Safety and Tolerability of the Treatment of Youth-Onset Type 2 Diabetes

The TODAY experience

TODAY Study Group*

OBJECTIVE—Data related to the safety and tolerability of treatments for pediatric type 2 diabetes are limited. The TODAY clinical trial assessed severe adverse events (SAEs) and targeted nonsevere adverse events (AEs) before and after treatment failure, which was the primary outcome (PO).

RESEARCH DESIGN AND METHODS—Obese 10- to 17-year-olds ($N = 699$) with type 2 diabetes for <2 years and hemoglobin A_{1c} (A1C) ≤8% on metformin monotherapy were randomized to one of three treatments: metformin, metformin plus rosiglitazone (M + R), or metformin plus lifestyle program (M + L). Participants were followed for 2–6.5 years.

RESULTS—Gastrointestinal (GI) disturbance was the most common AE (41%) and was lower in the M + R group ($P = 0.018$). Other common AEs included anemia (20% before PO, 14% after PO), abnormal liver transaminases (16, 15%), excessive weight gain (7, 9%), and psychological events (10, 18%); the AEs were similar across treatments. Permanent medication reductions/discontinuations occurred most often because of abnormal liver transaminases and were lowest in the M + R group ($P = 0.005$). Treatment-emergent SAEs were uncommon and similar across treatments. Most (98%) were unrelated or unlikely related to the study intervention. There were no deaths and only 18 targeted SAEs (diabetic ketoacidosis, $n = 12$; severe hypoglycemia, $n = 5$; lactic acidosis, $n = 1$). There were 62 pregnancies occurring in 45 participants, and 6 infants had congenital anomalies.

CONCLUSIONS—The TODAY study represents extensive experience managing type 2 diabetes in youth and found that the three treatment approaches were generally safe and well tolerated. Adding rosiglitazone to metformin may reduce GI side effects and hepatotoxicity.

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Diabetes is increasing in prevalence worldwide and results in considerable morbidity and mortality at an estimated annual cost of more than $174 billion in the U.S. alone (1). Although typically a disease of adults, over the last two decades type 2 diabetes has become an important pediatric disorder. On the basis of data from the SEARCH for Diabetes in Youth Study Group (2) and a review by Fagot-Campagna et al. (3), by the mid-1990s, type 2 diabetes accounted for 16–45% of youth with diabetes in the U.S. (3), and by 2001 this had risen to 22–76% (2), depending on race/ethnicity and geographic location. Despite the growing prevalence of youth-onset type 2 diabetes, long-term experience to define the efficacy and safety of treatment approaches is limited. Only metformin and insulin currently are approved by the Food and Drug Administration for treatment of type 2 diabetes in children.

The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial was designed to address the safety and efficacy of three distinct approaches to treatment of youth-onset type 2 diabetes. The rationale, design, and methods (4), baseline characteristics of the cohort (5), and primary outcomes (POs) (6) have been reported previously. The purpose of this article is to report the safety, tolerability, and event rates of the interventions used in TODAY, paying particular attention to the side effects of metformin (gastrointestinal [GI] symptoms, anemia, lactic acidosis) and rosiglitazone (hepatotoxicity, anemia, edema, weight gain, heart failure, fractures) previously reported in adults.

RESEARCH DESIGN AND METHODS

Study design

The TODAY study design and methods have been reported previously (4). Briefly, TODAY was a multicenter, randomized, three-arm, parallel-group clinical trial funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health. The collaborative study group included 15 clinical centers and a data coordinating center (these centers are listed in the Supplementary Data). Participants who met eligibility criteria at the end of run-in were randomized (1:1:1) to one of three groups: *1*) metformin alone (1,000 mg twice daily) (M); *2*) metformin plus rosiglitazone (4 mg twice daily) (M + R); or *3*) metformin plus an intensive lifestyle intervention (M + L) (7). Assignment to the M or M + R groups was double-blinded. Participants were recruited over 4.5 years and followed for 2–6.5 years.

The PO of TODAY was time to treatment failure, defined as either *1*) hemoglobin A_{1c} (A1C) ≥8% sustained for 6 months or *2*) the inability to wean from insulin within 3 months after acute metabolic decompensation. After reaching PO, rosiglitazone was discontinued, metformin was continued, and insulin glargine was started and titrated to achieve the glycemic target.

The protocol was approved by an external evaluation committee convened by the NIDDK and by the institutional

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*A complete list of the members of the TODAY Study Group can be found in the Supplementary Data online. The members of the writing group are listed in the APPENDIX.

See accompanying articles, pp. 1732, 1735, 1742, 1749, 1758, 1772, 1775, and 1777.

review board for the protection of human subjects of each participating institution. All participants provided informed consent and minor children confirmed assent according to local guidelines. An independent data and safety monitoring board (DSMB) convened by NIDDK reviewed progress, safety, and interim analyses throughout the study.

Study sample

Eligibility criteria included age 10–17 years (inclusive), type 2 diabetes based on American Diabetes Association criteria (8) for <2 years at randomization, BMI higher than the 85th percentile for age and sex, and the ability to complete a 2- to 6-month run-in period taking metformin monotherapy with A1C <8%. Exclusion criteria relevant to safety included creatinine clearance <70 mL/min/1.73 m^2; hepatic transaminase (aspartate aminotransaminase [AST] or alanine aminotransferase [ALT]) >2.5 times the upper limit of normal (×ULN); hematocrit (Hct) <30% or hemoglobin (Hgb) <10 g/dL; or women who were pregnant, planning pregnancy, or failed to practice appropriate contraception.

A total of 699 participants were randomized and monitored every 2 months in the first year and quarterly thereafter. Study visits included physical examination (including blood pressure, assessment of peripheral edema, anthropometrics); laboratory assessments (A1C, Hgb/Hct, AST/ALT, serum creatinine, vitamin B_{12}); and assessments of interim adverse events (AEs).

Recording and reviewing of adverse events

The TODAY clinical trial assessed serious AEs (SAEs) and targeted nonserious AEs before and after PO. The Supplementary Data gives definitions and study-specific responses for targeted AEs and definitions for study-specific SAEs.

Adverse events. Targeted nonserious AEs were recorded using an electronic online Safety and Comorbidity Tracker developed for TODAY and were reviewed regularly by the safety and monitoring committee (SMC) that was blinded to treatment group. The purposes of tracking AEs were to *1*) identify treatment-related AEs and facilitate adherence to study-specified guidelines and algorithms, *2*) determine whether AEs were occurring at a higher than anticipated overall rate or a disproportionate rate at one center compared with others, and *3*) permit tabulation of rates of AEs associated with study interventions. Targeted nonserious AEs included clinically manifest heart failure, anemia, renal impairment, excessive weight gain (defined as a >10% increase in BMI between visits), edema, psychological events, recurrent mild hypoglycemia, GI symptoms, and mildly (1.5–2.5 ×ULN) or definitively elevated (>2.5 ×ULN) AST, ALT, or both.

Serious adverse events. SAEs were classified as *1*) death, *2*) life threatening medical event, *3*) birth of a baby with a congenital anomaly, *4*) hospitalization or prolongation of hospitalization, *5*) disability, *6*) overdose of study medication, or *7*) event requiring intervention to prevent an SAE. In addition, the study specified the following SAEs of particular interest: severe hypoglycemia, diabetic ketoacidosis (DKA), and lactic acidosis. Causation of SAEs was assigned by the investigator as not, unlikely, possibly, or probably related to study participation or interventions. Using the SAE Tracker, each SAE was reviewed by the TODAY SMC (see below).

Safety monitoring. An SMC consisting of study group members held biweekly conference calls to review events and other issues related to safety. SMC members were masked to treatment group assignments and the chair reported any concerns to the Committee for Oversight of Procedures and the steering committee. Any event category that occurred more often than a predetermined frequency was referred to the Committee for Oversight of Procedures to consider a need for further referral to the independent DSMB. Before participant enrollment, the DSMB developed criteria for interim assessment of safety and treatment success or futility. The DSMB met twice yearly (and as needed) for unmasked assessments.

Statistical methods

Descriptive statistics are reported as median, mean ± SD, or percentage. The number of participants experiencing AEs and SAEs were analyzed using logistic regression (SAS PROC GENMOD, version 9.2; SAS Institute Inc., Cary, NC). Rates and counts of AEs and SAEs were analyzed using zero-inflated Poisson regression (SAS PROC GENMOD). To examine whether any AEs of treatments were altered by discontinuation of rosiglitazone and initiation of insulin therapy (Lantus, Sanofi-Aventis, Bridgewater, NJ) at the time of PO, the effect of treatment group, after adjusting for sex, race/ethnicity, age at baseline, and economic status, was analyzed separately before and after PO or censoring (i.e., study termination without PO). Analyses included all randomized participants in their assigned treatment groups. The study was powered for the PO only; the secondary outcomes reported here are considered exploratory. $P < 0.05$ is considered statistically significant.

RESULTS—Characteristics of the randomized cohort overall and by group are shown in Table 1. Participants were 14.0 ± 2.0 years old and had diabetes for 7.8 ± 5.8 months at the time of randomization. Nearly two-thirds were women; about 80% were from racial/ethnic minority groups (32.5% non-Hispanic black, 39.7% Hispanic, 5.9% American Indian, 1.6% Asian) and 20.3% were non-Hispanic white. There were no statistical differences for any baseline variable by treatment group.

Targeted adverse events

The number of participants experiencing targeted AEs by treatment group assignment, before and after reaching PO, is shown in Table 2. Forty percent reported GI symptoms before PO and 44% after PO. Before PO, fewer participants reported GI symptoms in the M + R group (33 vs. 41% in the M group and 45% in the M + L group; $P = 0.0054$). Only five participants required protocol-driven medication dose reductions because of GI symptoms. The only two AEs that occurred with a frequency exceeding the predetermined thresholds for concern (3% in both cases) were definitively elevated liver transaminases (>2.5 ×ULN) and excessive weight gain (defined as a >10% increase in BMI between visits). After exceeding the threshold, these events were tracked in an unblinded manner by the DSMB, which identified no concerns. Definitively elevated liver transaminases occurred in 5.7% of the participants before PO and 5.0% after PO and were not significantly different among treatment groups. Mildly elevated transaminases (1.5–2.5 ×ULN) occurred in 10% before PO and 10% after PO. Before PO there was no difference among treatment groups, but after PO there was marginal significance across groups for mildly elevated transaminases ($P = 0.048$). Excessive weight gain occurred in 6.9% before PO and 8.8% after PO. There was no statistically significant difference among treatment groups for our defined AE of excessive weight gain.

Table 1—*Baseline characteristics overall and by treatment group*

Characteristics	Overall (N = 699)	Metformin (n = 232)	M + R (n = 233)	M + L (n = 234)
Age (years)	14.0 ± 2.0	14.1 ± 1.9	14.1 ± 2.1	13.8 ± 2.0
Duration of diabetes (months)	7.8 ± 5.8	7.8 ± 6.0	8.0 ± 5.7	7.6 ± 5.8
Female sex (%)	64.9	63.1	65.7	66.0
BMI (kg/m^2)	34.9 ± 7.6	35.8 ± 8.1	35.0 ± 7.7	34.1 ± 7.1
BMI z score	2.23 ± 0.47	2.27 ± 0.45	2.22 ± 0.49	2.19 ± 0.48
A1C (%)	7.1 ± 2.2	7.3 ± 2.2	7.0 ± 2.3	7.1 ± 2.2
Hemoglobin (mg/dL)	13.4 ± 1.6	13.4 ± 1.6	13.4 ± 1.6	13.4 ± 1.5
Hematocrit (%)	39.6 ± 4.0	39.6 ± 4.1	39.7 ± 4.1	39.6 ± 3.9
AST/SGOT (U/L)	26.9 ± 21.1	28.5 ± 23.8	25.8 ± 20.4	26.2 ± 18.7
ALT/SGPT (U/L)	34.0 ± 33.7	37.1 ± 34.4	30.5 ± 29.3	34.1 ± 36.5
Creatinine clearance (mL/min)	158 ± 37	162 ± 36	157 ± 40	156 ± 35

Data are presented as mean ± SD unless otherwise indicated. SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase.

Anemia occurred in 20% of participants before PO and 14% after PO. There was no difference in the percentage of participants experiencing anemia among treatment groups before PO, but after PO more participants in the M group experienced anemia than in the M + R group (19 and 10%, respectively; P = 0.014). The occurrence of repeated mild hypoglycemia was low (3.9% before and 2.5% after PO). Before PO, the percentage of participants experiencing repeated mild hypoglycemia was similar between groups. However, when the M + R group was compared with the other two (non-rosiglitazone) groups combined, more participants taking rosiglitazone (6.9%) experienced repeated mild hypoglycemia than those not taking rosiglitazone (2.4%; P = 0.03). After PO, fewer participants experienced repeated mild hypoglycemia in the M + L group (0.9%) compared with M + R (3.3%; P = 0.020) and M (3.3%; P = 0.013) groups. Except for psychological events, which occurred in 10% before and 18% after PO, the remaining AEs were infrequent, such that an assessment of between group differences was not possible.

Table 3 shows the number of targeted AEs (per 100 participant-years of exposure) by treatment group assignment before and after reaching PO and represents 1,782 participant-years of exposure before PO and 876 participant-years after PO. In Table 3, participants could be recorded as experiencing multiple episodes of an event if the event resolved and then recurred. It should be noted that upon reaching PO, rosiglitazone was discontinued in all participants. Only edema before PO showed a difference between groups (1.26 in the M, 0.97 in the M + R, 0.33 in the M + L groups; P = 0.029), with only the significant difference that between M + L and M groups.

Although rosiglitazone has been reported to increase the risk of bone fractures (9), after controlling for age, sex, race/ethnicity, and socioeconomic status (household income and education at baseline), there was no difference in fracture rate among treatment groups.

Serious adverse events

Table 4 shows SAEs overall and by study group assignment before and after PO; 42 events were recorded in more than one category. Most categories contained insufficient numbers of events to be statistically meaningful, and there were no differences among the groups in the categories for which analysis was possible. Hospitalization was responsible for 91 and 94% of the SAEs before and after PO, respectively. The vast majority of SAEs (89%) were not related to study participation or intervention and 98% were either not or unlikely related. Only two SAEs were deemed probably related and two possibly related. Of these four events, two were severe hypoglycemia, one was hypoglycemia resulting in hospitalization, and one was an episode of DKA occurring in a participant for whom study medication had been discontinued for safety reasons (definitively elevated transaminases; see below). There were no participant deaths during the TODAY study. There were 12 cases of DKA (in 11 participants) and 5 occurrences (in 5 participants)

Table 2—*Participants with targeted adverse events overall and by treatment group*

	Before primary outcome					After primary outcome				
AEs	Overall (N = 699)	M (n = 232)	M + R (n = 233)	M + L (n = 234)	P*	Overall (N = 319)	M (n = 120)	M + R (n = 90)	M + L (n = 109)	P*
Heart failure	0	0	0	0	—	1	0	1	0	—
Anemia	140	50	50	40	0.3795	45	23	9	13	0.0367[a]
Renal impairment	2	0	1	1	—	0	0	0	0	—
LFTs										
1.5–2.5 × ULN	73	27	21	25	0.6496	32	17	8	7	0.0482[a]
>2.5 × ULN	40	18	9	13	0.1260	16	4	2	10	0.0906
Edema	9	3	4	2	0.4729	5	1	1	3	—
Excessive weight gain	48	10	21	17	0.3592	28	6	13	9	0.4665
Psychological	69	19	25	25	0.4885	58	22	12	24	0.3016
Repeated mild hypoglycemia	27	5	16	6	0.0939	8	4	3	1	0.0286[b,c]
GI symptoms	280	96	78	106	0.0181[c]	139	55	36	48	0.2753

LFT, liver function test. *Event categories with no P value recorded had too few events to be statistically analyzed. [a]M vs. M + R significant. [b]M vs. M + L significant. [c]M + R vs. M + L significant.

Table 3—*Number of targeted adverse events per 100 participant-years of exposure overall and by treatment group*

	Before primary outcome					After primary outcome				
AEs	Overall	M	M + R	M + L	*P**	Overall	M	M + R	M + L	*P**
Participant-years of exposure (per 100 years)	17.82	5.56	6.18	6.08		8.76	3.40	2.43	2.93	
Heart failure	0.00	0.00	0.00	0.00	—	0.11	0.00	0.41	0.00	—
Anemia	11.11	12.59	11.65	9.20	0.6130	6.28	7.95	4.12	6.13	—
Renal impairment	0.11	0.00	0.16	0.16	—	0.00	0.00	0.00	0.00	—
LFTs										
1.5–2.5 × ULN	4.66	5.94	3.72	4.44	0.7186	4.34	6.18	4.12	2.39	—
>2.5 × ULN	2.58	3.96	1.78	2.14	0.1289	2.05	1.18	0.82	4.09	—
Edema	0.84	1.26	0.97	0.33	0.0285[a]	0.80	0.59	0.41	1.36	—
Excessive weight gain	2.75	1.80	3.40	2.96	0.4801	3.54	1.77	6.59	3.07	—
Psychological	4.71	4.50	4.85	4.77	0.9745	8.22	7.36	7.82	9.54	0.3958
Repeated mild hypoglycemia	1.96	1.26	3.40	1.15	0.1528	0.91	1.18	1.24	0.34	—
GI symptoms	26.03	27.35	22.82	28.10	0.4172	26.60	25.61	26.77	27.60	0.4715

LFT, liver function test. *Event categories with no *P* value recorded had too few events to be statistically analyzed. [a]M vs. M + L significant.

of severe hypoglycemia. Despite a study requirement for appropriate contraceptive measures while taking study medication, there were 62 pregnancies in 45 participants during the TODAY study, and 6 (10%) were associated with a congenital anomaly. For those planning pregnancy, study medication was discontinued before attempts at conception. For those young women who became unexpectedly pregnant, study medication was discontinued at the first indication of pregnancy. Pregnancy tests were performed on all female participants at every visit. The 14 life-threatening SAEs were not significantly different among groups; of these, 7 were psychiatric hospitalizations due to suicidal ideation/attempt, 2 were DKA, 1 was severe hyperglycemia and ketosis (without acidosis), 2 were infections (one associated with a deep vein thrombosis, the other a postpartum infection), and 1 was lactic acidosis associated with asthma. This case of lactic acidosis (lactate level 9.8 mmol/L) occurred in a 15-year-old girl assigned to the M group during a severe asthma exacerbation. Aside from asthma, she was asymptomatic and the elevated lactate resolved within 12 h of asthma treatment. This was assessed by the local investigator and the SMC and determined to be unlikely related to metformin use. A single event of congestive heart failure occurred 6 days postpartum after a pregnancy complicated by hypertension. Although this occurred in a participant in the M + R group, the subject already had been off rosiglitazone for approximately 2 years 9 months before the heart failure developed. Therefore, this event was classified as not related to study intervention or participation. No life-threatening SAEs were classified as probably related, and the only one classified as possibly related to study participation was an episode of DKA occurring in a participant for whom study medication was discontinued 2 months earlier because of definitively elevated liver transaminases (AST, 211 IU/L; ALT, 256 IU/L).

Discontinuations of study medication and primary outcome

The TODAY protocol specified blinded dose reduction/discontinuation in response to certain targeted AEs (definitively elevated transaminases, severe hypoglycemia, intercurrent illness, edema, anemia, and renal impairment). Overall, 85 AEs occurring in 67 participants (9.6%) resulted in protocol-driven discontinuation of study medication or permanent dose reduction, consistent with protocol-driven safety algorithms; 65% of these medication alterations (55 of 85 occurring in 42 participants) were due to elevated liver transaminases. Adjustment because of transaminase elevation was significantly different among treatment groups (28 in the M group, 8 in the M + R group, 19 in the M + L group; *P* =

Table 4—*Serious adverse events overall and by treatment group*

	Before primary outcome				After primary outcome			
SAEs	Overall (*n* = 119)	M (*n* = 28)	M + R (*n* = 33)	M + L (*n* = 58)	Overall (*n* = 144)	M (*n* = 49)	M + R (*n* = 46)	M + L (*n* = 49)
Life threatening	8	4	1	3	6	1	5	0
Hospitalization	108	24	32	52	136	47	45	44
Disability	1	0	0	1	0	0	0	0
Requires intervention to prevent SAE	15	6	2	7	12	3	3	6
Congenital abnormality*	2	1	0	1	4	1	0	3
Event from overdose of study medication	0	0	0	0	2	0	0	2
Lactic acidosis	1	1	0	0	0	0	0	0
Severe hypoglycemia	4	0	1	3	1	1	0	0
DKA	3	2	1	0	9	4	2	3

Rows below do not sum to total because each event could have more than one summary characteristic checked. *Of 62 pregnancies in 45 participants.

0.005). The remaining events were of such low frequency that no group differences could be detected. A post hoc analysis of the effect of certain presumed side effects of rosiglitazone (edema, elevated transaminases) upon medication dose reductions showed that the rate of dose alterations due to liver transaminase elevations differed in the M + R group. A lower rate was observed in the participants treated with rosiglitazone than in those not taking rosiglitazone (0.93 vs. 2.61 per patient-year; $P < 0.005$). Finally, those who had discontinued permanently or reduced study medication did not reach PO sooner than those who did not.

Anemia and plasma vitamin B_{12} concentrations

Anemia was diagnosed in 20% of participants before PO, whereas 14% had either an initial diagnosis or a reoccurrence after PO. Before PO, cases of anemia occurred almost equally among all three treatment groups. After PO, there were more anemia events in the M group compared with the M + R group. Only a single participant in the M + L group required a permanent reduction in medication dose because of anemia. Since all participants in this trial were taking metformin, which can impair absorption of vitamin B_{12} (10,11) and contribute to anemia, we examined plasma concentrations of vitamin B_{12} in all participants. Additional tests to identify the causes of anemia (such as iron studies) were performed at the discretion of local clinic staff, but these data were not collected for analysis. Median vitamin B_{12} concentrations were similar across treatment groups at baseline and 2 years, and the proportion of participants with vitamin B_{12} concentrations in the deficient (<203 pg/mL), borderline (203–299 pg/mL), and normal (≥300 pg/mL) ranges were also similar among treatment groups. There was no meaningful change in vitamin B_{12} concentrations over time. When classified as deficient, borderline, or normal, lower vitamin B_{12} concentrations were significantly associated with anemia. At 2,695 participant visits during which both Hgb/Hct and vitamin B_{12} were assessed, 315 participants had anemia and, of these, 100 were associated with deficient or borderline vitamin B_{12} values. Those study participants who had anemia tended to have lower vitamin B_{12} concentrations at the visit at which anemia was detected than those without anemia (median 355 with vs. 408 without; $P < 0.0001$). These median values were, however, in the normal range. The prevalence of anemia among women was more than twice that of men (32 vs. 15%; $P < 0.0001$).

CONCLUSIONS—Our data demonstrate that the three treatment approaches are all generally safe and well tolerated by adolescents. Other than a high rate of reported GI disturbances (41%), there were few treatment-related AEs overall and little difference in the frequency of AEs and SAEs among treatment groups. The high rate of GI events is not unexpected because all participants were taking metformin, which has been associated with GI symptoms in more than a quarter of children (12) and adults (13) in clinical trials of shorter duration. The prevalence of GI events in the M + R group (33%) was significantly lower than in the M + L (45%) or the combined nonrosiglitazone (43%) groups. The reason for this difference is unclear, but it cannot be attributed to any disparity in metformin dose or medication compliance, which were similar among the three treatment arms (6).

It is notable that the M + R group did not have more AEs than the other two groups. Peripheral edema and excessive weight gain are known adverse effects of rosiglitazone as well as other thiazolidinediones (14–18). However, peripheral edema occurred in only 1.7% of participants in the M + R group, which was not significantly more than in the other two groups and compares favorably to the 4–6% occurrence of edema in similar trials of adults (17,18). In addition, using the protocol-defined AE criteria set a priori (>10% increase in BMI between visits), excessive weight gain occurred in 9.0% of the M + R group compared with 4.3 and 7.3% in the M and M + L groups, respectively (not statistically significant). The study has reported gains in BMI in the M + R group, which increased significantly more over 60 study months than BMI in either the M or M + L groups (6). The apparent contradiction between equivalent incidence of excessive weight gain between 3-month visits across treatment and significantly higher BMI across 60 months in the M + R group can be explained by the specificity of the study's definition of excessive weight gain as an AE, which was designed primarily to provide an early signal of safety concerns. Studies of overweight adults treated with rosiglitazone have shown a gain in BMI ranging from 1.1 kg/m^2 after 12 weeks (17) to 0.35 after 24 weeks (15), which compares to about 0.4 at 12 weeks and 0.7 at 24 weeks among participants in TODAY's M + R group (6). Weight gain from rosiglitazone seems to be a potential problem in children and adolescents, as it is in adults.

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of elevated liver transaminases in the U.S. and is strongly associated with type 2 diabetes (19). Because of hepatotoxicity associated with troglitazone, we were particularly concerned about potential hepatic effects of rosiglitazone. Although liver transaminase elevations were common, there were no significant differences in the event rates of mildly or definitively elevated liver transaminases among the treatment groups either before or after PO (Table 3). Therefore, based on 1,782 patient-years of experience during the TODAY study, there is no evidence of hepatotoxicity related to rosiglitazone in youth with type 2 diabetes. Furthermore, the need for permanent dosage reductions and medication discontinuations due to elevated liver transaminases was significantly lower in the M + R group.

The etiology of the elevated transaminases was not formally evaluated as part of this study. Nonetheless, participants with abnormal AST or ALT levels underwent an evaluation for other causes of liver disease. In the preponderance of cases, no genetic, infectious, or autoimmune cause of elevated transaminases was identified. Therefore, we suspect that the high rate of abnormal liver transaminases reflects a high prevalence of NAFLD in these obese pediatric participants with type 2 diabetes. The prevalence of NAFLD in obese children is estimated to be 9.6% (20), and this incidence is estimated to approach 50% in obese youth with type 2 diabetes (21). Because hepatic steatosis is strongly associated with insulin resistance (22), the high incidence of elevated liver transaminases in the TODAY study likely reflects the magnitude of hepatic insulin resistance in children with type 2 diabetes. Examining the effect of insulin-sensitizing agents on NAFLD, Nadeau et al. (21) reported that five of six children with type 2 diabetes showed an improvement in liver transaminases after treatment. We postulate that the trend toward decreased frequency of transaminase abnormalities and the reduced number of medication dose adjustments in the M + R group may be the result of improved insulin

sensitivity (23). Similar effects of rosiglitazone have been described in adults (14,24).

Although anemia was commonly observed over the course of this study, it was distributed equally across treatment groups. Metformin can impair vitamin B_{12} absorption and presumably increase the risk of megaloblastic anemia (10,11). Since all treatment groups in the TODAY study were taking metformin, we cannot assess the effects of metformin on vitamin B_{12} and anemia in this study. Although our data demonstrate that lower vitamin B_{12} concentrations were associated with anemia, the majority of participants with anemia did not exhibit vitamin B_{12} deficiency. Since anemia was more than twice as prevalent in young women as in young men, we speculate that the principal cause of anemia in this group was iron deficiency secondary to menstrual blood loss.

We were reassured to confirm a very low incidence of renal impairment; mounting evidence suggests that renal complications (macroalbuminuria, dialysis, transplantation) in youth-onset type 2 diabetes can manifest within the first 10 years of disease (25,26). Severe hypoglycemia also occurred infrequently, as might be expected from the treatments used in the TODAY study, which rarely predispose patients to hypoglycemia in the absence of exogenous insulin therapy. Nearly 1 in 10 pregnancies resulted in congenital malformation; this is nearly twice the frequency reported in a recent meta-analysis (27). Finally, the high rate of psychological AEs in the TODAY study is consistent with a previously reported 19% prevalence of neuropsychiatric diseases in children at the time of diagnosis of type 2 diabetes (28).

Type 2 diabetes is a serious medical condition in adolescents, with high morbidity and limited treatment options. The PO data from the TODAY study showed that M + R had the greatest efficacy in maintaining glycemic control, suggesting that aggressive action against hyperglycemia in the early stages of the disease using a combination of pharmacologic approaches may be warranted (6). Although rosiglitazone is no longer widely available because of concerns of increased risk of myocardial infarction (29), the TODAY experience demonstrates that combining rosiglitazone with metformin provides greater durability of glycemic control without a significant increase in AEs. The spectrum of antidiabetic agents to emerge since the inception of the TODAY study is remarkable and includes agents with diverse mechanisms of action. Although the treatment options used in the TODAY study were safe and well tolerated, the safety and efficacy of additional agents in adolescents must be evaluated swiftly to reduce the growing number of young adults at risk for the devastating consequences of poorly controlled type 2 diabetes.

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N.H.W., S.M.W., M.W.H., and K.J.N. researched data, contributed to the discussion, wrote the manuscript, and reviewed and edited the manuscript. L.P., R.G., and D.E.H. researched data, contributed to the discussion, and reviewed/edited the manuscript. T.P. researched data and reviewed and edited the manuscript. S.D.C. and S.N. contributed to the discussion and reviewed and edited the manuscript. L.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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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/.

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