning fasting sample, drawn prior to the insulin clamp, with the respective radioimmunoassay kits from Millipore. Other fasting laboratory evaluations included total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, and hemoglobin A1c (The Diabetes Control and Complications Trial (DCCT)-calibrated); assays were performed by standard methods in the CTRC laboratory.

Activity Questionnaires and Body Composition

All participants were sedentary, defined as performing less than 3 hours per week of regular exercise. A 3-day pediatric physical activity recall questionnaire and accelerometers were used to confirm sedentary status and to estimate habitual physical activity,[8,14,15] reported as a 3-day average of daily

metabolic equivalents. Body composition was assessed by dual-energy x-ray absorptiometry scan as previously reported.[8,14]

Insulin Sensitivity

Insulin sensitivity (glucose infusion rate in mg/kg per min and mg/lean kg/min) was calculated from a hyperinsulinemic–euglycemic clamp (80 $mU \cdot m^{-2} \cdot min^{-1}$ insulin) after an overnight intravenous insulin infusion to normalize glycemia in participants with diabetes as previously described.[8,14]

Exercise Testing

Measurements were made using an exercise bicycle ergometer (Medical Graphics Corp, Minneapolis, MN) and a metabolic cart (Medgraphics CPX/D, Medical Graphics Corp, St. Paul, MN) as previously described.[8,14] For all bicycle tests, oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation were measured, breath-by-breath, at rest and during exercise. Arm blood pressures (by auscultation) and heart rates (by 12-lead ECG) were obtained every minute during exercise. Cardiac status was continuously monitored throughout each test by 12-lead ECG. The respiratory exchange ratio was calculated as VCO_2/VO_2. Subjects were excluded if peak respiratory exchange ratio was ≤ 1.1.

As previously reported, a maximal graded bicycle ergometer protocol was performed in conjunction with the use of a metabolic cart to determine peak oxygen consumption (VO_2peak).[8,14] VO_2peak was reported in milliliter per min, milliliters per kilogram per minute and milliliters per lean kg from dual-energy x-ray absorptiometry per minute.

Echocardiography

Resting supine 2-dimensional and tissue Doppler echocardiography was performed, using a Vivid 7 (General Electric, Waukesha, WI) ultrasound system, to exclude left ventricular systolic dysfunction (ejection fraction <50%), regional wall motion abnormalities, pericardial disease, or significant valvular pathology. Image analysis was completed with EchoPAC software (General Electric, Waukesha, WI). Left ventricular dimensions and ejection fraction were obtained by standard m-mode and 2-dimensional volumetric method-of-discs analysis.[16] Left ventricular mass (LVM) was calculated as $LVM=0.8\times 1.05\times[(IVSd+PWd+LVIDd)^3-LVIDd^3)]$, where IVSd indicates interventricular septal end diastole, PWd indicates posterior wall septal end diastole, and LVIDd indicates left ventricular diameter at end diastole.[16] Indexed LVM was calculated as $LVM/height^{2.7}$.[17] Left ventricular hypertrophy was defined as indexed LVM values greater than 90th percentile for age and sex-specific reference data.[18]

Using traditional pulse wave blood and tissue Doppler, the mitral inflow peak E and A wave velocities, deceleration time, and myocardial systolic (S′) and early diastolic (E′) velocities at the lateral and septal mitral valve annuli were measured using standard protocols.[19]

Speckle tracking was performed with EchoPAC software. Global LS curves were obtained from each of the 2 standard apical views and 1 parasternal long-axis view. The parasternal short axis view at the papillary muscles was used to obtain circumferential strain. In each view the endocardium was traced in end-diastole. The epicardium was traced by defining the myocardial thickness such that the entire myocardium was included while excluding the pericardium. The software then generated strain curves by tracking and averaging the relative speed and location of defined patterns or "speckles" within each segment. Only those segments that had an adequate number of traceable speckles were included. In order to obtain valid results, adequate tracking in at least 4 of the 6 segments had to be verified; otherwise, values from that view were discarded. Per standard techniques,[20] peak strain was measured on strain curves at the time of aortic valve closure. Global circumferential strain was obtained from the curves in the short-axis view that measured global strain as if the entire left ventricle was one segment (rather than an average of the individual segments). LS was calculated as an average of the maximum global strain from the 3 views. Strain is interpreted in absolute values (eg, strain of −15% is lower than strain of −16%).

Statistical Analysis

Analyses were performed in SAS (version 9.4 for Windows; SAS Institute, Cary, NC). Variables were checked for the distributional assumption of normality using normal plots. Leptin was positively skewed and natural log transformed (ln [leptin]). ANOVA was used for comparison of continuous variables across the 3 groups (T2D, obese control, and lean control); 2-sample *t* tests were employed to evaluate between-group differences, and least-square means were calculated for the adjusted models. Due to the small number of observations in each group, we also used the Kruskal–Wallis test and obtained similar *P*-values to ANOVA. For categorical variables we used χ^2 and Fisher's exact test. Linear regression models were employed to examine the associations between ln[leptin], adiponectin and VO_2peak, and echocardiogram variables, unadjusted, adjusted for age, and sex (model 1) and adjusted for age, sex, and BMI (model 2). As sensitivity analyses, we also adjusted for Tanner stage instead of age and obtained similar results. As our analyses were considered hypothesis generating, we did not adjust for multiple comparisons. R^2 and semipartial R^2 were represented with a 95% CI. Significance was based on an α-level of ≤ 0.05.

Results

Clinical Characteristics

Adolescents with T2D were slightly older than the obese and lean participants, with pubertal status similar to the obese participants and slightly more advanced than the lean participants (Table 1). The 3 groups did not significantly differ in baseline level of physical activity or sex distribution, and BMI *z*-score and fat mass were similar between the obese and T2D participants (Table 1).

Adolescents with T2D and obese nondiabetic participants had significantly greater leptin concentrations than lean nondiabetic participants. Adiponectin was significantly lower in adolescents with T2D compared to both obese and lean nondiabetic controls (Table 1). These differences remained significant after adjusting for age and/or Tanner stage.

Adolescents with T2D had a higher resting heart rate and reduced peak exercise capacity (VO_2peak) compared with lean nondiabetic controls, and also reduced compared to obese nondiabetic controls, despite similar Tanner stage, BMI *z*-score, and habitual level of physical activity (Table 1). Systolic blood pressure was higher in the youth with T2D compared with both obese and lean nondiabetic controls, and also higher in the obese nondiabetic controls than lean nondiabetic controls. Diastolic blood pressure was higher in the youth with T2D compared with the lean nondiabetic controls (Table 1).

Differences in Measures of Left Ventricular Size Between T2D, Obese, and Lean Participants

Volumetric analysis of 2-dimensional echographic images demonstrated significant differences between the groups

Table 1. Differences in Clinical Parameters Between Groups

Variables	Type 2 Diabetes (n=37)	Obese (n=41)	Lean (n=33)	*P* Value ANOVA/χ^2
Age, y	15.4±2.3*	14.4±2.0	14.9±2.1	0.06
Gender (% female)	70%	71%	55%	0.23
Tanner stage	4.7±0.8†	4.7±0.7†	4.1±1.0	0.002
BMI *z*-score	2.1±0.5†	2.0±0.4†	0.1±0.7	<0.0001
Diabetes duration‡ (y)	4.6 (1.5–8.0)	—	—	—
HbA1c (%)	8.2±2.4*	5.2±0.3	5.1±0.3	<0.0001
HbA1c, mmol/mol	66±26*	34±2	33±3	<0.0001
Insulin sensitivity, mg/lean kg/min	7.0±5.2*	15.2±5.7†	19.7±4.1	<0.0001
Insulin sensitivity, mg/kg per min	3.6±2.9*	8.6±3.3†	14.6±3.8	<0.0001
Fat mass, kg	37.9±12.6†	35.6±11.5†	13.0±5.7	<0.0001
% Fat	41.3±6.2†	41.5±5.2†	23.3±8.8	<0.0001
Lean mass, kg	50.2±9.7†	47.1±9.6†	40.8±9.0	<0.0001
Adiponectin, μg/mL	5.9±3.0*	8.6±3.6	9.2±3.6	<0.0001
Leptin§, ng/mL	27.9 (23.1–33.6)†	31.7 (27.3–36.9)†	5.8 (3.9–8.7)	<0.0001
METs	64.1±16.7	60.2±13.2	62.2±14.1	0.48
Resting systolic blood pressure, mm Hg	122±12*	116±9†	112±8	<0.0001
Resting diastolic blood pressure, mm Hg	71±11†	68±10	66±7	0.03
Resting heart rate, beats/min	71±13*	64±9	64±10	0.07
VO_{2peak}, mL/lean kg/min	37.6±7.5*	43.5±8.3†	47.6±8.6	<0.0001
VO_{2peak}, mL/kg per min	20.4±4.2*	24.2±5.5†	34.3±8.2	<0.0001
VO_{2peak}, mL/min	1859±446	2007±462	1876±582	0.39

Continuous variables are expressed as mean±SD, unless otherwise specified. BMI indicates body mass index; HbA1c, hemoglobin A1c; METs, metabolic equivalents; VO_{2peak}, peak oxygen consumption.

*P<0.05 compared to obese and lean.

†P<0.05 compared to lean.

‡Median, p25 to p75.

§Geometric mean, 95% CI.

(Table 2). The diastolic septal and posterior walls (IVSd and left ventricular posterior wall end diastole) were significantly thicker in adolescents with T2D compared to both lean and obese controls. LVM and indexed LVM were also significantly greater in adolescents with T2D compared to obese and lean controls (Table 2 and Figure 1). Overall, these data are consistent with a tendency towards cardiac hypertrophy in the adolescents with T2D, and 18% of adolescents with T2D had LVM consistent with clinically significant left ventricular hypertrophy. End-diastolic volume was also largest in adolescents with T2D, but not significantly different from obese controls. Left ventricular diameter at end diastole and left

Table 2. Differences in Echo Parameters Between Groups

Variables/Categories	Type 2 Diabetes (n=37)	Obese (n=41)	Lean (n=33)	*P* Value ANOVA/Fisher's Exact
Measures of left ventricular size				
LVIDd, cm	4.4±0.5	4.5±0.4*	4.3±0.4	0.04
LVIDs, cm	2.8±0.5	3.0±0.3*	2.7±0.5	0.04
FS (%)	36.2±7.3	34.7±6.2	37.6±7.5	0.22
IVSd, cm	0.88±0.16†	0.76±0.15	0.79±0.15	0.002
LVPWd, cm	0.92±0.15†	0.81±0.14	0.80±0.14	0.001
End-diastolic volume, cm^3	91.8±18.7*	91.1±24.8*	76.1±20.5	0.01
End-systolic volume, cm^3	29.8±8.7	30.5±10.3	26.7±8.6	0.26
Ejection fraction (biplane) (%)	67.6±6.5	66.5±6.1	65.2±5.0	0.34
LVM, g	129.4±36.1†	115.1±29.8	106.9±30.6	0.01
LVMI, $g/m^{2.7}$	33.3±8.4†	31.0±10.5	27.3±6.1	0.02
LVH (%)	18%*	17%*	5%	0.20
IVSd >1 cm (%)	18%†	4%	0%	0.004
LVPWd >1 cm (%)	21%*	8%	3%	0.02
Traditional echo and tissue Doppler measurements				
Mitral peak E velocity, m/s	0.93±0.16	0.93±0.14	0.94±0.15	0.99
Mitral peak A velocity, m/s	0.47±0.10*	0.49±0.12*	0.40±0.08	0.002
Mitral inflow E/A	2.1±0.6*	2.0±0.6*	2.4±0.7	0.01
Deceleration time, ms	134±107*	129±96*	197±44	0.002
Lateral peak E′, cm/s	16.7±3.5§	18.4±4.3	18.2±2.5	0.07
Lateral peak A′, cm/s	8.0±2.7†	7.6±2.4*	5.6±1.4	<0.0001
Lateral E/E′	5.9±1.5*	5.3±1.3	5.2±1.0	0.08
Septal peak E′, cm/s	13.3±3.0	13.9±2.9	14.1±1.6	0.39
Septal peak A′, cm/s	7.4±2.3*	6.8±0.2*	5.5±0.2	0.0005
Septal E/E′	7.3±1.7	7.0±1.6	6.7±1.3	0.30
Speckle tracking parameters				
Longitudinal strain (%)§	−17.5±2.6	−16.1±3.1*	−18.0±2.1	0.03
Circumferential strain (%)§	−18.9±4.6†	−21.5±3.5	−22.0±4.2	0.04
Apical rotation	7.0±2.2	5.9±2.2	7.3±5.0	0.42
Basal rotation	−3.5±6.4	−5.3±4.3	−6.7±2.2	0.52
Torsion	11.1±8.3	11.4±5.1	14.9±3.2	0.37

Continuous variables are expressed as mean±SD. E/A is the ratio of the early (E) to late (A) ventricular filling velocities; FS, fractional shortening; IVSd, interventricular septal end diastole; LVH, left ventricular hypertrophy; LVIDd, left ventricular internal diameter end diastole; LVIDs, left ventricular internal diameter end systole; LVM, left ventricular mass; LVMI, left ventricular mass index; LVPWd, left ventricular posterior wall end diastole.

*$P<0.05$ compared to lean.

†$P<0.05$ compared to obese and lean.

§Strain is interpreted in absolute values (eg, −15% is lower than −16%).

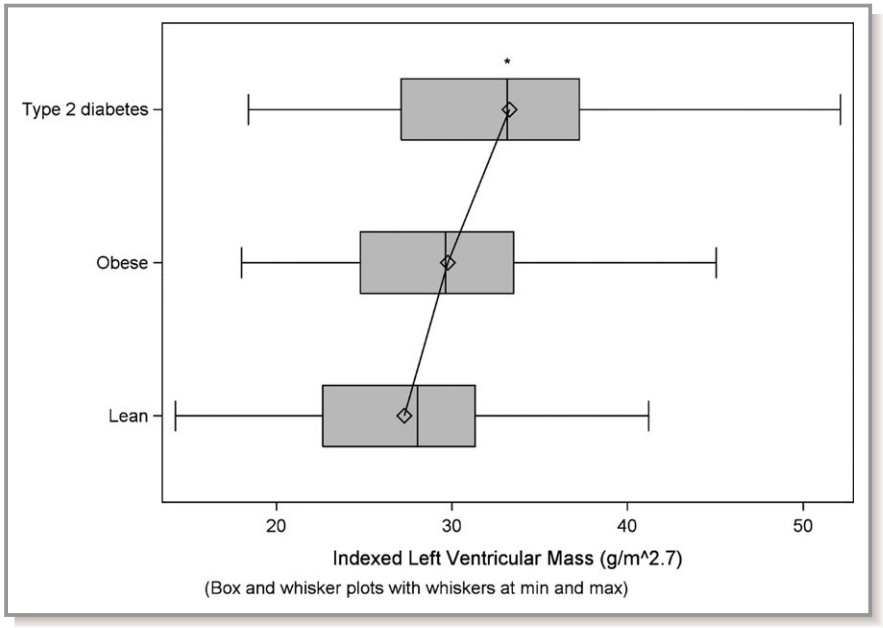

Figure 1. LVMI in adolescents with type 2 diabetes (T2D), and in obese and lean adolescents. The figure shows vertical box plots with whiskers at min and max for indexed LVM in adolescents with T2D (n=37), obese (n=41), and lean (n=33). The vertical lines in the boxes represent the median values, and the diamonds represent mean values. ANOVA was used for comparisons of the continuous variables across the 3 groups. **P*=0.03 compared to obese adolescents, and *P*=0.0007 compared to lean adolescents. LVMI indicates indexed left ventricular mass.

ventricular diameter at end systole were within normal limits for all groups, but significantly greater in obese controls compared to lean controls. No significant differences were observed in left ventricular diameter at end diastole or left ventricular diameter at end systole between adolescents with T2D and obese controls (Table 2).

Differences in Traditional Echocardiographic and Tissue Doppler Measurements Between T2D, Obese and Lean Participants

Albeit in the normal ranges, mitral E/A (the ratio of the early (E) to late (A) ventricular filling velocities) and deceleration time were significantly lower in the T2D and obese control group compared to lean controls, consistent with early signs of diastolic dysfunction (Table 2). Septal peak A′ was significantly higher in adolescents with T2D and obese controls compared to lean controls (Table 2). No significant differences were appreciated among the 3 groups for septal peak E′ (Table 2). Lateral peak A′ was higher in the T2D versus lean control group, showing a stronger atrial contraction (Table 2). However, fractional shortening and ejection fraction did not differ between groups, indicating preserved systolic function.

Differences in Speckle Tracking Measurements Between T2D, Obese, and Lean Participants

Speckle tracking analysis demonstrated significantly lower CS in participants with T2D compared to obese and lean nondiabetic counterparts (Table 2 and Figure 2). There was no significant difference in LS between participants with T2D and the obese or lean control group (Table 2). However, the obese control group had significantly lower LS than the lean control group (Figure 3). No differences in apical rotation, basal rotation, or torsion were noted among the 3 groups (Table 2). LVM (β±SE: 0.04±0.02, *P*=0.02), but not-indexed LVM was associated with LS. Neither LVM nor indexed LVM was associated with CS or VO_2peak in adolescents with T2D (data not shown).

Relationships Between Cardiopulmonary Fitness and Cardiac Function

In the whole cohort (lean, obese, and T2D), VO_2peak was weakly associated with CS (β±SE: −0.13±0.06, *P*=0.04, R^2=0.07), but did not reach significance for LS (*P*=0.07). In adolescents with T2D, VO_2peak remained significantly

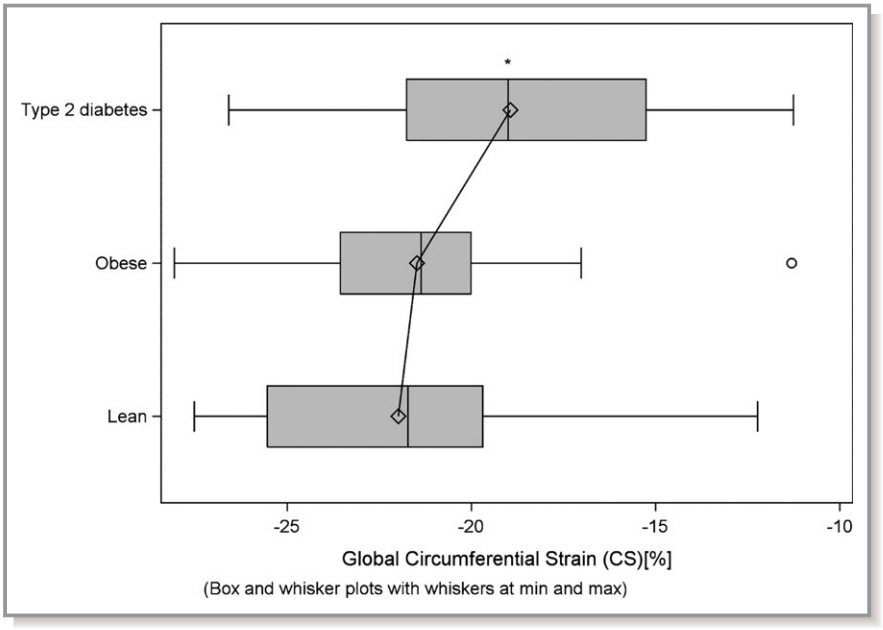

Figure 2. CS in adolescents with type 2 diabetes (T2D), obese and lean adolescents. The figure shows vertical box plots with whiskers at min and max for CS in adolescents with T2D (n=37), obese (n=41) and lean (n=33). The vertical lines in the boxes represent the median values, and the diamonds represent mean values. ANOVA was used for comparisons of the continuous variables across the 3 groups. *P=0.04 compared to obese adolescents, and P=0.02 compared to lean adolescents. CS indicates circumferential strain.

associated with CS after adjusting for age, sex, and insulin sensitivity (β±SE: −0.73±0.26, P=0.02), and CS explained a greater amount of the variance in VO_2peak (adjusted model, semipartial R^2=0.31 [95% CI: 0.00–0.58]). VO_2peak was not associated with LS (P=0.12) in T2D youth.

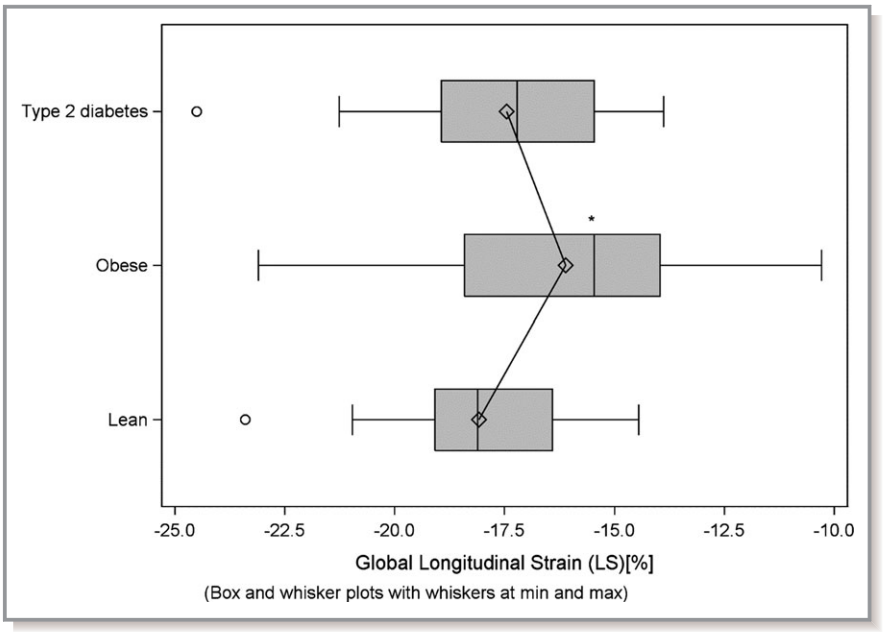

Figure 3. LS in adolescents with type 2 diabetes (T2D), and in obese and lean adolescents. The figure shows vertical box plots with whiskers at min and max for LS in adolescents with T2D (n=37), obese (n=41), and lean (n=33). The vertical lines in the boxes represent the median values, and the diamonds represent mean values. ANOVA was used for comparisons of the continuous variables across the 3 groups. *P=NS compared to T2D adolescents, and P=0.01 compared to lean adolescents.

Relationships Between Conventional Risk Factors, Cardiopulmonary Fitness, and Cardiac Function in Adolescents With T2D

Regarding hemoglobin A1c, systolic blood pressure, diastolic blood pressure, and diabetes duration, none was significantly associated with VO_2peak or CS in adolescents with T2D (data not shown). Conversely, systolic blood pressure was associated with LS (β±SE: −0.13±0.04, P=0.003).

Relationships Between Insulin Sensitivity, Cardiopulmonary Fitness, and Cardiac Function in Adolescents With T2D

Insulin sensitivity was positively associated with VO_2peak (β±SE: 0.64±0.27, P=0.02, R^2=0.18) and remained significant after adjusting for age (Table 3) and fat mass, respectively (P=0.04). In contrast, insulin sensitivity was not significantly associated with LS or CS (Table 3).

Relationships Between Leptin, Cardiopulmonary Fitness, and Cardiac Function in Adolescents With T2D

Ln(leptin) concentration was positively associated with LS (β±SE: 1.87±0.86, P=0.04, R^2=0.19), but the association lost significance after adjusting for BMI (Table 3). Ln(leptin) was also associated with VO_2peak (Table 3).

Relationships Between Adiponectin, Cardiopulmonary Fitness, and Cardiac Function in Adolescents With T2D

Adiponectin concentration was inversely associated with CS in adolescents with T2D (β±SE: −0.69±0.26, P=0.02, R^2=0.28, Figure 4). Adiponectin remained inversely associated with CS after adjusting for sex, age, and BMI (Table 3). Adiponectin was also positively associated with VO_2peak (β±SE: 0.81±0.37, P=0.04, R^2=0.13), and remained significant after adjusting for age, sex, and BMI (Table 3).

Relationships Between Body Composition, Cardiopulmonary Fitness, and Cardiac Function in Adolescents With T2D

Fat mass was positively associated with LS (β±SE: 0.11±0.04, P=0.01, R^2=0.28, Figure 5), and the association remained significant after adjusting for sex and Tanner stage (P=0.006). Lean mass was also associated with LS (β±SE: 0.11±0.05, P=0.04, R^2=0.19), and remained significant after adjusting for sex and Tanner stage (P=0.02).

Table 3. Associations Adjusted for Age in Adolescents With Type 2 Diabetes

	LS	CS	VO_{2peak}/lean kg
Fat mass			
Unadjusted	0.11±0.04, P=0.01	0.03±0.10, P=0.80	−0.08±0.10, P=0.44
Model 1: age and sex	0.11±0.04, P=0.009	0.09±0.11, P=0.43	−0.08±0.10, P=0.45
Lean mass			
Unadjusted	0.11±0.05, P=0.04	0.13±0.11, P=0.26	−0.24±0.12, P=0.05
Model 1: age and sex	0.17±0.05, P=0.005	0.33±0.14, P=0.03	−0.33±0.12, P=0.01
Ln(leptin)			
Unadjusted	1.87±0.86, P=0.04	0.35±1.84, P=0.85	−3.70±1.96, P=0.07
Model 1: age and sex	2.11±0.94, P=0.04	0.16±2.22, P=0.94	−3.87±1.86, P=0.049
Model 2: age, sex, and BMI	1.78±1.02, P=0.10	0.16±2.22, P=0.94	−3.82±2.08, P=0.08
Adiponectin			
Unadjusted	−0.21±0.16, P=0.20	−0.69±0.26, P=0.02	0.81±0.37, P=0.04
Model 1: age and sex	−0.20±0.17, P=0.26	−0.72±0.28, P=0.02	0.80±0.37, P=0.04
Model 2: age, sex, and BMI	−0.14±0.18, P=0.44	−0.70±0.30, P=0.04	0.82±0.39, P=0.04
IS			
Unadjusted	0.00±0.09, P=0.97	−0.24±0.22, P=0.30	0.64±0.27, P=0.02
Model 1: age and sex	0.03±0.07, P=0.73	−0.30±0.22, P=0.19	0.59±0.28, P=0.046
Model 2: age, sex, and BMI	0.07±0.09, P=0.43	−0.32±0.25, P=0.23	0.65±0.31, P=0.049

Data presented as β±SE from linear regression models. BMI indicates body mass index; CS, circumferential strain; IS, insulin sensitivity; Ln, natural log; LS, longitudinal strain; VO_{2peak}, peak oxygen consumption.

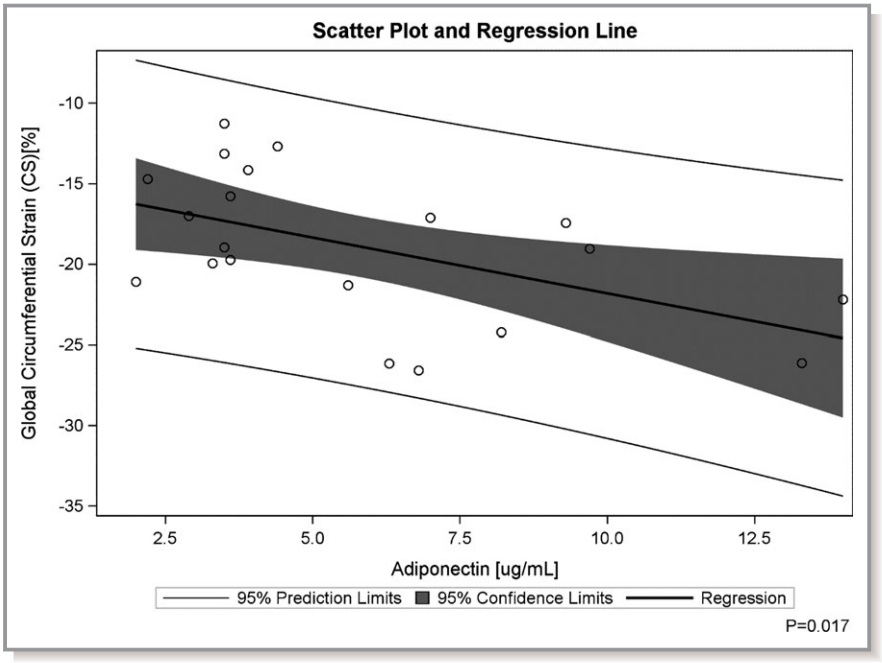

Figure 4. Association between adiponectin and global circumferential strain (CS) in adolescents with type 2 diabetes (T2D). Scatter plot and regression line. Linear regression employed to model relationship between CS and adiponectin in adolescents with T2D. β±SE: −0.69±0.26, *P*=0.02.

Conclusions

Early CVD, including atherosclerosis and diabetic cardiomyopathy, are anticipated to be major lifetime causes of excess morbidity and mortality in people with youth-onset T2D. As such, it is critical to identify early cardiac changes in adolescents with T2D prior to the development of overt clinical heart disease. This study demonstrated that adolescents with T2D had reduced CS compared to both nondiabetic lean and obese peers, as well as evidence of increased ventricular mass and wall thickness, hypertension, and higher resting heart rate. In addition, adolescents with T2D and those with obesity both had early signs of cardiac dilation and diastolic dysfunction. Notably, in obese nondiabetic youth, LS and not CS was reduced compared to lean nondiabetic peers, which is consistent with a previous report.[21] Because reductions in LS are reported to occur prior to a reduction in CS in adults with diabetes,[22] our observations may represent early changes in myocardial strain in obese nondiabetic adolescents, and more advanced changes in adolescents with T2D. Reduced CS, which was associated with reduced exercise capacity, may represent the earliest evidence of cardiac abnormality in T2D.

Interestingly, adiponectin, an adipokine with proposed cardiotrophic properties,[10] rather than glycemia and traditional CVD risk factors, was associated with CS and cardiopulmonary fitness, emphasizing the importance of considering nontraditional risk factors when examining the changes in myocardial mechanics observed in adolescents with T2D.

The complexities of myocardial mechanical changes in diabetic cardiomyopathy are not well understood. Since reduced ejection fraction, the conventional measurement of systolic function, is typically a late marker of disease, most recent studies focus on diastolic parameters as earlier evidence of cardiac abnormalities.[23–25] Indeed, mitral inflow pattern and diastolic tissue velocities from traditional tissue Doppler correlate with disease severity better than ejection fraction.[24,26] In adults with T2D, diastolic dysfunction is associated with development of heart failure.[27]

We have previously reported that cardiac pulmonary wedge pressure was elevated in premenopausal, otherwise healthy women with T2D compared to nondiabetic controls, which suggests diastolic dysfunction early on in the course of diabetes.[28] Data on cardiac function in pediatric T2D are limited to a few studies.[1,7,29–31] Shah et al[1] reported decreased diastolic function in adolescents with T2D and obesity compared to lean controls. Left ventricular hypertrophy, which is common in adolescents with T2D, is a strong independent predictor of CVD.[29] We have previously demonstrated left ventricular hypertrophy in 29% of a smaller cohort of adolescents with T2D,[8] and in 18% to 21% of adolescents in this cohort, depending on definition. Whalley et al also demonstrated functional cardiac abnormalities in adolescents

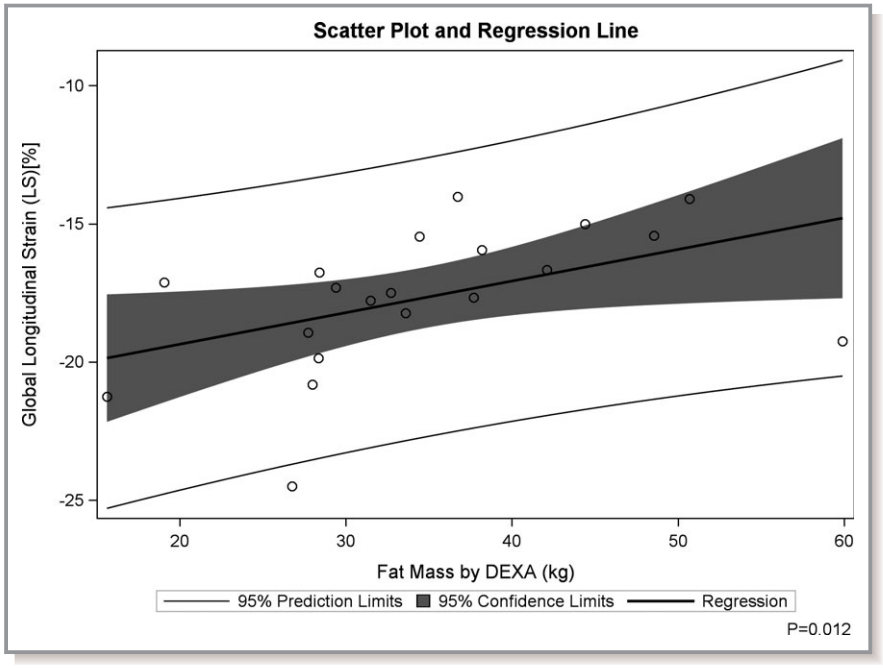

Figure 5. Association between fat mass and global longitudinal strain (LS) in adolescents with type 2 diabetes (T2D). Scatter plot and regression line. Linear regression was employed to model relationship between LS and fat mass in adolescents with T2D. β±SE: 0.11±0.04, *P*=0.01. DEXA indicates dual-energy x-ray absorptiometry.

with T2D, but their study was small and limited to girls with poorly controlled T2D.[29] The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study performed traditional echocardiography on 542 young adults (average age 18 years) and found high/normal LV wall thickness, LV shortening fraction, and left atrial internal dimension, predicted by obesity and elevated blood pressure.[7] However, TODAY did not include nondiabetic control groups, and rather compared their findings with previously published norms. As a consequence, the investigators were unable to determine whether the abnormal findings they observed were related to obesity or physical activity versus diabetes status. In addition, none of the above studies examined associations between cardiac function and adipokines (eg, adiponectin or leptin) or measured insulin sensitivity, and did not include cardiac strain by speckle tracking, or cardiopulmonary fitness.

In this study, we employed speckle tracking (Figures 6 and 7), an echocardiography technique that permits measurement of myocardial systolic deformation, or strain, in multiple directions. Previous studies in adults with heart failure have linked abnormal strain, identified by speckle tracking, with increased morbidity. For example, abnormal strain predicted heart failure in patients with both systolic cardiomyopathy and with heart failure with preserved ejection fraction; 20% of these patients have diabetes.[32,33] In studies of adult diabetic cardiomyopathy, strain has proven to be a more sensitive marker of CVD severity than either ejection fraction or tissue Doppler,[34] and thus may be the earliest marker of systolic dysfunction. Abnormal CS has also been shown to predict incident heart failure in asymptomatic individuals without any known CVD.[35] CS may also be a mediator of CVD, as studies have shown that CS may mediate vascular regulation, atherosclerosis, and remodeling.[36–38]While strain imaging is able to detect subclinical LV systolic dysfunction in adults with T2D,[34,39] it has not been examined in adolescents with T2D. In our cohort, despite relatively short diabetes duration (median 4.6 years) and no overt clinical cardiovascular problems, we found reduced CS in adolescents with T2D compared to lean and obese controls, prior to overt changes in ejection fraction. Thus, our data may support the role of strain imaging as an early, sensitive, and noninvasive marker of cardiac dysfunction in youth.

Assessment of echocardiographic strain patterns in early cardiac dysfunction has revealed that LS precedes CS.[22] In fact, in adults with T2D, the subendocardial fibers, which mediate longitudinal motion, appear to be affected first.[22] Therefore in early, well-controlled diabetes without significant complications, LS is reportedly decreased initially, with a paradoxical increase in CS, preserving overall LV ejection fraction.[39] With a longer duration of diabetes and more comorbidities, CS is reportedly most affected, and may not include abnormalities in LS.[40,41] Alterations in circumferential motion are consistent with dysfunction of midwall fibers and may signify increased damage to deeper layers.[22,40] The strain pattern we observed in adolescents suggests that LS becomes abnormal with adolescent obesity and progresses to

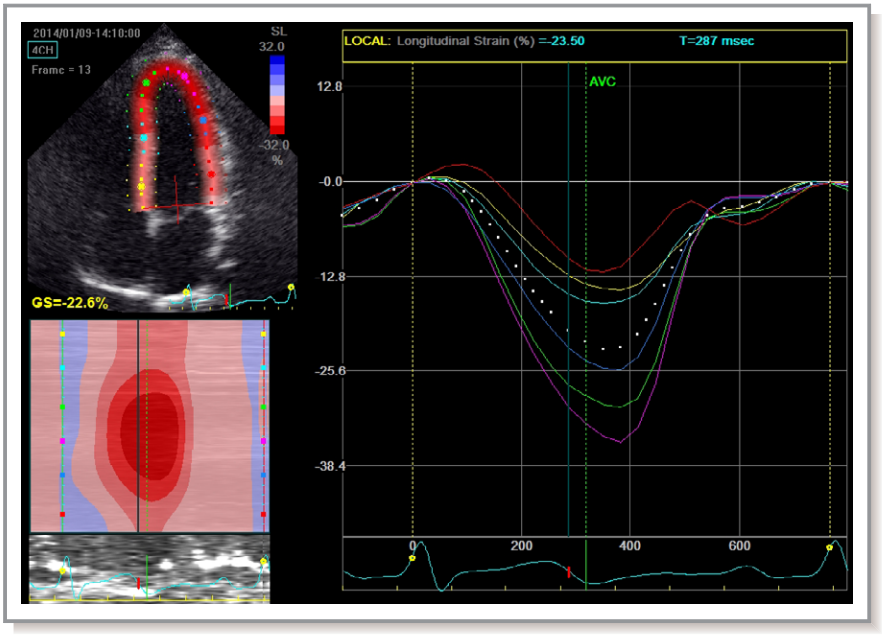

Figure 6. Speckle tracking. Speckle tracking analysis of 4-chamber view of the left ventricle in a patient with type 1 diabetes. Each color of the curve represents a region of the myocardium, with the dotted curve representing global value. This curve represents left ventricular longitudinal global strain.

more significant CS abnormalities when this obesity progresses to T2D. The severity of these abnormalities in youth is of concern, as the strain pattern we observed predicts a high risk for cardiovascular events.[42] In fact, in adults with overt systolic cardiomyopathy, mortality is associated with CS, rather than LS.[33] Observing a change in strain in adolescents with T2D is a major and ominous finding. Similarly, youth with T2D also have concerning evidence of other comorbidities

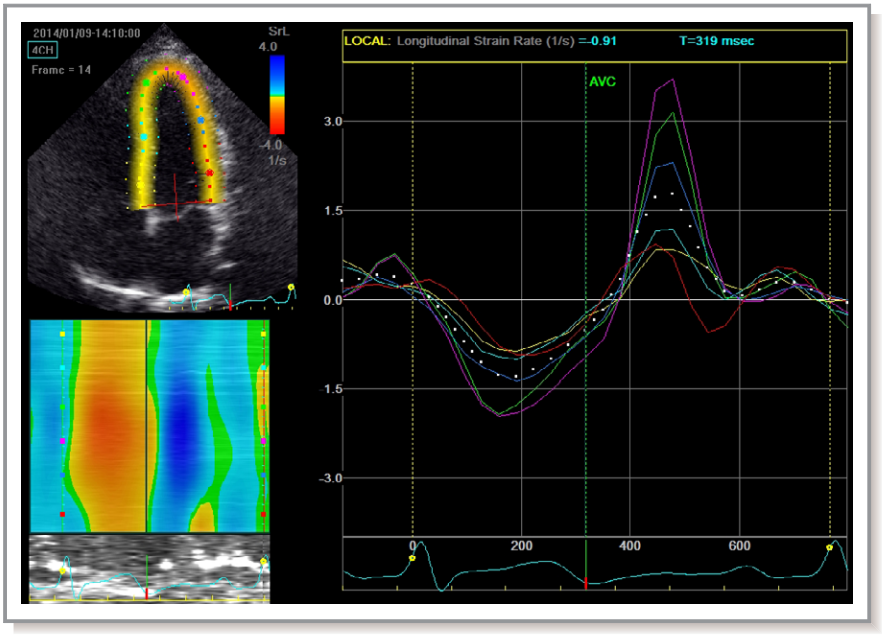

Figure 7. Speckle tracking. Speckle tracking analysis of 4-chamber view of the left ventricle in a patient with type 1 diabetes. Each color of the curve represents a region of the myocardium, with the dotted curve representing global value. This curve represents left ventricular longitudinal global strain rate.

already present at the time of diabetes diagnosis, including significant renal disease, fatty liver disease, and sleep apnea. Moreover, the correlation between strain measures and reduced cardiopulmonary fitness suggests that abnormal strain is already having negative physiological consequences, as fitness is highly correlated with mortality.

We previously demonstrated reduced peak exercise capacity in a smaller cohort of adolescents with T2D, and a strong relationship between cardiopulmonary fitness and insulin sensitivity.[8] Our findings in the present study confirm our initial findings in a larger group, and for the first time we demonstrate relationships between leptin, adiponectin, and peak exercise capacity in adolescents with T2D.

Adiponectin is an adipokine that is reported to be cardioprotective,[10] and studies also suggest that low adiponectin levels may contribute to the development of insulin resistance and inflammation in adults,[43] but data in adolescents are scarce. High plasma adiponectin levels are associated both with a lower risk of myocardial infarction in men[44] and a moderately decreased risk for coronary heart disease in men with T2D.[45] Recent studies also found that adiponectin influences cardiac remodeling and suppresses pathological cardiac growth.[46,47] In response to pressure overload caused by aortic constriction, adiponectin knockout mice demonstrate enhanced concentric cardiac hypertrophy and increased mortality.[46,47] The role of adiponectin in the setting of cardiac hypertrophy may be attributed to the modulation of cardiac intracellular growth signaling, including the AMPK cascade.[48] A major observation from our study was the finding of independent associations between low adiponectin and reduced CS, and low adiponectin and low VO_2peak. These findings potentially suggest an independent protective role of adiponectin in cardiovascular function in adolescents with T2D. Leptin is another cardiotrophic adipokine, and we demonstrated a positive relationship between leptin and LS in adolescents with T2D (ie, the greater the concentration of leptin the worse the strain). Obesity and T2D are associated with elevated leptin concentrations and consequent downregulation of leptin receptors.[11] This leptin resistance has been proposed to be associated with cardiac hypertrophy in diabetic animal models.[11,49] Furthermore, recent data demonstrate a direct effect of leptin on aldosterone secretion, endothelial dysfunction, and cardiac fibrosis,[50] which may explain the relationship between leptin and LS in adolescents with T2D.

Our study has important limitations. To minimize the effect of sample size, we obtained detailed physiological measurements: dual-energy x-ray absorptiometry for fat mass, "gold-standard" fitness testing, and hyperinsulinemic–euglycemic clamp studies; however, we did not have data on 24-hour ambulatory blood pressure measurements. We also controlled pre-study diet and physical activity, included both lean and BMI-similar obese control groups, and chose groups similar in pubertal stage and habitual level of physical activity. The wide CIs of the semipartial R^2 reflect the limited observations with data on both strain and cardiopulmonary fitness. Another limitation to the present study includes the cross-sectional design that prevents determination of causality, and whether the progression of LS to CS, and the associations between strain and cardiopulmonary fitness, adiponectin, and CS hold true longitudinally, and for that reason the data should be viewed as hypothesis generating. Moreover, while our sample size is modest, it is quite representative of the overall population of youth with T2D.[51] No formal a priori power calculations were performed with speckle tracking outcomes for this study, and randomization does not apply because there was no treatment modality. It is also unknown whether the changes we report are reversible; thus, future directions include longitudinal measurements of myocardial strain and exercise performance after interventions such as weight loss, exercise, and improvement in insulin sensitivity and/or glycemic control.

In conclusion, adolescents with T2D demonstrate significant changes in myocardial structure and mechanics that correlate with decreased cardiopulmonary fitness compared to equally obese and to lean sedentary nondiabetic peers. Adolescents with T2D also had significantly lower adiponectin levels than the nondiabetic participants, and low adiponectin was associated with abnormal CS and peak exercise capacity independent of adiposity. These observations may represent the earliest changes of cardiac abnormalities in T2D, and future research should continue to assess cardiac strain to provide important insight into severity and progression of myocardial dysfunction in adolescents with T2D.

Sources of Funding

Support for this study was provided by NCRR K23 RR020038-01, NIH BIRCWH K12 5K12HD057022-04, Adult GCRC NIH Grant #M01-RR00051, Pediatric CTRC NIH Grant #MO1 RR00069, NIH/NCRR Colorado CTSI Grant UL1 RR025780, T32 DK063687, NIH/NCATS Colorado CTSI UL1 TR000154, Center for Women's Health Research, VA Merit, Thrasher Pediatric Research Foundation; Colorado Clinical and Translational Sciences Institute (CCTSI) Co-Mentored Pilot Grant TL1 RR025778, American Heart Association (AHA) 13CRP14120015, American Diabetes Association (ADA) 7-11-CD-08, Juvenile Diabetes Research Foundation (JDRF) Award #11-2010-343, R56 DK088971, and ADA 1-11-JF-23. Drs Nadeau and Bjornstad are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

Drs Bjornstad, Truong, Dorosz, Cree-Green, Pyle, Regensteiner, Reusch, and Nadeau, Ms. Baumgartner and Mr Coe have no conflict of interest to disclose.

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