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A Comparison of Average Daily Risk Range Scores for Young Children with Type 1 Diabetes Mellitus Using Continuous Glucose Monitoring and Self-Monitoring Data

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Abstract

Background: Young children with type 1 diabetes are vulnerable to glycemic excursion. Continuous glucose monitoring (CGM), combined with variability statistics, can offer a richer and more complete picture of glycemic variability in young children. In particular, we present data for the Average Daily Risk Range (ADRR) and compare ADRR scores calculated using CGM versus self-monitoring of blood glucose (SMBG) data for young children.

Methods: CGM and SMBG data from 48 young children with type 1 diabetes (mean age, 5.1 years) were used to calculate two separate ADRR scores, using SMBG data (ADRRs) and CGM data (ADRRc), for each child. Additionally, we calculated mean amplitude of glycemic excursion (MAGE) scores for children to examine the concurrent validity of the ADRRs and ADRRc.

Results: Young children's mean ADRRc score was significantly greater than their ADRRs score (55 ± 12 and 46 ± 11, respectively; $P < 0.001$). In addition, 74% of the time the children's ADRRc score reflected greater variability risk than their ADRRs score. Examining the concurrent validity, children's ADRRc scores correlated positively with MAGE scores calculated using their CGM and SMBG data, whereas their ADRRs scores only correlated with MAGE scores calculated using SMBG.

Conclusions: ADRR scores generated for young children with type 1 diabetes demonstrate a high risk for glucose variability, but ADRR scores generated from CGM data may provide a more sensitive measure of variability than ADRR scores generated from SMBG. In young children with type 1 diabetes, ADRR scores calculated from CGM data may be superior to scores calculated from SMBG for measuring risk of excursion.

Introduction

Young children with type 1 diabetes (less than 7 years) are highly susceptible to extreme blood glucose variability.[1,2] This increased vulnerability is conferred based on several factors, including young children's increased insulin sensitivity and variability in their activity levels and food intake.[1] Unfortunately, glycosylated hemoglobin A1c, a traditional measure of glycemic control, may miss glucose variability in young children because it only provides a measure of long-term average glucose levels.[2,3] Similarly, in a previous study, we contend that for research purposes, the typical frequency of parents' daily self-monitoring of blood glucose (SMBG) checks may not be adequate to fully capture glucose variability in young children.[3] Thus, continuous glucose monitoring (CGM) may offer the best method for measuring glucose levels in young children.

CGM is a relatively new technology that is available for clinical use and research in patients with type 1 diabetes. CGM is a nearly continuous measure of glucose levels in young children because it measures and reports a glucose level every 5 min. This can allow for a closer examination of young children's glucose patterns and may allow for better identification of glucose excursions, especially during times of the day when parents may not be regularly checking (e.g., night time).

In our past research using CGM in young children we have explored glucose variability using two new and less established measures, the Continuous Overall Net Glycemic Action (CONGA) and Mean of Daily Differences (MODD).[3] The

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CONGA provides a measure of short-term intraday variability, whereas the MODD examines interday variability by calculating the mean of the absolute value of the difference between glucose levels measured at the same time on two consecutive days.[4] Our results demonstrated that using the CONGA and MODD, young children with type 1 diabetes demonstrated greater glycemic variability than older youth with type 1 diabetes.[3]

In the current study, we focused on short-term glycemic variability in young children using the Average Daily Risk Range (ADRR). The ADRR is a valid, diabetes-specific measure of variability that yields a score that corresponds to a patient's risk for variability (<20, low risk; 20–40, moderate risk, >40, high risk).[5] The ADRR has several advantages over the CONGA and MODD. First, the ADRR is more sensitive to hypoglycemic excursion than the other measures.[4,5] This may be particularly important in young children, where excursion below the normal range could increase young children's risk for a hypoglycemic seizure.[1] Second, the ADRR can be calculated using SMBG data in addition to CGM data, which may make it a more practical measure of variability than the other measures.[5] Finally, there are several glucometer software programs that automatically calculate the ADRR; thus it may be more familiar to patients and to other providers.

Despite the fact that the ADRR can be calculated from SMBG data, we predict that in young children with type 1 diabetes ADRR scores calculated using SMBG (ADRRs) will be less sensitive to variability than ADRR scores calculated using CGM data (ADRRc). We base this prediction on the fact that CGM can collect more individual glucose readings per day than SMBG and even collect values overnight, when it may be more difficult for parents and young children to test regularly.[3,6] If our prediction is true it will have direct implications for research and intervention studies that use glycemic variability as an outcome variable as well as implications for clinical management. Additionally, having a more accurate measure of risk for glucose variability is important in the development of the artificial pancreas and specifically in the tailoring of control algorithms for young children.[7,8] Therefore, the purpose of this study was to examine both ADRRs and ADRRc data for a sample of young children with type 1 diabetes. In addition, to examine the validity of the ADRR scores using the two different data sources, we proposed to examine correlations between young children's two ADRR scores and their mean amplitude of glycemic excursion (MAGE) scores, the current gold standard for measuring variability.[9,10] The two central hypotheses guiding this study were (1) young children's ADRRc scores would be more sensitive and reflect greater variability than young children's ADRRs scores and (2) young children's ADRRc scores would show better concurrent validity with MAGE scores than their ADRRs scores.

Research Design and Methods

This study used CGM data collected from children with type 1 diabetes (2–7 years old). The data from two independent research studies were combined for the analyses. For both studies, families were recruited from one of two pediatric diabetes centers in the Midwestern United States. The inclusion criteria for families were as follows: child's age less than 8 years old, time since diagnosis of at least 1 year, and the family needed to be English speaking. Families were excluded if children were not following an intensive insulin regimen (e.g., insulin pump or multiple daily injection) or parents reported a severe psychological disorder within the last year that required hospitalization.

Procedure

Human subject's approval was obtained ahead of accrual of subjects. Families were recruited to participate by telephone and in-clinic solicitation. Parents, who agreed to the studies, completed an informed consent form during the first study home visit. In addition, children and their parents worked with a trained member of the study team to place a continuous glucose sensor in the child. Families were instructed to proceed with their typical schedules for daily activities and diabetes management while children wore the continuous glucose sensors. We asked all families to leave the continuous glucose sensor in their child for at least 72 h (no longer than 96 h) in order to try to capture glucose data representative of the child's typical levels. After the 72-h monitoring period, parents or a trained research team member removed the continuous glucose sensor and collected the monitor, and a research team member downloaded children's home blood glucose meter and insulin pump (when available) to obtain information related to the child's typical diabetes management. Families received a copy of their child's continuous glucose data and small remuneration for completing either study. A medical chart review to obtain children's most recent glycosylated hemoglobin A1c was completed to obtain a surrogate marker of children's average glycemic control.

Measures

CGM. The Minimed CGMS® Gold™ (Medtronic, Northridge, CA) was used to measure children's glucose levels for the two larger studies. This CGM system provides a relatively noninvasive approach to measuring glucose concentrations over a continuous 24-h period for up to 3 days. The system was specifically selected for the research because it is a blinded system and thus does not provide real-time glucose data that could have altered parents' daily diabetes management routine or children's typical activities. Consistent with the CGM procedure manual, children wore the sensor on their buttocks or abdomen. The individual sensors were inserted just under the skin and into subcutaneous tissue using a spring-loaded insertion device. In addition, to minimize any discomfort related to placing the sensors, a member of the research team applied lidocaine/prilocaine cream to the insertion site to numb the external tissue. While in place, the CGM device recorded children's average glucose concentrations every 5 min. After the sensing period ended, these data were then downloaded on to a central research computer and converted to a spreadsheet for analyses. For this study, the mean duration of CGM trace was 65 ± 19 h (782 ± 228 individual CGM readings). Data lost from the sensor were primarily because of sensor error or parents forgetting to calibrate the sensor at least two times per 24-h period.

SMBG. Children's daily SMBG data were gathered from their home blood glucose meters at the final study appointment. As part of the larger studies, parents were specifically instructed to proceed with their normal routine for diabetes

management and did not receive any guidance on the number of times to check blood glucose daily. At least 14 days (no more than 1 month) of SMBG were collected, which included the time children were wearing the CGM device. For the current analyses, children were excluded if they had less than three checks per day for at least 14 days, which is consistent with the minimum number of SMBG checks required to calculate variability scores.[5] The mean number of SMBG checks for the final sample was 92 ± 37 checks.

Demographic questionnaire. All parents completed a standardized demographic questionnaire to obtain information concerning sample characteristics for children and parents (e.g., child age, gender, family socioeconomic status). Parents completed this form at the first study visit.

Data analyses

Demographic data for families were analyzed according to means, SDs, and frequency as appropriate. The primary analyses involved calculating and then comparing the ADRR scores for young children using both their CGM and SMBG data. To calculate young children's ADRR scores, the original formula of Kovatchev et al.[5] was used separately for young children's CGM and SMBG data. As a second measure of glucose variability and a measure of concurrent validity, MAGE scores were calculated using both children's CGM (MAGEc) and SMBG (MAGEs) data. To calculate children's MAGEc, we used the modified algorithm developed by Baghurst.[9] To evaluate Hypothesis 1, we calculated a bivariate correlation between children's ADRRs and ADRRc scores. In addition, we compared children's ADRRs and ADRRc scores using a paired sample t test, and we compared categories for each child's ADRRs and ADRRc scores to calculate the mean percentage of ADRR categories that matched. To evaluate Hypothesis 2, we calculated bivariate correlations for young children's ADRRs, ADRRc, MAGEs, and MAGEc scores. An a priori α level was set at 0.01 for the correlations to control for multiple tests.

Results

The final sample consisted of 48 children with type 1 diabetes. The children had a mean age of 5.1 ± 1.2 years. There were 26 boys and 22 girls in the sample, and the majority of children (85%) reported using an insulin pump for diabetes management. Children had a mean daily average glucose level of 11.0 ± 2.0 mmol/L, as measured by CGM. They had a mean glycosylated hemoglobin A1c level of 8.06 ± 1.0%, which is within the target range for young children with type 1 diabetes.[1] Table 1 includes a summary of our main outcomes as well as glucose data for each participant. It is notable that children had a mean ADRRs of 46 ± 11 and a mean ADRRc of 55 ± 12, both of which exceeded 40, indicating a high risk for glycemic variability.

Specific to Hypothesis 1, the bivariate correlation between children's ADRRs and ADRRc scores was not significant ($r = 0.13$, $P = 0.18$), suggesting poor reliability between these two scores despite the fact that these correlations were conducted within-subject and the SMBG data overlapped in time with when children wore the CGM device. In addition, the results of a paired sample comparison revealed a significant difference between children's ADRRs and ADRRc scores ($t_{47} = 3.92$, $P = 0.001$), with children's ADRRc score demonstrating a higher risk for glycemic variability. Comparing children's individual ADRRs and ADRRc scores by category, we found that approximately 40% of children had a mismatch in their ADRR category and that 74% of the time, children's ADRRc score reflected a greater risk for variability than their ADRRs score. Looking specifically by category, 83% of children had an ADRRc score of >40, whereas 69% of children had an ADRRs score of >40. For moderate variability (ADRR score = 20–39), 17% of children had an ADRRc score in this range versus 29% of children's ADRRs score. Finally, for low risk for variability (ADRR score <20), 0% of children had an ADRRc score in this range, whereas 2% of children had an ADRRs score in this range.

Specific to Hypothesis 2, bivariate correlations were computed to examine the relations between children's MAGEs and MAGEc scores with their ADRRs or ADRRc scores. The results of the correlations relating children's ADRRs to their MAGE scores were mixed. Specifically, there was no correlation between children's ADRRs and their MAGEc scores ($P = 0.12$, $P = 0.43$), although there was a strong correlation between children's ADRRs and their MAGEs scores ($r = 0.88$, $P = 0.001$). These mixed results suggest that children's ADRRs may have passable concurrent validity when considering variability measures using SMBG data only. In contrast, children's ADRRc significantly correlated with both their MAGEs ($r = 0.41$, $P = 0.004$) and MAGEc ($r = 0.61$, $P = 0.001$) scores, suggesting better concurrent validity across methods of glucose measurement.

Discussion

This study demonstrated that ADRR scores calculated using CGM data (ADRRc) showed greater variability than ADRR scores calculated using children's SMBG data (ADRRs). Specifically, in a paired comparison, we found children's ADRRc scores were significantly greater than children's ADRRs scores. Likewise, when we looked across ADRRs and ADRRc categories, we found that 74% of the time, children's ADRRc score reflected greater variability than their ADRRs score and that with the ADRRc, no child was categorized as low risk for variability compared with one child (2%) who was in the low-risk category based on his or her ADRRs score. Thus, our data suggest that using CGM data, the ADRR will be more sensitive to glucose variability in young children, which may have important implications if using the ADRR as an outcome measure in clinical research and in developing control algorithms as part of a closed-loop insulin system.[7,8] In this study we also looked at the concurrent validity of the two measures of ADRR using young children's MAGE scores calculated from either their CGM (MAGEc) and SMBG (MAGEs) data.[9,10] Our findings revealed mixed results for children's ADRRs, suggesting a passable level of concurrent validity. However, we found strong correlations between children's ADRRc scores and both measures of the MAGE, indicating better concurrent validity for the ADRRc.

This study advances our knowledge of the management of type 1 diabetes in young children in the following ways. First, as shown in other studies, using CGM results in a richer and more complete picture of glycemic excursion in young children than SMBG.[3] As a result clinical investigators using the

Table 1. Study Outcomes and Individual Participant Characteristics

Variable	*Mean ± SD*	r *ADRRs*	r *ADRRc*
ADRRs	54 ± 12.5		
ADRRc	46 ± 10.8		
MAGEs (mmol/L)	9.7 ± 2.1	0.88*	0.41*
MAGEc (mmol/L)	8.7 ± 1.6	0.12	0.61*

Age (year)/gender	*HbA1c (%)*	*Mean blood glucose (mmol/L)*		*ADRRs*	*ADRRc*	*MAGEs (mmol/L)*	*MAGEc (mmol/L)*
		CGM	*SMBG*				
7/F	6.6	8.0	9.4	32	38	6.9	8.3
6/M	6.8	10.1	10.2	58	45	10.3	8.7
7/M	6.8	7.8	9.9	28	53	7.8	7.7
4/M	7.0	8.8	10.7	46	74	10.0	8.0
6/M	7.0	10.4	11.6	29	45	6.2	9.9
5/M	7.1	9.9	9.3	41	32	6.7	7.7
5/F	7.1	9.4	8.5	38	51	8.0	7.5
5/M	7.2	11.8	11.8	65	47	10.3	9.7
6/F	7.2	9.9	10.5	34	45	10.0	6.5
4/M	7.4	8.9	11.1	51	51	9.9	8.8
5/F	7.4	9.9	9.8	54	36	9.5	6.6
6/M	7.4	10.1	12.4	25	48	9.5	4.4
6/F	7.4	9.5	9.1	55	41	8.9	7.9
3/M	7.5	9.6	9.2	43	58	9.0	9.7
3/F	7.5	10.1	9.9	77	31	7.7	12.2
5/M	7.5	11.0	11.3	40	47	7.7	8.8
5/F	7.5	10.4	11.4	52	53	10.6	7.9
6/M	7.5	10.3	10.3	36	52	7.7	9.0
6/F	7.5	9.3	9.5	40	49	9.0	7.3
4/M	7.7	12.4	9.9	48	53	10.2	11.3
5/F	7.7	14.9	12.4	43	65	10.0	10.8
6/F	7.8	10.0	9.0	20	54	6.9	9.4
6/F	7.8	11.5	12.1	60	69	11.5	10.4
6/F	7.8	11.8	12.3	38	41	9.3	7.7
5/F	7.9	10.8	12.4	56	61	12.4	10.4
3/M	8.0	15.7	15.0	60	45	11.5	9.2
4/M	8.0	13.0	11.5	56	59	11.0	9.2
6/F	8.0	8.3	10.5	36	76	10.3	7.8
3/M	8.1	11.9	10.4	36	66	8.7	9.2
6/F	8.1	11.0	10.9	61	50	11.0	9.0
2/M	8.3	7.1	7.4	53	25	6.4	9.2
6/M	8.3	9.0	13.9	60	56	11.6	11.3
6/F	8.3	11.1	15.2	67	75	12.9	7.8
5/M	8.4	13.8	11.4	56	69	12.6	11.8
5/M	8.6	14.9	14.2	47	54	11.3	8.6
6/M	8.6	12.3	13.7	56	54	12.4	10.8
6/M	8.6	12.1	12.7	81	51	11.2	10.1
6/F	8.7	10.3	10.9	56	49	9.2	6.3
5/M	8.8	14.8	12.6	56	65	13.7	10.0
5/F	8.8	12.1	12.2	59	49	11.9	8.0
6/M	8.8	10.4	12.8	39	47	6.7	8.2
6/F	8.9	11.2	11.8	54	63	12.2	9.4
5/M	9.0	10.7	12.7	40	56	12.5	6.2
5/M	9.1	10.9	9.9	44	57	9.0	9.3
5/F	9.2	11.2	11.1	51	49	11.1	8.5
2/F	9.3	11.5	10.2	42	30	7.9	7.0
5/M	12.7	11.4	10.9	35	58	9.4	6.0

*$P < 0.01$.

ADRRc, average daily risk range using continuous glucose monitoring; ADRRs, average daily risk range using self-monitoring of blood glucose; CGM, continuous glucose monitoring; HbA1c, glycosylated hemoglobin A1c; MAGEc, mean amplitude of glycemic excursion using continuous glucose monitoring; MAGEs, mean amplitude of glycemic excursion using self-monitoring of blood glucose; SMBG, self-monitoring of blood glucose.

ADRR may want to calculate these scores using CGM versus SMBG data to ensure they are capturing a more accurate measure of risk of excursion in young children with type 1 diabetes. Second, our data suggest that in young children, an ADRR score calculated using CGM data may be as accurate a measure of excursion as calculating a MAGE score for young children.[9] This has important practical implications because calculating the ADRRc can be fully automated using a spreadsheet (e.g., Excel [Microsoft, Redmond, WA]), whereas the MAGE requires some hand calculations and thus can be very labor intensive. Third, our results have practical implications for the development and release of closed-loop insulin delivery systems in young children. These systems rely on control algorithms that balance the release of insulin with children's blood glucose levels, and key to the success of these algorithms is their sensitivity to predicting high and low glucose levels.[8] Young children are vulnerable to greater glucose variability than older youth[3] and adults[5] with type 1 diabetes, and our results demonstrate that children's ADRRc scores are more sensitive to variability than their ADRRs scores. Thus, researchers working to customize control algorithms for young children may obtain better risk predictions if they use ADRRc versus ADRRs scores. Finally, our study presents typical ADRR scores for young children with type 1 diabetes, which may serve as benchmark data for future research and intervention studies.

Our study has some limitations. First, this article combines the glucose data from two samples of young children who participated in two separate clinical research projects. In both cases, families were asked to follow a typical schedule for their daily activities and diabetes management. However, as all the families knew they were participating in research, we are unable to rule out the possibility of a Hawthorne effect. To further validate our ADRR scores as normative of young children, it may be helpful to compare our data with personal CGM data collected via a medical chart review, as these personal CGM data may be relatively free of a Hawthorne effect. Second, for this study, 85% of children were on an insulin pump, which is likely higher than the normal distribution in most clinics. This high rate of pump usage is because one of the studies from which these data were drawn specifically recruited young children on an insulin pump. Therefore, we expect our data may not generalize to young children who are conventionally managed and may demonstrate a very different pattern of glucose variability.

In summary, young children with type 1 diabetes typically experience glycemic variability.[1,2] The ADRR provides a measure of risk for glycemic variability and is easy to calculate using either CGM or SMBG data.[5] However, the results of our current analyses suggest that for young children, ADRR scores calculated using CGM data may be a more sensitive measure of risk for excursion than scores calculated using children's SMBG and thus may be a better measure of excursion for use in clinical research and patient care.

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Author Disclosure Statement

All authors declare that no competing financial interests exist.

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