Cardiac Biomarkers in Youth with Type 2 Diabetes Mellitus: Results from the TODAY Study

Samuel S. Gidding, MD[1], Fida Bacha, MD[2], Petter Bjornstad, MD[3], Lorraine E. Levitt Katz, MD[4], Lynne L. Levitsky, MD[5], Jane Lynch, MD[6], Jeanie B. Tryggestad, MD[7], Ruth S. Weinstock, MD PhD[8], Laure El ghormli, MS[9], and Joao A. C. Lima, MD[10], for the TODAY Study Group*

Objectives To examine cardiac biomarkers over time in youth-onset type 2 diabetes, and relate serum concentrations to cardiovascular disease risk factors, and left ventricular structure and function.

Study design TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) was a multicenter randomized trial of 3 treatments including 521 participants with type 2 diabetes, aged 10-17 years, and with 2-6 years of follow-up. Participants were 36% male, obese, and ethnically diverse. Annual serum concentrations of brain natriuretic peptide, troponin, tumor necrosis factor (TNF)-α, receptors 1 and 2 were related to blood pressure, body mass index, hemoglobin A1c, and left ventricular ejection fraction, diastolic function, relative wall thickness, and mass.

Results Elevated concentrations of brain natriuretic peptide (≥100 pg/mL), TNF-α (≥5.6 pg/mL) and troponin (≥0.01 ng/mL), were present in 17.8%, 18.3%, and 34.2% of the cohort, respectively, at baseline, and in 15.4%, 17.1%, and 31.1% at the end of the study, with wide variability over time, without persistence in individuals or clear relationship to glycemia or cardiovascular structure/function. TNF receptors concentrations were increased at baseline and not significantly different from end-of-study concentrations. Adverse echocardiographic measures were more likely in the highest TNF receptor tertile (all $P < .05$): higher left ventricular mass (39.3 ± 9.0 g/m$^{2.7}$), left atrial internal dimension (3.7 ± 0.4 cm) and E/Em ratio, a measure of diastolic dysfunction (6.2 ± 1.9). After adjustment for body mass index, these relationships were no longer significant.

Conclusions Elevated serum concentrations of cardiac biomarkers were common in youth with type 2 diabetes, but their clinical significance is unclear and will require further long-term study. *(J Pediatr 2018;192:86-92).*

Trial registration ClinicalTrials.gov NCT00081328.

Youth with type 2 diabetes (T2D) are at high lifetime risk for cardiovascular disease (CVD).[1] The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study, a randomized clinical trial of 3 glycemic control treatments in newly diagnosed youth with T2D, reported that CVD risk worsened over 2-6 years.[2-4] Adverse profiles of inflammatory markers including high-sensitivity C-reactive protein, interleukin-6, plasminogen activator inhibitor-1, and homocysteine were described, and these did not improve.[4] Cross-sectional echocardiographic studies of adolescents with T2D demonstrate high concentrations of left ventricular (LV) mass, high measures of relative wall thickness to cavity dimensions, high left atrial (LA) size, and possible diastolic dysfunction.[5-7] In adults with T2D, measurement of cardiovascular and inflammatory biomarkers adds to CVD risk stratification.[8,9]

BMI	Body mass index
BNP	brain natriuretic peptide*
BP	blood pressure*
CVD	cardiovascular disease*
HbA1c	Hemoglobin A1c
LA	left atrial*
LV	left ventricular*
T2D	Type 2 diabetes*
TNF-R1	tumor necrosis receptor 1*
TNF-R2	tumor necrosis receptor 2*
TNF-α	tumor necrosis factor alpha*
TODAY	Treatment Options for type 2 Diabetes in Adolescents and Youth*
Troponin	high-sensitivity troponin*

From the [1]Nemours Cardiac Center, Alfred I. DuPont Hospital for Children, Wilmington, DE; [2]Texas Children's Hospital, Baylor College of Medicine, Houston, TX; [3]University of Colorado Anschutz Medical Campus and Children's Hospital Colorado, Aurora, CO; [4]Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [5]Massachusetts General Hospital, Boston, MA; [6]University of Texas Health Science Center San Antonio, San Antonio, TX; [7]University of Oklahoma Health Sciences Center, Oklahoma, OK; [8]Department of Medicine, SUNY Upstate Medical University, Syracuse, NY; [9]George Washington University Biostatistics Center, Rockville; and [10]Johns Hopkins Hospital, Johns Hopkins University, Baltimore, MD

*List of additional members of the TODAY Study Group is available at www.jpeds.com (**Appendix**).

Funded by the National Institute of Diabetes and Digestive and Kidney Disease and National Institutes of Health (U01-DK61212, U01-DK61230, U01-DK61239, U01-DK61242, U01-DK61254, and T32-DK063687), the National Center for Research Resources General Clinical Research Centers Program (M01-RR00036 [Washington University School of Medicine], M01-RR00043-45 [Children's Hospital Los Angeles], M01-RR00069 [University of Colorado Denver], M01-RR00084 [Children's Hospital of Pittsburgh], M01-RR01066 [Massachusetts General Hospital], M01-RR00125 [Yale University], and M01-RR14467 [University of Oklahoma Health Sciences Center], and by the NCRR Clinical and Translational Science Awards (UL1-RR024134 [Children's Hospital of Philadelphia], UL1-RR024139 [Yale University], UL1-RR024153 [Children's Hospital of Pittsburgh], UL1-RR024989 [Case Western Reserve University], UL1-RR024992 [Washington University in St Louis], UL1-RR025758 [Massachusetts General Hospital], and UL1-RR025780 [University of Colorado Denver]). R.S.W. has participated in multicenter clinical trials sponsored by Medtronic Minimed Inc, Diasome Pharmaceuticals Inc, Calibra Medical Inc, and Mylan GmbH Inc. L.L.L is a consultant for Eli Lilly. The other authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2017.09.012

Cardiac biomarkers, including brain natriuretic peptide (BNP), and high-sensitivity troponin (troponin), have been associated with adverse cardiac structure or function changes in adults with T2D.[10] Tumor necrosis factor alpha (TNF-α), an inflammatory marker, is also associated with the presence of T2D. A study of Asian Indians with youth-onset T2D showed this relationship in obese and nonobese patients. Laboratory studies have implicated TNF in regulation of myocardial cell function.[11] Two large cohort studies of T2D suggest TNF receptor 1 (R1) and TNF receptor 2 (R2) predict future kidney disease, CVD, and total mortality.[12-14]

There are limited longitudinal data on cardiac biomarkers in children and adolescents, including at-risk populations, such as those with youth-onset T2D. The purpose of this report is to determine the (1) natural history of BNP, troponin, TNF-α, TNF-R1, and TNF-R2 over time in youth with T2D, (2) relationship of these cardiac biomarkers to CVD risk factors and hemoglobin A1c (HbA1c), and (3) relationships of these biomarkers to echocardiographic measures of LV structure and function. The finding of worsening biomarker profiles over time or a relationship to cardiac structure and function would suggest subclinical diabetic cardiomyopathy in this young population.

Methods

The TODAY study was a multicenter, randomized clinical trial (ClinicalTrials.gov: NCT00081328) of 3 treatments for T2D in youth: metformin alone, metformin and intensive lifestyle, and metformin and rosiglitazone.[2] Eligibility included age 10-17 years, T2D duration <2 years, body mass index (BMI) ≥85th percentile, negative pancreatic autoantibodies, fasting C-peptide >0.6 ng/mL, and an adult caregiver willing to support study participation. Subjects were excluded for refractory hypertension or creatinine clearance <70 mL/min. The primary objective was to compare treatment arms on time with treatment failure (HbA1c ≥8% [≥64 mmol/mol] for 6 months or sustained metabolic decompensation requiring insulin). One-half of the cohort reached the primary endpoint and results demonstrated that adding rosiglitazone to metformin was associated with more durable glycemic control.[2]

The protocol was approved by an External Evaluation Committee convened by the National Institute of Diabetes and Digestive and Kidney Disease and by the Institutional Review Boards for the Protection of Human Subjects of each participating institution. All participants provided informed consent and minor children confirmed assent according to local guidelines. A Data and Safety Monitoring Board convened by the National Institute of Diabetes and Digestive and Kidney Disease reviewed progress, safety, and interim analyses throughout the study.

Assessments were obtained at months 0, 12, 24, 36, 48, and 60, as previously described.[5] These included measurements of height, weight, blood pressure (BP) and laboratory testing. Hypertension was defined as BP ≥130/80 mm Hg or ≥95th percentile for age, sex, and height[2,3] and was treated with an angiotensin-converting enzyme inhibitor. Additional medications were added as needed.

HbA1c and cardiac biomarkers measurements were performed at the Northwest Lipid Research Laboratory, University of Washington, Seattle, Washington. Blood samples were collected yearly in EDTA tubes, centrifuged, frozen immediately upon sample processing and stored in 24/7 monitored -80°C freezers. Analyses were performed immediately after samples were thawed. Serum BNP concentrations were measured by ELISA (Raybio Tech Inc, Norcross, Georgia), with intra-assay and interassay coefficient of variations of 10% and 12%, respectively. Troponin, TNF-α, TNF-R1, and TNF-R2 assays were performed using a Multiplex protein arrays system using magnetic beads (R&D systems, Minneapolis, Minneapolis, and EMD Millipore Inc, Gibbstown, NJ). Intra-assay and interassay CVs were 6.5% and 11% for troponin respectively, 7.2% and 12.5% for TNF-α, 3.0% and 3.3% for TNF-R1, and 2.3% and 2.8% for TNF-R2.

Two-dimensional guided echocardiograms were performed on participants during the last year of the study according to American Society of Echocardiography standards by certified technicians as previously described.[5,15] Images were transferred to a central reading laboratory where MMode measurements of LV wall thicknesses in diastole, LV dimensions in systole and diastole, and dimension were performed; tissue Doppler imaging was used to measure diastolic function. The tricuspid annular plane systolic excursion was measured to assess right ventricular function. Study quality was graded and only studies of fair or better quality were included. Quality control procedures showed a coefficient of variation for repeat measurement of all parameters of <10%.

Statistical Analyses

Statistical analyses of the biomarker data were performed on TODAY participants (n = 521) with at least 2 annual assessments including baseline. TODAY participants completed an average of 4 annual examinations (SD, 1; min-max, 2-6). Abnormal risk categories, based on current consensus, were applied to 3 of the 5 cardiac biomarkers (BNP, ≥100 pg/mL[16]; troponin, ≥0.01 pg/mL[17]; TNF-α, ≥5.6 pg/mL[18]). A cutoff of ≥0.04 pg/mL[19] for troponin was also examined.

Participants were grouped into 3 categories for BNP, troponin, and TNF-α: (A) always normal (values less than the cutoff at all annual visits), (B) intermittent (at least 1 visit with a value ≥l to the cutoff), and C) always high (values greater than or equal to the cutoff at all annual visits). TNF-R1 and TNF-R2 were normally distributed and analyzed as continuous variables or by tertiles. Generalized linear models were used to assess the relationships between treatment group, race-ethnicity, T2D parameters, risk factors, or echocardiography parameters with the cardiac biomarkers concentrations at (a) baseline, (b) end of the study, and (c) grouped into categories (always abnormal, intermittent, always normal). Models evaluating longitudinal data accounted for the multiple observations per participant as appropriate. Analyses included all data available up to as many as 6 annual visit time points (range, 24-60 months). Sensitivity analyses were conducted on those with a minimum of 4 visits (n = 340) to ensure reported results were not biased by those with fewer visits.