# Changes in Treatment Adherence and Glycemic Control During the Transition to Adolescence in Type 1 Diabetes

Joseph R. Rausch, phd<sup>1</sup> Korey K. Hood, phd<sup>1</sup> Alan Delamater, phd<sup>2</sup> Jennifer Shroff Pendley, phd<sup>3</sup> JENNIFER M. ROHAN, MA<sup>1,4</sup> GRAFTON REEVES, MD<sup>5</sup> LAWRENCE DOLAN, MD<sup>6</sup> DENNIS DROTAR, PHD<sup>1,4</sup>

**OBJECTIVE**—To test models of unidirectional and bidirectional change between treatment adherence and glycemic control in youth with type 1 diabetes.

**RESEARCH DESIGN AND METHODS**—We conducted a 2-year longitudinal, multisite study of 225 youth with type 1 diabetes recruited at the cusp of adolescence (aged 9–11 years) to describe the mutual influences of glycemic control as measured by  $HbA_{1c}$  and treatment adherence as measured by blood glucose monitoring frequency (BGMF) during the transition to adolescence.

**RESULTS**—HbA<sub>1c</sub> increased from 8.2 to 8.6% (P < 0.001) and BGMF decreased from 4.9 to 4.5 checks per day (P < 0.02) during the 2-year period. Changes in the BGMF slope predicted changes in HbA<sub>1c</sub>. A change (increase) in HbA<sub>1c</sub> was associated with a change (decrease) in BGMF of 1.26 (P < 0.001) after controlling for covariates.

**CONCLUSIONS**—The magnitude of the effect of declining treatment adherence (BGMF) on glycemic control in young adolescents may be even greater than declines observed among older adolescents. BGMF offers a powerful tool for targeted management of glycemic control for type 1 diabetes during the critical transition to adolescence.

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he importance of glycemic control in reducing future complications in type 1 diabetes is well recognized. Although improvement of glycemic control can result in significant risk reduction for future diabetes-related complications, suboptimal glycemic control has major consequences on long-term health outcomes (1,2). Moreover, suboptimal glycemic control that is established during early adolescence (3) may be very difficult to change, even with state-of-the-art behavioral intervention (4).

Although significant declines in treatment adherence have been observed as children with type 1 diabetes enter puberty and experience increased insulin resistance (3,5–8), the course of glycemic control and potentially modifiable factors that predict change in glycemic control in this age group are not well understood. Moreover, most studies examining glycemic control in pediatric type 1 diabetes have not described predictors of change in glycemic control over time, particularly during early adolescence. One exception is Helgeson et al. (9), whose single-site study found that treatment nonadherence, as defined by lower frequency of blood glucose monitoring (BGM), predicted a decline in glycemic control, especially among youth (N = 132) with type 1 diabetes aged 10-14 years. Berg et al. (10) and Palmer et al. (11,12) have also studied youth (aged 10–14 years) with type 1 diabetes, with a focus on the role of autonomy, coping, and parental involvement in diabetes management.

To our knowledge, no study with pediatric patients who are transitioning to adolescence has evaluated 1) the rate at which treatment adherence predicts change in glycemic control; or, 2) whether the adherence-glycemic control relationship is bidirectional, that is, involving mutual influence. A bidirectional relationship between these variables is both plausible and clinically relevant from the standpoint of patients, families, and health care providers. For example, if adolescents have above-target hemoglobin HbA<sub>1c</sub> values, they may receive more intensive intervention aimed at adherence promotion. However, the use of glycemic control data as a proxy for and to guide future management of treatment adherence for adolescents may mask other contributors to above-target HbA<sub>1c</sub> values such as insulin dosing and glycemic variability. Moreover, if the level of glycemic control does not predict trajectories of adherence, this global strategy of clinical management may need to be revisited in favor of more specific adherence promotion approaches.

To address this important gap in predictive models of glycemic control and to inform practice, the current study tested models of unidirectional and bidirectional change between treatment adherence and glycemic control for youth with type 1 diabetes. We studied a homogeneous (by age), relatively large sample of 239 youth with type 1 diabetes recruited during late childhood/early adolescence (aged 9-11 years) to describe the course of and clinically relevant influences on glycemic control as children with type 1 diabetes transition through adolescence. In the context of clinically relevant covariates, among them pubertal status and method of diabetes treatment, we tested the validity of a unidirectional model in which adherence (at baseline and longitudinal change) predicted changes in glycemic control versus a bidirectional model in which adherence and glycemic

From the <sup>1</sup>Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; the <sup>2</sup>Department of Pediatrics, University of Miami, Miami, Florida; the <sup>3</sup>Division of Behavioral Health, Alfred I. duPont Hospital for Children, Wilmington, Delaware; the <sup>4</sup>Department of Psychology, University of Cincinnati, Cincinnati, Ohio; the <sup>5</sup>Division of Pediatric Endocrinology, Alfred I. duPont Hospital for Children, Wilmington, Delaware; and the <sup>6</sup>Division of Endocrinology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.

Corresponding author: Dennis Drotar, dennis.drotar@cchmc.org. Received 7 November 2011 and accepted 8 February 2012. DOI: 10.2337/dc11-2163

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control predicted one another in this cohort over 2 years.

## RESEARCH DESIGN AND METHODS

## Participants and procedures at baseline

Participants were youth with type 1 diabetes and their maternal caregivers who were followed up at pediatric diabetes clinics at three university-affiliated medical centers in the U.S. Each site's institutional review board approved the study. Data were collected as part of an ongoing, 3-year longitudinal study. For the purpose of the present analysis, baseline predictors of 2-year outcome data were considered. Baseline data have been described (13–15). This is the first report from this study that has focused on treatment adherence and the prediction of glycemic control at 2 years after baseline.

Caregivers and children were recruited during a routine outpatient clinic visit. Potentially eligible participants were identified by clinic staff and then approached by research staff, who explained the study procedures and verified eligibility. Inclusion criteria included duration of type 1 diabetes for at least 1 year, age 9 to 11 years at the time of recruitment, English speaking, no known plans to move out of the area within the next 3 years, and absence of secondary causes of a type 1 diabetes diagnosis (e.g., cystic fibrosis). Exclusionary criteria included current involvement in foster care, presence of severe psychiatric disorders or comorbid chronic conditions (e.g., renal disease) that required burdensome ongoing treatment regimens, or diagnosis of mental retardation.

Of the 361 eligible participants who were approached, 240 (66.5%) consented and participated. Reasons for not participating included being too busy (n = 54), no transportation (n = 3), and other (n = 64). Signed informed consent was obtained from a parent or legal guardian, written assent from children aged 11 years, and verbal assent from children aged younger than 11 years according to the guidelines established by each site's institutional review board. After enrollment, one child was diagnosed with monogenic diabetes of the young (16), was no longer treated with insulin, and hence, removed from the study and analysis.

The 2-year follow-up yielded 225 youth (aged 11–14 years) with type 1

diabetes and their maternal and paternal caregivers. Overall attrition from baseline to 2 years was 3.3% (n = 8). Reasons for discontinuing participation included child and/or family was no longer interested in the research (n = 2), the family moved out of the area (n = 1), the patient changed endocrinologists and the doctor was not affiliated with the hospital (n = 1), the family was too overwhelmed to participate in research (n = 1), and families would not schedule a research visit and were dropped from the study (n = 3). Missing data due to noncompletion of visits included 13 at 1 year and 14 at 2 years. There were no significant differences between those who participated in the 1- and 2-year follow-up visits and those who did not complete the 1- and/or 2-year study visit with respect to baseline disease duration, age, race, income, household composition (1 vs. 2 parents), child's sex, insulin delivery method at baseline, 12, and 24 months, or  $HbA_{1c}$  obtained at baseline, 6, and 18 months.

# Sample characteristics: baseline to 2 years

The demographic and medical characteristics of our sample at baseline through the 2-year follow-up are reported in Table 1. At 2 years, the sample (mean age, 12.62 years) had a comparable percentage of boys (46.2%) and girls (53.8%) and included a majority of non-Hispanic white youth (75.6%), but higher percentages of Hispanic white youth (13.3%) than are typical in studies of type 1 diabetes. Most the sample (68.4%) received insulin via subcutaneous insulin infusion (i.e., insulin pump or pod).

#### **Measures: primary outcomes**

#### Treatment adherence: BGM frequency.

BGM frequency (BGMF) was chosen as the indicator of treatment adherence given its central role in diabetes management and its robust association with glycemic control in multiple studies (9,17). Children and adolescents received \$5 cash for supplying the researchers with a meter and/or logbook at the time of the study visit. BGMF results were obtained from the child's blood glucose meter(s) for the previous 2 weeks starting with the day before the assessment visit. If one or more of the meters (e.g., a school meter) were not available at the time of the study visit, the information was obtained from the child's logbook (baseline, 17%; 1 year, 17%; 2 years, 15%). Data from the meters or logbooks were available for

98.7% of patients at baseline, 97.8% at 1 year, and 96.5% at 2 year.

**Glycemic control:** HbA<sub>1c</sub>. Blood samples were obtained at 6-month intervals from baseline to 2 years after baseline by a finger stick during the study visit. Samples from each study site were analyzed by one central laboratory to ensure standardization of results across sites. Samples were analyzed using the TOSOH-G7 method (reference range, 4.0–6.0%).

#### Measures: covariates

Site. Site location (Cincinnati Children's Hospital Medical Center in Cincinnati, Ohio; Alfred I. duPont Hospital for Children in Wilmington, Delaware; and University of Miami Diabetes Research Institute in Miami, Florida [Joe DiMaggio Children's Hospital], Miami Children's Hospital]) was assessed across time points and considered a covariate in the analy-

**Sex.** The child's sex (male, female) was assessed at baseline and considered as a covariate.

**Ethnicity and race**. Ethnicity and race were assessed at baseline and categorized as non-Hispanic white; non-Hispanic other; or Hispanic.

Maternal education. Maternal education was assessed at baseline and categorized as follows: did not finish high school; obtained high school diploma or equivalent; obtained some college or college degree.

Household composition. Household composition was assessed at baseline and categorized as one or two caregiver involvement.

**Pubertal status.** Pubertal status, as measured by Tanner stage based on provider examination, was assessed across time points, but the baseline status was used as the covariate.

**Insulin delivery method.** Insulin delivery method was assessed across all time points, allowed to vary across time, and was categorized as pump/pod or injections.

**Duration.** Type 1 diabetes duration in years was assessed across all time points and allowed to vary across time.

**Age.** Youth age in years was assessed across all time points and allowed to vary across time.

#### Approach to statistical analysis

We ultimately had two primary goals for examining changes in  $HbA_{1c}$  and BGMF: First, we were interested in the prediction of the  $HbA_{1c}$  slope from the BGMF slope

Table 1—Demographic and medical characteristics of sample at baseline, 1 year, and 2 years

	Baseline	1 year	2 years
Child's age (years)*	10.54 (0.94) 9.0–12.09	11.59 (0.97) 9.86–13.22	12.62 (0.96) 10.95–14.39
Diabetes duration (years)	4.41 (2.46) 1–11	5.43 (2.49) 2–12	6.46 (2.43) 3–13
Pubertal status (Tanner exam)	1.73 (0.91) 1-5	2.49 (1.19) 1-5	3.10 (1.14) 1–5
HbA <sub>1c</sub> (%)	8.20 (1.37) 5.7–16.8	8.31 (1.38) 5.6–14.5	8.51 (1.41) 5.7–13.4
Child's sex			
Male	109 (45.61)	103 (45.6)	104 (46.2)
Female	130 (54.39)	123 (54.4)	121 (53.8)
Child's ethnicity			
Non-Hispanic white	179 (74.9)	171 (75.7)	170 (75.6)
Non-Hispanic other	27 (11.3)	26 (11.5)	25 (11.1)
Hispanic	33 (13.8)	29 (12.8)	30 (13.3)
Site			
Cincinnati Children's Hospital	108 (45.2)	106 (46.9)	106 (47.1)
Alfred I. duPont Hospital for Children	84 (35.1)	78 (34.5)	76 (33.8)
UMDRI	47 (19.7)	42 (18.6)	43 (19.1)
Insulin regimen			
Conventional/multiple daily injection	109 (45.6)	76 (33.6)	67 (29.8)
Pump/pod	130 (54.4)	150 (66.4)	154 (68.4)
Household composition			
One caregiver	51 (21.3)	46 (20.4)	47 (20.9)
Two caregivers	188 (78.7)	180 (79.6)	178 (79.1)
Maternal caregiver relationship			
Biological mother	228 (97.4)	207 (92)	209 (92.9)
Adoptive mother	2 (0.9)	2 (0.9)	2 (0.9)
Stepmother	0 (0)	1 (0.4)	2 (0.9)
Grandmother	4 (1.7)	4 (1.7)	4 (1.7)
Maternal education			
No high school diploma or equivalent	9 (3.8)	6 (2.7)	7 (3.1)
High school diploma or equivalent	70 (29.3)	68 (30.1)	65 (28.9)
Some college or college degree	159 (66.5)	151 (66.8)	152 (67.6)

Continuous data are expressed as mean (SD) range, and categoric data as *n* (%). UMDRI, University of Miami Diabetes Research Institute. \*Note: four children were recruited at age 11 but were not seen for baseline visits until after they turned 12 years of age due to study visit cancellations and reschedules.

where we examined a statistical model with the  $HbA_{1c}$  slope as the outcome variable, the BGMF slope was the primary predictor, and we also controlled for the initial levels of  $HbA_{1c}$  and BGMF from their respective trajectories (i.e., the intercepts) and the set of covariates detailed in the previous section.

Our second goal was to investigate predictors of the slopes for each of HbA<sub>1c</sub> and BGMF using a bivariate, bidirectional regression model. The focus of this model was on the relationships between each of the slopes for HbA<sub>1c</sub> and BGMF and the HbA<sub>1c</sub> and BGMF intercepts to establish the existence of a potential bidirectional relationship. Consistent with our first statistical model, we also included the set of covariates, detailed in the previous section, in the bidirectional model. The covariates used in each of these statistical models were included based on their documented associations with glycemic control and adherence, as well as their ability to provide a richer context to the data. Sample size estimates were based on a multiple regression analysis in which the outcome is the participant-specific trajectory, calculated separately for each participant. Sample size calculations indicated relatively small increments in  $R^2 = 0.03-0.04$  that can be detected with 0.80 power, and P < 0.05 between self-management, adherence, and glycemic control.

These analyses were done in MPlus 5.2 software using maximum likelihood estimation to account for missing data and estimation of parameters for trajectories. Statistical significance was defined as P < 0.05.

#### **RESULTS**

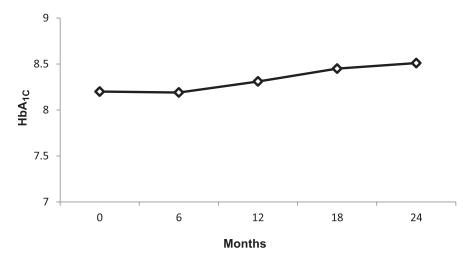
## Trajectory analyses for HbA<sub>1c</sub> and BGMF

The slopes for  $HbA_{1c}$  and BGMF were calculated in a manner so that they corresponded to change in units per year. The average intercept or  $HbA_{1c}$  was 8.2 (95%

CI 8.0–8.4; P < 0.001), whereas the average slope over time was 0.2 (0.1–0.3; P < 0.001). This reflected an increase in HbA<sub>1c</sub> over time. Thus, an individual following the average trajectory for HbA<sub>1c</sub> had an initial HbA<sub>1c</sub> value of 8.2% and a total change of 0.4% on HbA<sub>1c</sub> across the 2-year time span, yielding a final HbA<sub>1c</sub> of 8.6%. Figure 1 illustrates the raw data for the average values of HbA<sub>1c</sub> at each time point.

For BGMF, the average intercept was 4.9 (95% CI 4.7-5.2; P < 0.001), and the average slope over time was -0.2 (-0.0 to -0.3; P = 0.02), reflecting a decrease in the frequency of BGM. An individual following the average trajectory for BGMF started with 4.9 BGM checks per day initially, changed by a total of -0.4 checks per day across the entire study, and ultimately yielded a final value of 4.5 checks per day by the end of the study. Figure 2 illustrates the raw data for the average values for BGMF at each time point. The average daily BGMF for the entire

#### Treatment adherence and glycemic control



**Figure 1**—Average values of  $HbA_{1c}$  at each time point.

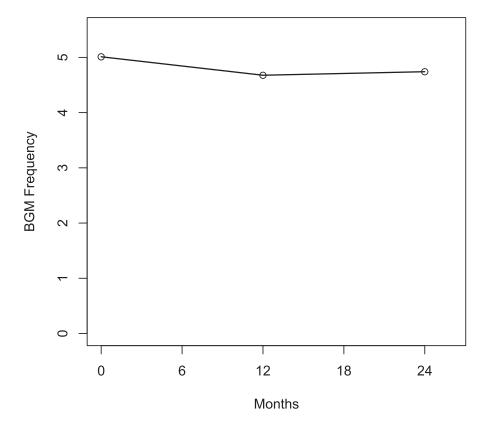
sample was 5.01 (SD, 1.73) at baseline, 4.68 (1.97) at 1 year, and 4.74 (2.04) at 2 years.

# Description of unidirectional regression of HbA<sub>1c</sub> slope on BGMF slope

The results for the unidirectional regression model for the  $HbA_{1c}$  slope with the BGMF slope as a predictor are reported in Table 2, where the BGMF slope is a statistically significant predictor of

HbA<sub>1c</sub> slope ( $\beta = -1.26$  [95% CI -0.49 to -2.03], P = 0.001). Importantly, neither of the HbA<sub>1c</sub> nor BGMF intercepts are statistically significant, nor are any of the covariates of interest.

The regression coefficient of -1.26 reflects that every change of -1.0% on the BGMF slope was associated with a change of -1.26% on HbA<sub>1c</sub> slope, after controlling for the covariates of interest. Thus, as an example, an individual trajectory, which initially has an HbA<sub>1c</sub> of 8.2%



**Figure 2**—Average values of BGMF at each time point.

(the average value for  $HbA_{1c}$  in this model) and changed to a final  $HbA_{1c}$  value of 10.8% by the end of the study, is expected to yield a drop of approximately -2.0 blood glucose checks per day for the BGMF trajectory (e.g., starting the study with five checks per day and ending the study with three checks per day) across the 2-year time span. The number of blood glucose checks at the end of the study was below the standard of care for BGMF, which is four to six checks per day across the sites.

# Description of bidirectional regression model predicting HbA<sub>1c</sub> and BGMF slopes

The results for the bidirectional regression model are reported in Table 2. This Table illustrates that the HbA<sub>1c</sub> intercept  $(\beta = -0.19 [95\% CI - 0.06 to -0.32],$ P < 0.01) and BGMF intercept ( $\beta = -0.23$ [-0.10 to -0.36], P < 0.001) both are statistically significant predictors of the HbA<sub>1c</sub> slope, whereas only the BGMF intercept predicted the BGMF slope ( $\beta = 0.26$ [0.02-0.50], P = 0.03). Several covariates such as site (Cincinnati Children's Hospital Medical Center versus Miami sites;  $\beta$  = -0.30 [-0.01 to -0.59], P = 0.04), type of insulin delivery at baseline ( $\beta = 0.25$ [0.05-0.45], P = 0.01), and pubertal status at baseline ( $\beta = -0.15 [-0.27 \text{ to } -0.03]$ , P = 0.02) were statistically significant and uniquely accounted for variance in the HbA<sub>1c</sub> slopes. However, none of these covariates were statistically significant in the regression model predicting the BGMF slope.

**CONCLUSIONS**—Our findings documented significant deterioration in glycemic control over a 2-year period as youth with type 1 diabetes transition to adolescence. Treatment adherence defined as BGMF, which also deteriorated over the course of the study period, demonstrated a robust effect on change in glycemic control after controlling for clinically relevant covariates. Specifically, one less check of blood glucose per day across this 2-year period predicted an increase in HbA<sub>1c</sub> of 1.26% (e.g., 8.0–9.26%). The clinical significance of this finding is difficult to ascertain.

Although the influence of treatment adherence on glycemic control has been relatively well documented in older adolescents (3,5–7), our findings document the substantial impact of declining adherence on subsequent glycemic control for youth with type 1 diabetes whose

Table 2—Results for bidirectional regression model and unidirectional regression model for  $HbA_{1c}$  slope based on  $HbA_{1c}$  and BGMF trajectories

	Bidirec		Unidirectional regression model based for HbA <sub>1c</sub> slope			
	$HbA_{1c}$ slope as outcome		BGMF slope as outcome		HbA <sub>1c</sub> slope as outcome	
Variable	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	Р
BGMF slope	_	_	_	_	-1.26 (-0.49 to -2.03)	0.001
HbA <sub>1c</sub> Int	-0.19 (-0.06 to -0.32)	0.004	0.17 (-0.07 to 0.41)	0.16	0.10 (-0.17 to 0.37)	0.48
BGMF Int	-0.23 (-0.10 to -0.36)	< 0.001	0.26 (0.02-0.50)	0.03	0.08 (-0.19  to  0.35)	0.54
CCHMC vs. Miami	-0.30 (-0.01 to -0.59)	0.04	0.36 (-0.24 to 0.96)	0.24	0.11 (-0.59  to  0.81)	0.76
Delaware vs. Miami	-0.21 ( $-0.49$ to $0.07$ )	0.15	0.38 (-0.21 to 0.97)	0.20	0.22 (-0.49 to 0.93)	0.55
Age	0.02 (-0.08 to 0.12)	0.65	-0.08 (-0.28  to  0.12)	0.43	-0.09 (-0.33  to  0.15)	0.47
Education	-0.09 (-0.25 to 0.07)	0.25	0.15 (-0.18  to  0.48)	0.36	0.11 (-0.27 to 0.49)	0.57
Duration	-0.01 (-0.05 to 0.03)	0.60	-0.01 ( $-0.08$ to $0.06$ )	0.74	-0.03 ( $-0.11$ to $0.05$ )	0.52
Married (vs. not married)	0.19 (-0.03  to  0.41)	0.10	0.02 (-0.44 to 0.48)	0.92	0.25 (-0.26  to  0.76)	0.34
White (vs. nonwhite)	0.10 (-0.16 to 0.36)	0.44	-0.15 ( $-0.69$ to $0.39$ )	0.58	-0.03 ( $-0.63$ to $0.57$ )	0.93
Male (vs. female)	0.13 (-0.04 to 0.30)	0.14	-0.34 ( $-0.70$ to $0.02$ )	0.06	-0.30 (-0.77  to  0.17)	0.21
Baseline						
Insulin regimen	0.25 (0.05-0.45)	0.01	-0.31 ( $-0.72$ to $0.10$ )	0.13	-0.10 (-0.59  to  0.39)	0.70
Tanner stage	-0.15 (-0.27 to -0.03)	0.02	0.10 (-0.14 to 0.34)	0.43	-0.05 (-0.33 to 0.23)	0.71

Cells in boldface are statistically significant at P < 0.05 level. CCHMC, Cincinnati Children's Hospital Medical Center; Miami, University of Miami Diabetes Research Institute (includes both the Miami Children's Hospital and the Joe DiMaggio sites). Int, intercept.

baseline glycemic control data were obtained at the onset of adolescence. These data suggest that the magnitude of the effect of declining BGMF on glycemic control in young adolescents may be even greater than declines observed among older adolescents. Early adolescence may represent a critical transition period in treatment adherence for which targeting preventive intervention should be targeted toward preserving BGMF and thus altering the potential trajectory of increased and suboptimal glycemic control. Our results are consistent with Driscoll et al. (18), who found that BGMF increased before clinic visits for children with lower HbA<sub>1c</sub> values.

The absence of a bidirectional effect of glycemic control on treatment adherence also has useful clinical implications for clinical assessment and treatment planning. The findings affirm the observation that glycemic control is not a valid proxy for treatment adherence (19). In other words, the clinician who obtains an above-target HbA<sub>1c</sub> value for a particular patient and family and then assumes poor treatment adherence may miss other relevant contributors to glycemic control such as dosing, timing of insulin administration, and variability and frequency of BGM. This clinical management strategy may also have the unintended effect of demotivating patients and families, especially if they have been trying to adhere to

treatment recommendations but still have an above-target HbA<sub>1c</sub>. Alternatively, data from this study suggest that readily available data concerning treatment adherence (e.g., number of daily blood glucose checks) does predict glycemic control and can be used as a primary method to guide targeted clinical management. In particular, those youth who demonstrate a decreasing BGMF during early adolescence can be targeted for intensive interventions to increase their BGMF.

Several limitations should be considered when interpreting our findings. Although the homogeneity in ages of our sample is a strength because of its developmental specificity, it also limits the generalizability of our findings, as does the sample demographics that included a majority of white and more educated families. In addition, the findings were limited to a 2-year follow-up. We also used BGMF as an indicator of treatment adherence. Although there is substantial support for this objective measure of treatment adherence in pediatric type 1 diabetes (17,20), BGMF may not fully capture the multidimensional nature of treatment adherence. However, our experience suggests that youth and families in this age group who are not checking as frequently as is prescribed are also not fully engaging in other adherence behaviors, due to lack of blood glucose data to make necessary changes in insulin or to other variables such as insufficient diabetes knowledge, support, or motivation. Finally, adherence is one of a number of variables (e.g., the well-documented (7,8) effect of hormonal changes during the onset of puberty) that can influence glycemic control. In the current study, pubertal status at baseline was associated with changes in glycemic control, but this effect was controlled for in our analysis. However, the absence of a bidirectional effect of glycemic control on treatment adherence may reflect the influence of puberty.

Future research should address these limitations by studying broader, more representative samples across a more extended period of time. Our subsequent analyses will describe prediction of change in glycemic control over 3 years when prospective data collection is complete. The present findings might be extended to identify subgroups of adolescents with differing trajectories of glycemic control and clarify how individual differences in trajectories of treatment adherence map onto glycemic control. The frequency of BGM, which is readily available to practitioners in their routine care of adolescents with type 1 diabetes, offers a powerful tool for targeted management of type 1 diabetes, especially when combined with data concerning recent trajectories of glycemic control.

#### Treatment adherence and glycemic control

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J.R.R., J.M.R., and D.D. researched data, contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript. K.K.H. contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript. A.D. and L.D. contributed to discussion and reviewed and edited the manuscript. J.S.P. researched data, contributed to discussion, and reviewed and edited the manuscript. G.R. reviewed and edited the manuscript. D.D. 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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