Relationship Between Parental Diabetes and Presentation of Metabolic and Glycemic Function in Youth With Type 2 Diabetes: Baseline Findings From the TODAY Trial

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OBJECTIVE
Children whose parents have diabetes are at increased risk for developing type 2 diabetes. This report assessed relationships between parental diabetes status and baseline demographics, anthropometrics, metabolic measurements, insulin sensitivity, and β-cell function in children recently diagnosed with type 2 diabetes.

RESEARCH DESIGN AND METHODS
The sample included 632 youth (aged 10–17 years) diagnosed with type 2 diabetes for <2 years who participated in the TODAY clinical trial. Medical history data were collected at baseline by self-report from parents and family members. Youth baseline measurements included an oral glucose tolerance test and other measures collected by trained study staff.

RESULTS
Youth exposed to maternal diabetes during pregnancy (whether the mother was diagnosed with diabetes prior to pregnancy or had gestational diabetes mellitus) were diagnosed at younger ages (by 0.6 years on average), had greater dysglycemia at baseline (HbA1c increased by 0.3% [3.4 mmol/mol]), and had reduced β-cell function compared with those not exposed (C-peptide index 0.063 vs. 0.092). The effect of maternal diabetes on β-cell function was observed in non-Hispanic blacks and Hispanics but not whites. Relationships with paternal diabetes status were minimal.

CONCLUSIONS
Maternal diabetes prior to or during pregnancy was associated with poorer glycemic control and β-cell function overall but particularly in non-Hispanic black and Hispanic youth, supporting the hypothesis that fetal exposure to aberrant metabolism may have long-term effects. More targeted research is needed to understand whether the impact of maternal diabetes is modified by racial/ethnic factors or whether the pathway to youth-onset type 2 diabetes differs by race/ethnicity.
The prevalence of type 2 diabetes among adolescents has increased by 30% in the past decade (1). Once considered an adult disease, type 2 diabetes now represents 20–50% of new cases of youth-onset diabetes and disproportionately affects minority racial and ethnic groups (1). Obesity in the young clearly contributes to the emergence of type 2 diabetes, but other factors are likely involved. Youth with type 2 diabetes often have an affected parent, suggesting a genetic component to disease development. Previous studies have reported that maternal effects are stronger than paternal (2–5) and relate to the degree of gestational dysglycemia (6). In addition, it has been observed that exposure to diabetes during pregnancy may affect offspring through epigenetic mechanisms (2,7). The impact of the in utero environment is illustrated by the threefold higher risk of developing diabetes in offspring exposed to an intrauterine diabetic environment compared with unexposed siblings (8).

Several reports have described the effects of parental diabetes on various physiological measures in nondiabetic offspring and on the incidence of type 2 diabetes (5,9,10), but information on the effect of parental diabetes on adolescents with newly diagnosed type 2 diabetes is limited. Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) was a multicenter randomized clinical trial of diabetes treatment modalities for the management of recent-onset type 2 diabetes in youth and has the largest and best-characterized group of youth with type 2 diabetes to date (11). A recent report from TODAY (12) examined relationships between various parental characteristics and youth outcomes in those families with a parent who signed informed consent agreeing to be actively involved in the youth’s diabetes care and management. Those data showed that having a parent with diabetes was associated with a youth’s higher HbA1c at baseline and decreased ability to maintain glycemic control on randomized treatment over time. In this study, we used self-report data collected at baseline on all biological parents of the TODAY youth participants to more closely examine the effect of parental diabetes status on metabolic and glycemic function in the youth at baseline (prior to start of randomized treatment), including effects related to exposure to diabetes during pregnancy. Measures of insulin secretion and β-cell function were further analyzed by racial/ethnic subgroup.

RESEARCH DESIGN AND METHODS

The rationale, design, and methodology of TODAY were reported previously (13). Materials developed and used for the TODAY standard diabetes education program and the intensive lifestyle intervention program are available at the public site https://today.bsc.gwu.edu/. Briefly, the study group of 15 participating clinical centers enrolled 699 multiethnic youth aged 10–17 years between July 2004 and February 2009 who had been diagnosed with type 2 diabetes within the previous 2 years, had a BMI ≥85th percentile for age and sex, had a fasting C-peptide >0.6 ng/mL, and were negative for diabetes autoantibodies (GAD-65 and tyrosine phosphatase). Prior to randomization, participants completed a 2- to 6-month run-in period in which they demonstrated mastery of standard diabetes medications, maintained glycemic control (HbA1c <8% [<64 mmol/mol]) on metformin alone (500–1,000 mg twice daily), and demonstrated adherence to study medication and visit attendance. Participants who successfully completed the run-in phase were randomized to one of three treatment arms: metformin monotherapy, metformin plus rosiglitazone, or metformin plus an intensive lifestyle intervention program. The primary objective of TODAY was to compare the three arms in terms of time to treatment failure (i.e., loss of glycemlc control), defined as either HbA1c ≥8% (≥64 mmol/mol) over a 6-month period or inability to wean from temporary insulin therapy within 3 months after acute metabolic decompensation (11). The protocol was approved by an external evaluation committee convened by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health and by the institutional review board for each of the participating institutions. All participants provided both informed parental consent and minor child assent.

Measurements and Outcomes

Parental medical history was obtained at the baseline visit through interview with a parent, adult caregiver, or other knowledgeable family member. Information collected on the biological parents included parental age at participant birth, current height and weight, and diabetes history, including age at diabetes diagnosis and whether the mother had diabetes during the pregnancy. Responses were used to classify mother’s diabetes status as during the pregnancy (a combination of diagnosed before or during the pregnancy) (“during”), after the youth participant’s birth (“after”), or never diagnosed (“never”). The during category grouped together mothers diagnosed with diabetes prior to or during the pregnancy in order to assess the effect of fetal exposure to the maternal diabetic environment. Paternal diabetes was dichotomized as “ever” or “never.”

Demographic and anthropometric data collected on youth at baseline included age, duration of diabetes, sex, birth weight, height, weight, percent body fat from DEXA, and waist circumference (14). Anthropometric measures were made by trained certified staff members, and BMI was calculated as weight in kilograms divided by the square of height in meters. Race/ethnicity was determined by self-report on two separate items: 1) participants checked Hispanic/Latino ethnicity yes or no and 2) participants checked as many racial categories as needed. Participants were categorized as non-Hispanic black, non-Hispanic white, Hispanic, or other (combination of categories that were too small for separate analysis).

HbA1c, measurements and oral glucose tolerance tests (OGTTs) were performed at baseline and processed immediately according to standardized procedures at the TODAY central laboratory (13). Insulin sensitivity was calculated as the inverse of fasting insulin (1/IF), the C-peptide index (CPI) as the ratio of the incremental C-peptide and glucose responses over the first 30 min of the OGTT (CPI = ΔC30/ΔG30), and the C-peptide oral disposition index (CPODI), a measure of β-cell function relative to insulin sensitivity, as the product of insulin sensitivity multiplied by the CPI (CPODi = 1/IF × ΔC30/ΔG30) (15). We used C-peptide instead of insulin to compute the index and oral disposition index because of the potential influence of ethnic differences in insulin clearance (16). The HOMA index was not included in the present analysis, as HOMA has
Table 1—Participant characteristics collected at baseline by maternal and paternal diabetes status

|                                  | Maternal diabetes status (n = 632) | Paternal diabetes status (n = 494) |
|----------------------------------|-----------------------------------|-----------------------------------|
|                                  | D (n = 215, 34%)                  | P*                                |
| Demographic                      |                                   |                                   |
| Age at diagnosis (years)         | 13.3 ± 2.2                        | 13.6 ± 2.1                        |
| Duration of diabetes (months)    | 7.6 ± 5.7                         | 8.4 ± 6.3                         |
| Male                             | 42.3                              | 28.0                              |
| Race/ethnicity†                  |                                   |                                   |
| Non-Hispanic black               | 31.6                              | 30.6                              |
| Hispanic                         | 40.5                              | 40.1                              |
| Non-Hispanic white               | 20.5                              | 21.0                              |
| Other                            | 7.4                               | 8.3                               |
| Parental (self-report)           |                                   |                                   |
| Maternal BMI (kg/m²)             | 34.5 ± 9.6                        | 35.2 ± 9.7                        |
| Maternal age at birth (years)    | 28.7 ± 6.0                        | 27.9 ± 6.1                        |
| Paternal age at birth (years)    | 317.7 ± 7.4                       | 317.8 ± 8.0                       |
| Anthropometric                   |                                   |                                   |
| Birth weight at term (g)‡        | 3,678 ± 788                       | 3,247 ± 765                       |
| BMI z score                      | 2.3 ± 0.5                         | 2.2 ± 0.5                         |
| % body fat from DXA              | 37.5 ± 6.6                        | 37.9 ± 6.3                        |
| Waist circumference (cm)         | 107.5 ± 16.4                      | 109.8 ± 18.2                      |
| Metabolic                        |                                   |                                   |
| HbA₁c (%)                        | 6.2 ± 0.8                         | 6.1 ± 0.8                         |
| HbA₁c (mmol/mol)                 | 44.2 ± 8.5                        | 43.9 ± 8.2                        |
| Fasting blood glucose (mg/dL)    | 116.1 ± 26.8                      | 111.4 ± 25.4                      |
| 2-h blood glucose (mg/dL)        | 217.3 ± 66.8                      | 209.7 ± 61.7                      |

Data are mean ± SD or %. Models evaluating anthropometric and metabolic outcomes were adjusted for participant’s sex, race/ethnicity, and age at baseline. If the overall test was significant, pairwise comparisons across the three maternal diabetes status categories were performed and significant comparisons were reported. A, after pregnancy; D, during pregnancy; N, never. *P values from generalized linear models examining differences in TODAY participants by maternal or paternal diabetes status; P values <0.05 (in boldface type) are considered statistically significant. †Other race/ethnicity was excluded from testing. ‡At term defined as within 2 weeks of due date.
been shown to offer no advantage over the simpler fasting indices (i.e., inverse of fasting insulin) in adolescents with type 2 diabetes (17). Negative values for the CPI and suspected nonfasting blood results were treated as missing values.

Sample
The analysis was performed on TODAY participants for whom maternal diabetes history was available (632 of 699 [90.4%]). Comparison of the analysis sample with the 67 not included showed they were equivalent for baseline demographics (sex, race/ethnicity, birth weight, months since type 2 diabetes diagnosis) and weight metrics (BMI z score, waist circumference), but those not included were 6 months older at study entry (14.4 vs. 13.9 years old, \( P = 0.0457 \)). For the 632 participants with available maternal diabetes history, paternal diabetes history was available for 494. Those with complete parental diabetes history did not differ from those without paternal diabetes history for baseline characteristics described above.

Statistical Methods
Generalized linear models were used to examine differences in TODAY participants at baseline by maternal and/or paternal diabetes status. All models evaluating anthropometric and metabolic outcomes in the youth were adjusted for sex, race/ethnicity, and age at baseline. Insulin sensitivity, CPI, and CPoDI were log transformed prior to testing to normalize the distributions. Pairwise comparisons were performed if the overall test was significant. For exploration of whether race/ethnicity modified the association between maternal diabetes and β-cell function indices, an interaction term between race/ethnicity and maternal diabetes status was tested in models similar to those described above. A \( P \) value <0.05 was considered significant without adjustment for multiple comparisons, and all analyses were considered exploratory. SAS, version 9.3 (SAS Institute, Cary, NC), was used for all analyses.

RESULTS
In the analysis sample of 632, 215 (34%) of mothers had diabetes during the pregnancy, 77 (36%) of whom were diagnosed prior to the pregnancy; 101 (16%) were diagnosed after the pregnancy, and 316

![Figure 1](image-url)

Figure 1—Insulin sensitivity (inverse fasting insulin) and β-cell function (CPI and CPoDI) were compared by maternal (left) and paternal (right) diabetes status. Maternal diabetes was categorized as during pregnancy, after pregnancy, or never diagnosed; paternal diabetes categories are ever or never diagnosed. Testing was performed separately for each parent in models adjusted for participant’s sex, race/ethnicity, and age at baseline, and significant \((P < 0.05)\) comparison categories are shown linked. Variables were log transformed to normalize the distributions. CPoDI, oral disposition index.
(50%) were never diagnosed with diabetes. Of the 494 with paternal data, 158 (32%) of biological fathers reported having been diagnosed with diabetes by the baseline visit.

**Baseline Anthropometric and Metabolic Outcomes**

Baseline participant anthropometric and metabolic outcomes by joint parental diabetes status* are compared in Table 1.

**Baseline Metabolic Control**

A history of parental diabetes had an overall detrimental relationship with metabolic status in the youth, with the influence of maternal diabetes being greater than paternal (Table 1). Participants whose mothers had diabetes during pregnancy or after pregnancy had increased fasting and 2-h post-challenge blood glucose concentrations compared with those whose mothers never had diabetes. HbA1c was increased (P < 0.0001) by 0.3% (3.4 mmol/mol) in those whose mothers had diabetes during pregnancy compared with those never diagnosed, while those whose mothers were diagnosed after pregnancy had intermediate but still significantly different values. Paternal diabetes status had no relationship with blood glucose measures from OGTT, but there was a small difference (P = 0.0241) of 0.1% (1.8 mmol/mol) greater HbA1c in the ever versus never groups.

**Baseline Insulin Sensitivity and Secretion**

Insulin sensitivity was not related to parental diabetes status. In contrast, insulin secretion and CPoDI were lower in those born to mothers who were ever diagnosed with diabetes compared with those whose mothers never had diabetes. There was no difference between those whose mothers had diabetes during pregnancy versus those who were diagnosed after. There was no significant effect of paternal diabetes on measures of insulin secretion other than a trend (P = 0.12) for lower CPI in the youth born to fathers diagnosed with diabetes (Fig. 1).

**Maternal and Paternal Diabetes Status Combined**

In the sample of 494 who had both maternal and paternal diabetes data, parental diabetes status was regrouped to analyze differences in anthropometric and metabolic outcomes by whether only the mother, only the father, neither, or both parents had ever been diagnosed with diabetes. The maternal and after groups were collapsed because previous analysis produced similar results. There were no between-group differences in racial/ethnic composition (data not shown). HbA1c and 2-h glucose were significantly higher and CPI was significantly lower in those with a parental history of diabetes, regardless of whether it was the mother, father, or both who had been diagnosed. Fasting glucose was higher and CPoDI lower in the mother-only group versus the neither parent group, but the father-only group was no different than the neither group (Table 2).

### Table 2—Baseline participant anthropometric and metabolic outcomes by joint parental diabetes status*

| Parental diabetes status (n = 494) | B (n = 79) | MO (n = 174) | FO (n = 78) | N (n = 163) | P† |
|-----------------------------------|-----------|-------------|------------|------------|----|
| **Anthropometric**                |           |             |            |            |    |
| Birth weight at term (g)          | 3,427 ± 676 | 3,703 ± 780 | 3,180 ± 687 | 3,312 ± 588 | 0.0009b vs. FO, MO vs. FO, MO vs. N |
| BMI z score                       | 2.3 ± 0.5  | 2.2 ± 0.4   | 2.2 ± 0.5  | 2.2 ± 0.5  | 0.5600 |
| % body fat from DXA               | 37.9 ± 6.4 | 37.5 ± 6.8  | 37.9 ± 6.3 | 37.2 ± 5.8 | 0.8361 |
| Waist circumference (cm)          | 108.8 ± 18.4 | 107.9 ± 14.6 | 110.8 ± 18.2 | 107.9 ± 16.3 | 0.4089 |
| **Metabolic**                     |           |             |            |            |    |
| HbA1c (%)                         | 6.1 ± 0.8  | 6.1 ± 0.8   | 6.1 ± 0.7  | 5.8 ± 0.6  | <0.0001b vs. N, MO vs. N, FO vs. N |
| HbA1c (mmol/mol)                  | 43.7 ± 8.3 | 43.1 ± 8.4  | 42.9 ± 8.2 | 39.8 ± 6.8 | 0.0001b vs. N, MO vs. FO, MO vs. N |
| Fasting blood glucose (mg/dL)     | 114.7 ± 25.4 | 115.8 ± 27.9 | 108.0 ± 25.2 | 104.1 ± 19.6 | <0.0001b vs. N, MO vs. FO, MO vs. N |
| 2-h blood glucose (mg/dL)         | 210.9 ± 65.0 | 214.2 ± 65.0 | 208.6 ± 58.5 | 183.4 ± 59.5 | <0.0001b vs. N, MO vs. N, FO vs. N |
| Insulin sensitivity [1/(l/l) (mL/µU)]† | 0.047 ± 0.030 | 0.048 ± 0.033 | 0.052 ± 0.037 | 0.047 ± 0.037 | 0.4961 |
| CPI [ΔAC0/ΔG30] (ng/mL per mg/dL)† | 0.062 ± 0.051 | 0.066 ± 0.062 | 0.077 ± 0.068 | 0.098 ± 0.084 | <0.0001b vs. N, MO vs. N, FO vs. N |
| CPoDI [1/Insulin sensitivity] (mL/µU)† | 0.0028 ± 0.0026 | 0.0029 ± 0.0027 | 0.0035 ± 0.0035 | 0.0040 ± 0.0035 | 0.0074b vs. N, MO vs. N |

Data are mean ± SD. B, both parents; FO, father only; MO, mother only; N, neither. *Parental diabetes status determined from self-report as ever or never diagnosed with diabetes. †P values from generalized linear models examining differences in TODAY participants by parental diabetes status; P values < 0.05 (in boldface type) were considered statistically significant. Models were adjusted for participant’s sex, race/ethnicity, and age at baseline. If the overall test was significant, pairwise comparisons were performed and significant comparisons were reported. Variables were log transformed to normalize the distributions.
(P = 0.0147), indicating that the relationship between maternal diabetes status and the indexes differed across the racial/ethnic groups. Figure 2 compares measures of β-cell function and insulin secretion (CPI and CPoDI) by race/ethnicity and by whether the mother was ever diagnosed with diabetes. Among non-Hispanic blacks and Hispanics, both CPI and CPoDI were significantly lower in those with mothers diagnosed with diabetes; there was no difference in non-Hispanic whites. In the group with mothers never diagnosed with diabetes, CPI and CPoDI were significantly lower in non-Hispanic whites than in non-Hispanic blacks or Hispanics; there were no racial/ethnic differences in the group with mothers ever diagnosed. In addition, there was no effect of paternal diabetes within and between racial/ethnic groups for either CPI or CPoDI; i.e., the interaction of paternal diabetes status with race/ethnicity was not significant in the models.

Youth BMI z score was significantly lower (P = 0.031) in the non-Hispanic white participants whose mothers were never diagnosed with diabetes (mean 2.0), after adjustment for age and sex, compared with the other groups (2.2–2.3). However, adjustment for BMI z score in the analysis did not have an impact on any of the findings shown in Fig. 2.

In our sample, maternal BMI among non-Hispanic blacks (37.5 ± 9.8) was significantly different from that among Hispanics (32.9 ± 8.0, P < 0.0001) and among non-Hispanic whites (32.3 ± 9.0, P < 0.0001). However, these differences in maternal BMI by race status did not differ across the three maternal diabetes groups.

CONCLUSIONS
In this sample of 632 youth with recent-onset type 2 diabetes, those exposed to diabetes during pregnancy (whether the mother was diagnosed with diabetes prior to pregnancy or had frank gestational diabetes mellitus) were diagnosed at younger ages on average and had greater dysglycemia at study baseline compared with those who were not exposed. These findings were associated with reduced β-cell function, as insulin sensitivity was unaltered by either maternal or paternal diabetes status. In addition, lower β-cell function in study participants whose mothers had ever been diagnosed with diabetes was found in racial/ethnic groups at higher risk of diabetes.

The relationship between maternal diabetes and participant’s baseline metabolic status appears modest but may be meaningful considering the constraints on the sample examined. Prior to randomization into the trial and collection of baseline measurements, all participants had to maintain HbA1c ≤8.0% (≤64 mmol/mol) for at least 2 months on metformin alone, meaning that individuals with the poorest glycemic control were excluded. In this context, the increase in baseline HbA1c from 5.9 to 6.2% (41 to 44 mmol/mol) in those youth exposed to an intrauterine diabetes environment compared with those whose mother was never diagnosed may be meaningful, as the value approaches the threshold for vascular complication risk (18).

Comparing outcomes between those whose mothers had diabetes during pregnancy with either those with a paternal history of diabetes or those whose mothers developed diabetes after delivery has been used to assess whether the effects reflect genetic transmission or exposure to a diabetic environment in utero. In our
study as in others (2–6), the influence of maternal diabetes was stronger than that of paternal diabetes. Furthermore, β-cell function was equivalently lower in those whose mothers had diabetes during pregnancy versus after birth compared with those youth whose mothers were never diagnosed with diabetes, suggesting transmission of a maternal factor independent of diabetes status at time of gestation. These findings are similar to those reported by Kelstrup et al. (9) in studies of nondiabetic adult offspring of women with diabetes during pregnancy. However, it is possible that, in our sample, mothers reporting diagnosis after the pregnancy either actually had gestational diabetes mellitus that was undiagnosed or had mild dysglycemia that did not meet the diagnostic threshold but was sufficient to affect the offspring’s β-cell function. In support of the latter, the birth weight of offspring born to our mothers with diabetes diagnosed after pregnancy was intermediate between those whose mothers had diabetes during pregnancy and those whose mothers never had diabetes. Data from Kelstrup et al. (9) also suggest that there is subtle dysglycemia during pregnancy in mothers with positive family history of diabetes but without overt diabetes during pregnancy.

The relationships we observed between maternal diabetes status and youth participant baseline β-cell function and disease presentation are concordant with other reports. Results from the SEARCH for Diabetes in Youth Study show that youth with type 2 diabetes are more likely to have been exposed to maternal diabetes during pregnancy than nondiabetic control subjects (7) and that youth whose mothers had diabetes during pregnancy were diagnosed at younger ages compared with those whose mothers had diabetes diagnosed later (4). A reduction in β-cell function is also evident in nondiabetic offspring with a family history of diabetes and typically is more pronounced when the mother is affected (5,10).

The differences by maternal diabetes across race/ethnicity found in subgroup analysis require replication and additional research given our current understanding of the pathogenesis of type 2 diabetes. SEARCH found no effect of race/ethnicity on the influence of maternal diabetes status on presentation (6), and several other reports have demonstrated that maternal diabetes exposure reduced β-cell function in predominantly European populations (2,5,9). Thus, non-Hispanic white individuals are not immune to the effects of maternal diabetes on insulin secretion. The fact that the non-Hispanic white participants whose mothers were never diagnosed with diabetes had indices of β-cell function as low as those with mothers reporting diagnosis of diabetes suggests additional factors have affected β-cell function by the time these adolescents presented with type 2 diabetes. For example, there may have been racial/ethnic differences in mothers of TODAY participants related to diabetes control during gestation or in quality of perinatal care received.

The strengths of our study are a well-characterized, large cohort representative of youth with type 2 diabetes early in the course of the disease. Limitations include obtaining data on parents retrospectively and by self-report. Race/ethnicity was based on the youth participant’s self-report and may not reflect how the mothers and fathers would characterize themselves. Also, we were unable to assess severity or type of diabetes (i.e., type 1 vs. type 2) in mothers and fathers, though it would appear that type 1 diabetes was uncommon in mothers, as the majority were diagnosed during or after the pregnancy and the frequency of remission after birth was high (60%). Because our main objective was to examine the effects of exposure of offspring to maternal diabetes during gestation, the focus was on the presence or absence of diabetes rather than type. Correct ascertainment of parental dysglycemia is supported both by prior studies demonstrating validity of diabetes history by questionnaire (7,19) and by the fact that birth weights of offspring from mothers with diabetes during pregnancy were increased as expected. Future studies that would distinguish the effects on offspring according to parental diabetes type would be of interest.

In conclusion, the impact of parental diabetes on offspring is evident even post-diagnosis in the adolescent with type 2 diabetes. The relationships are complex and likely mediated by both genetic and fetal environmental factors (e.g., intrauterine hyperglycemia resulting in epigenetic changes) that influence β-cell function. Racial/ethnic distinctions evident in this sample are consistent with a growing body of evidence indicating racial/ethnic differences among various factors related to the development of type 2 diabetes.

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