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Metformin monotherapy in youth with recent onset type 2 diabetes: experience from the pre-randomization run-in phase of the TODAY study

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Abstract

Background—TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) is a federally-funded multi-center randomized clinical trial comparing three treatments of youth-onset type 2 diabetes.

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Members of the writing group have no conflicts of interest or financial arrangements to disclose.

Members of the TODAY Study Group are listed in the on-line appendix.

Objective—To describe the experience of youth participating in a 2–6 month run-in period in preparation for randomization into TODAY.

Subjects—An ethnically diverse sample of 927 youth, 65.4% female, aged 13.7 ± 2.0 years old, with type 2 diabetes for a median of 2 months (0.7–7.8 months, 25th–75th percentiles).

Methods—A run-in period was conducted to achieve HbA1c <8% with metformin monotherapy and diabetes education, and to evaluate adherence to pill taking, visit attendance, and other procedures.

Results—At entry, mean BMI and z-BMI were 35.6 ± 7.7 and 2.3 ± 0.4 , respectively, mean HbA1c was $7.7 \pm 2.2\%$, only 42.5% were on a hypoglycemic treatment, and 35.6% had HbA1c <8%. Co-morbid conditions were common; 18.8% had hypertension, 24.2% had elevated cholesterol, and 6.5% had abnormal liver enzymes. After a median 71 days of run-in, 90.9% had HbA1c <8%, 77.9% had HbA1c <7%, and 46.4% had HbA1c <6%. Of the 772 youth achieving the target HbA1c <8%, 704 (91.2%) were randomized; non-adherence to metformin treatment was the main cause for non-randomization. Youth proceeding to randomization decreased weight by 0.68 kg and HbA1c by 1.45% compared to a weight gain of 0.71 kg and HbA1c decrease of 0.74% in the non-randomized youth ($p=0.01$ in both cases). Change in z-BMI was not significantly different between the two groups, however.

Conclusions—Most youth with recent onset type 2 diabetes can achieve target HbA1c <8.0% with short-term metformin monotherapy and standard diabetes education.

Keywords

type 2 diabetes; pediatric onset; clinical trial; metformin; hemoglobin A1c

Introduction

Rising rates of childhood obesity over the past two decades (1) have led to increased rates of type 2 diabetes in youth (2–5). The effectiveness of therapies used in adults with type 2 diabetes has not been well studied in youth with type 2 diabetes. Metformin monotherapy with standard diabetes education is generally recommended in adults with new onset type 2 diabetes, but limited data are available concerning this treatment approach in newly diagnosed youth. To address this, the National Institute of Diabetes and Digestive and Kidney Diseases funded a collaborative group to develop and conduct the TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) study, a randomized clinical trial comparing three therapies. Trial methods, rationale, design, and baseline participant characteristics at randomization have been reported (6,7). Briefly, the TODAY study had a screening phase and a run-in phase, followed by the randomized controlled trial. The pre-randomization run-in phase required participants to be weaned from any non-metformin diabetes treatments and to be treated with metformin monotherapy.

The youth entering the run-in phase of the TODAY trial can provide clinically relevant experience regarding success with metformin therapy aimed at achieving target HbA1c levels <8% as well as a description of the prevalence of co-morbid conditions in this cohort. The ethnic and geographic diversity of this sample of youth with type 2 diabetes adds to its clinical relevance and the generalizability of observations for the practicing clinician.

This report describes changes in glycemic control and weight management in obese youth with recently diagnosed type 2 diabetes participating in the TODAY pre-randomization run-in period, and compares those who achieved target HbA1c values and were randomized with those who were unable to meet criteria for randomization.

Methods

Study Design

The TODAY trial consisted of a screening phase and a run-in phase followed by the clinical trial. Screening (n=1,211) was conducted from May 2004 to September 2008 and aimed to identify eligible youth with antibody negative, c-peptide positive diabetes (6,8). The TODAY clinical trial (n=704 participants), conducted from November 2004 through February 2011, was a randomized, parallel-group clinical trial designed to evaluate the relative glycemic efficacy and safety of three treatments for type 2 diabetes in youth: metformin alone, metformin plus rosiglitazone, and metformin plus an intensive lifestyle program (6,7,9). Assignment to rosiglitazone was double blind, but assignment to the lifestyle program was not. Participants were recruited from 15 clinical centers (see study group listing in on-line appendix). Eligible youth were 10–17 years of age, diagnosed with type 2 diabetes <2 years, had a BMI 85th percentile at diagnosis of type 2 diabetes or at screening, were accompanied by an adult caregiver who agreed to support the youth's study participation, and were able to complete the run-in period successfully.

The protocol was approved by an External Evaluation Committee and by Institutional Review Boards at participating institutions. Participants provided informed consent and minors confirmed assent according to local guidelines. A Data and Safety Monitoring Board reviewed progress and safety regularly.

Run-in (Pre-Randomization) Period Objectives

After initial screening for eligibility, the run-in phase (n=927 participants) aimed to: (1) establish a relatively homogeneous study cohort regarding therapy prior to randomization; (2) determine participants' tolerance of metformin 1000 mg twice daily but no less than 500 mg twice daily; (3) discontinue other diabetes medications; (4) ensure glycemic control (HbA1c <8%) without ketonuria for at least 2 months with metformin monotherapy; (5) provide standard diabetes education with demonstration of participant mastery; and (6) assess ability of potential participants and their families to adhere to the protocol. The run-in phase lasted from 2 to 6 months; participants who did not complete an initial run-in period successfully could make a second attempt *de novo* starting with screening procedures if the reason for failure had been suitably addressed in the opinion of the site clinician.

Run-in Period Procedures

Participants completed tasks similar to those required once enrolled and randomized, e.g., taking study medications (2 capsules twice daily), completing nutrition and activity diaries, and keeping appointments. The metformin dose, masked to the participant/family, was titrated to study treatment level.

A standard diabetes education (SDE) program, developed for this study (10), was delivered by a certified diabetes educator (CDE) and materials were provided in a workbook in English or Spanish. Materials described type 2 diabetes physiology, treatment, blood glucose monitoring, record keeping, glycemic targets, healthy eating, and physical activity goals, and provided progressive skill building in a developmentally appropriate and culturally sensitive manner. Delivery options included in-person, group, or telephone sessions at the study site, the participant's home, or a mutual location such as a library, youth center, or restaurant. The education program consisted of a minimum of six sessions, each lasting 60–90 minutes and each ending with mastery activities.

Both participant and adult caregiver attended scheduled visits, which included HbA1c testing, at least every other month. Participants brought nutrition and activity logs to visits.

A 'no show' was defined as occurring when a scheduled visit was missed without the participant/family first calling to reschedule or cancel. Data collected included demographic characteristics, physical examination, anthropometrics, laboratory tests (blood and urine), medication counts, and mastery of SDE (6). Youth participants and family members were compensated for their travel to run-in visits.

Run-in Adherence Assessment

As the run-in phase aimed to establish target HbA1c values <8% with metformin monotherapy, non-metformin treatments were weaned and metformin was titrated to a minimum of 500 mg twice daily and a maximum of 1,000 mg twice daily. Study staff assessed the ability of participants and their families to adhere to study procedures, assessments, and interventions. Satisfactory completion of behavioral tasks, including monitoring and logging of glucose levels, taking study medication, keeping nutrition and activity logs, and attending scheduled visits, were examined and tallied according to checklists by clinic study staff for a two-month period. Adherence to metformin was measured by pill counts; adherence to scheduled blood glucose monitoring was determined by meter download. Clinic study staff reviewed participant nutrition and activity records and assessed their completeness and validity.

To achieve run-in adherence criteria, participants had to take at least 80% of their pills each week for 8 out of 12 weeks, were allowed no more than one missed ('no show') visit, and both youth and accompanying adult caregiver had to complete SDE with demonstrated mastery scores of at least 80% on all lesson quizzes and skills tests.

Laboratory and Physical Data

Blood samples were analyzed at the Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle (6). The Adult Treatment Panel III (ATPIII) guidelines were used to characterize lipid abnormalities (11). Blood pressure percentiles were determined using a CDC program that adjusted for sex, age, and height (12).

Data Analysis

Descriptive statistics are presented for the overall sample and comparing participants who successfully completed run-in and criteria necessary for randomization versus participants who failed to reach target HbA1c values <8% or other eligibility criteria for randomization. Comparisons were performed using analysis of variance for normally distributed continuous variables, the Kruskal-Wallis test for non-normally distributed continuous variables, and the chi-square test for categorical variables. A p-value <0.05 was considered significant, with no adjustment for multiple comparisons.

Results

Reasons for non-randomization following run-in

The 223 subjects not randomized were classified according to single major reason for ineligibility. One-quarter (25.9%, n=58) did not achieve HbA1c levels <8%, 10.4% (n=23) could not be weaned from other hypoglycemic medications (e.g., insulin), and 8.5% (n= 19) could not tolerate metformin at study levels. Nearly half (45.3%, n=101) of those failing run-in were non-adherent to metformin therapy (representing 10.9% of the 927 subjects enrolled in run-in). Other reasons for failure to advance to randomization included study visit nonattendance (0.9%), inability to master SDE (0.9%), safety concerns (2.4%, e.g., abnormal LFTs), and subject refusal to proceed with study participation (5.7%).

Characteristics of run-in participants

As shown in Table 1, 65.4% of participants were female, 81.7% belonged to racial/ethnic minority groups, mean age was 13.7 years, median time from diagnosis of type 2 diabetes was 63 days, less than half (42.5%) were receiving some form of hypoglycemic treatment, and 91.9% lived with at least one biological parent. Most (86.7%) presented with acanthosis nigricans and, as expected according to eligibility criteria, were obese (average BMI 35.6 m/kg² and z-BMI 2.3). Mean HbA1c at entry into run-in was 7.7% and almost two-thirds (64.4%) met the level required for randomization of <8%.

Glycemic control with metformin monotherapy during run-in

Of the 927 run-in participants, 90.9% achieved HbA1c <8%, 77.9% achieved HbA1c <7%, and 46.4% achieved HbA1c <6%. Of the 772 who reached target HbA1c <8%, only 704 (91.2%) also met all randomization criteria for enrollment into the TODAY clinical trial. Of the 223 participants who did not meet inclusion criteria for randomization at the end of run-in, 105 were unable to achieve HbA1c <8% on metformin monotherapy. Only a few individuals who failed the initial run-in made a second attempt starting *de novo* with screening and a second run-in period; 10 (1.4%) of the 704 participants subsequently randomized underwent a second run-in period compared with 15 of the 223 who did not qualify for randomization (6.7%).

In addition to the difference in glycemic control between those proceeding to randomization and those not, the non-randomized subgroup had a longer duration of type 2 diabetes compared to those randomized (median 86 and 56 days, respectively, $p<0.01$). There was also a modest difference in the racial distribution between groups, with a slightly higher percentage of non-Hispanic Black participants and a slightly lower percentage of Hispanic and non-Hispanic White participants in the non-randomized group compared with the randomized group ($p=0.02$).

During run-in, weight decreased by a mean of 0.68 kg in participants meeting the randomization criteria, while there was a mean weight gain of 0.71 kg in the non-randomized group (Table 2, $p<0.01$). Figure 1A shows the distribution of weight loss in 2 kg increments in the two groups. The change in weight did not translate into significant change in z-BMI during the run-in interval.

Initial and final run-in HbA1c levels differed significantly between the randomized and the non-randomized participants with means of 7.5% and 8.5%, respectively ($p<0.0001$), at screening and 6.0% and 8.0%, respectively ($p<0.01$), at the end of the run-in period. Over two-thirds of those who proceeded to randomization had acceptable HbA1c levels <8% initially compared to only half of those who did not (Table 1). There was a significantly greater improvement in glycemic control in those randomized, with an HbA1c decrement of 1.45% versus 0.74% in those non-randomized ($p<0.01$). Figure 1B shows the distribution of change in HbA1c. There were 11 participants (8 who proceeded to randomization) who reduced their HbA1c by >7%; all began run-in with values >12%. C-peptide levels were not different between those who were randomized and those who were not (Table 1).

Co-morbid Conditions

There was a substantial presence of co-morbid indicators in this cohort (see bottom of Table 2). Overall, 18.8% of participants had a blood pressure >95th percentile according to age, gender, and height, 37.6% had LDL-cholesterol ≥100 mg/dL, 24.2% had total cholesterol ≥180 mg/dL, and 6.5% had abnormal liver function tests. There was no difference in blood pressure, LDL-cholesterol, or liver function tests between those randomized and those not. Mean total cholesterol was significantly lower in the former group (156.3 mg/dL) compared

to the latter failure group (168.7 mg/dL, $p<0.01$). Average triglycerides were significantly higher in non-randomized participants (195.4 mg/dL and 127.0 mg/dL, respectively, $p<0.01$) and correlated with their HbA1c ($r=0.07$, $p=0.03$). Higher mean HDL-cholesterol was evident in the non-randomized group (41.6 mg/dL) versus the randomized group (39.8 mg/dL) and related to higher total cholesterol.

Discussion

Reports of the early management of type 2 diabetes in youth is limited. It is unclear if response to therapy in this age group is similar to that observed in adults or if the course of the disease in youth is more aggressive. The TODAY study is the largest clinical trial of treatment regimens for pediatric type 2 diabetes and addresses some of these issues. Examination of the pre-randomization period of this trial provided the opportunity to understand better the short-term responsiveness of youth early in the course of their type 2 diabetes to metformin monotherapy, the initial therapy generally recommended for adults with type 2 diabetes. The finding that 90.9% of the 927 participants who entered run-in achieved or maintained HbA1c $<8\%$ suggests that metformin monotherapy can be effective in youth with type 2 diabetes, at least early in the course of the disease.

There were differences between those who did and did not meet randomization criteria. Not surprisingly, a greater proportion of those who successfully completed the run-in period had HbA1c levels $<8\%$ at the screening visit. Duration of type 2 diabetes was about one month longer in the non-randomized group. There were more non-Hispanic Blacks and fewer Hispanics and non-Hispanic Whites in the group that did not meet randomization criteria. All youth in the TODAY study were required to enroll with a committed adult caregiver who would also participate. Family support has consistently been associated with improved youth outcomes (13–15). Very few ($<1\%$) failed run-in due to visit nonattendance.

The primary reasons for failure to randomize were related to diabetes treatments and included inability to adhere to metformin dosing schedule. While $\sim 45\%$ of the failure group was unable to demonstrate medication adherence, this represents only about 11% of all those who entered run-in. As for the main trial, the run-in period required twice daily treatment with a short-acting metformin preparation. Adherence might have been improved if long-acting metformin preparations had been available. The demographics of the TODAY run-in participants are similar to those reported by the population-based cohort in the SEARCH study (16,17). Co-morbid conditions were similarly prevalent in this sample. Triglycerides were the only co-morbid condition associated with randomization status; however, we cannot infer a causal relationship as triglyceride levels may have been a proxy for glycemic control.

In conclusion, the TODAY pre-randomization experience supports the current practice of using metformin as initial oral therapy in youth with new onset type 2 diabetes along with standard diabetes education. Knowledge gained about co-morbidities, family support, etc. may prove useful to other researchers and clinicians dealing with this patient population. The 704 youth randomized to the 3 treatment intervention arms ended participation in TODAY after 2–6 years of treatment. Future findings should provide additional needed guidance concerning treatment approaches for youth with type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ATPIII	Adult Treatment Panel III
BMI	Body Mass Index
CDE	Certified Diabetes Educator
LFT	Liver Function Tests
SDE	Standard Diabetes Education
TODAY	Treatment Options for type 2 Diabetes in Adolescents and Youth

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Figure 1. Distribution of Change in Weight and HbA1c of Participants during Run-in (Pre-Randomization Phase) of TODAY

Figure 1A. The 704 participants who met all randomization criteria, including HbA1c <8% on metformin monotherapy, experienced significantly more weight loss than the 223 who did not meet criteria. Six participants lost >10 kg (5 among the successes and 1 among the failures).

Figure 1B. A greater proportion of the 704 participants who met all randomization criteria, including HbA1c <8% on metformin monotherapy, experienced a decline in HbA1c compared with the 223 who did not meet criteria. Eleven participants had HbA1c decline by >7% during run-in (8 among the successes and 3 among the failures).

Table 1

Characteristics* of Participants at Start of Run-in

	OVERALL (N=927)	RANDOMIZED		P-value
	YES (N=704)	NO (N=223)		
Age (years)	13.7 (2.0)	13.7 (2.0)	13.9 (2.0)	0.10
Duration of diabetes (days)				<0.01
25 th percentile	22	20.5	31	
50 th percentile	63	56.5	86	
75 th percentile	203	182.5	286	
Gender female	65.4%	64.9%	66.8%	0.60
On diabetes treatment	42.5%	41.3%	46.2%	0.20
BMI (m/kg ²)	35.6 (7.6)	35.5 (7.5)	36.0 (7.8)	0.39
z-BMI	2.3 (0.4)	2.3 (0.4)	2.3 (0.4)	0.99
Acanthosis present	86.7%	86.6%	87.3%	0.77
HbA1c (%)	7.7 (2.2)	7.5 (2.0)	8.5 (2.6)	<0.01
HbA1c (categories)				
< 8%	64.4%	69.1%	49.5%	
8–10%	19.4%	18.2%	23.2%	
> 10%	16.2%	12.5%	27.3%	
C-peptide (ng/mL)	4.0 (2.1)	4.1 (2.1)	3.9 (2.1)	0.38
Race/ethnicity [†]				0.02
American Indian	6.2%	6.1%	6.5%	
Non-Hispanic Black	34.3%	31.5%	43.2%	
Hispanic	39.5%	41.1%	34.6%	
Non-Hispanic White	18.3%	19.6%	14.3%	
Asian	1.7%	1.7%	1.4%	
Living with biological parents				0.24
Both	38.1%	38.8%	36.1%	
Mother only	49.0%	46.9%	55.6%	
Father only	4.8%	5.1%	3.7%	
Neither	8.1%	9.2%	4.6%	

* Mean (sd), percent, or percentile.

[†] Race/ethnicity was determined by self report on two separate items. For data analysis, 25 (3.6%) who reported belonging to more than one racial group were assigned to a racial/ethnic group according to the following priority of risk for type 2 diabetes in youth: AI > Hispanic > NHB > NHW (5).

Table 2

Participant Characteristics and Outcomes during Run-in

	OVERALL	RANDOMIZED		<i>P-value</i>
	(N=927)	YES (N=704)	NO (N=223)	
<i>25th, 50th, 75th percentiles</i>				
Days from screening to run-in	18, 25, 36	18, 25, 35	19, 27, 45	
Run-in length (days)	59, 70, 91	62, 71, 89	23, 57, 109	
		<i>mean (SD) or %</i>		
Weight change [*] (kg)	−0.43 (4.01)	−0.68 (3.91)	0.71 (4.27)	<0.01
z-BMI change [*]	−0.046 (0.123)	−0.049 (0.108)	−0.033 (0.177)	0.15
HbA1c [†] change [*]	−1.33 (1.91)	−1.45 (1.84)	−0.74 (2.14)	<0.01
Last HbA1c				
< 8%	90.9%	100.0%	46.9%	
8–10%	6.0%	--	35.2%	
> 10%	3.1%	--	17.9%	
Co-morbid conditions [‡]				
Total cholesterol (mg/dL)	159.3 (43.5)	156.3 (36.8)	168.7 (59.0)	<0.01
HDL cholesterol (mg/dL)	40.2 (9.9)	39.8 (9.4)	41.6 (11.4)	0.02
Triglycerides (mg/dL)	143.5 (332.7)	127.0 (90.9)	195.4 (657.0)	<0.01

* Change from screening visit to final run-in visit.

[†] HbA1c sample size N=704 for randomized and N=145 for non-randomized for an overall N=849.

[‡] Only statistically significant variables are given; those tested but not significant were systolic blood pressure, diastolic blood pressure, LDL cholesterol, and liver function tests.