Effects of Metformin, Metformin Plus Rosiglitazone, and Metformin Plus Lifestyle on Insulin Sensitivity and β-Cell Function in TODAY

TODAY Study Group*

OBJECTIVE—The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) trial demonstrated that combination therapy with metformin plus rosiglitazone provided superior durability of glycemic control compared with metformin alone, with significantly lower treatment failure rates (38.6 vs. 51.7%), and metformin plus lifestyle was intermediate. Herein we describe the temporal changes in measures of β-cell function and insulin sensitivity over a 4-year period among the three treatments.

RESEARCH DESIGN AND METHODS—TODAY participants (699) were tested periodically with an oral glucose tolerance test to determine insulin sensitivity (1/fasting insulin [$1/I_F$]), insulinogenic index ($\triangle I_{30}/\triangle G_{30}$) or C-peptide index ($\triangle C_{30}/\triangle G_{30}$), and β-cell function relative to insulin sensitivity (oral disposition index [oDI]).

RESULTS—During the first 6 months, metformin plus rosiglitazone exhibited a significantly greater improvement in insulin sensitivity and oDI versus metformin alone and versus metformin plus lifestyle; these improvements were sustained over 48 months of TODAY. Irrespective of treatment, those who failed to maintain glycemic control had significantly lower β-cell function (~50%), higher fasting glucose concentration, and higher HbA_{1c} at randomization compared with those who did not fail.

CONCLUSIONS—The beneficial change in insulin sensitivity and the resultant lower burden on β-cell function achieved in the first 6 months with metformin plus rosiglitazone appear to be responsible for its superior glycemic durability over metformin alone and metformin plus lifestyle. However, initial β-cell reserve and HbA_{1c} at randomization are independent predictors of glycemic durability. Therefore, efforts to preserve β-cell function before significant loss occurs and to reduce HbA_{1c} may be beneficial in the treatment of youth with type 2 diabetes.

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Despite the escalating rates of obesity-driven type 2 diabetes in youth, therapeutic options remain limited to metformin, the only FDA-approved oral hypoglycemic agent for children, and insulin when the former fails (1). Even though metformin was effective in the short-term over 16 weeks (2), it remained unknown whether this effect was durable until the results of the TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) trial showed >50% failure rates on metformin over an average follow-up of 3.86 years (3). TODAY was a multicenter, randomized clinical trial that compared metformin monotherapy (M) with metformin plus rosiglitazone (M+R) or metformin plus intensive lifestyle intervention (M+L) on time to treatment failure, i.e., loss of glycemic control defined as either $HbA_{1c} \geq 8\%$ over a 6-month period or inability to wean from temporary insulin therapy within 3 months of acute metabolic decompensation (3,4). The results revealed that the combination of M+R was superior to M in sustaining durable glycemic control, and M+L was intermediate (3).

Similar to adults, the pathophysiology of type 2 diabetes in youth involves peripheral and hepatic insulin resistance, together with impaired β-cell function, which progressively worsens over time (5–9). The deterioration in β-cell function in youth appears to be accelerated compared with that observed in adults (10–14). Cross-sectional observations, including the TODAY study, show an inverse relationship between HbA_{1c} and β-cell function but not insulin sensitivity, suggesting that residual β-cell function relative to insulin sensitivity is a determinant of glycemic control in youth with type 2 diabetes (5,15). Based on the TODAY outcome of better glycemic durability with M+R, we hypothesized that the combination of M+R was superior in improving β-cell function relative to insulin sensitivity compared with M or M+L. We describe the temporal changes in measures of β-cell function and insulin sensitivity derived from an oral glucose tolerance test (OGTT) over a 4-year period among the three treatments of TODAY.

RESEARCH DESIGN AND METHODS

Study design

Detailed description of the TODAY protocol and the primary outcome results have been published (3,4,16,17). In brief, the TODAY trial consisted of a screening phase and a run-in phase followed by the randomized clinical trial. After initial screening, eligible participants entered a 2–6-month run-in period with goals of weaning from nonstudy diabetes

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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.

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medications, tolerating metformin up to a dose of 1,000 mg twice daily but no less than 1,000 mg/day, attaining HbA_{1c} <8.0% for at least 2 months on metformin alone, and demonstrating adherence to study medications and visit attendance (4,16,17). After the run-in phase, 699 overweight youths, 10–17 years of age, with a mean duration of diagnosed type 2 diabetes of 7.8 months, were randomly assigned to receive M, M+R, or M+L (3,4). HbA_{1c} was obtained at screening, randomization, and every study visit thereafter. OGTTs were performed after a 10–14-h overnight fast, at randomization, and at 6 and 24 months and annually thereafter, and blood samples were analyzed for glucose, insulin, and C-peptide. This report uses temporal data related to measures of insulin sensitivity, secretion, and glycemic control from the randomized participants.

Assays and calculations

All assays were performed at the TODAY central laboratory (Northwest Lipid Research Laboratory, University of Washington, Seattle, WA) (4). HbA_{1c} (high-performance liquid chromatography), C-peptide (two-site immunoenzymatic assay), and insulin (double-antibody radioimmunoassay) were performed as previously described (15).

Insulin sensitivity was calculated as 1/fasting insulin ($1/I_F$), which correlates strongly with hyperinsulinemic-euglycemic clamp–derived in vivo insulin sensitivity in obese youth with or without type 2 diabetes (18). During the OGTT, the insulinogenic index ($\triangle I_{30}/\triangle G_{30}$) and C-peptide index ($\triangle C_{30}/\triangle G_{30}$) were calculated as the ratio of the incremental insulin, C-peptide, and glucose responses over the first 30 min of the test, as reported for the TODAY baseline (15). These indices reflect similar trends in first-phase insulin from the hyperglycemic clamp in obese youth across the glucose tolerance spectrum (19). The oral disposition index (oDI), a measure of β-cell function relative to insulin sensitivity, was calculated as the product of insulin sensitivity multiplied by the insulinogenic index ($1/I_F \times \triangle I_{30}/\triangle G_{30}$ and $1/I_F \times \triangle C_{30}/\triangle G_{30}$). In obese youth, the oDI correlates strongly with clamp-derived DI, identifies comparable decrements in β-cell function across the glucose tolerance groups (as does the clamp DI), and has analogous predictive power to that of clamp DI for the 2-h glucose concentration of the OGTT (20). We used the C-peptide index of insulin secretion ($\triangle C_{30}/\triangle G_{30}$) in addition to the insulinogenic index ($\triangle I_{30}/\triangle G_{30}$), since some participants had received insulin prior to screening/enrollment in TODAY, which could have potentially resulted in circulating insulin antibodies interfering with the insulin assay. In addition, differences in insulin clearance in different racial groups (21,22) could confound the insulinogenic index data. Metabolic assessments performed after participants reached the primary end point of treatment failure are not reported because accurate assessment of β-cell function is hindered by the impact of exogenous insulin therapy on the parameters of insulin secretion. Thus, treatment group differences in the above measures over time may be influenced by the successive removal of subjects reaching treatment failure. Sensitivity analyses were used to assess the potential impact of bias.

Statistical methods

Of the 2,043 insulinogenic index values obtained through the 4-year visits, 75 (3.67%) were ≤0, and for the C-peptide–based index, 74 (3.61%) were ≤0. Although mathematically possible, such values were judged biologically implausible and were treated as missing values, similar to approaches used in adult type 2 diabetes trials (12). These improbable responses were observed in 64 subjects (average of 1.13 per such subject), of whom 18 had a response ≤0 at baseline, necessitating their exclusion from the longitudinal analyses. There were a total of 74 missing oDI values due to the combination of 72 missing insulin sensitivity values and insulinogenic index ≤0.

Kruskal-Wallis or *F* tests were used to compare baseline variables among the treatment groups for continuous variables, and the χ^2 test was used for categorical variables. Longitudinal linear models were used to estimate mean levels of the parameters over time within groups over the follow-up period using all available data. Analyses of the reciprocal of fasting insulin, insulinogenic index, and oDI used the natural log transformation to better approximate a normal distribution. Mean change from baseline to 6 months, describing the acute effects of therapy on the outcomes, and the average rate of change from 6 months to 48 months were estimated from linear contrast of the model-estimated means over time (12). Data in the figures are presented as baseline adjusted geometric means ± SE asymmetric limits (obtained as exp [mean ± SE of the log values]). Baseline predictors for glycemic failure and odds ratios (ORs) were examined by multiple logistic regression.

RESULTS

Demographic and metabolic characteristics

Screening, entry, and run-in information were described previously (4,15–17). Mean screening HbA_{1c} levels were not different among the three groups (M, 7.6 ± 2.0%; M+R, 7.4 ± 2.0%; M+L, 7.4 ± 2.0%). At randomization (Table 1), age, sex, race/ethnicity, BMI, waist circumference, and duration of diabetes were similar among the three treatment groups. Fasting insulin was highest and insulin sensitivity lowest in the M group before adjusting for age, sex, BMI, and race. After these adjustments, the between-group difference in insulin sensitivity disappeared. There were no differences in the remaining metabolic parameters, including randomization HbA_{1c}, fasting glucose, insulinogenic index, and oDI, among the three groups.

Temporal patterns of insulin sensitivity, insulinogenic index, and oDI

Only participants with a baseline and follow-up evaluation for each outcome measure contributed data to the longitudinal analyses of the measures depicted in Fig. 1. The longitudinal models present data over 48 months of follow-up by treatment group for insulin sensitivity (Fig. 1*A*), insulinogenic index (Fig. 1*B*), and oDI (Fig. 1*C*). During the first 6 months, insulin sensitivity and oDI increased in the M+R group relative to the other two groups but fell thereafter in all groups similarly.

Table 2 shows the short-term (first 6 months) effect of therapy as the mean percent change from baseline to 6 months, and the longer-term (chronic) effect as the rate of change, percent per year, from 6 to 48 months. M+R produced a significantly greater short-term increase in insulin sensitivity and oDI over the first 6 months than M or M+L, whereas the decline in the insulinogenic index among the three groups was similar. Thereafter (6–48 months), the decline in insulin sensitivity and β-cell function relative to insulin sensitivity was parallel among the three groups.

Table 1—*Demographic and metabolic characteristics of TODAY participants by treatment groups at randomization*

	M (n = 232)	M+R (n = 233)	M+L (n = 234)	P	Adjusted P
Demographic characteristics					
Age at randomization (years)	14.1 ± 1.9	14.1 ± 2.1	13.8 ± 2.0	NS	
Race/ethnicity (%)				NS	
Non-Hispanic black	33.2	27.5	36.8		
Hispanic	39.2	43.4	36.8		
Non-Hispanic white	21.1	20.2	19.7		
Other	6.5	9.0	6.8		
Female (%)	62.9	65.2	65.8	NS	
Months since diagnosis	5 (4–9)	6 (4–11)	5 (4–9)	NS	
BMI (kg/m^2)	35.8 ± 8.1	35.0 ± 7.7	34.1 ± 7.1	NS	
BMI z score	2.3 ± 0.4	2.2 ± 0.5	2.2 ± 0.5	NS	
Waist circumference (cm)	110.3 ± 16.6	109.0 ± 17.1	106.6 ± 16.2	NS	
Metabolic characteristics					
HbA_{1c} (%)	6.1 ± 0.7	6.0 ± 0.7	6.0 ± 0.8	NS	NS
Fasting glucose (mg/dL)	111.4 ± 24.2	112.1 ± 26.3	109.4 ± 25.9	NS	NS
Fasting insulin (μU/mL)	34.6 ± 25.1	29.7 ± 20.3	29.1 ± 22.6	0.0045	0.020
Insulin sensitivity, $1/I_F$ (mL/μU)	0.044 ± 0.033	0.051 ± 0.043	0.053 ± 0.053	0.0258	NS
Insulinogenic index, $\Delta I_{30}/\Delta G_{30}$ (μU/mL per mg/dL)	1.49 ± 1.55	1.30 ± 1.32	1.70 ± 3.04	NS	NS
C-peptide index, $\Delta C_{30}/\Delta G_{30}$ (ng/mL per mg/dL)	0.079 ± 0.067	0.073 ± 0.061	0.090 ± 0.179	NS	NS
oDI ($1/I_F \times \Delta C_{30}/\Delta G_{30}$)	0.003 ± 0.002	0.003 ± 0.004	0.004 ± 0.009	NS	NS
oDI ($1/I_F \times \Delta I_{30}/\Delta G_{30}$)	0.049 ± 0.042	0.054 ± 0.061	0.064 ± 0.103	NS	NS

Continuous data are presented as mean ± SD or median (first–third quartile). Unadjusted P values were calculated from F tests and/or Kruskal-Wallis test for continuous variables. P values for categorical variables were calculated using the χ^2 test. Adjusted P values are adjusted by sex, baseline BMI, race/ethnicity, and age at randomization. Fasting insulin, $1/I_F$, $\Delta I_{30}/\Delta G_{30}$, $\Delta C_{30}/\Delta G_{30}$, $1/I_F \times \Delta C_{30}/\Delta G_{30}$, and $1/I_F \times \Delta I_{30}/\Delta G_{30}$ were analyzed using natural log transformation for the F tests.

Baseline characteristics in those who failed versus did not fail treatment

Those reaching the primary outcome of treatment failure in TODAY, regardless of treatment group assignment, had significantly higher HbA_{1c} levels and fasting glucose concentrations at randomization (Table 3) and lower insulinogenic index, C-peptide index, and oDI compared with those who did not fail. Insulin sensitivity was not different between those who failed versus those who did not fail in each treatment group. In the M treatment group, more non-Hispanic blacks failed; in the M+R group, fewer females failed. Duration of diagnosed diabetes was significantly different between those who failed and did not fail in the M+L treatment group, but not in the other two treatment groups.

To identify baseline predictors of treatment failure, logistic regression analysis was performed, with the outcome being treatment failure and the independent variables at randomization being diabetes duration, HbA_{1c}, and oDI in addition to age, sex, race/ethnicity, and BMI. The best prediction model for failure included randomization oDI (P = 0.0071) and HbA_{1c} ($P < 0.0001$). Replacing oDI in the model with insulinogenic index (P = 0.0521) or insulin sensitivity (P = ns) showed no predictive power for either. OR analyses revealed that for every 0.5% increase in HbA_{1c} at randomization, the OR for future glycemic failure was 1.83 (95% CI 1.59–2.12), and for every 0.002 unit increase in oDI at randomization, the OR for glycemic failure was 0.84 (0.74–0.95).

Similar to randomization HbA_{1c}, screening HbA_{1c} (4,15) was higher in those who failed to maintain glycemic control versus those who did not fail (8.0 ± 2.1 vs. 7.1 ± 1.8%, $P < 0.001$). Using logistic regression analysis to identify screening predictors of treatment failure (independent variables in the model included age, sex, race/ethnicity, duration of diabetes, and HbA_{1c}), screening HbA_{1c} was the only significant ($P < 0.001$) predictor of glycemic failure, with OR of 1.12 (95% CI 1.08–1.17) for every 0.5% increase in screening HbA_{1c}.

Temporal patterns of insulin sensitivity, insulinogenic index, and oDI in those who failed versus did not fail treatment

Figure 2 shows the change in insulin sensitivity (*A*), insulinogenic index (*B*), and oDI (*C*), with the three therapeutic groups combined, in those who failed treatment and those who did not. Data are shown for up to 36 months because in the group who failed therapy, once the subjects were put on insulin, they were not included in the analysis, as stated above. Due to successive failure, the remaining numbers of subjects dwindled over time, with only 15 subjects available before primary outcome at 48 months, which did not allow for adequate statistical analysis. Insulin sensitivity was not different over time between those who failed versus those who did not fail, but insulinogenic index and oDI deteriorated rapidly and progressively over time in those who failed in contrast to those who did not fail.

CONCLUSIONS—The present investigation demonstrates that *1*) over the first 6 months, the M+R group exhibited a statistically significant greater acute improvement in insulin sensitivity and oDI versus the other two groups, *2*) after the first 6 months and up to 4 years, the changes in glucose homeostasis parameters were not different among the three treatment groups, *3*) HbA_{1c} and oDI were significant baseline predictors of glycemic failure, *4*) insulinogenic index and oDI were ~40–50% lower at baseline in those who failed to maintain glycemic control versus those who did not fail,

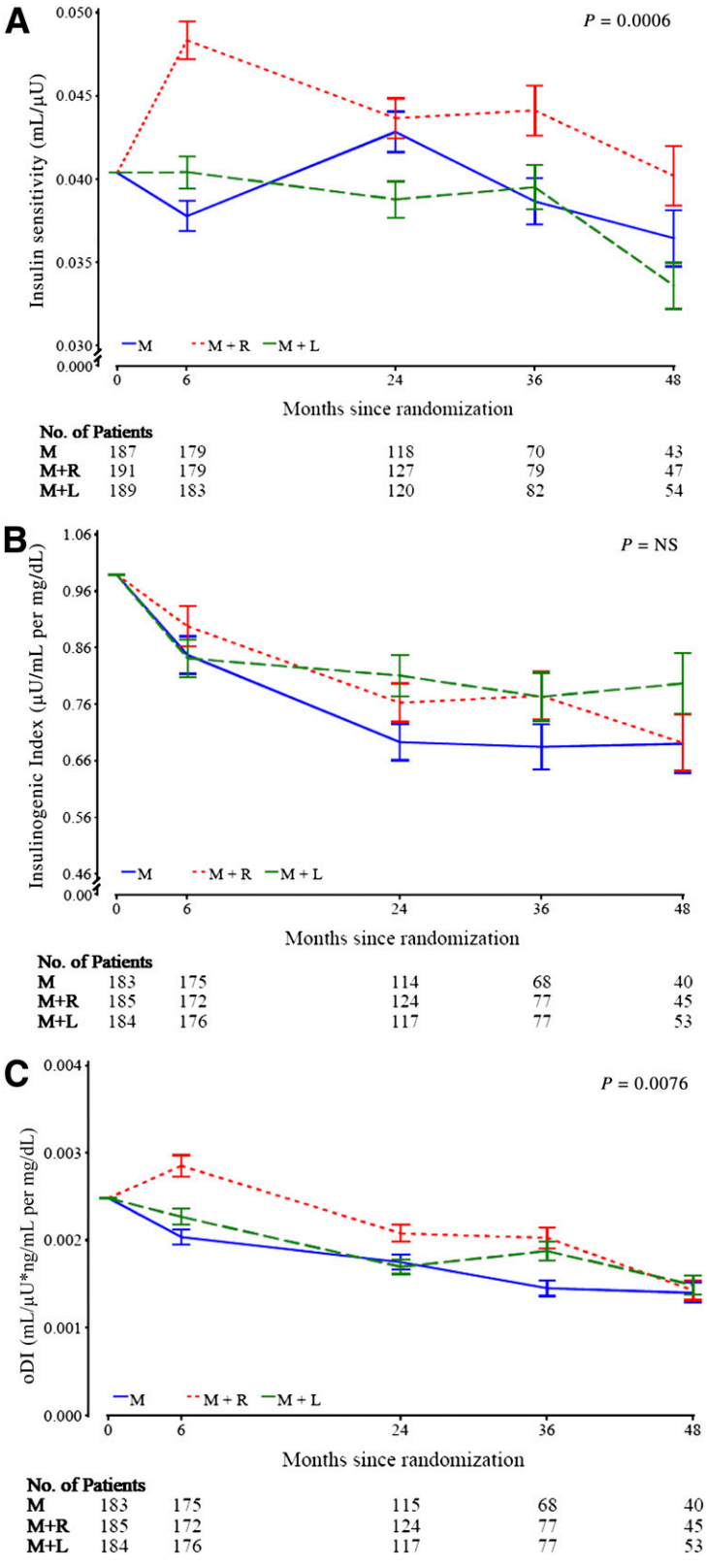

Figure 1—*Baseline adjusted geometric mean ± SE asymmetric limits (obtained as exp[mean ± SE of log values]) of OGTT-derived measures of insulin sensitivity ($1/I_F$) (A), insulinogenic index ($\triangle I_{30}/\triangle G_{30}$) (B), and oDI ($[1/I_F] \times [\triangle C_{30}/\triangle G_{30}]$) (C) in the three treatment groups over 48 months of follow-up in TODAY, analyzed using log-transformed values. The P value refers to the overall effect of treatment group assignment in the longitudinal models for the various parameters under question within the groups.*

and 5) insulinogenic index and oDI deteriorated rapidly and progressively in those who failed versus those who did not fail therapy, but insulin sensitivity over time was not different between the two groups.

The pathogenesis of youth-onset type 2 diabetes involves peripheral and hepatic insulin resistance combined with β-cell failure, which progressively worsens (5–9). Thus, therapeutic approaches that directly improve or preserve β-cell function or those that improve insulin resistance and consequently lessen the burden on the β-cell are desirable. Limited longitudinal data in youth using clamp methodology show that there is a relatively rapid deterioration of β-cell function over time with no significant change in peripheral or hepatic insulin sensitivity in the absence of weight or BMI change (10,11,23). After a median duration of 20 months of diagnosed diabetes, youth with type 2 diabetes lost on average 20% per year of their first-phase insulin or C-peptide secretion measured with the hyperglycemic clamp (11). These data are consistent with the TODAY data (Table 2), which show 20–35% decline in β-cell function per year, depending on treatment group. These data in youth and adolescents contrast with adult data showing a lower rate of decline in β-cell function. The ADOPT (A Diabetes Outcome Progression Trial) study of drug-naive adults with type 2 diabetes showed that the insulinogenic index declined at a rate of ~7–11% per year (12). In the UK Prospective Diabetes Study, the estimated rate of decline of β-cell function, using the homeostasis model assessment %B index, was ~7% per year (13,14).

The TODAY study allowed the prospective evaluation of changes in glucose metabolism over 4 years in patients randomized to M, M+R, or M+L. In the first 6 months, M+R improved insulin sensitivity by ~20%. Even though this change was statistically significant, it is uncertain if it was clinically meaningful, especially bearing in mind the severity of insulin resistance in youth with type 2 diabetes (50% lower in vivo insulin sensitivity compared with age-, BMI-, and adiposity-matched nondiabetic controls) (5). This acute improvement in insulin sensitivity in the M+R group may have translated to lowering the short-term secretory burden on the β-cells. Whereas the insulinogenic index did not differ among the three treatment groups, either in the short- or

Table 2—*Changes in OGTT-derived measures of insulin sensitivity, insulinogenic index, and β-cell function relative to insulin sensitivity (oDI) for the full TODAY cohort from randomization to 0.5 years and rates of change among means from 0.5 to 4 years based on a longitudinal model adjusted for baseline factors*

Variable	M	M+R	M+L	Pairwise comparison *P* value		
				M vs. M+R	M vs. M+L	M+R vs. M+L
Insulin sensitivity $1/I_F$ (mL/μU)						
n	220	224	224	—	—	—
Mean % change from 0 to 0.5 years	−4.93 (−12.35 to 3.13)	21.63 (12.15–31.90)	1.71 (−6.16 to 10.25)	<0.0001	NS	0.0022
Rate of change from 0.5 to 4 years (% per year)	−3.57 (−14.82 to 9.17)	−11.68 (−21.55 to −0.57)	−11.01 (−20.57 to −0.31)	NS	NS	NS
Insulinogenic index $\Delta I_{30}/\Delta G_{30}$ (μU/mL per mg/dL)						
n	217	221	220	—	—	—
Mean % change from 0 to 0.5 years	−24.44 (−33.86 to −13.69)	−19.91 (−29.97 to −8.40)	−24.96 (−34.29 to −14.31)	NS	NS	NS
Rate of change from 0.5 to 4 years (% per year)	−14.31 (−30.03 to 4.95)	−16.39 (−31.00 to 1.33)	−5.02 (−20.95 to 14.13)	NS	NS	NS
C-peptide index $\Delta C_{30}/\Delta G_{30}$ (ng/mL per mg/dL)						
n	218	221	221	—	—	—
Mean % change from 0 to 0.5 years	−22.24 (−30.18 to −13.41)	−13.71 (−22.62 to −3.78)	−18.72 (−27.01 to −9.49)	NS	NS	NS
Rate of change from 0.5 to 4 years (% per year)	−27.15 (−38.04 to −14.33)	−29.52 (−39.64 to −17.69)	−16.73 (−28.19 to −3.45)	NS	NS	NS
oDI ($1/I_F \times \Delta I_{30}/\Delta G_{30}$)						
n	217	221	220	—	—	—
Mean % change from 0 to 0.5 years	−29.31 (−38.80 to −18.33)	−4.85 (−17.71 to 10.02)	−24.06 (−32.21 to −12.33)	0.0045	NS	0.0306
Rate of change from 0.5 to 4 years (% per year)	−12.55 (−30.04 to 9.33)	−25.30 (−39.56 to −7.66)	−12.65 (−28.64 to 6.93)	NS	NS	NS
oDI ($1/I_F \times \Delta C_{30}/\Delta G_{30}$)						
n	217	221	219	—	—	—
Mean % change from 0 to 0.5 years	−26.42 (−36.14 to −15.22)	2.98 (−10.66 to 18.70)	−18.09 (−28.85 to −5.71)	0.0010	NS	0.0251
Rate of change from 0.5 to 4 years (% per year)	−25.87 (−40.20 to −8.11)	−37.80 (−49.27 to −23.73)	−23.69 (−37.20 to −7.29)	NS	NS	NS

For the log-transformed insulin sensitivity, insulinogenic index, and oDI, results are presented as a percentage change from baseline and mean rates of change (percent per year) and 95% CI.

long-term, the β-cell function relative to insulin sensitivity remained relatively stable in the M+R group but deteriorated (~25%) in the M and M+L groups in the short-term (Table 2). After the first 6 months, there were no significant group differences in the decline in oDI; all showed continued deterioration. Similar to our data, results from the adult ADOPT study showed that, during the first 6 months, insulin sensitivity increased more in the rosiglitazone group than the metformin group (12,24). However, contrary to our findings, the ADOPT study showed a continued increase in insulin sensitivity in both groups after the first 6 months, whereas in TODAY, there was continued and comparable deterioration in insulin sensitivity in all three groups. The mean percent change in insulin sensitivity with metformin monotherapy in TODAY was remarkably lower (−4.93% [95% CI −12.3 to 3.1]) than that in ADOPT (~13%) (12). This could be indicative of a more severe impairment in peripheral insulin sensitivity in youth with type 2 diabetes that may not be adequately managed with the hepatic insulin sensitizer metformin, but may require more potent peripheral insulin sensitizers.

In the TODAY cohort, M+R provided superior durability of glycemic control compared with M, with significantly lower treatment failure rates (38.6 vs. 51.7%), whereas M+L was intermediate (46.6%) and not significantly different from either of the other two groups. These treatment failure rates are in stark contrast to adult studies showing lower failure rates; 21% with metformin monotherapy and 15% with rosiglitazone monotherapy at 5 years (25). These higher failure rates in youth despite combination therapy (M+R) in TODAY are suggestive of a more severe disease process in youth.

Irrespective of treatment group assignment, those who ultimately failed to maintain glycemic control were metabolically in a more advanced disease state at baseline, characterized by higher HbA_{1c} and fasting glucose levels, lower insulinogenic index, and ~50% lower β-cell function relative to insulin sensitivity, with no difference in insulin sensitivity (Table 3). Moreover, logistic regression analyses revealed that both HbA_{1c} and oDI were significant independent baseline predictors of glycemic failure. For every 0.5% increase in HbA_{1c} at the time of randomization, the OR for failure increased to 1.83, and for every doubling of oDI, the OR

Table 3—*Randomization demographic and metabolic characteristics of TODAY participants who failed versus those who did not fail treatment by treatment group*

	Metformin			
	Failed (*n* = 120)	Did not fail (*n* = 112)	*P*	Adjusted *P*
Demographic characteristics				
Age at randomization (years)	14.1 ± 2.0	14.0 ± 1.9	NS	—
Race/ethnicity (%)			0.0207	—
Non-Hispanic black	42.5	23.2		
Hispanic	33.3	45.5		
Non-Hispanic white	18.3	24.1		
Other	5.8	7.1		
Female (%)	63.3	62.5	NS	—
Months since diagnosis	6 (4–11)	5 (4–8)	NS	—
BMI (kg/m^2)	36.2 ± 7.8	35.3 ± 8.4	NS	—
BMI *z* score	2.31 ± 0.44	2.23 ± 0.45	NS	—
Waist circumference (cm)	111.8 ± 17.0	108.8 ± 16.1	NS	—
Metabolic characteristics				
HbA_{1c} (%)	6.5 ± 0.7	5.7 ± 0.5	<0.0001	<0.0001
Fasting glucose (mg/dL)	122.6 ± 27.1	100.3 ± 14.1	<0.0001	<0.0001
Fasting insulin (μU/mL)	34.3 ± 23.0	34.9 ± 27.2	NS	NS
Insulin sensitivity, $1/I_F$ (mL/μU)	0.05 ± 0.04	0.04 ± 0.03	NS	NS
Insulinogenic index, $\Delta I_{30}/\Delta G_{30}$ (μU/mL per mg/dL)	1.24 ± 1.39	1.75 ± 1.66	0.0002	<0.0001
C-peptide index, $\Delta C_{30}/\Delta G_{30}$ (ng/mL per mg/dL)	0.06 ± 0.06	0.10 ± 0.07	<0.0001	<0.0001
oDI ($1/I_F \times \Delta I_{30}/\Delta G_{30}$)	0.04 ± 0.04	0.06 ± 0.04	0.0001	<0.0001
oDI ($1/I_F \times \Delta C_{30}/\Delta G_{30}$)	0.002 ± 0.002	0.004 ± 0.002	0.0001	0.0001
	Metformin + rosiglitazone			
	Failed (*n* = 90)	Did not fail (*n* = 143)	*P*	Adjusted *P*
Demographic characteristics				
Age at randomization (years)	14.1 ± 2.2	14.0 ± 2.1	NS	—
Race/ethnicity (%)			NS	—
Non-Hispanic black	31.1	25.2		
Hispanic	46.7	41.3		
Non-Hispanic white	13.3	24.5		
Other	8.9	9.1		
Female (%)	53.3	72.7	0.0025	—
Months since diagnosis	6 (4–12)	5 (4–10)	NS	—
BMI (kg/m^2)	35.0 ± 7.7	35.0 ± 7.7	NS	—
BMI *z* score	2.23 ± 0.53	2.22 ± 0.47	NS	—
Waist circumference (cm)	110.5 ± 17.3	108.0 ± 16.9	NS	—
Metabolic characteristics				
HbA_{1c} (%)	6.3 ± 0.8	5.8 ± 0.7	<0.0001	<0.0001
Fasting glucose (mg/dL)	123.7 ± 30.5	105.0 ± 20.2	<0.0001	<0.0001
Fasting insulin (μU/mL)	32.2 ± 23.1	28.2 ± 18.3	NS	NS
Insulin sensitivity, $1/I_F$ (mL/μU)	0.05 ± 0.06	0.05 ± 0.03	NS	NS
Insulinogenic index, $\Delta I_{30}/\Delta G_{30}$ (μU/mL per mg/dL)	0.94 ± 0.91	1.54 ± 1.49	<0.0001	<0.0001
C-peptide index, $\Delta C_{30}/\Delta G_{30}$ (ng/mL per mg/dL)	0.05 ± 0.04	0.09 ± 0.07	<0.0001	<0.0001
oDI ($1/I_F \times \Delta I_{30}/\Delta G_{30}$)	0.04 ± 0.05	0.07 ± 0.07	<0.0001	<0.0001
oDI ($1/I_F \times \Delta C_{30}/\Delta G_{30}$)	0.002 ± 0.003	0.004 ± 0.004	<0.0001	<0.0001
	Metformin + lifestyle			
	Failed (*n* = 109)	Did not fail (*n* = 125)	*P*	Adjusted *P*
Demographic characteristics				
Age at randomization (years)	13.7 ± 2.0	13.9 ± 2.0	NS	—
Race/ethnicity (%)			NS	—
Non-Hispanic black	37.6	36.0		
Hispanic	39.5	34.4		

Continued on p. 1755

Table 3—*Continued*

	Metformin + lifestyle			
	Failed (n = 109)	Did not fail (n = 125)	P	Adjusted P
Non-Hispanic white	16.5	22.4		
Other	6.4	7.2		
Female (%)	69.7	62.4	NS	—
Months since diagnosis	6 (4–12)	5 (3–7)	<0.0001	—
BMI (kg/m^2)	34.1 ± 6.6	34.1 ± 7.5	NS	—
BMI z score	2.19 ± 0.46	2.18 ± 0.46	NS	—
Waist circumference (cm)	105.8 ± 15.7	107.3 ± 16.6	NS	—
Metabolic characteristics				
HbA_{1c} (%)	6.3 ± 0.8	5.7 ± 0.6	<0.0001	<0.0001
Fasting glucose (mg/dL)	119.6 ± 29.4	100.3 ± 18.1	<0.0001	<0.0001
Fasting insulin (μU/mL)	31.2 ± 26.3	27.3 ± 18.6	NS	NS
Insulin sensitivity, $1/I_F$ (mL/μU)	0.05 ± 0.07	0.05 ± 0.03	NS	NS
Insulinogenic index, $\Delta I_{30}/\Delta G_{30}$ (μU/mL per mg/dL)	1.16 ± 3.08	2.18 ± 2.93	<0.0001	<0.0001
C-peptide index, $\Delta C_{30}/\Delta G_{30}$ (ng/mL per mg/dL)	0.05 ± 0.07	0.12 ± 0.23	<0.0001	<0.0001
oDI ($1/I_F \times \Delta I_{30}/\Delta G_{30}$)	0.04 ± 0.05	0.09 ± 0.13	<0.0001	<0.0001
oDI ($1/I_F \times \Delta C_{30}/\Delta G_{30}$)	0.002 ± 0.003	0.006 ± 0.012	<0.0001	<0.0001

Continuous data are presented as mean ± SD or median (first–third quartile). Unadjusted P values were calculated from F tests and/or Kruskal-Wallis test for continuous variables. P values for categorical variables were calculated using the χ^2 test. Adjusted P values are adjusted by sex, baseline BMI, race/ethnicity, and age at randomization. Fasting glucose, fasting insulin, $1/I_F$, $\Delta I_{30}/\Delta G_{30}$, $\Delta C_{30}/\Delta G_{30}$, $1/I_F \times \Delta C_{30}/\Delta G_{30}$, and $1/I_F \times \Delta I_{30}/\Delta G_{30}$ were analyzed using natural log transformation for the F tests.

decreased to 0.84. Analyses of longitudinal data between those who failed to maintain glycemic control and those who did not fail demonstrated a lack of beneficial effects of treatment among those who failed. Whereas the pattern of insulin sensitivity over time was similar between those who failed and those who did not fail, insulinogenic index deteriorated rapidly and relentlessly in those who failed (Fig. 2), with a similar pattern of progressive deterioration in oDI over time in those who failed (~27% by 6 months, ~56% by 24 months, and ~67% by 36 months). Thus, when β-cell impairment is far advanced, as was the case in those who failed to maintain glycemic control, none of the three treatments proved effective in maintaining glycemic durability.

Studies of youth with type 2 diabetes have demonstrated a strong inverse relationship between HbA_{1c} and β-cell function relative to insulin sensitivity (5). In the TODAY study, at screening and randomization, insulin secretion indices declined with increasing HbA_{1c} quartiles (15). This inverse relationship between HbA_{1c} and β-cell function may either reflect the impact of deficient insulin secretion on the outcome of glycemic control or could be viewed as a glucotoxic phenomenon impairing β-cell function. In the current study, the group that failed to maintain glycemic control already had significantly impaired oDI at randomization compared with the group that did not fail, and did not show beneficial effects of treatment. This observation, combined with our findings that both HbA_{1c} and oDI are predictors of glycemic failure, would suggest that treatment before significant β-cell impairment and deterioration in glycemic control occur may be prudent in achieving better therapeutic success in youth with type 2 diabetes.

Since it was not feasible to institute clamp experiments across the many participating clinics in TODAY, we used surrogate estimates of insulin sensitivity and β-cell function derived from the OGTT. These surrogate estimates correlate strongly with clamp-measured parameters in youth (18–20). A potential limitation of TODAY is that in 3.6% of the tests, the value for the insulinogenic index was ≤0. This is in complete agreement with previous adult trials of type 2 diabetes (12) and is reported in individuals with normal and impaired glucose tolerance (24). Because of the high failure rates, statistical analysis was not possible past the 36-month visit in the cohort that failed since the number of subjects became very limited (15 subjects at 48 months). Lastly, despite the favorable therapeutic outcome of M+R in TODAY, a limitation is the use of rosiglitazone. However, TODAY was designed and initiated prior to the discovery of the adverse effects of rosiglitazone (26).

In summary, changes in insulin sensitivity and β-cell function relative to insulin sensitivity in the first 6 months of treatment appear to be responsible for the different degrees of glycemic durability observed with M+R, M, and M+L. The former provided favorable, albeit short-term, changes in both parameters, translating to the lowest treatment failure rates in TODAY. However, initial β-cell reserve and HbA_{1c} were important determinants of glycemic durability. Regardless of treatment assignment, those youth who failed to maintain glycemic control had severe impairment of β-cell function at the beginning of the trial and experienced progressive and faster loss of β-cell function compared with those with durable glycemic control.

APPENDIX—The members of the writing group are as follows: Silva Arslanian, MD (chair), Children's Hospital of Pittsburgh; Laura Pyle, PhD, George Washington University Biostatistics Center; Marisa Payan, MS, George Washington University Biostatistics Center; Fida Bacha, MD, Baylor College of Medicine; Sonia Caprio, MD, Yale University School of Medicine; Morey W. Haymond, MD, Baylor College of Medicine; Lynne L. Levitsky, MD, Massachusetts General Hospital for Children; Robin Goland, MD, Columbia University; Neil H. White, MD, Washington University in St. Louis; and Steven M. Willi, MD, Children's Hospital of Philadelphia.

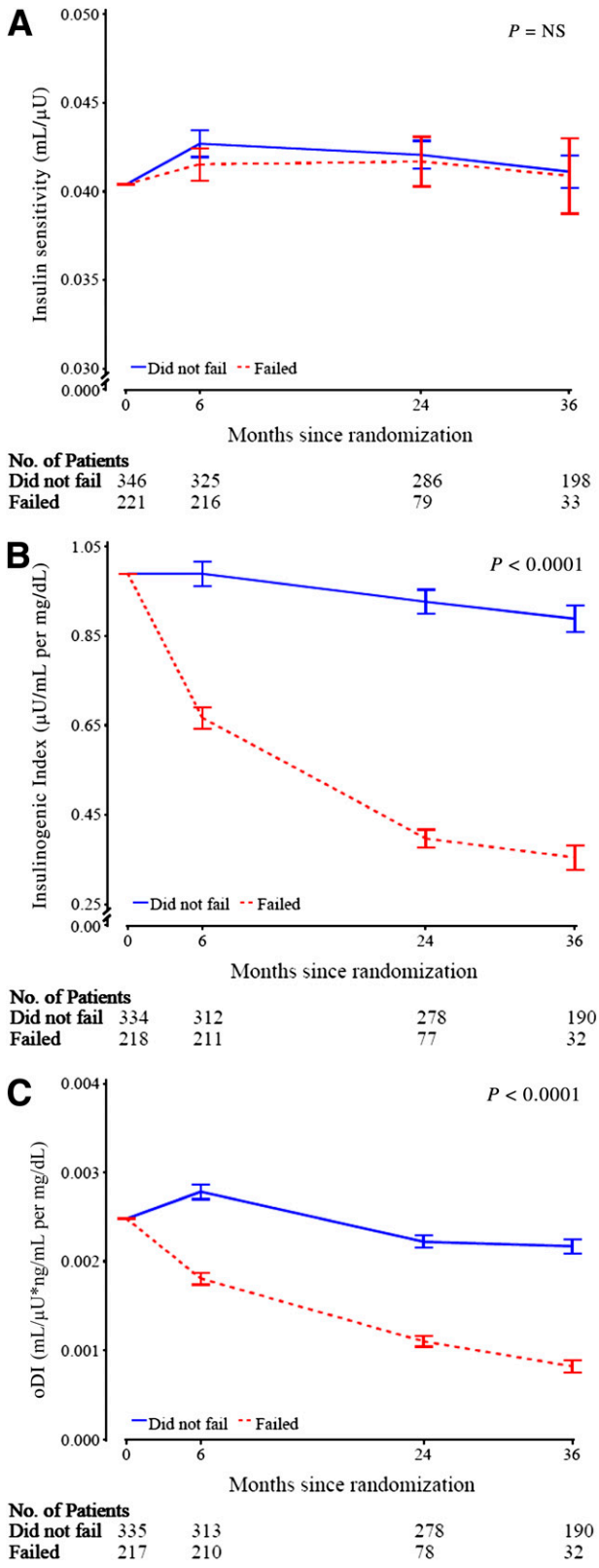

Figure 2—*Baseline adjusted geometric mean ± SE asymmetric limits (obtained as exp[mean ± SE of log values]) of OGTT-derived measures by treatment failure with the three treatment groups combined, analyzed using log-transformed values.* A*: Insulin sensitivity* ($1/I_F$). B*: Insulinogenic index* ($\triangle I_{30}/\triangle G_{30}$). C*: oDI* ($[1/I_F] \times [\triangle C_{30}/\triangle G_{30}]$). *The* P *value refers to the overall effect of failed vs. not failed group assignment in the longitudinal models for the various parameters under question within the two groups.*

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S.A., S.C., M.W.H., N.H.W., and S.M.W. researched data, contributed to the discussion, and wrote, reviewed, and edited the manuscript. L.P., F.B., L.L.L., and R.G. researched data, contributed to the discussion, and reviewed and edited the manuscript. M.P. researched data. 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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