Journal of Diabetes Science and Technology
Volume 5, Issue 4, July 2011

ORIGINAL ARTICLE

Hypoglycemia Impairs Quality of Blood Glucose Simulation in a Clinical Decision Support System

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Abstract

Background:

Clinical decision support systems allow for decisions based on blood glucose simulations. The DiasNet simulation tool is based on accepted principles of physiology and simulates blood glucose concentrations accurately in type 1 diabetes mellitus (T1DM) patients during periods without hypoglycemia, but deviations appear after hypoglycemia, possibly because of the long-term glucose counter-regulation to hypoglycemia. The purpose of this study was to evaluate the impact of hypoglycemia on blood glucose simulations.

Method:

Continuous glucose monitoring (CGM) data and diary data (meals, insulin, self-monitored blood glucose) were collected for 2 to 5 days from 17 T1DM patients with poor glycemic control. Hypoglycemic episodes [CGM glucose <63 mg/dl (3.5 mmol/liter) for ≥20 min] were identified in valid (well-calibrated) CGM data. For 24 hours after each hypoglycemic episode, a simulated (DiasNet) glucose profile was compared to the CGM glucose.

Results:

A total of 52 episodes of hypoglycemia were identified in valid data. All subjects had at least one hypoglycemic episode. Ten episodes of hypoglycemia from nine subjects were eligible for analysis. The CGM glucose was significantly ($p < .05$) higher than simulated blood glucose for a period of 13 h, beginning 8 h after hypoglycemia onset.

Conclusions:

The present data show that hypoglycemia introduces substantial and systematic simulation errors for up to 24 h after hypoglycemia. This underlines the need for further evaluation of mechanisms behind this putative long-term glucose counter-regulation to hypoglycemia. When using blood glucose simulations in decision support systems, the results indicate that simulations for several hours following a hypoglycemic event may underestimate glucose levels by 100 mg/dl (5.6 mmol/liter) or more.

J Diabetes Sci Technol 2011;5(4):894-900

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Abbreviations: (CGM) continuous glucose monitoring, (SMBG) self-monitored blood glucose, (T1DM) type 1 diabetes mellitus

Keywords: clinical decision support systems, continuous glucose sensors, hypoglycemia, physiopathology, type 1 diabetes mellitus

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Introduction

People with type 1 diabetes mellitus (T1DM) must take over the regulation of blood glucose from the pancreas in order to avoid acute or chronic complications caused by abnormal blood glucose levels. This is achieved primarily by balancing insulin injections, meals, and exercise. Suboptimal blood glucose control with frequent or persistent episodes of hyperglycemia leads to a substantially increased risk of long-term complications, such as microvascular and macrovascular diseases in kidneys, eyes, and nerves.[1] Intensive control of the blood glucose, however, may increase the frequency and severity of hypoglycemic events,[1] which, for many diabetes patients, is the most feared complication of diabetes.[2,3]

To a large extent, people with diabetes have to take responsibility for managing their diabetes[4–7] because it is not practical or economically viable for specialists to manage their patients' diabetes on a day-to-day basis.[7] Various approaches intended to facilitate everyday decisions of patients have been suggested, ranging from educational courses to interactive computer programs.[8] Computer programs are computer-based decision support systems such as DiasNet,[9] AIDA,[10] and Librae,[11] all of which have been developed for educational (general) and advisory (specific) purposes alike. These decision support systems all simulate a blood glucose profile from input data on meals and insulin doses, some of which are on a patient-specific basis[9,11,12] and some are from information on physical activity.[11] The patient may apply the computer simulation program as a test environment for exploring their reaction to changes in insulin doses, insulin regimen, or meal size. From the simulations, the patient may select the changes in insulin or meals that seem to provide the best blood glucose outcome.

The DiasNet simulation tool is based on a metabolic model and implemented as a compartment model of human glucose metabolism and insulin kinetics in a Bayesian network.[9] Systematic errors in the metabolic model in hypoglycemia-free data appear to be small compared to the day-to-day variation of blood glucose seen in diabetes.[12] The tool has been tested in diabetes clinics in Italy, Denmark, and England and has been shown to help improve blood glucose control in patients with poorly controlled T1DM.[13]

It should be noted, however, that these rather encouraging results were based on a basic model, implementing only basal, normal physiology and not taking into account the broad range of events or conditions that may affect blood glucose concentrations and that may be necessary to fully describe and predict blood glucose metabolism. These include alcohol intake, exercise, disease/fever, and hypoglycemic episodes. Whether such events and conditions should be included in a model depends on their effect on simulation quality. Large deviations between blood glucose simulations based on normal basal physiology and measured data obtained when the event or condition is present would indicate that physiological mechanisms are affecting the measured data but not the simulations, implying that not all relevant physiology is implemented in the model. We have earlier used this approach to investigate the importance of alcohol intake.[14]

We have previously reported that, in self-monitored blood glucose (SMBG) data with episodes of hypoglycemia, measured blood glucose levels are consistently higher than the levels simulated by the model for a period of 10–12 h, beginning 6–8 h after hypoglycemic episodes.[15] This systematic discrepancy is seen only in data following hypoglycemia, indicating that hypoglycemia leads to a long-term counter-regulatory effect of some sort. Such a phenomenon has been recognized for many years, and it was originally described by Somogyi. The Somogyi effect was studied by several groups in the 1980s and 1990s,[16–19] but taken together, the findings have been inconclusive, probably because of discrepancies in the hypotheses of the studies regarding the temporal characteristics of the hyperglycemic response and in study design and patient selection. Currently, the long-term glucose counter-regulation to hypoglycemia is omitted from or even refuted in medical and diabetes textbooks.

Due to the limited temporal resolution, SMBG is insufficient to provide accurate data on the impact of hypoglycemia on simulation quality (whether due to the Somogyi effect or long-term glucose counter-regulation to hypoglycemia or other mechanisms). To our knowledge, no studies have evaluated the effect of hypoglycemia on simulation quality using continuous glucose monitoring (CGM).

In this article, we report a comparative pilot study of the impact of hypoglycemia on blood glucose simulation profiles by evaluating the long-term post-hypoglycemic discrepancy between CGM glucose data and simulated blood glucose profiles.

Methods

Study Design

We retrospectively analyzed continuous glucose profiles (48–120 h) by calculating the deviation between simulated (DiasNet) blood glucose profiles and measured CGM (CGMS®, Medtronic-MiniMed, Northridge, CA) glucose profiles after hypoglycemic episodes. The study was approved by the local ethics committee.

Patients

Seventeen T1DM patients with poorly controlled diabetes (judged by their diabetologist) from the diabetes clinic at the Royal Bournemouth Hospital, England, were included after giving written informed consent. The T1DM patients were consequently referred to the study if the clinic's diabetologist assessed that there was a clinical indication for CGM. The mean age of the subjects was 39.5 years (range: 25–63 years). Mean diabetes duration was 11.1 years (range: 3–42 years). Mean body mass index was 25.5 (range: 18.6–30.0). All subjects (9 male and 8 female) were treated with insulin in a multiple daily injection regimen. Mean daily dose of short-acting insulin (primarily Humalog, Eli Lilly) was 34.5 IU (range: 10–56 IU), and mean daily dose of long-acting insulin (Humulin NPH, Eli Lilly or Insulatard, Novo Nordisk or Lantus, sanofi-aventis) was 19.5 IU (range: 8–50 IU).

Diary

The patients were instructed to maintain a diary regarding all meals (grams of carbohydrates and time of ingestion) and all insulin injections (units of insulin and time of injection) for 3 days and to do at least four daily capillary blood glucose measurements (SMBG) with their regular glucose meters. The diary should also include any meal or insulin-related action taken in connection with hypoglycemia. The patients were instructed to live their everyday lives despite the sensor.

Continuous Glucose Monitoring Data

The CGMS continuous glucose sensor was inserted into the subcutaneous fat in the periumbilical region using the insertion needle provided with the sensor. The sensor utilizes the principle of glucose oxidase for its measurements. The sensor was left in place for 3 to 5 days for collection of data. The sensor data were transferred to a personal computer using the data transfer tool from the manufacturer. The CGM measurements were not available for the subjects during the data collection period.

Data Analysis and Statistics

Sensor data were calibrated using the Medtronic MiniMed CGMS software. We regarded days of CGM data valid if the number of measurements available for calibration ranged from two to seven (eight if a nocturnal measurement was present). The lower limit of two was the absolute minimum, as at least two measurements are needed in order to determine offset and gain in the Medtronic MiniMed CGMS calibration algorithm. The upper limit was set to seven (or eight), as diabetes patients doing frequent SMBG do up to seven (eventually eight, including a nocturnal) blood glucose measurements per day. Time with missing (or low voltage) sensor signal was excluded as invalid.

Hypoglycemic episodes were identified in the calibrated, valid CGM data. We defined an episode of hypoglycemia to consist of at least four consecutive measurements (equivalent to 20 min) below 63 mg/dl (3.5 mmol/liter). The beginning of the hypoglycemic episode was defined as the first measurement below 63 mg/dl and the end of the hypoglycemic episode as the last measurement below 63 mg/dl before at least three measurements equal to or above 63 mg/dl. Episodes of hypoglycemia preceded by confirmed or possible hypoglycemic episodes up to 20 h beforehand were excluded. Hypoglycemic episodes within 20 h after sensor insertion or a period of missing data were excluded. Continuous glucose monitoring data were averaged every 15 min (equivalent to every three CGM glucose measurements) in order to obtain the same temporal resolution of CGM data as of the simulated glucose profiles; these CGM profiles are referred to as CGM-15s.

The DiasNet simulation tool[9] was used to calculate decision support system glucose profiles. The input to the model is the diary data: meals (grams of carbohydrates and time of ingestion) and insulin injections (units of insulin and time of injection). The simulation model is calibrated to each individual patient using a few glucose measurements. This adjustment is done with a patient-specific model parameter, the so-called insulin sensitivity, which is estimated automatically by the DiasNet simulation tool. The output is blood glucose profiles calculated in 15 min steps based on state-of-the-art knowledge of normal physiology.

A simulated glucose profile was calculated for each included episode of hypoglycemia. For each of these simulations, the input was all diary-reported meals

and insulin injections for the entire data period. The calibration to the specific patient and hypoglycemic event was done using five CGM-15 glucose values near the hypoglycemic episode (two values 1 and 2 h before the beginning of the episode, one value at the beginning of the episode, and two values 1 and 2 h after the beginning of the episode).

The CGM-15 and simulated glucose profiles were compared for 24 h after hypoglycemia. The average CGM-15 and simulated glucose profiles were compared using Student's one-sided *t*-test. All analysis was performed using the Excel spreadsheet program (Microsoft Corporation, Redmond, WA).

Results are given as mean ± standard deviation.

Results

Total monitoring time was 54 days, valid monitoring time 45 days. Periods of nonvalid monitoring were caused by missing or low-voltage sensor signals (15 h) or by an invalid number of SMBG measurements for calibration (approximately 8 days).

Episodes of Hypoglycemia

All 17 patients had at least one hypoglycemic episode according to the CGM data. A total of 52 episodes of hypoglycemia occurred (median per patient: 3; range: 1–9). Forty-two of the episodes were excluded because of (i) occurrence less than 20 h after sensor insertion (23 episodes of hypoglycemia), (ii) invalid CGM data (3 episodes of hypoglycemia), or (iii) preceding hypoglycemia (16 episodes of hypoglycemia).

The 10 hypoglycemic episodes included in the analysis were found in data from 9 patients. For the 9 patients, an outline of the collected data with all hypoglycemic episodes together with indications of inclusion/exclusion (and reason for exclusion) is shown in **Figure 1**.

The hypoglycemic episodes were evenly distributed during the day; six episodes of hypoglycemia were found in the daytime (6 AM to 6 PM) and four at night (6 PM to 6 AM). There was no significant difference between nocturnal and daytime episodes.

Mean hypoglycemia blood glucose nadir was 54 ± 7 mg/dl (3.0 ± 0.4 mmol/liter) (according to CGM data). Five episodes of hypoglycemia with nadir = 40 mg/dl (2.2 mmol/liter; the lower detection limit of the CGMS) were found. Mean duration of the hypoglycemic episodes was 86 ± 61 min (according to the CGM data).

Comparison of Mean Glucose Profiles after Hypoglycemic Episodes

Mean glucose profiles (CGM-15 and simulated blood glucose) can be seen in **Figure 2**.

The CGM-15 glucose was significantly higher ($p < .05$) than the simulated glucose for a period of 13 h, beginning 8 h after the onset of hypoglycemic episodes. No significant difference was recorded within the first 8 h after the onset of hypoglycemic episodes, except for 1 h immediately after the onset of hypoglycemic episodes, where the CGM-15 glucose was significantly lower ($p < .05$) than the simulated glucose.

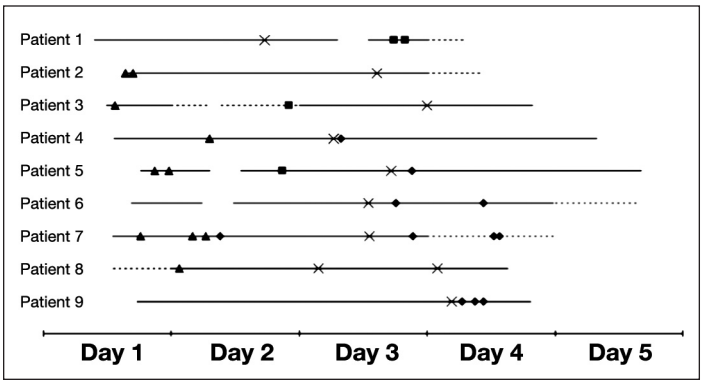

Figure 1. The temporal distribution of included and excluded hypoglycemic episodes [CGM glucose <63 mg/dl (3.5 mmol/liter) for at least 20 min] with indication of reason for exclusion (only profiles with included hypoglycemic episodes). The × indicates included episode of hypoglycemia. The square indicates hypoglycemic episodes excluded because of prior (0–20 h) invalid CGM data. The diamond indicates hypoglycemic episodes excluded because of prior (0–20 h) episodes of hypoglycemia. The triangle indicates hypoglycemic episodes excluded because of prior (0–20 h) sensor insertion. Full lines designate valid data, and dotted lines designate invalid data [days with <2 or >7 (8 if one is nocturnal) SMBG measurements].

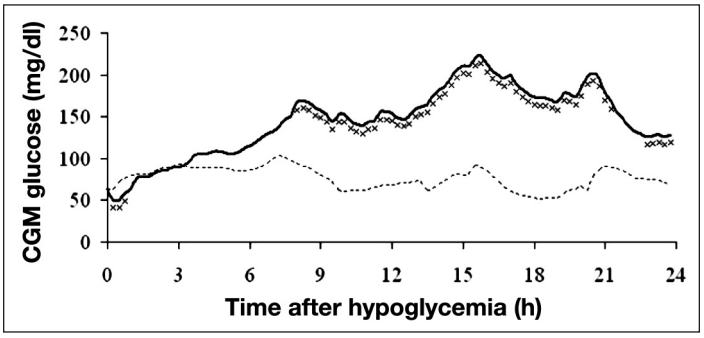

Figure 2. The mean glucose profiles (CGM: full line; simulated: broken line) for the first 24 h after the beginning of hypoglycemic episodes. The × indicates significantly higher or lower measured blood glucose than simulated blood glucose ($p < .05$).

Discussion

A systematic discrepancy between measured CGM data and DiasNet blood glucose simulations was analyzed to evaluate the impact of hypoglycemia on blood glucose simulations from a decision support system. Episodes of hypoglycemia were identified in CGM data, and CGM data were compared to simulated blood glucose profiles for a period of 24 hours following the onset of hypoglycemic episodes.

CGMS has been validated as a reliable method for continuous glucose assessment if calibrated properly with SMBG,[20–22] also during hypoglycemic[21] and hyperglycemic[22] conditions. Due to physiological and technical reasons, there are differences between interstitial glucose (as measured by CGM) and blood glucose (and, therefore, simulations applying to blood glucose data). It is, however, assumed that these differences are small compared to the differences found in the present study [12 h average difference of more than 100 mg/dl (5.6 mmol/liter)], and they are therefore not taken into account in this analysis.

The prevalence of hypoglycemia in our CGM data (17 of 17 patients) is consistent with findings of Høi-Hansen and colleagues[23] in diabetic patients with supranormal hemoglobin A1c and, at least to some extent, hypoglycemia unawareness.

The DiasNet simulation tool has been tested previously using data without hypoglycemic events, indicating that systematic errors in the metabolic model in hypoglycemia-free data are small compared to the day-to-day variation of blood glucose seen in diabetes and that the DiasNet simulation tool in hypoglycemia-free data produces precise blood glucose profile simulations.[12]

According to simulation theory, if blood glucose simulation tools calculate the average expected blood glucose for each patient, the intrapatient variation in the simulated data is cancelled or reduced significantly. Further, if the model is calibrated to each individual patient, the interpatient variation in the simulated data is cancelled or reduced significantly. This is the case for the DiasNet simulation tool. It should also be noted that the potential effect of different insulin types on the interpatient variation is cancelled or reduced significantly by a simulation model implementing average insulin absorption profiles for each type of insulin as done in DiasNet. This reduction in intrapatient and interpatient variation in the simulated data due to the characteristics of DiasNet implies that valid results can be produced with even a small number of hypoglycemic events in the CGM data set.

For the first hour after the onset of hypoglycemic episodes in our study, the simulation tool predicted significantly ($p < .05$) higher glucose levels than measured. Despite maximum average difference of 22 mg/dl (1.2 mmol/liter) indicates a relatively good prediction quality of the simulation tool. Eight hours after hypoglycemia, our data revealed significantly lower simulated than measured glucose levels for a period of more than 13 h. Maximum difference was 139 mg/dl (7.7 mmol/liter) 17 h after beginning of hypoglycemic episodes, and average difference during the time interval 8–21 h after hypoglycemia onset was 104 mg/dl (5.8 mmol/liter). Even in the last hour of analysis (23–24 h after hypoglycemic episode start), the CGM glucose was significantly higher ($p < .05$) than anticipated by the simulation tool.

The CGM data after hypoglycemia can be considered as hypoglycemia intervention data, and the simulated glucose profiles can be considered as hypoglycemia-free control data. Using these analogies, the results can be compared to results regarding the Somogyi effect or long-term glucose counter-regulation to hypoglycemia from studies that use the intervention-control design. In that sense, the 8 h delay of the pronounced simulation quality impairment after episodes of hypoglycemia reported here is consistent with the findings of Gale and associates,[17] Tordjman and coworkers,[19] Stephenson and Schernthaner,[24] and Havlin and Cryer[25] that no significant differences in glucose concentration are seen within the first 4–8 h after hypoglycemia when comparing blood glucose profiles after hypoglycemic episodes with control blood glucose profiles. It should be noted, however, that, although our results for the 0–8 h period after the beginning of episodes of hypoglycemia are similar to these previous reports, these studies concluded that prolonged hyperglycemia did not occur following hypoglycemia. Our data, based on the 8–24 h findings do not support this conclusion. The 8–21 h overshoot of CGM glucose compared to the simulated glucose profile corresponds very well to the results for the 8–12 h period after hypoglycemia reported by Bolli and colleagues.[18] The overshoot, however, is not in accordance with the findings of Hirsch and associates.[16]

An important limitation of our pilot study is that it is based on a very limited sample. In addition, it should be acknowledged that, even though the exclusion of 42 out of the 52 episodes of hypoglycemia found in the data was based on rational and objective criteria, a

potential selection bias, and thereby a distortion of the results, cannot be excluded. The purpose of our study was to focus on the impact of hypoglycemia on blood glucose simulations. Therefore, because our results do not contribute to the discussion of the potential causal mechanisms of the Somogyi hypothesis (which may, for example, include induced insulin resistance), a more in-depth discussion of this subject based on our findings does not seem to be appropriate. Furthermore, it should be emphasized that, because the patients are poorly controlled, it is possible that our observations in this study are seen only in this group of patients, and the results, therefore, cannot readily be generalized to the entire population of people with diabetes. Impaired quality of decision support system simulations after hypoglycemia limits the applicability of such systems. If decision support systems are to provide reliable advice to people with poor glycemic control accompanied by recurrent hypoglycemia, the simulation tools need to be accurate in all relevant situations, including hypoglycemia. This requires enhancement of the knowledge base of the simulation tools. Even though our pilot study is based on a very limited sample, the results emphasize the need for further evaluation of the mechanisms behind the substantial impact of hypoglycemia on the quality of decision support system simulations. One obvious mechanism to explore is the long-term glucose counter-regulation to hypoglycemia.

Conclusions

The present study indicates that hypoglycemic episodes have a substantial impact on the quality of blood glucose simulation. When using blood glucose simulations in decisions support systems, the results indicate that simulations for several hours following a hypoglycemic event may underestimate glucose levels by 100 mg/dl (5.6 mmol/liter) or more.

Funding:

The analysis work was funded by a Ph.D. grant from Aalborg University.

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