Insulin Sensitivity and Diabetic Kidney Disease in Children and Adolescents With Type 2 Diabetes: An Observational Analysis of Data From the TODAY Clinical Trial

Petter Bjornstad, Edward Nehus, Laure El ghormli, Fida Bacha, Ingrid M. Libman, Siripoom McKay, Steven M. Willi, Lori Laffel, Silva Arslanian, and Kristen J. Nadeau, on behalf of the TODAY Study Group

Background: Diabetic kidney disease is a major cause of premature mortality in type 2 diabetes mellitus (T2DM). Worsening insulin sensitivity independent of glycemic control may contribute to the development of diabetic kidney disease. We investigated the longitudinal association of insulin sensitivity with hyperfiltration and increased albumin excretion in adolescents with T2DM.

Study Design: Observational prospective cohort study.

Setting & Participants: 532 TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) participants aged 12 to 17 years with T2DM duration less than 2 years at baseline. The TODAY Study was a multicenter randomized clinical trial that examined the efficacy of 3 treatment regimens (metformin monotherapy, metformin plus rosiglitazone, or metformin plus an intensive lifestyle intervention program) to achieve durable glycemic control.

Predictors: Natural log–transformed estimated insulin sensitivity (reciprocal of fasting insulin), hemoglobin A_{1c} concentration, age, race-ethnicity, treatment group, body mass index, loss of glycemic control, and hypertension.

Outcomes: Hyperfiltration was defined as 99th percentile or higher of estimated glomerular filtration rate (≥140 mL/min/1.73 m^2) when referenced to healthy adolescents (NHANES 1999-2002) and albumin-creatinine ratio ≥ 30 μg/mg at 3 consecutive annual visits.

Results: Hyperfiltration was observed in 7.0% of participants at baseline and in 13.3% by 5 years, with a cumulative incidence of 5.0% over 5 years. The prevalence of increased albumin excretion was 6% at baseline and 18% by 5 years, with a cumulative incidence of 13.4%. There was an 8% increase in risk for hyperfiltration per 10% lower estimated insulin sensitivity in unadjusted and adjusted models ($P = 0.01$). Increased albumin excretion was associated with hemoglobin A_{1c} concentration, but not estimated insulin sensitivity.

Limitations: Longer follow-up is needed to capture the transition from hyperfiltration to rapid glomerular filtration rate decline in youth-onset T2DM.

Conclusions: Lower estimated insulin sensitivity was associated with risk for hyperfiltration over time, whereas increased albumin excretion was associated with hyperglycemia in youth-onset T2DM.

Complete author and article information (including a list of the members of the TODAY Study Group) provided before references.

Correspondence to L. El ghormli (elghorml@bsc.gwu.edu)

Am J Kidney Dis. 71(1): 65-74. Published online November 20, 2017.

doi: 10.1053/j.ajkd.2017.07.015

Diabetic kidney disease remains the leading cause of end-stage renal disease.[1] Early diabetic kidney disease, including hyperfiltration and increased albumin excretion, is common in youth with type 2 diabetes mellitus (T2DM) and progresses at an alarming rate. Prevalences of 24% for hyperfiltration and 34% for increased albumin excretion have been reported in a small cohort of 46 adolescents with T2DM.[2] We previously examined longitudinal data from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, showing that the prevalence of increased albumin excretion increased from 6.3% of participants at baseline to 16.6% by the end of the study period.[3] However, at the time of that publication, average follow-up was only 3.9 years, and laboratory data needed to assess hyperfiltration were not available.

Youth-onset T2DM appears to carry a particularly high risk for progressive diabetic kidney disease, significantly greater than in youth-onset type 1 diabetes or adult-onset T2DM of similar disease duration.[3-10] The early stages of diabetic kidney disease are clinically silent for many years, yet renal parenchymal damage progresses during this time.[11] Hyperfiltration is an early indicator of diabetic kidney disease, often preceding increased albumin excretion and kidney function decline.[12,13] Therefore, identification of clinical phenotypes that are associated with hyperfiltration and predictive of diabetic kidney disease progression is needed to improve outcomes in adolescents with T2DM. Specifically, reduced insulin sensitivity is associated with the development of future kidney disease in adults with and without T2DM.[14,15] Although the mechanisms underlying the relationship between reduced insulin sensitivity and diabetic kidney disease remain unclear, experimental evidence suggests that the energy profile of T2DM cannot accommodate the renal hypermetabolism of diabetic kidney disease.[16-18] Associations between insulin resistance and hyperfiltration have been reported in a small cross-sectional cohort of adolescents

with T2DM,[2] but data for hyperfiltration are lacking in larger cohorts, as are longitudinal hyperfiltration data in adolescents with T2DM. Cross-sectional relationships between insulin resistance and increased albumin excretion were previously reported in adolescents with T2DM in the SEARCH for Diabetes in Youth Study,[19] but longitudinal data for these relationships are also lacking. To our knowledge, there are no longitudinal data for the relationship between insulin sensitivity and hyperfiltration or increased albumin excretion in adolescents with T2DM.

Our aim was to add to our previous work by describing the prevalence and incidence of hyperfiltration (defined as estimated glomerular filtration rate [eGFR] ≥ 99th percentile for healthy controls) in the TODAY study of youth-onset T2DM at baseline and over 5 years, as well as extending the albumin excretion data previously reported out to 5 years. Moreover, we sought to investigate the longitudinal relationship between estimated insulin sensitivity and renal outcomes during the 5 years of study. Considering our previous cross-sectional data, we hypothesized that lower estimated insulin sensitivity in adolescents with T2DM would be associated with diabetic kidney disease, reflected by increased risk for hyperfiltration and increased albumin excretion.

Methods

Study Population and Design

The TODAY study (ClinicalTrials.gov identifier NCT00081328) was a multicenter randomized clinical trial designed to evaluate 3 treatment therapies in children and adolescents with T2DM. Beginning in July 2004 and ending in February 2009, a total of 699 participants were randomly assigned to metformin monotherapy, metformin plus rosiglitazone, or metformin plus an intensive lifestyle intervention program (materials developed and used for the TODAY standard diabetes education program and the intensive lifestyle intervention program are available to the public at https://today.bsc.gwu.edu). Eligibility criteria included youth 10 to 17 years of age with T2DM according to American Diabetes Association criteria with diabetes duration less than 2 years, body mass index (BMI) higher than the 85th percentile, negative testing for diabetes-associated autoantibodies, fasting C-peptide concentration > 0.6 ng/mL, and an adult caregiver willing to support study participation. Participants were excluded for refractory hypertension, defined as blood pressure ≥ 150/95 mm Hg despite appropriate medical therapy or a calculated Cockcroft-Gault creatinine clearance < 70 mL/min.[20] The primary objective of the parent study was to compare the 3 treatment arms in terms of time to treatment failure, classified as a loss of glycemic control (defined as hemoglobin A_{1c} [HbA_{1c}] ≥ 8% for 6 months or sustained metabolic decompensation requiring insulin). Half the cohort reached the primary end point, and results demonstrated that adding rosiglitazone to metformin therapy was associated with more durable glycemic control after an average follow-up of 3.86 years.[21] Insulin therapy was initiated at the time of the primary outcome. The protocol was approved by the institutional review boards of all participating institutions, and appropriate informed consent and assent were obtained.

This study is a secondary analysis using observational data from the parent TODAY clinical trial. Of 699 TODAY participants, 137 were excluded who did not have baseline estimated insulin sensitivity and/or eGFR data, leaving a final cohort of 532 participants. Excluded participants did not differ significantly on any demographic or baseline characteristic (sex, race-ethnicity, age, BMI, or HbA_{1c}) from the 699 in the original cohort. Analyses included data available for TODAY participants at each annual visit time points up to 60 months of follow-up.

Data Collection and Laboratory Analysis

The methods of the TODAY trial, including laboratory analyses, study definitions, and data collection protocols, have been previously reported in detail.[22] Briefly, samples were obtained at baseline and annually, processed immediately according to standardized procedures, and shipped on dry ice for analysis at the TODAY central biochemical laboratory.[23] Estimated insulin sensitivity was calculated annually as the reciprocal of fasting insulin (in units of mL/μU), which correlates strongly with hyperinsulinemic-euglycemic clamp–derived in vivo insulin sensitivity in obese youth with or without T2DM.[24] Creatinine concentrations in serum and urine were determined by using the Creatinine Plus enzymatic Roche reagent on a Modular P analyzer (Roche Diagnostics, Inc), which is traceable to the isotope-dilution mass spectrometry reference standard. Cystatin C in serum was measured immunochemically by using Siemens reagents (Siemens Healthcare Diagnostics Inc) on a Siemens nephelometer autoanalyzer (BNII). This method is standardized against the IFCC/ERM DA-471 Reference Material (RT Corp).

Measurements and Definitions of Study Outcomes

eGFR was calculated using the Zappitelli combined creatinine and cystatin C equation, $eGFR = 25.38 \times (1/\text{serum cystatin C})^{0.331} \times (1/\text{serum creatinine})^{0.602} \times (1.88^{\text{height}})$, which has demonstrated strong agreement with measured GFR in adolescents.[25,26] Due to the large variability in eGFRs over time in the cohort, a conservative approach was used in the present study to define the presence of hyperfiltration. First, elevated GFR was defined as eGFR at the 99th percentile or higher (≥140 mL/min/1.73 m^2) when referenced to a