ORIGINAL ARTICLE

Frequency of Mealtime Insulin Bolus as a Proxy Measure of Adherence for Children and Youths with Type 1 Diabetes Mellitus

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Abstract

Background: Electronic measures of adherence can be superior to patient report. In type 1 diabetes, frequency of blood glucose monitoring (BGM), as measured by patients' home blood glucose meters, has already been identified as a valid proxy of adherence. We present methodology to calculate adherence using insulin pump records and evaluate the reliability and validity of this methodology.

Subjects and Methods: Blood glucose meter data, insulin pump records, and corresponding hemoglobin A1c (HbA1c) levels were randomly gathered from clinical and research databases for 100 children and youths (referred to hereafter as youths) with type 1 diabetes (mean $\pm$ SD age, 12.7 ± 4.6 years). Youths' mean frequency of daily BGM was calculated. Additionally, we calculated a mean mealtime insulin bolus score (BOLUS): youths received 1 point each for a bolus between 0600 and 1000 h, 1100 and 1500 h, and 1600 and 2200 h (maximum of 1 point/meal or 3 points/day).

Results: Simple correlations between youths' HbA1c level, age, frequency of BGM, and insulin BOLUS scores were all significant. Partial correlations and multiple regression analyses revealed that insulin BOLUS scores better explain variations in HbA1c levels than the electronically recorded frequency of daily blood glucose measures.

Conclusions: Our procedures for calculating insulin BOLUS scores using insulin pump records demonstrate better concurrent validity with youths' HbA1c levels than that of the frequency of BGM with youths' HbA1c levels. Our analyses have shown that insulin bolus scoring was superior to the frequency of BGM in predicting youths' HbA1c levels.

Introduction

EXISTING RESEARCH SUGGESTS that adherence to daily diabetes self-care is important for improving health outcomes in children and youths (referred to hereafter as youths) with type 1 diabetes mellitus (T1DM).^{1,2} Adherence can be measured by patient self-report, but electronic measures are better able to quantify adherence in a way that is free of reporter bias.^{3,4} In particular, sampling downloads from diabetes care devices, such as patients' home blood glucose meters or insulin pumps, may be able to provide a measure of actual patient behavior. Past research supports the use of blood glucose monitoring (BGM) as an objective proxy measure of adherence.³ This measure has been found to correlate negatively with youths' hemoglobin A1c (HbA1c) level, suggesting that more frequent BGM is related to lower HbA1c levels.⁵⁻⁷ It is presumed that more frequent BGM may allow a youth to more readily identify and correct high blood glucose levels, which leads to better control. This is a reasonable

assumption because it is unlikely that youths would check their blood glucose frequently if they did not use these data as part of their self-care. However, the widespread adoption of continuous subcutaneous insulin infusion therapy by youths with T1DM provides another potential objective measure of adherence.² These devices can provide records of patients' frequency of insulin bolusing, as well as records of the amounts of insulin administered via either basal or bolus dosing. To date, no systematic method for examining adherence based on youths' insulin pump downloads has been identified.

In this study, we developed and evaluated the psychometric properties of a new scoring system to measure adherence based on youths' frequency of mealtime insulin boluses. The hypothesis we tested was that youths' mealtime insulin bolus scores (BOLUS) would negatively correlate with youths' mean glycemic control, as measured by HbA1c level. We also evaluated how youths' BOLUS scores compared with BGM values in explaining HbA1c variations.

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Subjects and Methods

The data for this study were collected from two sources. First, from a clinic database with 3,453 patient records, we randomly selected 85 youths and extracted their HbA1c values, BGM records, and insulin pump records from the most recent clinic appointments. Inclusion criteria for this data search were as follows: child age between 2 and 19 years old, a confirmed diagnosis of T1DM for at least 1 year, and use of an insulin pump for daily insulin administration. Second, to ensure adequate sampling of young children (children less than 7 years old; representing only 14% of the clinical database), 15 youths less than 7 years old were randomly drawn from a research database of young children. The inclusion criteria were as follows: child age between 1 and 6 years old, a confirmed diagnosis of T1DM for at least 1 year, and use of an insulin pump for daily insulin administration. Thus, the final sample consisted of 85 youths between 7 and 19 years of age and 15 youths less than 7 years old, for a total sample size of 100. The sample of 100 used in this analysis was comparable to the approximately 1,600 eligible youths who regularly seek care from the diabetes clinic where this study was conducted. The respective means for female gender, HbA1c, and age for the 100 versus 1,600 patients were as follows: 44% versus 47%; 8.8% versus 8.6%, and age, 12.7 years versus 13.1 years (all P values >0.25). Institutional approval was obtained prior to data retrieval, and all data were de-identified.

Procedure

The data collected for each youth included up to 14 days of self-monitoring blood glucose data, insulin pump use, and the HbA1c values that corresponded with these data. We also recorded youths' age, gender, and race/ethnicity in order to characterize the sample. Data were reviewed and independently coded for frequency of mealtime insulin boluses (BOLUS) and BGM by trained diabetes educators. Reliability of these measures was assessed in a random subset of records ($n=33$) using intraclass correlations (ICCs). In contrast to other correlation measures, the ICC method imposes identical rater scales, and therefore linear transformations of measures are not allowed. ICC is often used to assess for consistency of measures made by multiple observers; it was more appropriate for the current data than κ because youths' BOLUS scores were measured on an interval scale.⁸

Measures

Daily BGM. Youths' downloaded blood glucose records were reviewed, and the average daily frequencies of BGMs were recorded. Inter-rater reliability for this measure was an ICC of 0.995, nearly perfect ratings ($P=0.000001$). This high and significant ICC confirms inter-rater reliability.

Mealtime insulin bolus score (BOLUS). Youths' insulin pump records were collected from times that correspond to typical mealtimes. Youths were assigned a maximum of 1 point each for at least one bolus between 0600 and 1000 h, 1100 and 1500 h, and 1600 and 2200 h. Youths could earn a maximum of 3 points/day. These values were then averaged to obtain youths' insulin BOLUS scores. Raters were three certified diabetes educators (e.g., two primary and one rely). On average, it took less than 5 min to review a 14-day record and

calculate a BOLUS score. Inter-rater reliability for our measure of mealtime insulin bolus was an ICC of 0.897 ($P=0.0000001$). Again, this is a high and significant ICC that confirms inter-rater reliability.

Analyses

A priori, to assure an adequate sample size (n), we determined that $n=100$ provides a power of 0.80 and 0.99 when detecting absolute correlations from 0.28 to 0.42, respectively, between HbA1c values and youths' BOLUS scores. Data were evaluated for normality and outliers. Simple correlations were calculated to examine the association between average frequency of daily BGM, BOLUS scores, and HbA1c. Next, partial correlations were calculated to examine the association of these variables with HbA1c while controlling for the influence of the other variable. Finally, the results of the partial correlations were confirmed using stepwise and exploratory multiple regressions.

Results

The total sample size was 100 youths with T1DM. The mean age of children in the final sample was 12.7 ± 4.6 years. There were 56 boys, and 93 families self-reported the child's race as white. The mean HbA1c value for this sample was $8.8 \pm 1.6\%$. The number of BGM events in this group of youths was 3.97 ± 2.53 . Their mean BOLUS score was 2.37 ± 0.54 . Simple correlations revealed significant correlations between youths' HbA1c level and their age, BGM, and BOLUS score (see correlations in Table 1). Table 1 also gives quartile values of HbA1c, age, BGM, and BOLUS score, the mean HbA1c at each variable's quartile, and analysis of variance results

TABLE 1. CORRELATIONS AND STATISTICS BY QUANTILES OF AGE, HEMOGLOBIN A1C LEVEL, AND ADHERENCE SCORES

Correlation ^a	HbA1c	Age	BGM	BOLUS
HbA1c	1.00	0.20*	-0.29**	-0.52**
Age		1.00	-0.61**	-0.48**
BGM			1.00	0.49**
Quartiles (number of observations, $n=100$) ^b	HbA1c mean (%) for quartiles	Mean HbA1c (%) for quartile ^c		
		Age [#]	BGM*	BOLUS**
1 (25)	7.8	8.40 (8.1)	9.61 (1.7)	10.17 (2.0)
2 (25)	8.6	8.51 (13.7)	8.78 (3.6)	8.82 (2.5)
3 (25)	9.4	9.39 (16.5)	8.57 (5.4)	8.23 (2.9)
4 (25)	13.4	9.00 (19.7)	8.33 (10.6)	8.08 (3.0)

Significance: * $P < 0.05$, ** $P < 0.001$, # $P > 0.10$.

^aCorrelations are for continuous values of column variables versus each of three rows.

^bQuartiles of each variable when ranked from lowest to highest, and levels of significance are by analysis of variance for the test of the differences in mean hemoglobin A1c (HbA1c) by quartiles. F values for age, blood glucose monitoring (BGM), and BOLUS are, respectively, 2.02, 3.35, and 12.39, with P values as indicated.

^cFirst number in each row of this column is the mean value of HbA1c at each quartile of column 1 for this variable (i.e., age, BGM, and BOLUS); thus, the mean A1c for the third quartile of age is 9.39%. The second value shown in parentheses is the maximum value of that variable for each quartile; thus, for example, the third quartile of age runs from >13.7 to 16.5 years.

comparing mean HbA1c by each variable's quartile (see quartiles in Table 1). Analysis of variance reveals significant main effects for HbA1c by BGM and BOLUS quartile. The mean HbA1c levels for each of the quartiles of BGM and BOLUS of Table 1 are, respectively, 9.61%, 8.78%, 8.57%, and 8.33% versus 10.17%, 8.82%, 8.23%, and 8.08%. Additionally, the mean HbA1c differences of the first-to-fourth quartiles of BGM (9.61%–8.33%=1.28%) and those of BOLUS (10.17%–8.08%=2.09%) provide empirical evidence of the stronger association between HbA1c and BOLUS versus with HbA1c and BGM. This stronger association is confirmed in the following sections using partial correlation and multiple regression analysis.

Partial correlations

The partial correlation of the association between HbA1c level and youths' BGM while controlling for the influence of youths' BOLUS scores was not significant ($r = -0.08$, $P = 0.42$). In contrast, the partial correlation between HbA1c level and youths' BOLUS scores while controlling for the influence of youths' BGM was significant ($r = -0.46$, $P = 0.0001$). These suggest that even after controlling for the effects of BGM on youths' BOLUS scores and HbA1c levels, the BOLUS scores provide additional correlation with HbA1c level that is useful in explaining the latter.

Multiple regression. Confirming the results of the partial correlations, a multiple regression model examining the relation among HbA1c level and age, BGM, and youths' BOLUS score produced $R^2 = 0.28$, $F_{1,95} = 25.26$, $P = 0.0001$. Furthermore, during the stepwise regression, with age, BGM, and the BOLUS scores as covariates, only the BOLUS score was found to be significantly related to HbA1c level (full model, $P = 0.0001$; Table 2). Youths' age and BGM were included as possible covariates in Table 2 because it was anticipated that there would be significant correlations between these variables and HbA1c level. However, as confirmed by the stepwise model (BOLUS-only model in Table 2), once youths' BOLUS score entered the model, all other covariates were not found to be significantly related to HbA1c level. Interpreting the unstandardized coefficients of the model, we find that every 1 point increase in youths' BOLUS score is associated with a 1.5 unit (%) decrease in their HbA1c level (full model or BOLUS-only model, Table 2).

Discussion

We examined the validity and reliability of a new scoring system to measure adherence to insulin use via insulin pump download reports. Specifically, we coded the frequency of mealtime insulin boluses. Inter-rater reliability for our BOLUS score was very good, suggesting the operational definitions we provided to code insulin use were clear and easy to apply to insulin pump records. Current validity of our BOLUS scores were confirmed based on high and significant simple and partial correlations between youths' BOLUS scores and HbA1c levels. In addition, analyses demonstrated a more robust relation between youths' BOLUS score and HbA1c level than between youths' frequency of daily BGM and HbA1c level.

Multiple measures of treatment adherence have been studied in youths with T1DM.³ Although several self-report measures examine BGM frequency, the only objective measure of BGM frequency is that obtained from glucometer downloads. Glucometer-derived BGM frequency has been shown to correlate with glycemic control among children and adolescents, with a medium effect size.⁵ In one study, a decrease of one blood glucose check per day was associated with a 1.26% increase in HbA1c level.⁵ In contrast, self-report measures, although helpful in the absence of objective monitoring data, can be problematic because they are often time-intensive and require in-depth knowledge of the assessment tool by providers.³ In addition, they widely are considered less precise than glucometer-derived data,⁹ although glucometer-derived data can also suffer reliability issues¹⁰ and may not fully capture all available data if multiple glucometers are used by youth, and at least one recent study found that the Self-Care Inventory predicted glycemic control better than glucometer-derived monitoring frequency.³

Notably absent from the pediatric T1DM literature are any objective measures of treatment adherence based upon actual patient self-delivery of medication (i.e., insulin). With the increased adoption of continuous subcutaneous insulin infusion by youths with T1DM, adherence measures based on insulin bolusing are becoming more relevant and more applicable to a broad population. To develop our measure, we focused on the frequency of youths' mealtime insulin boluses because mealtimes occur daily and tend to follow a predictable schedule. In addition, studies have demonstrated that missed mealtime boluses can have a devastating impact on youths'

TABLE 2. THREE REGRESSION RELATIONSHIPS BETWEEN HEMOGLOBIN A1C AND AGE, FREQUENCY OF DAILY BLOOD GLUCOSE MONITORING, AND BOLUS SCORES

Model, variable ^a	Unstandardized coefficients		Standardized coefficient (β)	t value ^b	P
	β	SE			
Full ^c					
Age	-0.038	0.039	-0.110	-0.968	0.336
BGM	-0.066	0.072	-0.106	-0.923	0.358
BOLUS	-1.529	0.304	-0.522	-5.026	<0.0001
BGM-only ^c	-0.189	0.061	-0.296	-3.047	0.003
BOLUS-only ^c	-1.525	0.253	-0.521	-6.036	<0.0001

^aConstants for full, blood glucose monitoring (BGM)-only, and BOLUS-only models are 13.19, 9.56, and 12.434, respectively (all $P < 0.0001$).

^bF values for full, BGM-only, and BOLUS-only models are 12.3 ($P < 0.0001$), 9.3 ($P < 0.003$), and 36.5 ($P < 0.0001$), respectively.

^cAdjusted R^2 for full, BGM-only, and BOLUS-only models are 0.257, 0.078, and 0.264, respectively (P values same as those of F values).

glycemic control.^{11–13} Burdick et al.¹¹ determined that youths who missed at least one mealtime bolus per week had an average HbA1c level that was 0.8% higher than youths who did not miss any mealtime boluses. Likewise, Olinder et al.¹² reported average HbA1c levels 0.8% higher for youths who missed mealtime insulin boluses compared with youths who did not miss mealtime boluses, and another study found youths who skipped mealtime insulin boluses had an average HbA1c of 8.67%.¹³ There is also a study showing that missed snack time insulin boluses may be common for some youth with type 1 diabetes and related to daily episodes of glycemic excursion.¹⁴ However, the occurrence, frequency, and timing of snacks, characteristics that significantly complicate the creation of an operational definition of a “snack bolus,” are highly variable. Thus, we elected not to include snacks in our final measure. We also elected not to use a daily sum of all available boluses (e.g., food plus correction boluses) because the frequency and timing of correction boluses would be highly variable among youths and need to be tied to blood glucose data, which would complicate the calculation of an insulin bolus score. However, as a next step it may be useful to directly compare our mealtime BOLUS score and a “daily sum” BOLUS score with regard to their relative associations to HbA1c level.

We believe this study contributes to the literature in the following ways. First, to our knowledge, this is the first example of a specific coding strategy for calculating adherence based on insulin pump records. Specifically, we now present a simple-to-calculate, easily deployable, objective measure of adherence to mealtime insulin use. Second, because our new adherence measure uses insulin pump data, we potentially remove inaccuracy that might be introduced if patients use multiple glucometers throughout the day and/or do not enter glucose values into their insulin pump. Our BOLUS score can be calculated based on data downloaded from a single device without requiring additional patient-driven data entry. Third, our data suggest that for every 1 point increase in youths’ insulin bolus score, there was a 1.5 unit (%) decrease in youths’ HbA1c levels (full model and BOLUS-only model, Table 2). In contrast, every 1 point increase in youths’ frequency of daily BGM was associated with only a 0.19 unit (%) decrease in HbA1c level (BGM-only model, Table 2). This comparison suggests that measuring mealtime insulin bolus use is superior to the frequency of daily BGM in explaining variations in youths’ HbA1c levels. Finally, our results have practical implications for clinical research and management, where identifying a robust and objective adherence measure is important when examining behavioral changes and measuring outcomes.

Some strengths of the present study are its use of a relatively large and heterogeneous sample (i.e., age 1–19 years, any level of glycemic control) and our decision to compare our new adherence measure with frequency of daily BGM, one of the gold standards of adherence in T1DM. Some of the limitations of this study include its exclusive focus on youths using an insulin pump for daily insulin administration. Although insulin pump therapy is becoming more widely adopted among youths, our specific methodology for calculating the frequency of mealtime insulin boluses will not be applicable to youths receiving insulin via injections or an insulin pen, as these administration routes would require patient self-reports of insulin use. Second, our methodology

could be criticized because our mealtime windows sum to 12h, suggesting we may have been too liberal in our definition of mealtimes. This issue was carefully considered by the research team. Although we wanted to ensure that we provided individual mealtime periods that were sufficiently long enough to include most youths, we also wanted to focus primarily on mealtime insulin use versus snack time or correction boluses. To determine each mealtime window, we examined the default mealtimes used by insulin pump companies, we surveyed pump records from youths, and we sought recommendations from our colleagues. As a follow-up study, it may be useful to see if applying tighter individual mealtimes yields different relationships with HbA1c level when coding insulin pump records. Third, the study design was cross-sectional, precluding any speculation about causality and leaving unanswered the question of whether the association between BOLUS scores and glycemic control is stable over time. As further support of the validity of our insulin BOLUS score, it would be helpful to use longitudinal data to see whether the relationship with HbA1c level is stable over time and to see if youths’ BOLUS scores can reliably predict future HbA1c levels.

To summarize, objective proxy measures of adherence are helpful for clinical research and management.⁴ In T1DM, frequency of daily BGM has been used as a proxy measure of adherence and has been found to relate negatively with youths’ HbA1c level.^{3,5–7} Here, we present new methodology for calculating a proxy measure of adherence using insulin pump records. Our methodology focuses on calculating a mealtime insulin bolus score (BOLUS) based on the mean frequency of mealtime boluses per day. Our data demonstrate that this measure correlates negatively with youths’ HbA1c level and positively with youths’ BGM. In addition, our analyses suggest that youths’ BOLUS scores may be superior to frequency of BGM events in explaining variance in youths’ HbA1c levels. We conclude that the BOLUS score is likely a better measure of adherence than frequency of daily BGM.

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Author Disclosure Statement

No competing financial interests exist.

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