ORIGINAL ARTICLE

Is the Masked Continuous Glucose Monitoring System Clinically Useful for Predicting Hemoglobin A1C in Type 1 Diabetes?

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Abstract

Background: The masked continuous glucose monitoring system (Masked-CGMS) differs from standard CGMSs in three ways: (1) there is no feedback to the user so that no immediate regimen changes can be made; (2) it can only be worn for up to 5 days; and (3) there are no alarms to warn of hyperglycemia or hypoglycemia. Since 2008 masked-CGMS has become popular for identifying reasons that a patient's hemoglobin A1C does not correlate closely with his or her capillary blood glucose measurements. To date only one study addressing the clinical utility of Masked-CGMS for improving A1C in diabetes has been published. No studies are available specifically examining the variability and correlation of Masked-CGMS and A1C.

Subjects and Methods: We performed 156 Masked-CGMS studies (40 patients studied sequentially a maximum of four times each) in type 1 diabetes patients. We then analyzed the resulting interstitial glucose levels obtained from the Masked-CGMS compared with an A1C measurement performed within 1 week of the Masked-CGMS study.

Results: There was a very low correlation between the A1C and the Masked-CGMS-derived mean interstitial glucose level. This statistic did not provide sufficiently predictive information to be clinically useful for changing an individual patient's intensive insulin therapy regimen.

Conclusions: Our data demonstrate that a very weak correlation exists between 5 days of masked CGMS and a concurrently measured A1C level. For the individual type 1 diabetes patient, this relationship would unlikely to be clinically useful in altering the individual's treatment regimen.

Introduction

INTERSTITIAL CONTINUOUS glucose monitoring (CGM) has become standard therapy for patients with type 1 diabetes who want to know their interstitial glucose levels on a minute-to-minute basis and who wish to be notified by an alarm when their glucose levels exceed or are below a pre-determined set value.^{1–4} CGM is also valuable for identifying trends in glucose concentration so that preemptive corrective additional insulin doses can be administered (in the case of an upward trend) or carbohydrate ingested (in the case of a downward trend).^{5,6} More recently, CGM has been re-

commended for identifying patterns of glucose excursions so that corrections to the basal or preprandial doses of insulin can be made.^{7,8} For this reason, it is necessary that the patient not make acute adjustments in his or her diabetes regimen because these adjustments might obscure the glucose pattern that the CGM device is attempting to record. The use of CGM without immediate feedback information to the wearer has been referred to by various names, including “blinded CGM,” “professional CGM,” and “historical CGM.”⁹ To facilitate this specific use of CGM, the iPro™ CGM system (CGMS) (Medtronic, Inc., Minneapolis, MN) has been developed. This masked CGM device does not permit the

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FIG. 1. Individual mean interstitial glucose versus corresponding hemoglobin A1C observation points for each volunteer. Each volunteer had four 5-day continuous glucose monitoring sessions (separated by a 2-month interval) immediately preceded by a blood A1C measurement. There is no obvious common slope of the data points between the volunteers in this study, suggesting that a clinically useful relationship between these two variables does not exist.

diabetes patient to receive temporal feedback of his or her glucose values until after the completion of 3–5 days of glucose monitoring.

As might be expected, the iPro is often used by physicians to identify reasons why diabetes patients are not at recommended glycemic hemoglobin A1C targets.¹⁰ This approach makes logical sense because there are many times during the day and night that self-monitored capillary blood glucose is not measured. Although using the iPro CGMS for this purpose is relatively noninvasive, it does require physician training and resources to install the device, download the data, and interpret the results. In addition, the patient is billed for this service and is required to keep accurate records of meals, time of insulin injections and dosages, and activities during the 5-day iPro CGMS observation period.¹¹ This is a challenging, time-consuming process. To date, there is only one study examining the use of 5 days of iPro CGMS data to correct an insulin regimen in order to improve glycemic control as assessed by A1C.¹²

We hypothesized that there would be a strong correlation between a type 1 diabetes patient's A1C level and the mean interstitial glucose level that is provided by the iPro CGMS software. Thus, we analyzed 156 separate studies (40 patients studied four times each) in which the A1C specimen was drawn within 1 week of performing a 5-day iPro CGMS study to assess the correlation between the A1C and the interstitial

glucose. This time period would be similar to what is often used in clinical practice. Included in this study population were both patients on continuous subcutaneous insulin infusion and multiple daily insulin injections.

Subjects and Methods

All studies were performed on outpatients at the University of New Mexico Diabetes Research and Treatment Center. The protocol and consent form were approved by the University of New Mexico School of Medicine Institutional Review Board, and all volunteers signed the approved consent form prior to enrollment. Recruitment of type 1 diabetes volunteers was primarily through direct referral from the authors' diabetes clinics as well as advertisements in local newspapers. All volunteers came from the Albuquerque metropolitan area and were primarily cared for by physicians in private practice. Before entering the study, volunteers were required to have a history of type 1 diabetes for at least 1 year and a Sustacal® (Mead Johnson, Glenview, IL)-stimulated C-peptide level of less than 0.5 mg/dL. Volunteers with abnormal general chemistries or complete blood counts were excluded from the study. Only patients with an A1C level between 6.5% and 9.0% were evaluated because this is the most likely population that will undergo 5 days of iPro CGM

FIG. 2. Individual mean interstitial glucose versus corresponding hemoglobin A1C observation points for each volunteer during each of the four sequential continuous glucose monitoring system sessions, separated by a 2-month interval. There is no apparent sequence effect. The relationship for Periods 1 and 3 is statistically significant but not clinically useful owing to the large variance around the regression line.

evaluation. All volunteers had type 1 diabetes and were on either continuous subcutaneous insulin infusion or multiple daily insulin injections for insulin delivery.

Specific information on the volunteers is as follows: 17 males, 23 females; mean age, 42.3 years; mean body mass index, 26.5 kg/m²; mean duration of diabetes, 19 years; method of insulin delivery, 72.5% continuous subcutaneous insulin infusion, 27.5% multiple daily insulin injections; and ethnicity, 75% non-Hispanic white, 20% Hispanic white, and 5% other.

Volunteers were instructed to continue their usual daily activities. If the volunteers normally used a CGMS, they were instructed not to use it during the 5 days of iPro CGM. In addition, all volunteers kept a record of their meal intake, insulin injections, and activity patterns during the 5 days of iPro CGM. These parameters were recorded in a separate written notebook. The volunteers were also instructed not to make any changes in their insulin regimen until after the iPro CGMS period was complete. The iPro CGMS was placed on the abdomen of the volunteer by one of the authors (E.D.-V.) according to the manufacturer's recommendations. The device was removed by the volunteer following 5 days of use and mailed along with the notebook to the author (E.D.-V.) in a prepaid envelope. The data in the devices were downloaded using software provided by the manufacturer. Prior

to initiating the study, two devices containing data were downloaded to a computer, mailed to the author (E.D.-V.), and then downloaded again. The purpose of this was to determine if the mailings caused any changes in the data, which they did not.

Forty type 1 diabetes individuals meeting the above inclusion criteria were entered into the clinical trial. All volunteers were asked to complete four studies separated by at least 2 months each. However, primarily because of time constraints, all except two volunteers completed all four studies. The individual breakdown of the number of studies completed was as follows: one volunteer completed only one study, one volunteer completed only three studies, and 38 volunteers each completed all four studies. Sequential studies were performed to simulate the clinical practice of repeat iPro CGMS studies in select patients whose A1C did not reflect their reported glycemic parameters. Participants were seen in an outpatient clinic for evaluation on a monthly basis for a total of 8 months.

Results

In total, 180 individuals were prescreened via telephone, 99 of these individuals were screened in our clinic, and 40 who met the inclusion/exclusion criteria were enrolled into

FIG. 3. The median value for all four continuous glucose monitoring system sessions for each individual plotted against the corresponding median A1C levels drawn immediately preceded by the continuous glucose monitoring system sessions. A significant relationship was observed, but the large variability excludes a useful clinical prediction in an individual patient. The median value was used instead of the mean because of the presence of outliers for some of the volunteers' data.

the study. Participants were recruited from the greater Albuquerque, NM metropolitan area, and all study participants had at least an eighth grade literacy level. As explained above, two of the subjects dropped out of the study for personal family reasons before completing all four iPro CGMS sessions. No major adverse events were encountered during the study. Two volunteers developed minor skin irritation from the adhesive that held the iPro CGMS to the skin of the volunteer.

Figure 1 provides the four correlation points generated for each of the 40 diabetes volunteers. Visual inspection of these data shows that for any individual person, there was very little A1C predictive value for the corresponding mean 5-day interstitial glucose level as reported by the iPro CGM software. A clinically useful predictive relationship would permit a least squares best fit line to be drawn at a 45° angle from the lower left corner to the upper right corner for each individual's data plot. For the majority of individuals, this is not possible. However, because this approach is not statistically valid as the points are not necessarily independent of each other, a more sophisticated data analysis is given below.

Figure 2 plots each of the four separate observation periods for each individual, designated as time period 1–period 4. A least squares regression line is fitted for all individual correlation points for each time period. A statistically significant correlation was observed for time Period 1 and Period 3. These data indicate that for these two time periods, there was a positive correlation between the A1C value and the mean interstitial glucose concentration. However, the magnitude of the correlation was too low (a maximum R^2 of 20%) to be clinically useful for an individual patient.

Figure 3 depicts the median value for all four CGMS sessions for each individual plotted against the corresponding median A1C levels drawn immediately preceded by the CGMS sessions. When the data are condensed in this fashion, a significant relationship between the combined median A1C data points and the combined median iPro CGMS interstitial data points was observed. However, as is apparent from Figure 3, there is much scatter around the regression line so that for any given individual, a useful clinical relationship would be difficult to predict.

Data were further analyzed by repeated-measures of sensor average glucose concentration and A1C level taken every 2 months for a total of four observations per patient.

The repeated-measures data were analyzed with linear mixed model methods in Proc Mixed in SAS version 9.3 software.¹³ A random coefficient model allowing a unique linear relationship between A1C and sensor glucose for each patient was fitted. The random effect for sensor glucose was not significant (Likelihood ratio test, $P=0.82$), but the random effect for intercept was significant ($P<0.0001$) (i.e., the model does not find significantly different slopes among the patients, whereas it does find patients at differing levels of A1C). The fixed effect for sensor glucose was significant ($P=0.005$), with an estimated slope of $0.0042 (\pm 0.0015)$. What this means is that in the population studied, a greater sensor average glucose concentration is associated with a greater A1C value. However, that relationship was not observed within individual subjects. There is no universally agreed upon method of summarizing correlation in mixed models; we did calculate R_F^2 , a summary for the fixed effects, from Liu et al.,¹⁴ and obtained $R_F^2 = 7.4\%$. This

value is appropriate to summarize the strength of relationship seen in Figure 2 and is consistent with those in Figure 3.

Discussion

CGM has been a major advance in the treatment of type 1 diabetes.¹ This technique uses a hair-size sensor in the subcutaneous tissue to provide interstitial glucose readings approximately every 5 min in real time to the user.¹⁵ The cost to the patient for this technology is relatively high, approaching \$6/day for sensor replacement following the initial purchase of the system. The technology permits the user to respond to his or her changing glucose levels in real time (i.e., he or she can take additional insulin when his or her glucose levels are increasing above target values or ingest carbohydrate when his or her glucose values are trending downward toward hypoglycemic levels). This technology has been demonstrated to reduce the incidence of hypoglycemia and hyperglycemia in many patients, particularly if used on a daily basis.^{16,17}

As an extension to CGMS technology, Medtronic has released a modified CGMS system (iPro CGM) in which no real-time glucose feedback is available to the patient. The underlying concept for the use of this device is to permit the physician to download approximately 5 days of CGMS data during which no changes in the patient's diabetes regimen were made. Based on this information, the physician should be able to change the intensive insulin therapy regimen to prevent hypoglycemia or to improve the patient's A1C by preventing hyperglycemia. The advantages of this approach of using a masked feedback CGMS instead of the traditional real-time feedback CGMS are that the patient does not have to learn the intricacies of using CGMS, which can be challenging to many patients, and the necessity to purchase the CGMS hardware and sensors.

Pepper et al.¹² performed a retrospective study utilizing masked iPro CGM in a clinical practice setting. Their goal was to determine whether the use of 3-day masked CGM would result in an improved A1C level in 102 consecutive diabetes patients. A1C was measured prior to and up to 7 months after the masked CGM procedure. Both type 1 and type 2 diabetes patients were included in their cohort. A1C before masked CGM was $7.7 \pm 1\%$, compared with $7.8 \pm 1.1\%$ after masked CGM. Our results are consistent with their observations and provide a statistical basis for their lack of effectiveness of masked CGM in lowering A1C.

There are several limitations to our study that should be considered. First, we confined our population to patients with type 1 diabetes (in which rapid changes in blood glucose level are common). Whether our results are applicable to patients with other types of diabetes is unknown. However, most physicians use only 5 days of data before making a therapeutic change in the patient's regimen. Second, our study was primarily concerned with using the iPro CGM results for improving the patient's glycemic A1C target. It is possible that iPro CGM might be useful for other purposes, such as identifying periods of nocturnal hypoglycemia in specific patients who have previously reported unidentified episodes of very low blood glucose.^{18–20}

Our results suggest that 5 days of iPro CGM data have a very low predictive value in determining a concurrently measured A1C level, particularly for the individual patient. At least two reasons can be suggested to explain this obser-

vation. First, the A1C value is derived from blood hemoglobin and is directly influenced by circulating plasma glucose. This measurement contrasts with iPro CGMS data, which are determined from the glucose in the interstitial fluid. It has been shown that these two measurements do not always coincide, particularly when the blood glucose concentration is rapidly changing, a frequent occurrence in type 1 diabetes mellitus.^{21,22} Second, and probably more important, the A1C value is derived from glycosylation of hemoglobin over a 2–4-month period. This contrasts with iPro CGM data, which are obtained only for 5 consecutive days of observation, usually after the A1C is obtained. This glucose time frame may not be representative of the time frame during which the A1C was derived. In our study, this measurement did not provide a clinically useful correlation to the concurrently measured A1C level. Additional studies will be necessary to determine the optimal use for 5 days of masked CGM in order to benefit the patient and improve his or her intensive insulin therapy regimen.

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Author Disclosure Statement

No competing financial interests exist.

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