ORIGINAL ARTICLE

Association of HbA1c to *BOLUS* Scores Among Youths with Type 1 Diabetes

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Abstract

Background: Frequency of mealtime insulin bolusing (*BOLUS*) is a promising new objective assessment of adherence in youths with type 1 diabetes (T1D). As further confirmation of the validity of *BOLUS*, we compare the associations of glycated hemoglobin (HbA1c) values of T1D youths with the original scoring of *BOLUS* and two alternative scoring procedures: mean mealtime boluses within a 2-h meal window (*2h-BOLUS*) and total daily frequency of boluses (*TOTAL-BOLUS*). In addition, we assess HbA1c associations of these three procedures, including interaction terms for mealtime boluses plus correction boluses.

Subjects and Methods: Blood glucose meter data, insulin pump records, and HbA1c levels were collected from a combined clinical and research database for a random sample of 100 youths (mean age, 12.7 ± 4.6 years). Youths' pump records were scored using the published methodology and alternative procedures for evaluating insulin use.

Results: Youths' *BOLUS*, *TOTAL-BOLUS*, and mealtime boluses within a 2-h meal window (*2h-BOLUS*) scores are independently associated with youths' HbA1c level; all measures demonstrated stronger associations with youths' HbA1c than did frequency of glucose monitoring. The strongest association was between youths' *BOLUS* score and their HbA1c level. In multiple regression analyses, youths' *BOLUS* score better explains the variations in HbA1c levels than either youths' *2h-BOLUS* or *TOTAL-BOLUS* scores. When combined with *BOLUS* in the same relationships, *2h-BOLUS* and *TOTAL-BOLUS* were not found to have statistically significant coefficients. None of the bivariate relationships of HbA1c and interaction terms of mealtime and correction boluses was significant.

Conclusions: The original method for calculating *BOLUS* appears superior to alternative scoring methods in its association with youths' HbA1c levels.

Introduction

MANY CHILDREN AND ADOLESCENTS with type 1 diabetes (T1D) have difficulty adhering to their treatment regimen due to dependence on caregivers and psychological and physical burdens of T1D management.¹⁻³ This is an important concern because research has consistently shown that as adherence increases in youths, glycated hemoglobin (HbA1c) levels decrease.⁴ Presently, HbA1c is the gold standard measure of glycemic control in youths because of its predictive association with the development of long-term diabetes complications.

Until recently, the only objective measure in published research for predicting HbA1c levels was youths' frequency

of daily self-monitoring of blood glucose (SMBG). However, we have since published a description of a new objective measure of mealtime insulin use (*BOLUS*) calculated from insulin pump downloads.^{5,6} The *BOLUS* score is calculated using 2-week insulin pump downloads performed in the clinic during routine diabetes care visits by assigning 1 point if any food-associated insulin bolus occurs at breakfast (6–10 a.m.), lunch (11 a.m.–3 p.m.), or dinner (4–10 p.m.). The average score over 14 days, which can range from 0 to 3 points, is then calculated. In a cross-sectional study, we found a stronger association between youths' *BOLUS* scores and their HbA1c values than between youths' SMBG results and their HbA1c values, suggesting that *BOLUS* maybe superior

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to SMBG when explaining the variance in youths' HbA1c values.⁶ Likewise, in a follow-up prospective study, we found youths' *BOLUS* scores were superior to youths' SMBG in predicting future HbA1c values up to 12 months.⁵ Therefore the existing research suggests that the *BOLUS* score has potential to be a more effective measure of adherence than SMBG in youths and perhaps a more accurate proxy measure of glycemic control in youths than SMBG.

What continues to be unknown is whether the previously published measurement of adherence to *BOLUS* is, in fact, the best measurement for predicting HbA1c or if alternative methods in evaluating insulin use might be more effective. This gap in knowledge is important because if there are easier and more accurate methods of measuring adherence to insulin use in youths, those methods should be explored in order to improve available adherence measurement procedures.

The present work corrects this gap in knowledge by comparing alternative methods of scoring insulin use among youth. This work presents additional evidence for validity of the mealtime insulin *BOLUS* scores by comparing associations between youths' HbA1c values and the original *BOLUS* score versus alternate methods of measuring insulin use in youths. The alternative scoring procedures that we evaluate include one that uses tighter meal windows (mean mealtime boluses within a 2-h meal window [*2h-BOLUS*]), one that uses a total daily *BOLUS* frequency (*TOTAL-BOLUS*), and interactive terms that use a combination of mealtime insulin boluses and correction boluses.

Subjects and Methods

Data were obtained from a clinical database of approximately 3,000 patient records and a comparable research database containing approximately 50 patient records (all children younger than 7 years old). Inclusion criteria were as follows: child age between 1 and 19 years old, a confirmed diagnosis of T1D for at least 1 year, and use of an insulin pump for daily insulin administration. The research database was included in the data search to ensure an adequate sampling of young children with T1D, who otherwise represent only about 14% of the clinical database. A convenience sample of 100 patient records that met the inclusion criteria was randomly extracted from the databases (85 youths from the clinical database, 15 youths from the research database). Power analysis with StudySize version 3.0 software (Creo-Stat HB, Frolunda, Sweden) revealed that a sample size of 100 using generalized linear models of HbA1c as a function of three correlated covariates with multicollinearity of 0.30–0.40 and a simple correlation of a bolus measure of 0.40–0.48, respectively, would achieve a greater than 0.80 power. Institutional review board approval was obtained prior to the collection of study-related data.

Procedure

Data included the youths' demographic information, youths' 14-day blood glucose monitoring, 14-day insulin pump and glucometer download, and HbA1c levels from a single clinic appointment. Youths' mean frequency of daily SMBG was recorded by a team of certified diabetes educators using youths' 14-day glucometer download records. Using youths' 14-day insulin pump download, these coders also calculated youths' *BOLUS* score and *2h-BOLUS* score, as

well as recorded the *TOTAL-BOLUS* score from the report of the insulin pump download. The *BOLUS* and *2h-BOLUS* scores can be completed in less than 3 min by trained staff. Coders further calculated the interaction terms combining mealtime insulin use and corrections. Inter-rater reliability was examined for all of these scores using a random subset of the sample and intraclass correlations.

Measures

Frequency of daily serial SMBG. Youths' average daily frequency of SMBG was calculated using youths' 14-day blood glucose records. Inter-rater reliability was 0.995 ($P = 0.000001$), indicating a high degree of reliability among coders.

Mealtime insulin *BOLUS* score (*BOLUS*). Based on published methodology, youths' *BOLUS* scores were calculated using their 14-day insulin pump records. Youths were assigned a maximum of 1 point each for a food-associated *BOLUS* occurring between 0600 and 1000 h, 1100 and 1500 h, and 1600 and 2200 h. The maximum *BOLUS* score per day was 3.0. Inter-rater reliability was 0.897 ($P = 0.000001$), indicating a high degree of reliability.

The 2-h modified insulin *BOLUS* score (*2h-BOLUS*). To test the validity of a tighter definition of mealtimes, *2h-BOLUS* scores were calculated by applying only a 2-h window for mealtimes—0700–0900 h, 1100–1300 h, and 1700–1900 h—to youths' insulin pump records. Similar to the original scoring, youths were assigned a maximum of 1 point for a food-associated *BOLUS* occurring within one or more of these 2-h mealtime windows. The maximum *2h-BOLUS* score per day was 3.0. Inter-rater reliability was high at 0.934 ($P < 0.000001$).

Total *BOLUS* frequency (*TOTAL-BOLUS*). Using youths' insulin pump downloads, we calculated an average *TOTAL-BOLUS* frequency score per day by summing all reported boluses (e.g., mealtime and correction boluses) for each day and averaging these values over 14 days. Inter-rater reliability was high at 0.945 ($P < 0.000001$).

Total corrections for hyperglycemia (%*Total Corrections*). For youths who experienced episodes of hyperglycemia (>250 mg/dL), we calculated the percentage of time that youths corrected for the hyperglycemia using insulin across the 14 days. Inter-rater reliability was high at 0.952 ($P < 0.000001$).

Mealtime corrections for hyperglycemia (%*Meal Corrections*). For youths who experienced episodes of hyperglycemia (>250 mg/dL) at a mealtime, we calculated the percentage of times that youths corrected for the hyperglycemia in addition to dosing for the mealtime. Inter-rater reliability was high at 0.834 ($P < 0.000001$).

Interaction terms. We created two interaction terms—*BOLUS* $\times$ %*Meal Corrections* and *BOLUS* $\times$ %*Total Corrections*—which both accounted for mealtime insulin use plus the likelihood youths also corrected for hyperglycemia at either mealtimes or any time during the day, respectively, in order to see if including corrections for hyperglycemia improved the sensitivity of the *BOLUS* in explaining the variation in youths' HbA1c.

Analyses

Descriptive statistics were calculated to characterize the sample for youths' demographic and adherence data and HbA1c. Simple correlations examined the bivariate association between each of the insulin scores and youths' HbA1c levels. We also examined bivariate correlations between youths' HbA1c levels and their age, gender, and race (dichotomized white vs. not white because of sample limitations). Finally, a series of exploratory and stepwise multiple regressions were used to determine if the alternate scoring procedures of youths' insulin bolusing behavior (e.g., *2h-BOLUS*, *TOTAL-BOLUS*, *BOLUS* × %*Total Corrections*, *BOLUS* × %*Meal Corrections*) were superior to the original *BOLUS* scoring in predicting youths' HbA1c levels. In these regression models, the additional covariates of age, gender, SMBG, and race were included when significant. Steiger's Z test was used in the R statistical package (R Foundation for Statistical Computing, Vienna, Austria)⁷ to evaluate the difference in correlations between HbA1c and *BOLUS*, *2h-BOLUS*, and *TOTAL-BOLUS*, respectively.

Results

Cohort characteristics

Youths' mean scores for SMBG and the insulin use variables, as well as remaining sample characteristics, are included in Table 1.

Bivariate correlations

Youths' age, gender, and race each demonstrated weak but significant correlations with HbA1c (Table 2). With respect to adherence measures, youths' *BOLUS*, *TOTAL-BOLUS*, and *2h-BOLUS* scores independently associated with youths' HbA1c, and all measures demonstrated stronger associations with youths' HbA1c than did frequency of SBMG. That is, simple correlations between HbA1c and insulin bolus-derived measures were very significant with *P* values as follows: *BOLUS* (*P* < 0.001), *2h-BOLUS* (*P* = 0.001), and *TOTAL-BOLUS* (*P* = 0.001). The Pearson correlation coefficient was highest, however, for the relationship between the original mealtime insulin *BOLUS* score and HbA1c

(−0.54 vs. −0.37 for the *2h-BOLUS* score and −0.37 for the total *BOLUS* score) (Table 2). The difference in Pearson correlation coefficients between *BOLUS*:HbA1c and either *2h-BOLUS*:HbA1c or *TOTAL-BOLUS*:HbA1c was statistically significant (both *P* < 0.00001 using Steiger's Z and enhancement for the differences between two dependent correlations).

The correlation between frequency of SMBG and HbA1c was significant but remained lower than each of the insulin *BOLUS*-derived variables (−0.33; *P* < 0.01) (Table 2). In contrast, none of the correction *BOLUS*-derived measures (%*Meal Corrections*, %*Total Corrections*, *BOLUS* × %*Meal Corrections*, and *BOLUS* × %*Total Corrections*) exhibited a statistically significant correlation with HbA1c (Table 3).

Partial correlations and multiple regressions

Partial correlations between HbA1c level and youths' *2h-BOLUS* and *TOTAL-BOLUS* while controlling for youths' *BOLUS* scores were not significant ($r_{2h,HbA1c,BOLUS} = 0.05$, *P* > 0.60 and $r_{Total,HbA1c,BOLUS} = -0.025$, *P* > 0.80, respectively), suggesting that after controlling for the effects of *BOLUS*, youths' *2h-BOLUS* and *TOTAL-BOLUS* do not provide any additional association or information about HbA1c levels; for these data, they are inferior and redundant measures of adherence.

To confirm the results of the partial correlations, we explored a series of multiple regression models using theory and exploratory data analysis. In each model, we related either *BOLUS*, *2h-BOLUS*, or *TOTAL-BOLUS* to youths' HbA1c levels while controlling for race and other covariates. The results demonstrated that all models of youths' HbA1c and independent variable coefficients were significant (*P* < 0.01) when including one of either the *BOLUS*, *2h-BOLUS*, or *TOTAL-BOLUS* variables and the covariate race (Table 4; all other covariates were found to be insignificant). However, in a single model including the variables race, *2h-BOLUS*, *TOTAL-BOLUS*, and *BOLUS* ($R^2 = 0.29$, $F_{4,93} = 9.57$, *P* = 0.001), only race (1.059, *P* = 0.03) and *BOLUS* (−1.26, *P* = 0.001) had significant coefficients (i.e., *P* values) when associating with youths' HbA1c. In contrast, the coefficients and *P* values for *2h-BOLUS* (0.010, *P* > 0.96) and *TOTAL-BOLUS* (−0.045,

TABLE 1. CHARACTERISTICS OF THE *BOLUS* POPULATION (N = 100)

	Mean ± SD	Median (IQR)	Range
Age (years)	12.67 ± 4.61	13.67 (8.42, 16.38)	2.25, 19.67
Sex (% female)	44%		
White	93%		
HbA1c (n = 99)	8.88 ± 1.47	8.60 (7.90, 9.40)	5.70, 13.40
<i>BOLUS</i>	2.37 ± 0.54	2.46 (2.00, 2.86)	0.86, 3.00
<i>2h-BOLUS</i> (n = 98)	1.50 ± 0.73	1.50 (1.00, 2.07)	0, 2.86
<i>TOTAL-BOLUS</i> (n = 98)	4.59 ± 1.56	4.64 (3.50, 5.64)	0, 8.21
Frequency of SMBG (n = 99)	3.97 ± 2.53	3.64 (1.71, 5.43)	0, 10.64
% <i>Total Corrections</i> (n = 78)	0.66 ± 0.27	0.68 (0.50, 0.87)	0, 1.06
% <i>Meal Corrections</i> (n = 76)	0.67 ± 0.26	0.72 (0.54, 0.88)	0, 1.00
<i>BOLUS</i> × % <i>Total Corrections</i> (n = 78)	1.58 ± 0.76	1.59 (1.04, 2.14)	0, 3.00
<i>BOLUS</i> × % <i>Meal Corrections</i> (n = 76)	1.63 ± 0.74	1.71 (1.17, 2.22)	0, 3.00

All values are from n = 100 unless noted.

2h-BOLUS, mean mealtime boluses within a 2-h meal window; HbA1c, glycated hemoglobin; IQR, interquartile range; SMBG, self-monitoring of blood glucose.

TABLE 2. CORRELATION BETWEEN GLYCATED HEMOGLOBIN AND AGE, GENDER, NOT WHITE, FREQUENCY OF SELF-MONITORING OF BLOOD GLUCOSE, AND THREE *BOLUS* CALCULATIONS

Correlation ^a	HbA1c	Age	Gender	Not white	Frequency of SMBG	TOTAL-BOLUS	BOLUS	2h-BOLUS
HbA1c	1.00 (n=99)	0.21* (n=99)	-0.13 [†] (n=99)	0.20* (n=99)	-0.33 [†] (n=98)	-0.37 [†] (n=97)	-0.54 [†] (n=99)	-0.37 [†] (n=97)
Age		1.00 (n=100)	-0.11 [†] (n=100)	-0.06 [†] (n=100)	-0.61 [†] (n=99)	-0.45 [†] (n=98)	-0.48 [†] (n=100)	-0.54 [†] (n=98)
Gender			1.00 (n=100)	-0.01 [†] (n=100)	0.00 [†] (n=99)	0.13 [†] (n=98)	0.15 [†] (n=100)	0.07 [†] (n=98)
Not white				1.00 (n=100)	0.06 [†] (n=99)	-0.09 [†] (n=98)	-0.04 [†] (n=100)	0.00 [†] (n=98)
Blood glucose					1.00 (n=99)	0.42 [†] (n=97)	0.49 [†] (n=99)	0.54 [†] (n=97)
TOTAL-BOLUS						1.00 (n=98)	0.66 [†] (n=98)	0.61 [†] (n=98)
BOLUS							1.00 (n=100)	0.74 [†] (n=98)
2h-BOLUS								1.00 (n=98)

^aCorrelations are for continuous and nominal values of column variables versus each of eight rows. Significance (two-tailed): * $P < 0.05$, [†] $P < 0.01$, [‡] $P > 0.10$.

2h-BOLUS, mean mealtime boluses within a 2-h meal window; SMBG, self-monitoring of blood glucose.

$P > 0.65$) were insignificant both statistically and clinically. These several forms of analyses indicated that our original method for measuring daily adherence with *BOLUS* (i.e., the mean 14-day mealtime insulin *BOLUS* score) demonstrated better concurrent validity with youths' HbA1c levels than either the mean 14-day *TOTAL-BOLUS* scores or *2h-BOLUS* scores (e.g., compare Models 1, 2, and 3 of Table 4).

Additional analyses considered correction doses for hyperglycemia as correlates with HbA1c, as well as modifiers of the relationship between *BOLUS* score and HbA1c. None of the correction-dose-derived measures (%*Total Corrections*, %*Meal Corrections*) exhibited a statistically significant bivariate correlation with HbA1c (Table 3, Correlations). However, in a multivariate relationship, %*Total Corrections* was found to be related to HbA1c (Table 5, Model 1, $P < 0.05$). To assess whether correction insulin delivery interacted with mealtime insulin *BOLUS* delivery to improve association with HbA1c, interaction variables (*BOLUS* × %*Meal Corrections*, *BOLUS* × %*Total Corrections*) were evaluated for correlations with HbA1c. HbA1c was associated with only the *BOLUS* × %*Total Corrections* (Table 5, Model 2 [$P < 0.05$] but not Models 3, 5, or 6).

Discussion

The mealtime insulin bolus score (*BOLUS*) has been previously published as a new clinically deployable systematic scoring method to evaluate adherence to mealtime insulin use among youths with T1D.^{5,6} In the present study, we provide further validity for the *BOLUS* by comparing the original scoring rules with several alternative scoring rules. The present findings demonstrate that the *BOLUS* better explains youths' HbA1c levels than either the *2h-BOLUS*, which defines mealtimes using a tighter time window, or the *TOTAL-BOLUS*, which reflects the average number of all insulin boluses administered. In multivariable models, the *BOLUS* also showed a stronger association with youths' HbA1c than measures derived from correction insulin delivered for any high blood glucose value (%*Total Correction*) or specifically for mealtime hyperglycemia (%*Meal Correction*). Similarly, the *BOLUS* showed a better association with youths' HbA1c than interaction terms that combined the *BOLUS* plus correction insulin delivered at mealtimes (*BOLUS* × %*Meal Correction*); in contrast, an interaction term that combined the *BOLUS* plus correction insulin for any high blood glucose value (*BOLUS* × %*Total Correction*) was only marginally more associated with HbA1c than a model including only the *BOLUS* score. These new findings more definitively demonstrate the robustness of the original mealtime insulin bolus scoring method and suggest that an accurate proxy measure of youths' adherence and HbA1c may be obtained based on youths' mealtime insulin use alone.

It is well recognized from previous studies that numerous methodologies to assess diabetes treatment adherence are currently being used in practice and in research.⁸ Self-report measures are most commonly implemented but are limited by the reporter's ability to interpret questionnaire items and to exhibit accurate recall, thus impairing his or her objectivity.⁹ Ecological momentary assessment-based measures of adherence using mobile phone technology correlate well with self-report measures according to a pilot study; however, measures in that study were characterized by 41% missing

TABLE 3. CORRELATION BETWEEN GLYCATED HEMOGLOBIN AND NOT WHITE AND FIVE BOLUS CALCULATIONS

Correlation ^a	HbA1c	Not white	BOLUS	%Total Corrections	%Meal Corrections	BOLUS × % Total Corrections	BOLUS × % Meal Corrections
HbA1c	1.00 (n=99)	0.20* (n=99)	-0.54 [†] (n=99)	0.14 [‡] (n=77)	0.04 [‡] (n=75)	-0.14 [‡] (n=77)	-0.20 [‡] (n=75)
Not white		1.00 (n=100)	-0.04 [‡] (n=100)	0.02 [‡] (n=78)	0.02 [‡] (n=76)	0.02 [‡] (n=78)	0.01 [‡] (n=76)
BOLUS			1.00 (n=100)	0.19 [‡] (n=78)	0.16 [‡] (n=76)	0.64 [‡] (n=78)	0.60 [‡] (n=76)
%Total Corrections				1.00 (n=78)	0.92 [‡] (n=76)	0.85 [‡] (n=78)	0.83 [‡] (n=76)
%Meal Corrections					1.00 (n=76)	0.78 [‡] (n=76)	0.87 [‡] (n=76)
BOLUS × %Total Corrections						1.00 (n=78)	0.94 [‡] (n=76)
BOLUS × %Meal Corrections							1.00 (n=76)

Significance (two-tailed): * $P < 0.05$; [†] $P < 0.01$; [‡] $P > 0.05$.^aCorrelations are for continuous values of column variables versus each of five rows.

data and a failure to correlate with glycemic control.¹⁰ Prescription refill data have also been used to assess adherence, but this measure relies on the pharmacy to keep accurate records of refill information and, more importantly, discounts whether the patient is actually taking the medication after the prescription has been filled.¹¹

The most widely studied objective measure of adherence to date has been the frequency of SMBG, which has been demonstrated to inversely correlate with HbA1c values and thus glycemic control.^{3,12,13} However, reporting of SMBG can be inaccurate if patients are using multiple glucometers and/or are not inputting their glucose readings into their insulin pump. It also relies on the assumption that the patient consistently doses insulin after considering his or her blood glucose result.

Finally, others have reported a relationship between self-reported adherence to the T1D treatment regimen and HbA1c.^{14–17} Those studies, however, required subjects either to recall diet information from the prior 24 h prior to data collection¹⁴ or to complete a detailed questionnaire^{15,17} and, in one case, an interview in which they recalled diet information and mealtimes over a 4-week period,¹⁵ subjecting the measure to recall bias and increasing the burden on both patient and provider.

Several prior studies have reported a relationship between the frequency of missed insulin boluses and HbA1c. One study that included 100 youths 13.6 (±3.2) years of age revealed that HbA1c increased by 0.8% if any day in a 2-week period included fewer than three mealtime boluses and that HbA1c decreased by 0.2% for each additional insulin bolus of any type per day.¹⁸ The study further reported that breakfast insulin (or the breakfast meal) was missed in 70% of the youths studied and that missing breakfast or breakfast insulin on 1–3 days out of 14 was associated with a 0.5% increase in HbA1c; in contrast, missing breakfast or breakfast insulin on ≥4 days was associated with a 1.0% increase in HbA1c. Another study of 100 youths with T1D indicated that more than one missed meal bolus per week resulted in an HbA1c difference of 0.8%.¹⁵ A more recent study of insulin pump adherence behaviors among 31 youths found that as the number of days with three or more insulin boluses increased within a 2-week period, HbA1c decreased.¹⁹ Finally, the T1D Exchange, a network of >80 diabetes centers assessing health outcomes on >25,000 individuals with T1D across the United States, reported that the frequency of self-reported missed insulin doses among children and adolescents was higher in individuals with poor glycemic control and that the odds ratio for being in excellent control was 17 times higher for individuals with no self-reported missed insulin boluses.²⁰

Collectively, these studies established an important relationship between the frequency of insulin boluses and glycemic control; these studies were limited, however, by their use of self-reported insulin dosing habits, which are subject to recall bias,²⁰ their use of categorical rather than quantitative measures of missed insulin boluses,¹⁶ their limited representation of very young children with T1D,^{15,16,18,19} and the focus of one study on total insulin boluses per day,¹⁹ which we found to be less related to HbA1c than mealtime boluses. In addition, the prior studies did not directly compare the utility of measuring the frequency of blood glucose monitoring with the utility of measuring the frequency of insulin boluses, nor did they evaluate the utility of different methods

TABLE 4. REGRESSION RELATIONSHIPS BETWEEN GLYCATED HEMOGLOBIN AND AGE, GENDER, NOT WHITE, FREQUENCY OF SELF-MONITORING OF BLOOD GLUCOSE, AND THREE *BOLUS* CALCULATIONS

Model, variable ^a	F value	Adjusted R ^{2b}	β	SE	95% confidence interval		Standard coefficient (β)	t value
					Lower	Upper		
Model 1 (n=98)	22.65 [†]	0.31						
Not white			1.04	0.48	0.09	1.99	0.18	2.16*
<i>BOLUS</i>			-1.44	0.23	-1.90	-0.99	-0.53	-6.28 [†]
Model 2 (n=96)	10.77 [†]	0.17						
Not white			1.22	0.51	0.21	2.23	0.22	2.40*
<i>2h-BOLUS</i>			-0.72	0.18	-1.07	-0.36	-0.37	-3.99 [†]
Model 3 (n=96)	9.82 [†]	0.16						
Not white			1.04	0.52	0.02	2.06	0.19	2.02*
<i>TOTAL-BOLUS</i>			-0.32	0.09	-0.49	-0.15	-0.35	-3.75 [†]

^aDependent variable was glycated hemoglobin.

^bAdjusted R² P value is the same as those of the corresponding model's F value.

Significance (two-tailed): *P<0.05, [†]P<0.01.

2h-BOLUS, mean mealtime boluses within a 2-h meal window; SMBG, self-monitoring of blood glucose.

of scoring insulin boluses (e.g., mealtime insulin boluses, total boluses, correction boluses, etc.), which we found has a significant impact on the observed relationship between insulin bolus behavior and HbA1c. Although similar analyses of adults with T1D are limited, evidence indicates that missed insulin boluses occur with some frequency (20%) among adults with T1D and type 2 diabetes,²¹ suggesting that glycemic control among adults may also be impacted by insulin adherence.

In contrast to non-bolus-derived and self-report measures of adherence, the mealtime insulin bolus score directly and objectively evaluates the number of times youth are dosing insulin during standard mealtimes without the possibility for recall bias. Previous reports revealed that *BOLUS* demonstrates a stronger association with youths' HbA1c⁶ and also serves as a better predictor of future HbA1c at 12 months when compared with frequency of SMBG.⁵ In the present work, youths' *2h-BOLUS* and *TOTAL-BOLUS* scores were

TABLE 5. REGRESSION RELATIONSHIPS BETWEEN GLYCATED HEMOGLOBIN AND NOT WHITE AND FIVE *BOLUS* CALCULATIONS

Model, variable ^a	F value	Adjusted R ^{2b}	β	SE	95% confidence interval		Standard coefficient (β)	t value
					Lower	Upper		
Model 1 (n=76)	13.36 [†]	0.33						
Not white			0.98	0.52	-0.06	2.02	0.18	1.88 [‡]
<i>BOLUS</i>			-1.51	0.26	-2.04	-0.99	-0.55	-5.74 [†]
%Total Corrections			1.33	0.53	0.27	2.38	0.24	2.51*
Model 2 (n=76)	13.42 [†]	0.33						
Not white			0.93	0.52	-0.11	1.98	0.17	1.78 [#]
<i>BOLUS</i>			-1.94	0.34	-2.61	-1.27	-0.70	-5.75 [†]
<i>BOLUS</i> × %Total Corrections			0.61	0.24	0.13	1.09	0.31	2.53*
Model 3 (n=76)	9.94 [†]	0.32						
Not white			0.95	0.53	-0.11	2.01	0.17	1.78 [‡]
<i>BOLUS</i>			-1.80	0.80	-3.39	-0.20	-0.65	-2.25*
%Total Corrections			0.45	2.37	-4.27	5.17	0.08	0.19 [‡]
<i>BOLUS</i> × %Total Corrections			0.41	1.08	-1.75	2.57	0.21	0.38 [‡]
Model 4 (n=74)	11.18 [†]	0.29						
Not white			0.96	0.52	-0.08	1.99	0.18	1.84 [‡]
<i>BOLUS</i>			-1.47	0.28	-2.01	-0.92	-0.53	-5.33 [†]
%Meal Corrections			0.64	0.54	-0.43	1.72	0.12	1.19 [‡]
Model 5 (n=74)	11.32 [†]	0.30						
Not white			0.93	0.52	-0.10	1.97	0.18	1.80 [‡]
<i>BOLUS</i>			-1.68	0.34	-2.36	-1.00	-0.61	-4.96 [†]
<i>BOLUS</i> × %Meal Corrections			0.31	0.24	-0.16	0.79	0.16	1.31 [‡]
Model 6 (n=74)	8.43 [†]	0.29						
Not white			0.90	0.53	-0.15	1.95	0.17	1.71 [‡]
<i>BOLUS</i>			-1.98	0.80	-3.58	-0.37	-0.71	-2.46*
%Meal Corrections			-1.03	2.53	-6.07	4.00	-0.19	-0.41 [‡]
<i>BOLUS</i> × %Meal Corrections			0.76	1.12	-1.48	3.00	0.39	0.68 [‡]

Significance (two-tailed): *P<0.05, [†]P<0.01, [‡]P>0.05.

^aDependent variable, glycated hemoglobin.

^bAdjusted R² P value is the same as those of the corresponding model's F value.

not as strongly related to HbA1c as the *BOLUS* was, yet they were still more strongly associated with HbA1c than the frequency of youths' SMBG. This confirms that one may obtain a better proxy measure of adherence and HbA1c by measuring youths' mealtime or total insulin use rather than frequency of SMBG. In contrast, only one of the variables calculated to measure correction insulin use showed strong associations with youths' HbA1c levels. To allow calculation of the correction variables (*%Meal Correction*, *%Total Correction*, *BOLUS* $\times$ *%Meal Correction*, and *BOLUS* $\times$ *%Total Correction*), youths first had to experience blood glucose levels that exceeded 250 mg/dL. This decreased the sample size by approximately 25% and may have limited variability in the samples, which could explain the lack of significant associations between insulin correction dose-derived variables and youths' HbA1c.

However, another possible explanation is the complex relationship between insulin correction doses and glycemic variability. It is likely that some of the youths who attained the highest insulin correction scores experienced high blood glucose levels more often to prompt the correction bolus behavior. In contrast, other youths may have experienced more modestly elevated blood glucose levels for which they did not deliver a correction bolus. Such behavior could have led to lower insulin correction-derived scores and a paradoxically lower average glycemic level. In this respect, youths' insulin correction scores in various subgroups could have opposing associations with their HbA1c levels, leading to our findings of very weak, nonsignificant associations in some cases.

The present findings are clinically significant because they provide further evidence that diabetes care teams should assess for youths' mealtime insulin use in routine diabetes clinic visits as well as their frequency of SMBG. The *BOLUS*, now shown to be a more efficacious method of evaluating mealtime insulin use than other methods, is easy to compute by hand and can be readily integrated into diabetes clinic visits. In addition, it can be easily calculated using a spreadsheet, thus nearly fully automating the calculation. Our previous research suggests that every 1 point increase in youths' *BOLUS* score is associated with a 1.5 unit (%) decrease in youths' HbA1c levels. Thus, if targeted during routine diabetes care with health behavior change interventions, the *BOLUS* has the potential to become a robust target for treatments designed to decrease youths' HbA1c levels and improve health outcomes.

Multiple studies suggest that this may best be accomplished as part of a multicomponent intervention that also targets emotional, social, or behavioral processes.²² Thus in future studies the *BOLUS* should be evaluated in a treatment-outcome study to determine whether a behavioral intervention that improves youths' *BOLUS* scores leads to a significant and sustainable decrease in their HbA1c. Pilot data from a prior randomized trial are promising, indicating short-term improvement in HbA1c using an intervention (i.e., meal bolus alarms) that improved engagement with mealtime insulin boluses.²³ In future studies it will also be important to evaluate the associations between youths' *BOLUS* and insulin correction scores with measures of glycemic variability. Although *BOLUS* may provide a stronger proxy measure of youths' HbA1c than other insulin adherence measures, we do not know how it associates with glycemic variability. It is

possible that an adherence measure that accounts for meal-times plus insulin corrections may more strongly associate with glycemic variability than the *BOLUS* alone.

The present findings must be interpreted in the context of certain limitations.

First, use of the *BOLUS* is limited to youths who are on an insulin pump, which may limit its generalizability. However, data from a multiclinic study in the United States suggest that about 60% of youths with T1D use an insulin pump, with use rising to as high as 79% at some centers.²⁴ It seems likely that this number will increase as the technology improves and becomes more affordable, suggesting the *BOLUS* has the potential to become even more relevant as an adherence and treatment target in the future. "Smart" insulin pens may, in the future, provide a mechanism by which the *BOLUS* can be calculated for patients using multiple daily injection therapy.²⁵

Second, the *BOLUS* score requires review of the insulin pump download by trained personnel, whereas the *TOTAL-BOLUS* is precalculated on typical 2-week pump data reports. It is notable, however, that minimal skill is required to calculate the *BOLUS*, and the *BOLUS* can be calculated very quickly (<3 min) by visual scan of the 2-week download report. When a staff member reviews the report from the insulin pump download during a clinic visit, the staff member simply tallies the total number of mealtimes with any bolus across 14 days and then divides by the number of days.

Third, the use of retrospective data from an observational cohort has the potential to introduce bias into the sampling, although great care was taken to select a random sample from our data sources.

Fourth, the study's cross-sectional design and use of observational data prevent any evaluation of causality.

Fifth, the mealtime insulin bolus score by design does not capture the actual mealtimes of the patient, the accuracy of carbohydrate counting, or the degree to which patients deviate from their prescribed insulin dosing regimen. Problems with carbohydrate counting accuracy and with deviations from the prescribed insulin bolus regimen have been well documented among patients with T1D.^{26,27} Use of a bolus advisor appears to modestly reduce HbA1c and glycemic variability in a longitudinal observational study, but the degree to which accurate carbohydrate counting and accurate bolusing relate to overall glycemic control remains to be determined.²⁸

Finally, the present study only evaluated the relationship between *BOLUS* and mean glycemic control, with no attention given to glycemic variability, which has been the subject of much interest as a potential predictor for acute and chronic complications in T1D.²⁹⁻³¹ Strengths of the present study include its use of a relatively large and heterogeneous sample with enrichment for young children with T1D, as well as our thorough comparison of multiple scoring methods for evaluating insulin use in youths. Future research should include stratified analysis of the association between *BOLUS* and HbA1c in different age cohorts because adolescents are at particular risk for problems related to adherence, and case reports of adolescents manipulating data are well known to many diabetes care providers.

To summarize, the present study presents new results that lend additional support for clinical use of the *BOLUS*, a measure of mealtime insulin use in youths with T1D. Although

youths may dose insulin for food intake or to correct for hyperglycemia, we demonstrate that an accurate, parsimonious, and clinically deployable measure of youths' adherence to insulin may be achieved by simply evaluating their average frequency of insulin boluses at mealtimes, which can be performed in less than 3 min in a clinic setting. Youths' *BOLUS* has consistently been shown to better account for HbA1c than SMBG.^{5,6} Now that we have demonstrated that *BOLUS* is even more robustly associated with HbA1c than the precalculated *TOTAL-BOLUS* and other more complicated alternative insulin scoring methods, a barrier to routine use of the *BOLUS* is potentially removed, paving the way for greater uptake in the clinic and in research.

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Author Disclosure Statement

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