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A Novel Approach to Continuous Glucose Analysis Utilizing Glycemic Variation

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ABSTRACT

Background: Various methodologies have been proposed for analysis of continuous glucose measurements. These methods have mainly focused on the proportion of low or high glucose readings and have not attempted to analyze other dimensions of the data obtained. This study proposes an algorithm for analysis of continuous glucose data including a novel method of assessing glycemic variability.

Methods: Mean blood glucose and mean of daily differences (MODD) assessed the degree that the Continuous Glucose Monitoring System (CGMS®, Medtronic MiniMed, Northridge, CA) trace was representative of the 3-month glycemic pattern. Percentages of times in low, normal, and high glucose ranges were used to assess marked glycemic excursion. Continuous overall net glycemic action (CONGA), a novel method developed by the authors, assessed intra-day glycemic variability. These methods were applied to 10 CGMS traces chosen randomly from those completed by children with type 1 diabetes from the Royal Children's Hospital, Melbourne, Victoria, Australia and 10 traces recorded by healthy volunteer controls.

Results: The healthy controls had lower values for mean blood glucose, MODD, and CONGA. Patients with diabetes had higher percentages of time spent in high and low glucose ranges. There was no overlap between the CONGA values for patients with diabetes and for controls, and the difference between controls and patients with diabetes increased markedly as the CONGA time period increased.

Conclusions: We advocate an approach to the analysis of CGMS data based upon a hierarchy of relevant clinical questions alluding to the representative nature of the data, the amount of time spent in glycemic excursions, and the degree of glycemic variation. Integrated use of these algorithms distinguishes between various patterns of glycemic control in those with and without diabetes.

INTRODUCTION

THE AIM OF DIABETES THERAPY is to maintain blood glucose levels as close to normal as possible without compromising patient safety due to hypoglycemia.[1] Daily self-monitoring of blood glucose levels provides a limited view of glycemic control, while glycosylated hemoglobin (HbA1c) has proved to be a reliable marker reflecting average glucose control over a 2–3-month period.[2] Several methodologies have been proposed for the analysis of the intermit-

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tent glucose measures produced by daily self-monitoring. Kovatchev et al.,[3,4] for instance, have developed various indices for summarizing non-continuous data downloaded from a patient's glucose meter, including low blood glucose index, high blood glucose index, blood glucose risk index, and blood glucose rate of change.

In the past 10 years, various technologies allowing ambulatory continuous glucose measurement have become available. Such continuous glucose monitoring has demonstrated the wide degree of glycemic variation occurring in children with type 1 diabetes, even those with excellent HbA1c levels.[5–7] Whilst the hardware aspect of continuous glucose sensing has attained a reasonable degree of reliability and reproducibility, methods to analyze continuous glucose data are yet to be fully developed; methods suitable for analyzing intermittent data do not fully utilize the wealth of information provided by continuous glucose monitoring.

The purpose of this paper was to develop a new approach to the interpretation of continuous glucose data, utilizing the data obtained from a continuous glucose monitoring system. The method proposed is to answer a series of relevant hierarchical clinical questions:

1. How representative are the continuous glucose monitoring system data of average glycemic control within a 3-month period?
2. What is the amount of time with marked glycemic excursions?
3. What is the lability/variation of glycemic control?

This paper addresses these questions using some established methods and a novel algorithm and demonstrates their application in cohorts with and without diabetes.

PATIENTS AND METHODS

The continuous glucose monitor utilized in this study was the Medtronic MiniMed (Northridge, CA) CGMS®. The methods involving monitor application and data retrieval have been described in detail elsewhere.[8] Limitations to the MiniMed CGMS include the inability to measure interstitial tissue glucose values below 2.2 mmol/L or above 22.2 mmol/L. Data were downloaded using MiniMed Solutions version 1.7A.

CGMS recordings were obtained over 72-h periods from 10 children with type 1 diabetes (age range, 9.3–19.5 years) randomly chosen from the diabetes clinic at the Royal Children's Hospital (RCH), Melbourne, Victoria, Australia and from 10 healthy, adult controls without diabetes (age range, 30.0–46.5 years). Each CGMS trace was calibrated by a minimum of four finger-prick blood glucose measurements per 24-h period. A calibration point had to be carried out at least every 8 h for the data to be included in the analyses. Data cleaning entailed confirmation of regular calibration, identification of errors with paired sensor values, and review of missing data points or time points and was carried out using Stata™ statistical software (Stata Corp., College Station, TX).

Representative nature of the CGMS trace

To assess how representative a 72-h CGMS trace was for the average 3-month glycemic pattern of each patient we calculated the mean CGMS glucose value for the trace and the degree of inter-day glycemic variability. The mean CGMS glucose value was calculated as the arithmetic mean of glucose values within a given period.[9] HbA1c was assessed using the Bayer DCA 2000 immunoagglutination method (Calabria, Barcelona, Spain). Inter-day glycemic variation was assessed using the mean of daily differences (MODD). The absolute value of the difference between glucose values taken on two consecutive days at the same time was calculated; the MODD is the mean of these differences.[10] All readings of the trace where there was a reading 24 h previous were included in the calculation of the MODD.

Glycemic excursions

To assess the amount of time of marked glycemic excursion over the duration of the trace, the percentage of time was calculated for three defined glucose ranges after data cleaning: low (CGMS value <4 mmol/L), normal (CGMS value 4–12 mmol/L), and high (CGMS value >12 mmol/L).

Glycemic lability

When previous methods [M–value[11] and mean amplitude of glycemic excursions (MAGE)[12]] for assessing glycemic variation were evaluated, neither was found to be suitable for application to CGMS. A novel method, which describes intraday glycemic variation, has been devised by the authors. This measure has been named continuous overlapping net glycemic action (CONGA). For each observation after the first n hours of observations, the difference between the current observation and the observation n hours previous was calculated. CONGAn was defined as the standard deviation of the differences. Higher CONGA values therefore indicate greater glycemic variation. The choice of the time difference, n, will depend on the clinical question being addressed. We present results for CONGA1, CONGA2, and CONGA4, the time periods 1 h, 2 h, and 4 h, corresponding approximately to time between different activities in school, time between snacks, and time between meals. We also present results showing the relationship between CONGA values and the CONGA time period, n.

All formulae are listed in Table 1. Use of the Minimed CGMS at RCH has been approved by the RCH Human Research Ethics Committee.

TABLE 1. DEFINITION OF THE FORMULAE USED TO ASCERTAIN GLUCOSE VALUES

Name	*Formula*	
Mean glucose	$\frac{\sum_{t=t_1}^{t_k} GR_t}{k}$	k = number of observations (number of glucose readings for a given individual)
Adjusted M-value	$M_{GR} + M_W$ where $M_{GR} = \frac{\sum_{t=t_1}^{t_k} \left\lvert 10\times\log\frac{GR_t}{IGV}\right\rvert^3}{n}$ and $M_W = \frac{G_{max} - G_{min}}{20}$	M_{GR} = M-value for glucose readings M_W = correction factor for n <24 IGV = ideal glucose value (arbitrary number) G_{max} = maximum glucose reading G_{min} = minimum glucose reading k = number of observations (number of glucose readings for a given individual)
"J"-index	$J = 0.324 \times (MBG + SD)^2$	MBG = mean glucose levels SD = standard deviation of glucose levels
MAGE	$\sum \frac{\lambda}{x}$ if $\lambda > v$	λ = each blood glucose decrease from peak to nadir x = number of valid observations v = 1 SD of mean glucose for 24-h period
MODD	$\frac{\sum_{t=t_1}^{t_{k^*}} \lvert GR_t - GR_{t-1440}\rvert}{k^*}$	k^* = number of observations where there is an observation at the same time 24 h ago
CONGAn	$\sqrt{\frac{\sum_{t=t_1}^{t_{k^*}} (D_t - \overline{D})^2}{k^* - 1}}$ where $D_t = GR_t - GR_{t-m}$ and $\overline{D} = \frac{\sum_{t=t_1}^{t_{k^*}} D_t}{k^*}$	k^* = number of observations where there is an observation $n \times 60$ min ago $m = n \times 60$

Note that GR_t glucose reading at time t min after start of observations and t_i = time in minutes after start of observations of the i^{th} observation.

All calculations were performed using STATA version 8.0.

RESULTS

For clarity the data are summarized according to the clinical questions posed.

How representative are the CGMS data of average glycemic control within the same 3 months?

The HbA1c values for the cohort with diabetes ranged from 6.6% to 9.9%, which showed them to have a wide range of metabolic control such as is evident in most diabetes clinics. Mean blood glucose was calculated as a measure of glycemic control within the CGMS trace. The data in Table 2 show a wide variety of mean CGMS glucose values in the cohort with diabetes (6.0–16.2 mmol/L) compared with the relatively narrow range in the cohort without diabetes (4.8–5.8 mmol/L).

Consistency between days on a CGMS trace was assessed using the MODD. The mean MODD value for the patients with diabetes was 4.3 (range 2.9–8.1), whereas the mean in the healthy controls was 0.8 (range 0.5–1.2). A MODD value less than 1.0 means that the pattern of the trace was very similar on each of the 3 days recorded for that individual.

What is the amount of time of marked glycemic excursions?

The amount of time of marked glycemic excursion was based on the percentage of time spent in the high or low glucose ranges. Table 2 shows that none of the healthy control traces recorded high CGMS values (>12 mmol/L) and only 0–20.5% of time was spent with low CGMS values (<4 mmol/L). None of the healthy controls experienced symptoms of hypoglycemia. By contrast, the traces from the patients with diabetes recorded percentage of time rates of 2.3–88.9% in the high range and 0–29.1% in the low range.

What is the lability/variation of glycemic control?

The lability of glycemic control within a CGMS trace was assessed by calculating the

Table 2. Comparison of Continuous Traces from Controls Without Diabetes (ID 1–10) with Those from Children and Adolescents with Diabetes (ID 11–20)

ID	Type 1 diabetes	Mean blood glucose	MODD	CONGA1	CONGA2	CONGA4	HbA1c	% of time		
								Hypoglycemic	Normal	High
Controls										
1	No	4.8	1.2	1.1	1.2	1.2	—	20.5	79.5	0.0
2	No	5.0	1.1	1.2	1.1	1.5	—	19.4	80.6	0.0
3	No	5.2	0.9	0.6	0.9	1.2	—	15.4	84.6	0.0
4	No	5.3	0.6	0.4	0.4	0.5	—	0.0	100.0	0.0
5	No	5.3	0.8	0.6	0.7	1.0	—	4.2	95.8	0.0
6	No	5.4	0.5	0.7	0.9	0.9	—	0.6	99.4	0.0
7	No	5.6	0.6	0.7	0.9	1.0	—	0.3	99.7	0.0
8	No	5.6	0.8	0.6	0.7	0.8	—	0.5	99.5	0.0
9	No	5.8	0.6	0.6	0.7	0.7	—	0.0	100.0	0.0
10	No	5.8	0.8	0.5	0.6	0.7	—	0.3	99.7	0.0
Diabetes										
11	Yes	6.0	3.2	2.0	2.9	4.0	6.6	29.1	68.6	2.3
12	Yes	8.0	3.6	2.4	3.3	3.5	7.0	15.4	67.3	17.3
13	Yes	8.5	2.9	2.5	3.3	3.8	8.2	4.5	82.5	13.0
14	Yes	8.8	3.7	2.1	2.6	2.9	7.9	1.9	84.1	14.0
15	Yes	9.2	8.1	2.4	4.1	6.1	7.8	20.2	49.1	30.7
16	Yes	10.8	5.4	3.2	5.0	7.3	7.6	9.2	57.1	33.7
17	Yes	12.6	4.3	2.9	4.4	5.4	8.4	0.8	50.1	49.1
18	Yes	12.8	4.2	1.7	2.6	3.6	9.9	0.0	38.4	61.6
19	Yes	13.5	3.9	2.7	3.9	4.9	9.7	0.0	41.7	58.3
20	Yes	16.2	4.1	2.6	3.5	4.4	9.0	0.0	11.5	88.5

CONGA for 1, 2, and 4 h time differences. The group mean CONGA1 value in the group with diabetes was 2.5 (range 1.7–3.2) compared with the healthy control group value of 0.7 (range 0.4–1.2). For CONGA2 and CONGA4, the differences between the two groups were even more marked: The mean CONGA4 value in the diabetes group was 4.6, compared with 1.0 in the healthy group. Figure 1 shows the relationship between CONGA value and time period use to calculate CONGA for each of the patients and controls. For the healthy controls, the time period used to calculate the CONGA has little effect on the CONGA value. For the patients with diabetes, however, CONGA generally increases as the time period increases. The largest increases are seen in those patients with large glycemic swings over the period of the trace. This is illustrated in Figure 2b and c, which show the CGMS trace and CONGA values for patients with diabetes having low and high intra-day glycemic variation, respectively. For comparison, the CGMS trace and CONGA values for a healthy control are shown in Figure 2a.

DISCUSSION

The premise of our proposed approach to continuous glucose analysis is that there is no *one* measure that covers all aspects of glycemic control, and hence a multifaceted approach is warranted. CGMS provides clinically useful data over and above traditional diabetes outcome measures such as HbA1c and mean glucose values. Quantitative measures of inter- (MODD) and intra-day (CONGA) glycemic variation can now be assessed. There is no clinical reason why one would expect these metrics to correlate with HbA1c or mean glucose values. Clinical experience readily attests to patients having the same HbA1c but markedly varying degrees of glycemic variation. Conversely, there can be two patients with the same degree of intra-day or inter-day glycemic variation who have very different mean glucose levels or HbA1c values.

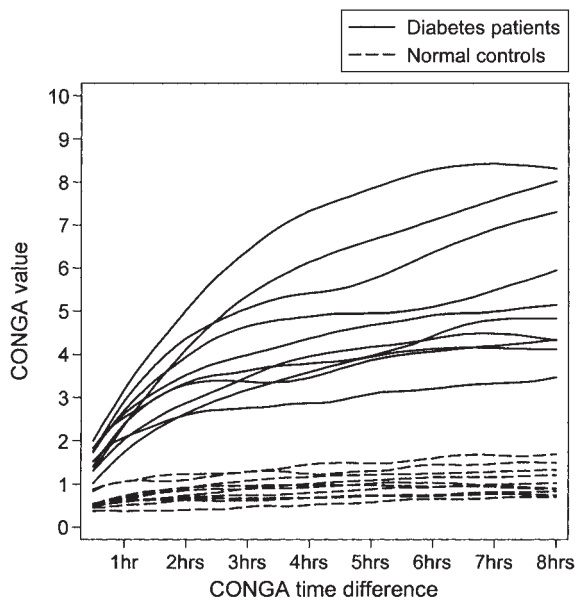

FIG. 1. Relationship between CONGA value and time period use to calculate CONGA for pediatric patients with diabetes (solid lines) and controls (dashed lines).

Continuous glucose monitoring provides both qualitative and quantitative data. Hence analysis of CGMS data can be problematic. We have proposed an approach to the analysis of CGMS data that is based upon relevant hierarchical clinical questions: How representative are the data? What is the percentage of time spent in major glycemic excursions? How variable or labile is the glycemic control? In order to provide answers to these questions we have explored the use of several algorithms in CGMS data obtained from groups with and without diabetes. As part of the new approach formulated, we have developed a novel algorithm, CONGA, to assess glycemic variation.

Prior to any use of CGMS data, investigators need to be confident that the data are accurate. To this end there should be at least four calibrations of the CGMS to intermittent finger-prick blood glucose values within each 24-h period as per the manufacturer's guidelines. The CGMS software calculates the acceptability of the data by comparing the inputted blood glucose values with paired sensor readings.

How representative are the CGMS data of average glycemic control within the same 3 months?

This question is of prime importance as it refers to the credibility of the CGMS data when attempting to extrapolate the CGMS findings to a relevant clinical period. In order to ascertain how representative a CGMS trace is of any

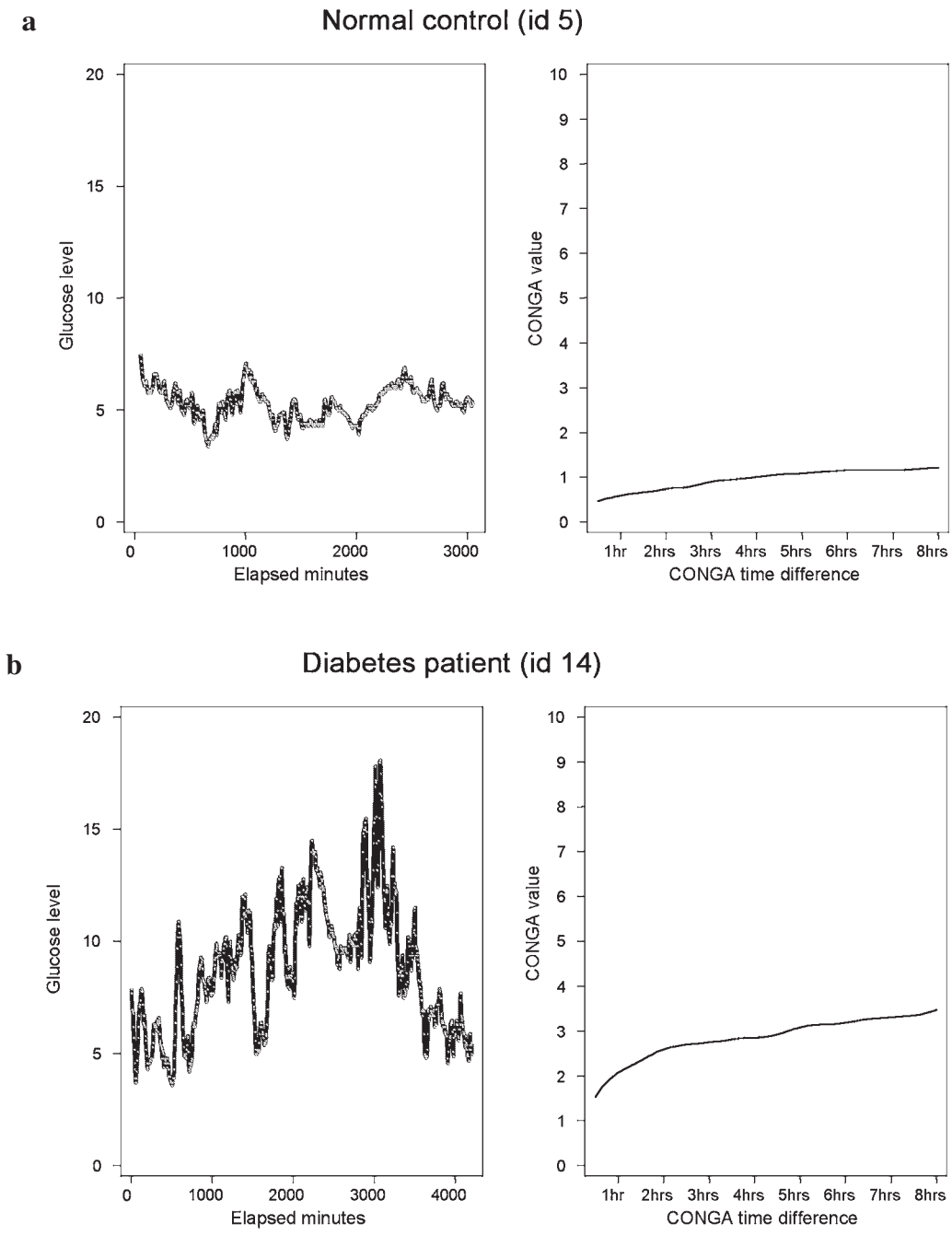

FIG. 2. CGMS trace and CONGA values for (**a**) a normal control, (**b**) a pediatric patient with diabetes having low intra-day glycemic variation, and (**c**) a pediatric patient with diabetes having high intra-day glycemic variation.

given period we have elected to summarize the sensor values obtained and to assess inter-day variation of the trace for consistency. The two aspects of CGMS data we have chosen to use in these analyses are the mean CGMS glucose value and the MODD. The use of mean CGMS glucose assumes that the distribution of CGMS values is not skewed; the mean does not directly measure amplitude or variation of the CGMS trace. Boland et al.[5] have shown correlations between mean CGMS glucose values and HbA1c. Although the mean CGMS glucose value cannot account for glycemic variation it can potentially be utilized as a surrogate marker for HbA1c within trace analysis. Because of the small size of the cohort with dia-

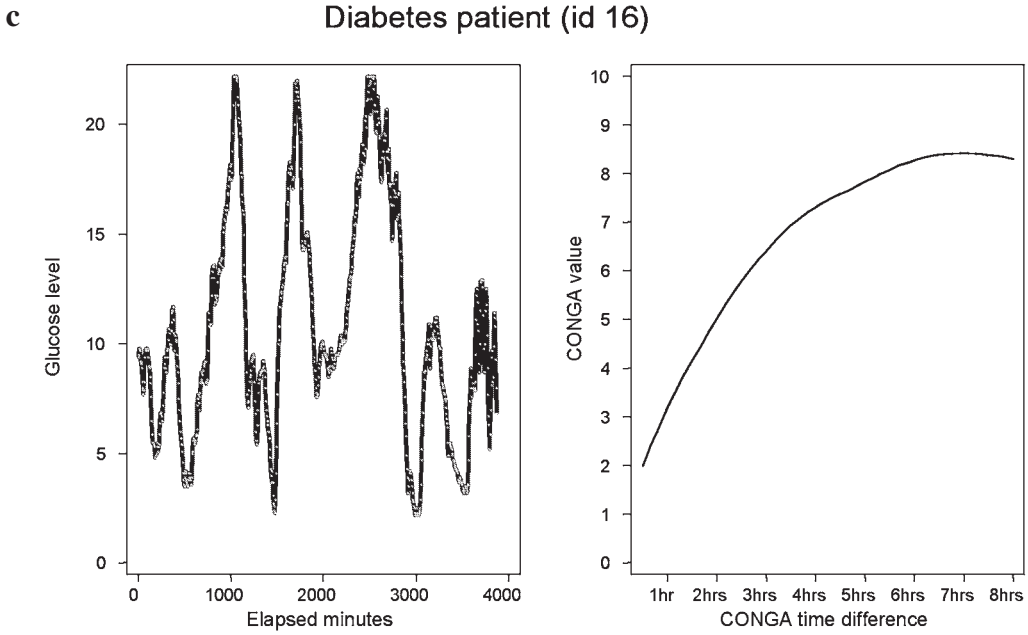

FIG. 2. (*Continued*)

betes assessed for this methods paper we did not attempt any statistical analyses comparing mean glucose values and HbA1c. Notwithstanding this we feel that the link between a 3-day CGMS recording and an independent measure of control such as HbA1c has already been established by Boland et al.[5] The clinical utility of CGMS is further enhanced by the integrated use of mean glucose data together with MODD, percentage of time in glycemic ranges, and CONGA.

The MODD value was derived by Molnar et al.[10] in 1972. This value was designed to illustrate inter-day variation of blood glucose levels. Care has to be taken in adapting this formula for use with continuous monitoring as occasional CGMS time intervals can be lengthened or shortened by 1 min, altering the time difference and affecting the final MODD calculation. A high MODD score is indicative of a large glycemic difference between days. MODD values have utility in that the degree of consistency in a CGMS trace can be assessed, and thus the degree to which observed daily patterns are ongoing and representative can be assessed. In our clinical experience, CGMS traces with high MODD values are indicative of irregular habits and require detailed contemporaneous lifestyle information prior to interpretation.

What is the amount of time spent in marked glycemic excursions?

Assuming the CGMS data are representative, then an assessment of the amount of time experienced by an individual in various glycemic ranges allows for a quantitative assessment of hypo- or hyperglycemia. Earlier CGMS studies have shown that occult hypoglycemia in childhood diabetes is a relatively common event.[6,7] In children, hypoglycemia may have adverse effects on cognitive function, potentially as significant as the long-term microvascular complications due to hyperglycemia.[13–16] Reliance only upon HbA1c and intermittent finger-prick testing may lead to a limited picture of overall metabolic control with little or no appreciation of glycemic excursions or variation.[9]

To ascertain the effect of marked glycemic excursions, the percentages of time spent in high and low glucose ranges were calculated. The percentage of time analyses proposed here have the advantage that CGMS data are summarized only in terms of time, an easily reproducible and comparable measure between subjects. Also, the percentage of time spent within various glycemic ranges is a useful clinical concept that can be used to adjust therapy. Notwithstanding the clinical utility of percent-

age time, it is a limited measure of continuous CGMS data. The values obtained are sum totals and not indicative of whether the time spent at or below a particular glucose level is within one prolonged episode or consists of many shorter episodes. Subanalyses of percentage of time during various periods (night, school time, etc.) may be more helpful in specific clinical contexts. Other literature dealing with CGMS data has used area under or above the CGMS curve to describe the degree of glucose deviation above or below a certain threshold.[6,17] The method has been used to describe the incidence of hypo- and hyperglycemia and the effect of new therapies.[6,17] Researchers using this method have analyzed data using the whole area under the curve of each 24-h glucose profile within the range of the CGMS (2.2–22.2 mmol/L), and have evaluated both mean value of the area for 3 days and the sum of the areas for the same 3 days.[6] Similar to mean CGMS glucose values, a relationship has been shown between HbA1c and mean 3–day glucose area under the curve values.[6] Another group evaluating a new therapy employed the incremental area under the curve using the trapezoidal rule to calculate postprandial glucose excursions.[17] In the context of CGMS, areas under the curve analyses are problematic in that the curve is truncated at glucose values under 2.2 mmol/L and over 22.2 mmol/L. Thus the area under the CGMS curve does not distinguish between extremes in glucose levels (for example, values of 23 mmol/L and 40 mmol/L are treated equally).

In this limited study we found that patients and controls experienced similar percentage of times of CGMS readings below 4 mmol/L (6% vs. 8%, respectively). There are potentially two explanations for this. First, the normal range for blood glucose levels extends down to 3 mmol/L. Thus CGMS readings between 3 and 4 mmol/L can be viewed as normal for the control subjects. In this study a cutoff value of 4 mmol/L was chosen because in patients with diabetes this is a level at which patients frequently experience symptoms of hypoglycemia and the level at which our pediatric patients are counseled to take remedial action. The second reason pertains to the accuracy of interstitial tissue CGMS readings compared with blood glucose at low glucose levels. In the control traces, the lowest recorded glucose level was 2.7 mmol/L. Out of a total of 6,488 5-min control readings, the glucose level was recorded between 2.7 and 3.0 mmol/L in only 35 occasions (0.5% of readings). The issue of sensor accuracy has been canvassed in the literature,[18–21] with discrepancies occasionally seen between interstitial tissue and blood glucose levels in detecting low glucose values. It is for these reasons that we are not advocating the use of the CGMS to assess the absolute degree of glycemic excursions; rather, we are advocating the use of the CGMS to assess patterns of glycemic excursions (i.e., percentage of time in and out of various glycemic ranges). In addition, we do not refer to CGMS values as indicating hyper-, normo-, or hypoglycemia; rather we prefer the use of the terms high, normal, or low glucose values in order to reinforce the point that the CGMS is not measuring blood glucose levels per se.

What is the lability/variation of glycemic control?

The importance of an understanding of the degree of variation/lability in glycemic control in childhood and adolescence is yet to be fully established. Reporting of improved psychosocial outcomes seen in children receiving continuous insulin therapy suggests that glycemic variation may be an important novel outcome measure in childhood diabetes.[22] Glycemic variation incorporates the frequency of glycemic excursions, including postprandial glycemia—a phenomenon increasingly recognized to be of importance in overall metabolic control.[23] Finally, glycemic variation may be a factor in determining the risk of severe hypoglycemia or diabetic ketoacidosis. Previous investigators have recognized the importance of trying to measure glycemic variation and have devised algorithms for use in postprandial experimental models.[11,12] Examples of such analyses include M–values and MAGE. The M–value is a measure of the stability of the glucose metabolism in comparison with an ideal glucose value.[9] The M–value was first described in an attempt at a quantitative analysis of postprandial blood glucose variation.[11] The M–value was originally de-

signed against a subjective standard of nine investigators' assessment of 72-h profiles from 20 patients with diabetes (six blood glucose measures per 24-h period) and has subsequently been extrapolated for use in the CGMS with little critical review.[24] The M–value is 0 in healthy controls, rising with increasing glycemic variation. In the context of diabetes, results are categorized as good (0–18), fair (19–31), or poor (>32) control.[11] Arbitrary cutoffs are required for administration of the formula with logarithmic transformation being required to increase the impact of hypoglycemic events on the index.[11] The original formula was later modified (Adjusted M–value; see Table 1)[9] for a higher arbitrary comparative glucose value when it was found that some cases the M–value was lower that of a reference group of healthy individuals. When originally devised, the authors acknowledged that the M–value was limited by the number of glucose values measured. To adjust for this, subsequent authors added an appendix (M_W) to the formula for calculations of 24 readings or fewer.[11] CGMS traces produce up to 288 readings in a day, and thus the appendix is now no longer applicable. As mentioned above, the M–value relies on selection of arbitrary glycemic reference points by the investigators. This introduces a bias effect that impedes the M–value's use in comparing separate studies that may use varying reference points. Further to this, hypoglycemia has a greater impact on the M–value than hyperglycemia, which limits the M value's usefulness as a true descriptor of glycemic variation.

In view of these disadvantages Wojcicki[25] proposed the "J"-index as an alternate formula for calculation of glycemic variation. The aim of this new index was to incorporate mean level and variability of glycemia utilizing one variable. The calculation summarized in Table 1 relates to glucose levels measured in mmol/L. This index has not been validated in continuous glucose monitoring and excludes hypoglycemia alarm states defined as severe hypoglycemia (<1.67 mmol/L) and continuous hypoglycemia (3 measurements <2.78 mmol/L).

The MAGE algorithm[12] was suggested in 1970 by the same investigators who devised MODD to quantitate glycemic excursion under controlled dietary/exercise conditions. The MAGE algorithm was designed to calculate the peaks and nadirs encountered in a day, generating a value for the variation around a mean glucose value. MAGE values differ from M–values in that the reference point is a mean value rather than an arbitrarily chosen cutoff. The degree of variation is calculated according to the standard deviation of postprandial glycemic excursion.[12] Definition of glycemic peaks and nadirs is arbitrary or subjective,[12] this being the main factor limiting its use in ambulatory, non-controlled CGMS analyses. MAGE uses the pooled results of arbitrarily designated glycemic peaks (chosen by the investigators in a non-reproducible fashion), and ignores blood glucose swings, which are designated as insignificant by the person interpreting the data. When MAGE was first proposed, hourly blood glucose measures were assessed. By way of comparison, CGMS records 12 measures per hour. In continuous monitoring the distinction between peaks and nadirs is unclear compared with the original hourly measurements used when MAGE was devised. Thus MAGE analysis ignores a large percentage of CGMS data. Notwithstanding this, MAGE has recently been used in conjunction with the CGMS in a diet- and exercise-controlled cohort with diabetes.[26] In that study the authors defined the standard deviation according to the mean CGMS glucose value, and defined CGMS glucose peaks and nadirs manually in a way that we have been unable to reproduce. In addition, the diet and activities of participants in the CGMS study by Alemzadeh et al.[26] were controlled. The necessity for such restrictions limits the use of MAGE in non-controlled, ambulatory CGMS use. Our attempts to use the MAGE analysis with the CGMS data presented in this study proved unsuccessful as we found identification of significant CGMS peaks and nadirs for the MAGE calculation to be inconsistent between investigators. No mathematical system could be devised that reliably, objectively, and consistently identified clinically relevant glycemic peaks and nadirs required for this calculation to be used with the CGMS.

There exists no established "gold standard" of glycemic variation against which to compare the M–value, J-index, or MAGE. Thus on the largely empiric and practical grounds summa-

rized above we have concluded that the M–value, J-index, and MAGE are inappropriate tools to analyze continuous glycemic data in a non-controlled or ambulant setting. Given the shortcomings of these existing algorithms to assess glycemic variation we have devised the CONGA as a novel method of consistently and objectively expressing glycemic variation. The CONGA is defined as the standard deviation of the differences and measures the overall intra-day variation of glucose recordings. The CONGA does not require arbitrary glucose cutoffs, logarithmic transformation, chosen peaks and nadirs, or defined meal or exercise times. The CONGA calculation is an expression of the variation shown during normal, ambulatory activity, which is more useful in the assessment of a child with diabetes. The CONGA formula is based on the premise that normoglycemia inherently allows for little glycemic variation, whereas glycemic control in diabetes will result in greater variation in blood glucose levels. High CONGA values will therefore reflect increased glycemic excursions consistent with less stable control, and low CONGA values will reflect stable glycemic control. Our data demonstrate the dramatic difference in glycemic variation between people with diabetes and healthy controls. Whilst both distributions are centered around zero, a much wider range of differences is evident in the subjects with diabetes.

CONCLUSIONS

The analysis of data produced from continuous glucose monitoring presents unique challenges. The wealth of data available from continuous glucose monitoring cannot be fully utilized with methods designed for intermittent glucose monitoring. In summary, the approach suggested for accurate CGMS analysis is depicted below according to what are the relevant clinical questions being asked of the data:

1. How representative are the CGMS data of average glycemic control within the same 3 months?
   - Mean blood glucose—is the value comparable to HbA1c?
   - MODD analysis—is there inter-day consistency?
2. What is the amount of time spent in marked glycemic excursions?
   - Percentage of time within glycemic range analyses
3. What is the lability/variability of glycemic control?
   - CONGA1, CONGA2, and CONGA4 analyses for intra-day variability

The measurement and analysis of continuous glucose readings have the potential benefit of increasing our understanding of glycemic control and generating a new independent outcome for diabetes, that of glycemic variation. CGMS can assist in this as both a quantitative and qualitative tool. The approach to CGMS interpretation advocated here allows for corroboration of glucose values with HbA1c, an analysis of inter-day glycemic variation, description of amount of time spent within various glucose ranges, and finally an analysis of intra-day glycemic variation. Continuing advances in the production of continuous glucose monitors should be paralleled by advances in the assessment of the data provided. The CONGA value, in particular, is a novel measure that is suitable for use in ambulant continuous glucose monitoring systems. Whether or not the CONGA value proves to be associated with other glycemic outcomes (hypoglycemia rates, risk of diabetic ketoacidosis, etc.) or behavioral variables is an area of ongoing enquiry. In the interim, we propose that the CONGA analysis, measuring glycemic variation, should be an integral component in the assessment of CGMS data.

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