Relationship of Cardiac Structure and Function to Cardiorespiratory Fitness and Lean Body Mass in Adolescents and Young Adults with Type 2 Diabetes

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Objective To investigate the relationships of cardiac structure and function with body composition and cardiorespiratory fitness (CRF) among adolescents with type 2 diabetes in the Treatment Options for Type 2 Diabetes in Adolescents and Youth study.

Study design Cross-sectional evaluation of 233 participants (median age 18.3 [min-max 12.4-24.2] years, 63% females, median hemoglobin A1c 6.8%) who had echocardiography measurements of left ventricular (LV) mass, ejection fraction, left atrial dimensions, LV diastolic function (early transmitral flow velocity to early mitral annular velocity ratio from tissue Doppler imaging), and right ventricular function (tricuspid annular plane systolic excursion [TAPSE]) and body composition (dual-energy x-ray absorptiometry) and CRF (cycle ergometry determination of physical work capacity at heart rate of 170 beats per minute).

Results LV mass correlated positively with CRF ($r = 0.5$, $P < .0001$), lean body mass (LBM) ($r = 0.7$, $P < .0001$), and fat mass (FM) ($r = 0.2$, $P = .00047$); LV ejection fraction did not. Early transmitral flow velocity to early mitral annular velocity was positively related to FM ($r = 0.14$, $P = .03$) and % body fat ($r = 0.18$, $P = .007$), and left atrial internal diameter correlated with FM ($r = 0.4$, $P < .0001$), LBM ($r = 0.3$, $P < .001$), and CRF ($r = 0.2$, $P = .0033$). TAPSE weakly correlated with CRF ($r = 0.2$, $P = .0014$) and LBM ($r = 0.13$, $P < .05$) but not with FM. In multivariable regression analyses, LBM ($\beta = 2.13$, $P < .0001$) and CRF ($\beta = 0.023$, $P = .008$) were related to LV mass independent of race, sex, age, hemoglobin A1c, hypertension, smoking, and diabetes medications. CRF ($\beta = 0.0002$, $P = .0187$) and hemoglobin A1c ($\beta = -0.022$, $P = .0142$) were associated with TAPSE.

Conclusions In youth with type 2 diabetes, LV size is related to physical fitness. LV ejection fraction is within normal limits. LV diastolic function is inversely related to FM. Greater fitness may counteract adverse effects of poor glycemic control on right ventricular function. *(J Pediatr 2016;177:159-66).*

Trial registration ClinicalTrials.gov: NCT00081328

The findings from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY)[1] indicated a high rate of dyslipidemia, microalbuminuria, and hypertension in youth with type 2 diabetes (T2D) at baseline, with progression of these cardiovascular risk factors over time.[2,3] Almost one-third of participants met criteria for the diagnosis of hypertension during an average period of 3.9 years of follow-up. Echocardiography performed in the last year of the study at a median of 4.5 years from diagnosis of T2D, and at an average age of 18 years, demonstrated high left ventricular (LV) mass associated with greater body mass index (BMI), greater blood pressure (BP), male sex, and African

BMI	Body mass index	M + L	Metformin plus an intensive lifestyle program
BP	Blood pressure	M + R	Metformin plus rosiglitazone
CRF	Cardiorespiratory fitness	PWC-170	Physical work capacity at a heart rate of 170 beats per minute
DXA	Dual-energy x-ray absorptiometry	RV	Right ventricle/ventricular
FM	Fat mass	TAPSE	Tricuspid annular plane systolic excursion
E/Em	Early transmitral flow velocity to early mitral annular velocity	TODAY	Treatment Options for type 2 Diabetes in Adolescents and Youth
HbA1c	Hemoglobin A1c	2D	2-dimensional
HR	Heart rate	T2D	Type 2 diabetes
LA	Left atrium/atrial		
LBM	Lean body mass		
LV	Left ventricle/ventricular		
M	Metformin alone		

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American race/ethnicity.[4] Physical activity measurements and physical fitness testing highlighted the sedentary nature and low overall fitness levels of this group of adolescents in comparison with data on obese youth from the National Health and Nutrition Examination Survey and other clinical studies.[5]

We sought to better understand echocardiographic determinants of cardiac structure and function and their relationship to fitness in T2D youth from TODAY. In healthy children, lean body mass (LBM) is a stronger determinant of LV mass than fat mass (FM).[6] In a group of lean and overweight 13-year-old children, a positive correlation was found between LV mass index and both lean mass and FM.[7] Exercise training at high intensity increases LV mass, but data on the relationship between fitness and heart size in obese youth with T2D are lacking.

We hypothesized that body composition and cardiorespiratory fitness (CRF) are associated with cardiac structure and function in obese adolescents with T2D. Therefore, we evaluated the relationships of measures of LV structure, LV systolic and diastolic function, as well as right ventricular (RV) function, with body composition and CRF in TODAY participants, while adjusting for diabetes treatment, glycemic control, and cardiovascular disease risk factors, including race, sex, BP, and smoking.

Methods

The TODAY study population consisted of 699 youth ≥85th percentile for BMI, aged 10-17 years, diagnosed with T2D ≤2 years, and negative for pancreatic autoantibodies (ClinicalTrials.gov: NCT00081328). Participants were randomized to 1 of 3 treatment arms: metformin alone (M), metformin plus rosiglitazone (M + R), and metformin plus an intensive lifestyle program (M + L). The primary outcome was defined as failure to maintain glycemic control (hemoglobin A1c [HbA1c] < 8%) on randomized treatment. At this point, insulin therapy was initiated and rosiglitazone was discontinued. Treatment with M + R was superior to M in preventing the need for chronic insulin therapy; M + L was not different from M or M + R.[1] The protocol was approved by the Institutional Review Boards for the Protection of Human Subjects of each participating institution. All participants provided informed consent/assent according to local guidelines.

Cardiovascular Risk Assessment and Treatment

BMI was calculated from height and weight (weight in kilograms divided by height in m^2). BP was taken with a CAS 740 monitor (CAS Medical Systems Inc, Branford, Connecticut) with standardized oscillometric cuff sizes. Participants with hypertension (defined as BP ≥95th percentile for age, sex, and height or ≥ 130/80 mm Hg, whichever was lower) received dietary counseling regarding a low-salt diet. If values remained elevated, study-supplied lisinopril was initiated and titrated to achieve target goals according to a predetermined algorithm.[2]

Echocardiography

Echocardiograms were performed in the last year of the study in 542 participants (of the 699 total randomized subjects) at a median of ~4.5 years from diagnosis of T2D at an average age of 18 years, 2-6 years after randomization in TODAY as previously reported.[4] The current cross-sectional analysis presents data for those participants who had body composition and CRF measured within 6 months of the echocardiogram (n = 233), with a median duration between the echocardiogram measures and body composition/physical work capacity at a heart rate (HR) of 170 beats per minute (PWC-170) of 56 (0-96) days. To describe in brief, M-mode and 2-dimensional (2D) measurements of LV and left atrial (LA) dimensions were performed and interpreted according to the guidelines of the American Society of Echocardiography at a core laboratory by the use of strict quality control procedures similar to those of the Coronary Artery Risk Development in Young Adults (ie, CARDIA) study.[8,9] LV mass (g) = 0.80 × 1.04 ([VSTd + LVIDd + PWTd]^3 − [LVIDd]^3) + 0.6; all measurements in diastole, LV ejection fraction ([LV end diastolic volume − LV end systolic volume]/LV end diastolic volume; volumes calculated by the Simpson rule), and LV relative wall thickness ([LV posterior wall thickness in diastole × 2]/LV end diastolic diameter) were calculated from 2D directed M-mode images of the LV according to the recommendations of the American Society of Echocardiography.[9] Tissue Doppler imaging analysis of the lateral mitral valve annulus during diastole was performed, and values from sequential beats were averaged; diastolic function was defined as the ratio of early transmitral flow velocity to early mitral annular velocity [E/Em].[10] RV function was assessed by tricuspid annular plane systolic excursion (TAPSE).[4]

Body Composition

Dual-energy x-ray absorptiometry (DXA) scans were performed at each clinical center according to study-specific guidelines for subject positioning standardized across the different DXA systems, as reported previously.[11]

Cardiorespiratory Fitness

CRF was assessed by a submaximal test with a cycle ergometry (818E bike; Quinton Monark, Seattle, Washington). Observed workload and HR were recorded up to 4 times at 60 rpm at 3-minute intervals. Workload at a HR of 170 beats per minute was estimated according to a best-fit equation. PWC-170 was calculated.[5] Previous studies show that the PWC-170 is a valid indicator for predicting maximal oxygen uptake, the reference measure for aerobic fitness.[12,13]

Statistical Analyses

Descriptive statistics presented are percent or median, minimum, and maximum. Analysis of variance was used to compare participant characteristics across the 3 treatment groups. Correlation analyses were used to evaluate bivariate relationships. Regression models were used to assess relationships among echocardiography outcomes and independent predictors, including age, sex, race-ethnicity, HbA1c, CRF, body composition measures, study treatment group, time on assigned treatment, and cardiovascular risk factors (diagnosis of hypertension or BP medication use, smoking). We compared unindexed LV mass to body composition measures to be able

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