Lipid Profiles, Inflammatory Markers, and Insulin Therapy in Youth with Type 2 Diabetes

Lorraine E. Levitt Katz, MD[1,*], Fida Bacha, MD[2,*], Samuel S. Gidding, MD[3], Ruth S. Weinstock, MD, PhD[4], Laure El ghormli, MS[5], Ingrid Libman, MD, PhD[6], Kristen J. Nadeau, MD[7], Kristin Porter, RN[6], and Santica Marcovina, PhD[8], for the TODAY Study Group[†]

Objectives Data regarding atherogenic dyslipidemia and the inflammation profile in youth with type 2 diabetes is limited and the effect of insulin therapy on these variables has not previously been studied in youth. We determined the impact of insulin therapy on lipid and inflammatory markers in youth with poorly controlled type 2 diabetes.

Study design In the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) multicenter trial, 285 participants failed to sustain glycemic control on randomized treatment (primary outcome, glycated hemoglobin A1c [HbA1c] at ≥8% for 6 months); 363 maintained glycemic control (never reached primary outcome). Statins were used for a low-density lipoprotein cholesterol of ≥130 mg/dL. Upon reaching the primary outcome, insulin was started. Changes in lipids and inflammatory markers (slopes over time) were examined.

Results Progression of dyslipidemia was related to glycemic control. In those with the primary outcome, insulin therapy impacted HbA1c modestly, and dampened the increase in total cholesterol, low-density lipoprotein cholesterol, and total apolipoprotein B, although statin use increased from 8.6% to 22% year after the primary outcome. The increase in triglycerides and plasma nonesterified fatty acids stabilized after insulin was started, independent of HbA1c. There was an increase in high-sensitivity C-reactive protein that continued after insulin initiation, related to HbA1c and percent overweight.

Conclusions Worsening dyslipidemia and inflammation over time raise concern regarding premature development of atherosclerosis in youth with type 2 diabetes. Insulin therapy has a limited benefit in the absence of glycemic control. Strategies to achieve better glycemic control are needed. *(J Pediatr 2017;■■:■■-■■).*

Trial registration ClinicalTrials.gov: NCT00081328.

The increasing prevalence of type 2 diabetes in youth is expected to contribute to an increase in diabetes-related complications, including cardiovascular disease.[1,2] This concern is heightened by the high prevalence of cardiovascular risk factors and markers of cardiovascular end organ injury in this population.[3] The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) trial was a multicenter, randomized clinical trial (ClinicalTrials.gov: NCT00081328) designed to compare the effect of 3 treatment regimens to maintain glycemic control in youth with recent-onset type 2 diabetes. The TODAY cohort provides a unique opportunity to examine the effects of insulin therapy in youth with type 2 diabetes with poor glycemic control on metformin (rosiglitazone was stopped upon insulin initiation).

apoB	Apolipoprotein B
BMI	Body mass index
HbA1c	Glycated hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
hs-CRP	High-sensitivity C-reactive protein
IL-6	Interleukin-6
LDL-C	Low-density lipoprotein-C
NEFA	Plasma nonesterified fatty acids
PAI-1	Plasminogen activator inhibitor-1
TODAY	Treatment Options for type 2 Diabetes in Adolescents and Youth
VA CSDM	Veterans Affairs Cooperative Study in type II Diabetes Mellitus

From the [1]Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [2]Texas Children's Hospital, Baylor College of Medicine, Houston, TX; [3]Nemours Cardiac Center, Alfred I. DuPont Hospital for Children, Wilmington, DE; [4]SUNY Upstate Medical University, Department of Medicine, Syracuse, NY; [5]George Washington University Biostatistics Center, Rockville, MD; [6]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA; [7]University of Colorado Anschutz Medical Campus, Aurora, CO; and [8]Northwest Lipid Research Laboratories, University of Washington, Seattle, WA

*Contributed equally.

†List of additional members of the TODAY study group is available at www.jpeds.com (**Appendix**).

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In light of the known accordance between glycemic control with dyslipidemia and markers of inflammation, we set out to explore the impact of reaching the primary outcome with subsequent initiation of insulin on these variables.

The objective of the current study was to determine the impact of insulin therapy on lipid profiles and inflammatory markers in the TODAY participants who reached primary outcome. We hypothesized that insulin therapy would ameliorate lipid abnormalities and chronic inflammation in obese youth with type 2 diabetes, related to improved glycemic control.

Methods

Details regarding the TODAY study design and methods have been reported.[4,5] In brief, 699 youth 10-17 years of age were enrolled between July 2004 and February 2009. Participants had type 2 diabetes of <2 years' duration using criteria of the American Diabetes Association, a body mass index (BMI) ≥85th percentile for age and sex, and negative pancreatic autoantibodies. Patients with refractory hyperlipidemia (n = 2)—total cholesterol >300 mg/dL or low-density lipoprotein cholesterol (LDL-C) of >190 mg/dL or triglycerides >800 mg/dL, despite appropriate medical therapy, were excluded from participation in the study. After randomization, participants were seen every 2 months in the first year and quarterly thereafter. Glycated hemoglobin A1c (HbA1c) was assessed at each visit and other laboratory measures including fasting lipid and inflammatory markers were determined at baseline, 6 months, and annually. The TODAY protocol was approved by the institutional review boards at each participating institution. Parents of children and adolescents provided written informed consent; children and adolescents provided assent.

When participants reached the primary outcome, metformin was continued, rosiglitazone was discontinued in the metformin plus rosiglitazone group, and insulin was added. After the initiation of insulin therapy, participants and clinicians remained masked to the original treatment assignment, but were unmasked to HbA1c. Initial insulin treatment was 0.2 U/kg glargine insulin each evening and was increased up to 1.0 U/kg/d (maximum 100 U) until fasting blood glucose levels reached 70-150 mg/dL.

Lipid-lowering medications, primarily atorvastatin, were initiated for persistent LDL-C levels of ≥130 mg/dL or triglyceride levels of 300-599 mg/dL after 6 months of nutrition and diabetes management per algorithm.[4] If triglycerides were ≥600 mg/dL, fibrate therapy could be initiated at the discretion of the physician, in addition to invigorating measures to achieve glycemic control, given the known relationships between hypertriglyceridemia and hyperglycemia.

Of the 699 TODAY participants, 34 of the 319 who reached the primary outcome were excluded from the preset analysis (12 had ≥1 full-term/preterm pregnancies, 1 required multiple episodes of temporary insulin treatment, and 21 reached primary outcome but never received insulin, that is, they reached the primary outcome right before the end of the study or were lost to follow-up after reaching the primary outcome). Comparison of these 21 excluded participants with the 285 included in the sample showed that those lost to follow-up were more likely to be male (13 of 21 [62%] were male vs 37% among the 285; $P = .0250$), but were not found different with respect to age at baseline, race/ethnicity, baseline Tanner stage, socioeconomic status (highest level of household education and income), duration of diabetes, baseline BMI, or baseline HbA1c. There were 363 TODAY participants who maintained glycemic control during the study and never started insulin.

All samples were shipped on dry ice to the Northwest Lipid Research Laboratory, University of Washington, Seattle, Washington. The methods and analytical performance for determination of HbA1c, lipids, separation of LDL-C fractions, apolipoprotein B (apoB) in plasma and in LDL-C fractions, plasma nonesterified fatty acids (NEFA), high-sensitivity C-reactive protein (hs-CRP), plasminogen activator inhibitor-1 (PAI-1), and homocysteine were described previously.[4] Analysis of interleukin-6 (IL-6) was performed using the human high-sensitivity magnetic beads-based method (EMD Millipore Inc, Billerica, Massachusetts). The assay sensitivity was 0.18 pg/mL. The intra-assay and interassay coefficients of variation were 7% and 8%, respectively, for the low-quality control samples and 6.8% and 8.4%, respectively, for the high-quality control.

Height (cm) and weight (kg) were measured as previously described[4] and used to calculate BMI in kg/m^2. Percent overweight, a weight-related metric measure now widely used for describing and tracking heavier children,[6] was defined as BMI minus BMI at the 50th percentile for age and sex based on Centers for Disease Control and Prevention growth charts, divided by BMI at the 50th percentile, times 100.

Statistical Analyses

Data are presented as mean and SD or percent. We used χ^2 tests or t tests to compare demographic and laboratory characteristics at time 0 between the TODAY participants who reached primary outcome and those who never reached it. For the group who reached the primary outcome, time 0 was defined as the date long-term insulin therapy was started; for those who did not reach the primary outcome, time 0 was defined as the midpoint in the study, resulting in equal duration in the study in the 2 groups.

Piecewise random coefficient modeling was used,[7,8] which allows for comparison of trends (slopes reflecting a change in outcome over time) corresponding with time before and time after a defined time 0. This method is appropriate for repeated measures data collected at uneven time intervals and allows for covariate adjustment.

SAS PROC MIXED (SAS version 9.3, SAS Institute Inc, Cary, North Carolina) was used to fit the piecewise random coefficient model. The model consisted of regressing each lipid or inflammatory marker outcome variable as a function of time relative to time 0, thereby obtaining 1 intercept (at time 0) and 2 slopes (one before and one after time 0) for each participant. The 2 times (relative to time 0) were included in the model as random effects. Intraclass correlations coefficients were calculated for each random effects model. The intraclass correlations coefficients obtained ranged from 55% to 71% for the

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