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HbA$_{1c}$ After a Short Period of Monotherapy With Metformin Identifies Durable Glycemic Control Among Adolescents With Type 2 Diabetes

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**OBJECTIVE**
To determine whether clinically accessible parameters early in the course of youth-onset type 2 diabetes predict likelihood of durable control on oral therapy.

**RESEARCH DESIGN AND METHODS**
TODAY was a randomized clinical trial of adolescents with type 2 diabetes. Two groups, including participants from all three treatments, were defined for analysis: 1) those who remained in glycemic control for at least 48 months of follow-up and 2) those who lost glycemic control before 48 months. Outcome group was analyzed in univariate and multivariate models as a function of baseline characteristics (age, sex, race/ethnicity, socioeconomic status, BMI, waist circumference, Tanner stage, disease duration, depressive symptoms) and biochemical measures (HbA$_{1c}$, C-peptide, lean and fat body mass, insulin inverse, insulinogenic index). Receiver operating characteristic curves were used to analyze HbA$_{1c}$ cut points.

**RESULTS**
In multivariate models including factors significant in univariate analysis, only HbA$_{1c}$ and insulinogenic index at randomization remained significant ($P < 0.0001$ and $P = 0.0002$, respectively). An HbA$_{1c}$ cutoff of 6.3% (45 mmol/mol) (positive likelihood ratio [PLR] 3.7) was identified that optimally distinguished the groups; sex-specific cutoffs were 6.3% (45 mmol/mol) for females (PLR 4.4) and 5.6% (38 mmol/mol) for males (PLR 2.1).

**CONCLUSIONS**
Identifying youth with type 2 diabetes at risk for rapid loss of glycemic control would allow more targeted therapy. HbA$_{1c}$ is a clinically accessible measure to identify high risk for loss of glycemic control on oral therapy. Adolescents with type 2 diabetes unable to attain a non–diabetes range HbA$_{1c}$ on metformin are at increased risk for rapid loss of glycemic control.

TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) was the first and largest randomized clinical trial to examine approaches to management of youth-onset type 2 diabetes. Among the primary findings of TODAY was that metformin monotherapy was inadequate for maintenance of glycemic control in almost half of participants after median time to failure of ~11 months (1). Furthermore,
there were distinct sex and racial/ethnic differences in the pattern of failure overall and across treatment arms. This degree of failure on monotherapy was higher than expected from studies of adults with type 2 diabetes (2,3) and only partially prevented by the addition of rosiglitazone. Taken together, the findings suggest that type 2 diabetes among adolescents can be more rapidly progressive than in adults (4–7).

On the other hand, ~50% of TODAY participants maintained durable glycemic control regardless of treatment group. This suggests that type 2 diabetes among adolescents is a heterogeneous disorder grossly divided between those who are and are not able to maintain glycemic control on oral therapy. If so, it would be of substantial clinical importance to properly classify patients early in the course of the disease so that appropriate treatment can be planned.

In this analysis, we address the hypothesis that readily available demographic and metabolic characteristics determined early in the course of type 2 diabetes can distinguish adolescents who will display long-term diabetes complications. During the trial, the investigators and the participants were blinded to specific HbA1c values but were informed if HbA1c was 1) ≥8% (≥64 mmol/mol), 2) 6–8% (42–64 mmol/mol) and increased from previous value by ≥0.8% (≥8.7 mmol/mol), or 3) ≤6% (≤42 mmol/mol) target). The primary objective was to compare the three treatment arms on time to treatment failure, 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.

The protocol was approved by an External Evaluation Committee convened by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health and by the institutional review boards of each participating institution. All participants provided written informed consent, and minor children confirmed assent according to local guidelines.

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/.

**Analysis Samples and Measures**

Two outcome groups were defined for analysis. Group designation was assigned irrespective of original treatment arm. Group 1 participants remained in glycemic control (i.e., did not reach the primary outcome, as defined above) for at least 48 months of follow-up, and group 2 reached the primary outcome before 48 months; beyond 48 months, sample size was inadequate for analysis and data are not included.

Demographic and baseline characteristics in the analysis were age, sex, race/ethnicity (classified as non-Hispanic black [NHB], Hispanic [H], non-Hispanic white [NHW], or other), household annual income, highest education level of parents or guardians, first-degree family history of diabetes, Tanner stage (by physician examination), months since diagnosis of type 2 diabetes, and presence of depressive symptoms based on the Children’s Depression Inventory (12) for participants age ≤15 years or the Beck Depression Inventory (13) for participants age ≥16 years.

Baseline measures were BMI, HbA1c at screening and randomization, C-peptide, and adiposity. Laboratories were performed by a central laboratory (8). Insulin sensitivity and β-cell function were derived from the 2-h oral glucose tolerance test as follows: insulin inverse = 1/insulin_{min Δ} and insulinogenic index = (insulin_{min 30} − insulin_{min 0})/ (glucose_{min 30} − glucose_{min 0}). Measures of adiposity were waist circumference and DXA measures of fat (kg) and lean (kg) body mass; in approximately one-quarter of the subjects, DXA scans were excluded owing to weight limitations (weight >140 kg).

**Statistical Analysis**

Logistic regression was used to model outcome group as a function of demographic variables, baseline characteristics, and baseline measures in univariate and multivariate analyses. Receiver operating characteristic (ROC) curve analyses were performed to identify optimal baseline HbA1c, cut points predictive of failure (as indicated by outcome group). The standard logistic regression model and the trapezoidal rule method were used to compute the total area under the curve (AUC) and its associated 95% CI in the overall analysis sample by sex, by race/ethnicity (NHB, H, NHW), and for the six sex-by-race/ethnicity combinations. Sensitivity and specificity were computed and the Youden index method was used to select the optimal threshold point from the ROC curve (14). The Youden index [maximum (sensitivity + specificity − 1)] maximizes the vertical distance from the line of equality to identify the point on the curve farthest from chance (15,16) and maximizes the classification rate. The positive likelihood ratio (PLR) [(sensitivity/1 − specificity)] was used to determine whether a baseline HbA1c cutoff usefully changed the probability of failing oral therapy; PLR >1 indicates the test result is associated with increased probability (17). P values <0.05 were considered significant. P values were considered exploratory and were not adjusted for...
multiple testing; the study was powered only for the time-to-failure primary outcome.

RESULTS
The assignment of participants into the two analysis groups is shown in Fig. 1. Demographic and baseline characteristics in group 1 (n = 172) versus group 2 (n = 305) are shown in Table 1. Group 1 had a significantly higher percentage of NHW and lower of NHB, a lower prevalence of depressive symptoms at the time of entry into the study, and a lower percentage of first-degree relatives with diabetes; total annual household income ($\geq$50,000) barely missed statistical significance (P = 0.0512). There were no differences by sex, treatment group, age, duration of diabetes, Tanner stage, or highest household education at study entry. There was also no difference in Tanner stage by sex in the analysis sample (90.5% of females and 87.3% of males were Tanner stage 4 or 5). There was no difference at any time between groups 1 and 2 in percentage of participants with study medication adherence $\geq$80% (data not shown).

In univariate analysis, screening and baseline HbA1c and baseline insulinogenic index were identified as the only significant metabolic factors distinguishing those with durable glycemic control irrespective of treatment group; participants with durable control had significantly lower HbA1c and higher insulinogenic index. Baseline measures of insulin sensitivity (fasting C-peptide and insulin inverse), measures of body fatness (BMI, waist circumference, and DXA fat mass), and DXA lean mass were not different between groups. Calculation of oral disposition index did not contribute beyond insulinogenic index alone (data not shown).

In multivariate models including all baseline demographic and metabolic factors significant in univariate analysis, only HbA1c and insulinogenic index remained significant (P < 0.0001 and P = 0.0002, respectively). This was also true when treatment assignment was included in the model. With all other variable values held as fixed, there was a 16% increase in the odds of failing within 48 months of treatment for each 0.1% (1.1 mmol/mol) increase in HbA1c from study baseline (after stabilization of HbA1c $<$8% [<$64 mmol/mol] during run-in but before start of study randomized treatment).

Similarly, there was a 16% increase in the odds of failing within 48 months of treatment for each 0.1-unit decrease in insulinogenic index from study baseline.

Figure 2 shows a shift in the distributions of baseline HbA1c for groups 1 and 2. Because HbA1c is easily obtained in clinical setting, this shift suggested a clinically practical basis for distinguishing between the groups. Overall, the Youden index identified an HbA1c cutoff of 6.3% (45 mmol/mol) that maximized correct classification of participants (Fig. 3A), with sensitivity 54%, specificity 86%, and PLR 3.7. Figure 3B shows a sex difference in HbA1c operator characteristics. Although both sexes had the same AUC (0.77), the ROC curves crossed, indicating that HbA1c had higher specificity in females and higher sensitivity in males. The Youden index identified HbA1c of 6.3% (45 mmol/mol) for females (sensitivity 59%, specificity 87%, and PLR 4.4) and 5.6% (38 mmol/mol) for males (sensitivity 88%, specificity 59%, and PLR 2.1) as the optimal cutoffs for classifying the risk of loss of durable control. This sex difference in optimal cutoff was true across race/ethnicity; the Youden index identified optimal HbA1c cutoffs of 6.3, 6.4, and 6.6% (45, 46, and 49 mmol/mol) for NHB, H, and NHW females, respectively, but 5.8% (40 mmol/mol) for NHB and 5.6% (38 mmol/mol) for H and NHW males. Figure 4 summarizes HbA1c cutoffs, AUC, and PLR overall and by sex and race/ethnicity in the sample of groups 1 and 2 combined. (Supplementary Table 1 gives sensitivity, specificity, and PLR overall by sex, race/ethnicity, and by the interaction of sex with race/ethnicity.)

Since the ADA recommends a treatment target of 6.5% (48 mmol/mol), this value is often used by diabetes health care providers as a cutoff for determining whether to alter therapy. We compared the cutoff of 6.3 vs. 6.5% (45 vs. 48 mmol/mol) in our analysis sample. Sensitivity for identification of participants who will lose glycemic control was 54 vs. 43%, while specificity rose from 86 to 91%. The PLR for an HbA1c of 6.3% (45 mmol/mol) was 3.7 vs. 5.0 for 6.5% (48 mmol/mol). At an HbA1c of 5.9% (41 mmol/mol), the PLR for loss of glycemic control was still $>2$. As expected from the sex-specific differences in Youden index, a cutoff of 6.5% (48 mmol/mol) had even lower sensitivity for identifying those likely to fail among males (35%, PLR 3.0) than females (48%, PLR 6.7). At an HbA1c of 6.0% (42 mmol/mol), the PLR for both males and females was $>2$.

CONCLUSIONS
The TODAY primary outcome analysis demonstrated that type 2 diabetes presenting during adolescence was characterized by
high rates of loss of glycemic control over a relatively brief period of time compared with adults (1). Although addition of rosiglitazone to metformin reduced the rate of loss of glycemic control by 23% over the course of the study, the median time to glycemic failure was the same regardless of treatment assignment. Furthermore, the incidence of loss of glycemic control plateaued over time regardless of treatment assignment. Taken together, these observations suggest that there may be subsets of adolescents with type 2 diabetes characterized as those at risk of losing glycemic control rapidly, those who will maintain glycemic control for a prolonged period of time, and those who may respond to addition of a second oral agent with improved maintenance of glycemic control. In particular, the early ability to distinguish patients who maintain glycemic control from those who are going to rapidly lose glycemic control would allow clinicians to identify high-risk patients who would benefit from closer monitoring and earlier intensification of therapy while supporting a less aggressive approach for those who are likely to maintain good glycemic control on metformin alone.

Table 1—Demographic and baseline characteristics by analysis group

|                          | Group 1: no PO <48 mo | Group 2: PO <48 mo | P       |
|--------------------------|-----------------------|--------------------|---------|
| n                        | 172                   | 305                |         |
| Treatment, n (%)         |                       |                    |         |
| M                        | 53 (30.8)             | 116 (38.0)         | 0.2453  |
| M+R                      | 58 (33.7)             | 86 (28.2)          |         |
| M+L                      | 61 (35.5)             | 103 (33.8)         |         |
| Sex, n (%)               |                       |                    |         |
| Female                   | 111 (64.5)            | 193 (63.3)         | 0.7845  |
| Male                     | 61 (35.5)             | 112 (36.7)         |         |
| Age (years)              | 13.8 (1.9)            | 14.1 (2.1)         | 0.1825  |
| Race/ethnicity, n (%)    |                       |                    |         |
| NHB                      | 47 (27.3)             | 117 (38.3)         | 0.0323  |
| H                        | 70 (40.7)             | 119 (39.0)         |         |
| NHW                      | 43 (25.0)             | 48 (15.7)          |         |
| Other                    | 12 (7.0)              | 21 (6.9)           |         |
| Months since diagnosis   | 8.1 (6.2)             | 8.7 (6.2)          | 0.3752  |
| Depressive symptoms, n (%)|                      |                    |         |
| No                       | 154 (91.1)            | 251 (83.4)         | 0.0217  |
| Yes                      | 15 (8.9)              | 50 (16.6)          |         |
| Tanner stage, n (%)      |                       |                    |         |
| ≥4                       | 155 (90.1)            | 271 (88.9)         | 0.6682  |
| ≤3                       | 17 (9.9)              | 34 (11.1)          |         |
| Household income ($), n (%)|                      |                    |         |
| Low (<25,000)            | 62 (39.7)             | 120 (45.0)         | 0.0512  |
| Mid (25,000–49,999)      | 46 (29.5)             | 93 (34.8)          |         |
| High (≥50,000)           | 48 (30.8)             | 54 (20.2)          |         |
| Household education, n (%)|                      |                    |         |
| Less than high school    | 46 (27.1)             | 80 (26.5)          | 0.4529  |
| High school, GED, business or technical school | 37 (21.8) | 85 (28.1) |         |
| College, no degree       | 57 (33.5)             | 93 (30.8)          |         |
| College degree           | 30 (17.6)             | 44 (14.6)          |         |
| First-degree family history of diabetes, n (%)|          |                    |         |
| No                       | 86 (50.6)             | 100 (33.3)         | 0.0003  |
| Yes                      | 84 (49.4)             | 200 (66.7)         |         |
| BMI (kg/m²)              | 34.0 (7.6)            | 35.1 (7.5)         | 0.1189  |
| Waist circumference (cm) | 107.1 (16.2)          | 109.2 (17.0)       | 0.1940  |
| HbA1c at screening (%)   | 6.79 (1.64)           | 8.05 (2.07)        | <0.0001 |
| HbA1c at screening (mmol/mol) | 51 (17.9) | 64 (22.6) | <0.0001 |
| HbA1c at randomization (%)| 5.68 (0.55)          | 6.39 (0.80)        | <0.0001 |
| HbA1c at randomization (mmol/mol) | 39 (6.0) | 46 (8.7) | <0.0001 |
| C-peptide (ng/mL)        | 3.71 (1.55)           | 3.91 (1.64)        | 0.1921  |
| DXA fat mass (kg)        | 32.9 (10.0)           | 33.0 (9.8)         | 0.9453  |
| DXA lean mass (kg)       | 55.6 (12.4)           | 54.0 (11.0)        | 0.2299  |
| Insulin inverse (mL/µU)  | 0.045 (0.027)         | 0.047 (0.037)      | 0.7956* |
| Insulinogenic index (µU/mL per mg/dL) | 2.04 (2.18) | 1.12 (2.08) | <0.0001* |

Data are mean (SD) unless otherwise indicated. GED, General Equivalency Diploma; M, metformin alone; M+L, metformin plus lifestyle program; M+R, metformin plus rosiglitazone; mo, months; PO, primary outcome, i.e., failure to maintain glycemic control on randomized treatment assignment. *Test performed on log transform to normalize distribution.
To examine this question, we analyzed the effect of demographic, anthropometric, and biochemical characteristics of the participants at the time of their randomization into TODAY on the likelihood of loss of glycemic control during follow-up. In univariate analysis, NHB race/ethnicity, depressive symptoms, first-degree family history of diabetes, and lower family income were all associated with rapid loss of glycemic control, as might be expected from previous literature in adults (18–21). Surprisingly, age, duration of diabetes, BMI, waist circumference, fat mass, and lean body mass at randomization had no effect on outcome, though this may be due, in part, to the relatively narrow range of each of these measures in the TODAY cohort (22). Among metabolic measures, only screening and baseline HbA1c and insulinogenic index were associated with maintenance of glycemic control; insulin sensitivity did not differ between the groups. We did not explore screening HbA1c further because the heterogeneous nature of the screened cohort in terms of treatment modalities made generalization of findings to a clinical population difficult.

In multivariate analysis, only baseline HbA1c and insulinogenic index remained significant irrespective of treatment assignment. Studies in adults (2,3) and previous studies in the TODAY cohort (23,24) have shown that β-cell function is a strong determinant of HbA1c. Therefore, HbA1c already reflects information about β-cell function. Although both measures were significant predictors of durable control, HbA1c is clinically more accessible than determination of insulinogenic index. Similarly, although demographic factors were shown to contribute to diabetes outcome in univariate analysis, it may be that the HbA1c value already reflects these contributions, and these factors, therefore, disappeared as significant contributors to prediction of glycemic control in multivariate analysis in this cohort. Given the limitations of our data, we can only speculate on how these factors affect HbA1c, perhaps through genetic, hormonal, nutritional, or behavioral influences on β-cell function. This analysis suggests that HbA1c obtained after a short course of metformin monotherapy in adolescents with type 2 diabetes can function as a simple clinical measure to predict outcome and allow more effective targeting of therapy to those at highest risk for loss of glycemic control.

The next question is whether there is a specific HbA1c cutoff value that is useful as a predictor of likely outcome. ROC analysis identified an HbA1c of 6.3% (45 mmol/mol) as the optimal Youden cutoff for correctly categorizing an individual’s risk for loss of glycemic control on oral therapy, with an AUC of 0.77. The optimal cutoff was similar for females, reflecting the >60% representation of females in the cohort, but was substantially lower for males. This cutoff is lower than the ADA-recommended
treatment target of 6.5% (48 mmol/mol) and probably lower than the level at which most clinicians would consider addition of a second agent. At a minimum, the analysis suggests that an HbA1c cutoff of 6.5% (48 mmol/mol) has low sensitivity for identifying those adolescents; a youth with HbA1c >6.5% (>48 mmol/mol) after a few months on metformin had a >70% chance of experiencing loss of glycemic control in a relatively short time on oral therapy alone. Indeed, both boys and girls with an HbA1c >6.0% (>42 mmol/mol) had approximately double the risk for failure as individuals with an HbA1c <6.0% (<42 mmol/mol). Together these data indicate that adolescents with type 2 diabetes who do not attain a non–diabetes range HbA1c after a few months on metformin are at increased risk for losing glycemic control, and the clinicians caring for these youth should not be reassured that HbA1c is “in target.” These findings do not suggest that there is benefit to treating patients to a lower HbA1c than the ADA target; we did not perform an intervention trial to test this question. Rather, the analysis suggests that HbA1c at the end of a relatively short course of metformin in these adolescents may reflect the severity of the underlying disorder and may be a marker of risk. Given the association of durable control with insulinogenic index and our previous demonstration that HbA1c is strongly determined by insulin secretion in these youth (23,24), those who are not able to get their HbA1c into the non–diabetes range within a few months are likely to have substantial deterioration in β-cell function already.

This analysis has a number of important strengths. First, although the analysis sample is composed of participants in a randomized clinical trial with rigorous eligibility criteria who remained in follow-up for at least 4 years, the demographics of the analyzed sample are comparable with demographics of the general population of youth-onset type 2 diabetes in the U.S. (25). Second, the participants in TODAY have been extensively characterized, allowing analysis of a broad set of demographic, anthropometric, and biochemical measures. Third, the cohort was followed longitudinally and all diabetes care was provided to the participants, allowing for analysis of causal relationships not possible in small and/or cross-sectional studies. On the other hand, despite the relatively large size of the TODAY cohort, the sample size is too small for

Figure 4 — The Youden index HbA1c cutoffs, AUC and its 95% CI, and PLR overall and by sex and racial/ethnic subgroups ("other" race/ethnicity not presented). AUC is a measure of diagnostic accuracy ranging from 0.0 to 1.0, where 0.5 is equivalent to a coin toss (the "curve" looks like a diagonal line); AUC values 0.6–0.7 represent poor ability to predict failure, values 0.7–0.8 represent fair ability, and 0.8–0.9 represent good ability. The TODAY cohort is predominantly female and minority, which affects the overall estimates. The male cutoffs are 0.5–0.10% below the female. The AUC 95% CI includes 0.50 only for NHW males (n = 35) indicating that the cutoff is equivalent to simply guessing. A PLR (sensitivity/1 – specificity) >1 indicates that the test result (HbA1c) is associated with presence of the disease, and the larger the PLR, the greater the likelihood of disease.
more than exploratory analysis of sex-by-racial/ethnic subgroups. In addition, the ROC analysis yields AUC values in the range indicating fair predictive ability for HbA1c, suggesting that there are other factors involved in determining likelihood of failure that are not fully reflected in HbA1c. However, despite this limitation, HbA1c remains the strongest predictor of likelihood of success or failure on metformin monotherapy in youth with type 2 diabetes and is an easily obtained clinical measure that may provide important clinical insight.

In summary, the population of youth with type 2 diabetes is heterogeneous and consists of subsets of individuals who are more or less likely to have durable glycemic control on oral therapy. Furthermore, the analysis demonstrates that HbA1c after a few months of metformin monotherapy was the strongest predictor of response, likely reflecting underlying insulin secretion. Finally, this finding may have important clinical insight.

The content is solely the responsibility of the authors and does not necessarily represent the views of the National Institutes of Health.

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The manuscript was written by P.Z. and revised by all other authors. P.Z. obtained the data used for the analysis. The analyses were performed by P.Z. and K.H. The authors and do not necessarily reflect the views of the National Institutes of Health.

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