Correlates of Medication Adherence in the TODAY Cohort of Youth With Type 2 Diabetes

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OBJECTIVE

To identify factors that predict medication adherence and to examine relationships among adherence, glycemic control, and indices of insulin action in TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth).

RESEARCH DESIGN AND METHODS

A total of 699 youth 10–17 years old with recent-onset type 2 diabetes and ≥80% adherence to metformin therapy for ≥8 weeks during a run-in period were randomized to receive one of three treatments. Participants took two study pills twice daily. Adherence was calculated by pill count from blister packs returned at visits. High adherence was defined as taking ≥80% of medication; low adherence was defined as taking <80% of medication. Depressive symptoms, insulin sensitivity (1/fasting insulin), insulinogenic index, and oral disposition index (oDI) were measured. Survival analysis examined the relationship between medication adherence and loss of glycemic control. Generalized linear mixed models analyzed trends in adherence over time.

RESULTS

In this low socioeconomic cohort, high and low adherence did not differ by sex, age, family income, parental education, or treatment group. Adherence declined over time (72% high adherence at 2 months, 56% adherence at 48 months, $P < 0.0001$). A greater percentage of participants with low adherence had clinically significant depressive symptoms at baseline (18% vs. 12%, $P = 0.0415$). No adherence threshold predicted the loss of glycemic control. Longitudinally, participants with high adherence had significantly greater insulin sensitivity and oDI than those with low adherence.

CONCLUSIONS

In the cohort, the presence of baseline clinically significant depressive symptoms was associated with subsequent lower adherence. Medication adherence was positively associated with insulin sensitivity and oDI, but, because of disease progression, adherence did not predict long-term treatment success.

The TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) clinical trial was conducted to evaluate three different treatments for type 2 diabetes in youth (1). The results of the TODAY trial revealed that 45.6% of participants, all with recently diagnosed (<2 years) youth-onset type 2 diabetes, lost glycemic control on randomized treatment usually by the end of the first year (2).

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**A complete list of the TODAY Study Group can be found in the Supplementary Data.*

Youth in the TODAY trial were expected to take two pills twice a day. After randomization, the TODAY trial used a predetermined 80% adherence cutoff, which is commonly applied in clinical trials (3), to monitor the adequacy of adherence to study medication during the trial. Rapoff (4) has discussed how adherence (or lack of) can bias clinical trials of promising therapies, especially in pediatric clinical trials. Most pediatric type 1 diabetes studies (5–7) consistently document a correlation between adherence and race, ethnicity, and socioeconomic status, and studies of adults with type 2 diabetes (8,9) have documented that depressed patients are less adherent to their diabetes regimen. There is a dearth of information in the literature regarding adherence to medication in pediatric patients with type 2 diabetes. One report (10) from a study of youth with type 2 diabetes at three clinical sites concluded that "compliance with medications and doctor's appointments is suboptimal in youth with type 2 diabetes." The objective of the current analysis was to identify factors that predicted medication adherence and to examine relationships among adherence, glycemic control, and indices of insulin action in the TODAY cohort.

RESEARCH DESIGN AND METHODS

TODAY Design and Primary Results

The collaborative study group included 15 clinical centers, a data coordinating center, and central laboratories and reading centers (Supplementary Data). Materials developed and used for the TODAY trial standard diabetes education program and the intensive lifestyle intervention program are available to the public at https://today.bsc.gwu.edu/. The TODAY study design has been reported (11) and is briefly summarized. Between July 2004 and February 2009, 699 youths between the ages of 10 and 17 years with type 2 diabetes were enrolled. To be eligible, all TODAY trial participants had to have received a diagnosis of type 2 diabetes using American Diabetes Association criteria $<$2 years before the time of randomization; have a BMI in $\geq$85th percentile; and have an adult caregiver (usually the mother) who agreed to support the youth participating in the study, including accompanying the youth to all visits and helping with diabetes tasks such as medication adherence. Youths had to take $\geq$80% of their metformin (M) for $\geq$8 weeks during a run-in period in order to be eligible for randomization. A total of 927 subjects entered the run-in phase, and 699 subjects were randomized and assigned to a treatment group. Eligible participants were randomized to one of the following three treatment arms: *1*) M alone (M), *2*) M plus rosiglitazone (M+R), and *3*) M plus an intensive lifestyle program (M+L). The primary objective of the TODAY trial was to compare the three arms on time to treatment failure (i.e., loss of glycemic control, defined as either an HbA_{1c} level of $\geq$8% over a 6-month period or an inability to wean from temporary insulin therapy within 3 months after acute metabolic decompensation). After an average follow-up period of 3.9 years, 319 subjects (45.6%) reached the primary outcome; the M+R arm was superior to the M arm ($P = 0.006$), and the M+L arm was intermediate but not different from M arm (2).

Study Medication Adherence Procedures

The dose for all treatment arms was two capsules twice daily. Masked study drug (M or M+R) was provided in 7-day blister packs separated into morning and evening two-pill doses. M and R were encapsulated together. All pills looked, smelled, and tasted the same. Study subjects were instructed to return all blister packs at their regular study visit. HbA_{1c} values were partially masked to the subject and the investigators. Investigators were not informed of the value, but were notified if the HbA_{1c} level was on target, stable, rising, or elevated.

For this analysis, adherence was measured while study subjects received randomized treatment (i.e., prior to the primary outcome [loss of glycemic control] or at the end of the study visit). Collection of adherence data (pill counts) and dispensing of the study drug occurred at each study visit (every 2 months in year 1 and then quarterly). Adherence was calculated as the percentage of the prescribed study drug taken, based on pill counts. If pill packs (empty, partial, or full) were not returned at a visit as instructed, then adherence could not be determined and was noted as missing. Adherence could be $>$100% if the number of pills taken based on empty containers brought to a visit was greater than the prescribed four pills per day. Outlier values were examined, and values $>$110% were excluded from the analysis.

At each visit, study staff evaluated and discussed adherence with the participant. There was no standardized behavioral intervention to address adherence. Based on adherence barriers identified in discussion with the participant and caregiver, study personnel worked with the participant on strategies to increase medication adherence. Participants could earn "points" for goal attainment, including medication adherence of $\geq$80%. Participants could earn up to 12 points per month (6 points for 100% medication adherence, 5 points for 90–99% adherence, or 4 points for 80–89% adherence; 3 points for glucose monitoring; 2 points for bringing back blister packs and a logbook to a visit; and 1 point for setting goals at the visit). Subjects who had $<$80% adherence did not earn points for medication adherence. Accumulated points could be exchanged for incentive items worth up to $150 per year. Adherence was monitored by the study group committees on Procedures Oversight and Retention and Adherence. Clinical centers below a target cutoff of 80% were contacted to address problems and provide support on both participant-specific and site-specific levels.

Factors and Measures

Race-ethnicity was determined by self-report. Participants were categorized as non-Hispanic black, non-Hispanic white, or Hispanic; categories that were too small for separate analysis were combined into Other (7%) and were not included in analyses by race-ethnicity. Household education was the highest education level attained by the parent/guardian; 15 education categories were collapsed into 4 for purposes of analysis. The annual household income of all persons living in the household in the past year was collected by self-report of family members present at the baseline visit; nine categories were collapsed into three for purposes of analysis. Percentage overweight, the recommended outcome for reporting changes in adiposity in youth, was calculated as percentage over median BMI for age and

sex (12–14). Health-related quality of life was measured by youth self-report on the generic scale (PedsQL 3.0) with impaired quality of life defined at a cutoff of 71.19 (15). Depressive symptoms were assessed using either the Children's Depression Inventory for participants <16 years of age or the Beck Depression Inventory II for those ≥16 years of age (16,17). Total scores were calculated for each instrument; a cutoff score ≥13 on the Children's Depression Inventory and ≥14 on the Beck Depression Inventory II indicated clinically significant depressive symptoms. The TODAY trial primary outcome, time to treatment failure, indicated durability of glycemic control. Three measures of insulin secretion/sensitivity were derived from the oral glucose tolerance test. Insulin sensitivity was calculated as 1/fasting insulin ($1/I_F$), also called the insulin inverse; this measure correlates strongly with hyperinsulinemic-euglycemic clamp–derived in vivo insulin sensitivity in obese youth with or without type 2 diabetes (18). The insulinogenic index was calculated as the ratio of the incremental insulin and glucose responses from baseline to 30 min ($\triangle I_{30}/\triangle G_{30}$) (19). This index reflects similar trends in first-phase insulin from the hyperglycemic clamp in obese youth across the glucose tolerance spectrum (18). 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 ($1/I_F \times \triangle I_{30}/\triangle G_{30}$); in obese youth as well as adults, the oDI correlates strongly with clamp-derived disposition index (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 oral glucose tolerance test (19,20).

Statistical Analysis

Study medication adherence is typically analyzed as a categorical or dichotomous variable; the continuous distribution was not appropriate even with transformation. Therefore, to be practically useful, a cutoff defining "adequate dose" (i.e., adequate to have the intended effect) is identified for monitoring purposes. The TODAY trial used a preplanned 80% cutoff, which is commonly applied in clinical trials (3) to assess the adequacy of adherence during the trial. The effect of adherence on treatment failure was analyzed using time-to-event survival methods, where time was entered as an interval for those who failed, and adherence and the interaction between adherence and treatment group were included in the model. The analysis was repeated for adherence cutoffs at 60%, 70%, and 90% adherence to determine whether there was a threshold effect. Tests of association between adherence and demographic and baseline characteristics used either the χ^2 test (for categorical characteristics) or ANOVA (for continuous variables). Generalized linear mixed models were used to compare adherence across treatment groups and over time. Study medication adherence cutoffs were applied to mean adherence prior to treatment failure, while the participant was still receiving the assigned study medication.

Measures of insulin secretion/sensitivity (insulin sensitivity, insulinogenic index, and oDI) were analyzed in models including time (visit number), study medication adherence, and their interaction, with a baseline measure of insulin secretion/sensitivity as a covariate. All measures of insulin secretion/sensitivity were log transformed to normalize the distribution. Significance was defined as $P < 0.05$ with no adjustment for multiple testing; the trial was powered for the primary outcome only.

RESULTS

Adherence Across Time by Treatment Group

Of the 699 subjects in the TODAY cohort, 42 were not included in the analysis (8 never returned after the baseline visit, and 34 reached the primary study outcome within the first 5 months of the study). Figure 1 plots the percentage of subjects with adequate study drug adherence (using the 80% cutoff) across time (months 2–48) by treatment group. As seen, overall adherence declined as a function of the number of months in the study ($P < 0.0001$) but was not different across treatment groups. When the analysis was repeated for adherence cutoffs at 60%, 70%, and 90%, results were similar to 80% (data not shown).

Factors Associated With Adherence

Baseline data and demographic characteristics by adherence status are shown in Table 1. For each participant, average adherence over time on randomized treatment was dichotomized at the 80% cutoff used during the study to monitor adequate adherence. Participants reporting clinically significant depressive symptoms at baseline were more likely to be in the lower-adherence group. Key characteristics that were not significant included sex, race-ethnicity, determinants of socioeconomic status, and randomized treatment group.

Durability of Glycemic Control

We examined the TODAY trial primary outcome (time-to-failure analysis) with adherence status. The model included the interaction between adherence status and treatment group. The analysis was performed for adherence cutoffs at 60%, 70%, 80%, and 90%. At all four adherence cutoffs, the results by treatment group were similar to the results for 80% adherence reported in the primary outcome article (2) (i.e., the only significant treatment group comparison was M vs. M+R). Failure was not associated with lower adherence to taking medication. Among those subjects who failed therapy, 62.5% had at least an 80% adherence to study medication on average compared with 50.3% in those who did not fail therapy by the end of the study ($P = 0.0018$).

Insulin Secretion/Sensitivity

Figure 2 shows longitudinal data at 6, 24, 36, and 48 months postrandomization and prior to glycemic failure for *1*) insulin sensitivity and *2*) insulinogenic index by study medication adherence status (cutoff 80%). In this analysis, there was no statistically significant interaction between adherence status and time in the study. On average, ≥80% medication adherence was associated with higher insulin sensitivity (Fig. 2*A*) ($P = 0.0012$) and higher oDI ($P = 0.0248$), but not with insulinogenic index (Fig. 2*B*) ($P = 0.4733$). There was a significant trend over time for the insulinogenic index ($P = 0.0076$) and oDI ($P = 0.0307$), but not insulin inverse ($P = 0.1291$). Analysis of medication adherence at other adherence cutoffs revealed similar relationships with insulin secretion/sensitivity.

CONCLUSIONS

The TODAY cohort demonstrated deterioration in study medication adherence over time, irrespective of treatment

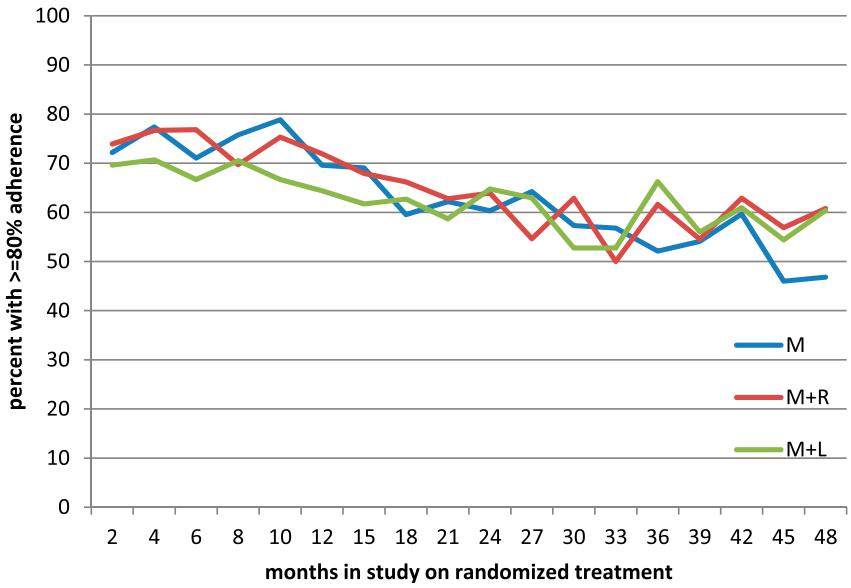

Figure 1—Data are shown through follow-up month 48. All data are from prior to treatment failure when participants were placed on a uniform diabetes management regimen. Adherence to medication significantly dropped over time ($P < 0.0001$), but there were no differences among treatment groups.

group assignment. Paradoxically, the current analysis found that those who reached the primary outcome actually had higher adherence levels than those who did not reach the primary outcome. Possible explanations include the following: *1*) patients who notice high glucose readings were more likely to take their medication and *2*) clinicians emphasized medication adherence more strongly and more frequently with participants whose blood glucose levels were higher.

Contrary to expectation, demographic factors (sex, race-ethnicity, household income, and parental educational level) did not predict medication adherence. The lack of correlation with these factors in the TODAY trial may be explained by the limited income and educational range of the families in the TODAY trial. Nearly half of the families in the TODAY trial had an annual income of <$25,000, and, for over half of the families, the highest level of parental education was a high school degree or lower. In addition, our run-in criteria selected for more adherent subjects. All subjects had to have >80% adherence to M therapy for ≥8 weeks before they could be randomized. This may have limited variability in medication adherence postrandomization. It is also possible that selecting for more adherent subjects in the run-in period also selected for subjects with a lower frequency of depressive symptoms.

Table 1—Baseline and demographic characteristics by overall adherence status

Characteristics	All (*n* = 657)	<80% (*n* = 292, 44%)	≥80% (*n* = 365, 56%)	*P* value
Age (years)	14.0 (2.0)	14.1 (1.9)	13.9 (2.1)	0.2809
Sex				0.8418
Female	419 (63.8%)	185 (63.4%)	234 (64.1%)	
Male	238 (36.2%)	107 (36.6%)	131 (35.9%)	
Race-ethnicity†				0.1036
Black non-Hispanic	209 (34.4%)	95 (36.0%)	114 (33.1%)	
Hispanic	266 (43.7%)	122 (46.2%)	144 (41.9%)	
White non-Hispanic	133 (21.9%)	47 (17.8%)	86 (25.0%)	
Highest household education				0.9894
Less than high school	173 (26.8%)	76 (26.5%)	97 (27.0%)	
High school, GED, business or technical school	159 (24.6%)	71 (24.7%)	88 (24.5%)	
College no degree	207 (32.0%)	91 (31.7%)	116 (32.3%)	
Graduate degree	107 (16.6%)	49 (17.1%)	58 (16.2%)	
Annual household income				0.2510
<$25,000	243 (41.2%)	114 (44.5%)	129 (38.6%)	
$25,000–49,999	201 (34.1%)	86 (33.6%)	115 (34.4%)	
≥$50,000	146 (24.7%)	56 (21.9%)	90 (27.0%)	
BMI (kg/m^2)	34.9 (7.6)	35.5 (7.9)	34.4 (7.3)	0.0681
BMI *z*-score	2.23 (0.46)	2.26 (0.44)	2.20 (0.48)	0.1102
Overweight (%)	78.9 (37.0)	81.3 (39.4)	77.0 (34.9)	0.1342
Impaired HRQOL	146 (22.6%)	72 (24.9%)	74 (20.7%)	0.2060
Depressive symptoms	93 (14.5%)	50 (17.7%)	43 (12.0%)	0.0415
Treatment group				0.2726
M	218 (33.2%)	88 (30.1%)	130 (35.6%)	
M+R	218 (33.2%)	98 (33.6%)	120 (32.9%)	
M+L	221 (33.6%)	106 (36.3%)	115 (31.5%)	

The values were reported as the mean (SD) or *n* (%), unless otherwise indicated. HRQOL, health-related quality of life. †Only the major three racial/ethnic groups are shown.

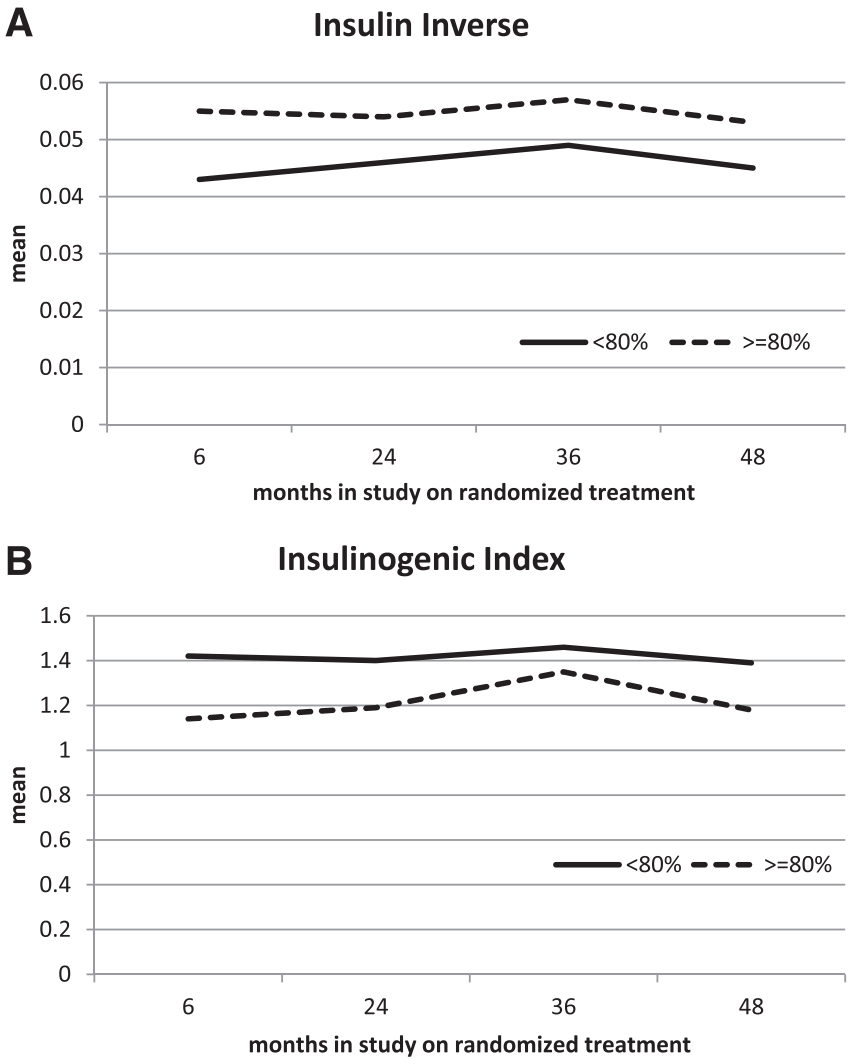

Figure 2—Data are from prior to treatment failure when participants were placed on a uniform diabetes management regimen. *A*: For insulin inverse, there was a significant difference between the adherence groups (i.e., the higher-adherence group had higher values of insulin inverse) ($P = 0.0012$), but the lines were parallel (no interaction) and flat (no visit or time trend). *B*: For the insulinogenic index, there was a significant difference over time ($P = 0.0076$), and a rise at month 36 was detected, which was the same in both adherence groups.

In the TODAY trial, baseline clinically significant depressive symptoms were more prevalent in the lower-adherence group, suggesting that regular screening for depressive symptoms should be undertaken to identify youth who were at high risk for poor medication adherence. In the TODAY study sample, ~15% scored at or above the cutoff for clinically significant depressive symptoms (21). These results are similar to those reported in the SEARCH study (22), which found that being female and of older age were risk factors for higher rates of clinically significant depressive symptoms in a pediatric sample of individuals with type 2 diabetes. Studies in adults with type 2 diabetes (23–28) consistently report that depressed patients are less adherent to their diabetes regimen and experience more physical complications of diabetes. Identifying youth who are at risk for poor medication adherence early in the course of disease would make it possible to provide support and, if needed, specific treatment. Although we were not able to determine whether the treatment of depressive symptoms changed adherence over time, our findings support the current guidelines for psychosocial screening in youth with diabetes (29,30). Clinicians may also need to evaluate adherence more carefully in patients with clinically significant depressive symptoms in order to identify and address barriers to adherence.

With regard to the TODAY study primary outcome, we did not find an adherence threshold that predicted loss of glycemic control. Adherence to oral medication was related to higher insulin sensitivity, as expected for the pharmacological mechanisms of action of M+R. However, improved insulin sensitivity was not adequate to compensate for the ongoing decline in β-cell function. These results are consistent with results in adults from the UK Prospective Diabetes Study (UKPDS), in which a continuous decline in β-cell function in adults with type 2 diabetes was seen, irrespective of glucose-lowering treatment (31). Furthermore, the durability of glycemic control in TODAY was not associated with lower adherence to medication (32). Unlike adults with type 2 diabetes, loss of glycemic control in the TODAY trial occurred around the end of the first year in a significant portion of the cohort. During this first year, adherence for the majority of the cohort was ≥80%. This points to the progressive nature of type 2 diabetes seen in approximately half of TODAY youth as well as other factors, including the effects of pubertal hormones. Compared with adult-onset diabetes, youth-onset type 2 diabetes is associated with faster deterioration in glycemic control (33) as well as insulin secretion (34). Other studies (35–38) have reported that youths with type 2 diabetes are also at higher risk for comorbidities (e.g., microalbuminuria and dyslipidemia) earlier in the course of disease progression.

The erosion of medication adherence seen in the TODAY trial is similar to the results of medication adherence deterioration over time in pediatric type 1 diabetes studies (39,40). Literature reviews of clinical trials and clinical practice (41–43) report that rates of adherence for adolescents with chronic illnesses vary, depending on the disease, the complexity of the treatment regimen, and the adherence measures used. However, there is a consensus across studies (4,44) that rates of adherence to medication are generally <50%, especially for adolescents. As incentives were used to improve medication adherence in the TODAY trial, the observed erosion of adherence over time may also relate in part to an initial response to incentives with subsequent habituation.

Limitations of the current report include the use of pill counts for measuring medication adherence and lack of adherence data when visits were missed. Pill counts as a measure of medication adherence often result in an overestimation of the actual number of pills taken. Rapoff (4) has written that this is especially true in pediatric patients. Our criterion of ≥80% adherence for ≥8 weeks prior to randomization may also have selected for a more adherent cohort than is typical for youths with type 2 diabetes. Participants received coaching to improve medication adherence and could earn incentives for better adherence to medication, providing greater opportunity to improve adherence than would be present in general clinical care. Data were not kept on the rate of incentives attained by subjects in the TODAY trial. Although our cohort was relatively homogeneous with regard to demographic factors, the cohort is representative of the pediatric population with diagnosed type 2 diabetes. Although we assessed for clinically significant depressive symptoms, we did not track treatment for identified clinically significant depressive symptoms. The SEARCH and TODAY studies showed a similar sex (female predominance) and ethnic/racial distribution (majority Hispanic or African American), family income (majority making <$50,000), BMI (*z*-score 2.1), family history of diabetes (>70% in both), and C-peptide level (~3.5 in both cohorts) (45–47).

In conclusion, medication adherence showed similar declines over time in all three treatment groups and was not related to race-ethnicity or socioeconomic status in this cohort of primarily minority youth characterized by low household income and low parental education levels. The only participant characteristic that was related to low medication adherence was the presence of baseline clinically significant depressive symptoms. We found that no cutoff of medication adherence in the TODAY trial was related to time to treatment failure. Although medication adherence was associated with better insulin sensitivity, it could not compensate for the progressive decline in β-cell function. These results support the literature that type 2 diabetes in many youths runs a progressive course. For patients whose glycemic control is deteriorating while receiving therapy with M, the assessment of adherence and barriers to adherence must be addressed. However, in youths who are taking most of their medication, near 100% adherence is still unlikely to maintain glycemic control, and, thus, clinicians should consider intensification of therapy (pharmacologic and/or nonpharmacologic) early in the course of the disease.

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References

1. Tamborlane WV, Klingensmith G. Crisis in care: limited treatment options for type 2 diabetes in adolescents and youth. Diabetes Care 2013;36:1777–1778
2. Zeitler P, Hirst K, Pyle L, et al.; TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med 2012;366:2247–2256
3. Walker EA, Molitch M, Kramer MK, et al.; DPP Research Group. Adherence to preventive medications: predictors and outcomes in the Diabetes Prevention Program. Diabetes Care 2006;29:1997–2002
4. Rapoff MA. *Adherence to Pediatric Medical Regimens*. New York, NY, Kluwer Academic/Plenum Publishers, 1999
5. Auslander WF, Thompson S, Dreitzer D, White NH, Santiago JV. Disparity in glycemic control and adherence between African-American and Caucasian youths with diabetes. Family and community contexts. Diabetes Care 1997;20:1569–1575
6. Miller KM, Beck RW, Bergenstal RM, et al.; T1D Exchange Clinic Network. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. Diabetes Care 2013;36:2009–2014
7. Gallegos-Macias AR, Macias SR, Kaufman E, Skipper B, Kalishman N. Relationship between glycemic control, ethnicity and socioeconomic status in Hispanic and white non-Hispanic youths with type 1 diabetes mellitus. Pediatr Diabetes 2003;4:19–23
8. Lustman PJ, Griffith LS, Clouse RE. Recognizing and managing depression in patients with diabetes. In *Practical Psychology for Diabetes Clinicians*. Anderson BJ, Rubin RR, Eds. Alexandria, VA, American Diabetes Association, 2003, p. 143–152
9. Katon W, Felz-Cornelis C. Treatment of depression in patients with diabetes: efficacy, effectiveness and maintenance trials, and new service models. In *Depression and Diabetes*. Katon W, Maj M, Sartorius N, Eds. Hoboken, NY, Wiley-Blackwell, 2010, p. 81–107
10. Nguyen TT, Jayadeva V, Cizza G, et al. Challenging recruitment of youth with type 2 diabetes into clinical trials. J Adolesc Health 2014;54:247–254
11. Zeitler P, Epstein L, Grey M, et al.; TODAY Study Group. Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes. Pediatr Diabetes 2007;8:74–87
12. Wilfley DE, Tibbs TL, Van Buren DJ, Reach KP, Walker MS, Epstein LH. Lifestyle interventions in the treatment of childhood overweight: a meta-analytic review of randomized controlled trials. Health Psychol 2007;26:521–532
13. Kalarchian MA, Levine MD, Arslanian SA, et al. Family-based treatment of severe pediatric obesity: randomized, controlled trial. Pediatrics 2009;124:1060–1068
14. Wilfley DE, Stein RI, Saelens BE, et al. Efficacy of maintenance treatment approaches for childhood overweight: a randomized controlled trial. JAMA 2007;298:1661–1673
15. Varni JW, Limbers CA, Burwinkle TM. Impaired health-related quality of life in children and adolescents with chronic conditions: a

comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes 2007;5:43
16. Kovacs M. *The Children's Depression Inventory Manual*. New York, NY, Multi-Health Systems, 1992
17. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II*. San Antonio, TX, Psychological Corporation, 1996
18. George L, Bacha F, Lee S, Tfayli H, Andreatta E, Arslanian S. Surrogate estimates of insulin sensitivity in obese youth along the spectrum of glucose tolerance from normal to prediabetes to diabetes. J Clin Endocrinol Metab 2011;96: 2136–2145
19. Brar PC, Koren D, Gallagher PR, Pendurthi B, Katz LEL. Comparison of oral and intravenous glucose tolerance test derived sensitivity and secretory indices in obese adolescents. Clin Pediatr (Phila) 2013;52:247–253
20. Utzschneider KM, Prigeon RL, Faulenbach MV, et al. Oral disposition index predicts the development of future diabetes above and beyond fasting and 2-h glucose levels. Diabetes Care 2009;32:335–341
21. Anderson BJ, Edelstein S, Abramson NW, et al.; TODAY Study Group. Depressive symptoms and quality of life in adolescents with type 2 diabetes: baseline data from the TODAY study. Diabetes Care 2011;34:2205–2207
22. Lawrence JM, Standiford DA, Loots B, et al.; SEARCH for Diabetes in Youth Study. Prevalence and correlates of depressed mood among youth with diabetes: the SEARCH for Diabetes in Youth study. Pediatrics 2006;117:1348–1358
23. De Groot M. Depression and diabetes. In *Psychosocial Care for People with Diabetes*. Young-Hyman D, Peyrot M, Eds. Alexandria, VA, American Diabetes Association, 2012, p. 1–16
24. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med 2001;63:619–630
25. Gross R, Olfson M, Gameroff MJ, et al. Depression and glycemic control in Hispanic primary care patients with diabetes. J Gen Intern Med 2005;20:460–466
26. Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 2000;23:934–942
27. Lustman PJ, Griffith LS, Freedland KE, Clouse RE. The course of major depression in diabetes. Gen Hosp Psychiatry 1997;19:138–143
28. Wagner JA, Tennen H. History of major depressive disorder and diabetes outcomes in diet- and tablet-treated post-menopausal women: a case control study. Diabet Med 2007;24:211–216
29. American Diabetes Association. (11) Children and adolescents. Diabetes Care 2015; 38(Suppl.):S70–S76
30. Delamater AM, de Wit M, McDarby V, Malik J, Acerini CL.; International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2014. Psychological care of children and adolescents with type 1 diabetes. Pediatr Diabetes 2014;15(Suppl. 20):232–244
31. U.K. Prospective Diabetes Study Group. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995;44:1249–1258
32. Zeitler P, Hirst K, Copeland KC, et al.; TODAY Study Group. HbA1C after a short period of monotherapy with metformin identifies durable glycemic control among adolescents with type 2 diabetes. Diabetes Care 2015;38:2285–2292
33. Levitt Katz LE, Magge SN, Hernandez ML, Murphy KM, McKnight HM, Lipman T. Glycemic control in youth with type 2 diabetes declines as early as two years after diagnosis. J Pediatr 2011;158:106–111
34. TODAY Study Group. Effects of metformin, metformin plus rosiglitazone, and metformin plus lifestyle on insulin sensitivity and β-cell function in TODAY. Diabetes Care 2013;36: 1749–1757
35. Dart AB, Martens PJ, Rigatto C, Brownell MD, Dean HJ, Sellers EA. Earlier onset of complications in youth with type 2 diabetes. Diabetes Care 2014;37:436–443
36. Constantino MI, Molyneaux L, Limacher-Gisler F, et al. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. Diabetes Care 2013;36:3863–3869
37. TODAY Study Group. Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. Diabetes Care 2013;36:1735–1741
38. Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG. Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. JAMA 2006;296:421–426
39. Jacobson AM, Hauser ST, Lavori P, et al. Adherence among children and adolescents with insulin-dependent diabetes mellitus over a four-year longitudinal follow-up: I. The influence of patient coping and adjustment. J Pediatr Psychol 1990;15:511–526
40. Kovacs M, Goldston D, Obrosky DS, Iyengar S. Prevalence and predictors of pervasive noncompliance with medical treatment among youths with insulin-dependent diabetes mellitus. J Am Acad Child Adolesc Psychiatry 1992;31:1112–1119
41. Bond WS, Hussar DA. Detection methods and strategies for improving medication compliance. Am J Hosp Pharm 1991;48:1978–1988
42. Quittner AL, Modi AC, Lemanek KL, Ievers-Landis CE, Rapoff MA. Evidence-based assessment of adherence to medical treatments in pediatric psychology. J Pediatr Psychol 2008; 33:916–936
43. Hanghøj S, Boisen KA. Self-reported barriers to medication adherence among chronically ill adolescents: a systematic review. J Adolesc Health 2014;54:121–138
44. Dunbar-Jacob J, Mortimer-Stephens MK. Treatment adherence in chronic disease. J Clin Epidemiol 2001;54(Suppl. 1):S57–S60
45. Mayer-Davis EJ, Beyer J, Bell RA, et al.; SEARCH for Diabetes in Youth Study Group. Diabetes in African American youth: prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. Diabetes Care 2009;32(Suppl. 2):S112–S122
46. Bell RA, Mayer-Davis EJ, Beyer JW, et al.; SEARCH for Diabetes in Youth Study Group. Diabetes in non-Hispanic white youth: prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. Diabetes Care 2009;32(Suppl. 2):S102–S111
47. Dabelea D, Mayer-Davis EJ, Saydah S, et al.; SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA 2014; 311:1778–1786