Developing and testing a novel study design for improving hypoglycaemia detection and prediction with continuous glucose monitoring data

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Abstract

Persons with Type 1 diabetes need continuous exogenous insulin supply throughout their life. Determining the optimal insulin treatment in relation to diet and physical activity is one of the main goals of diabetes management, but is difficult, especially for vulnerable populations, such as adolescents. Erroneous treatment may result in both repeated and severe low blood glucose events. Continuous glucose monitoring (CGM) may help in avoiding these events, but is inaccurate compared to traditional glucose monitoring. Models have been developed to significantly improve CGM's detection of insulin-induced events by using information from the CGM signal itself. Additional temporal data on insulin doses, diet and physical activity may improve hypoglycaemia prediction models. In this research, we present and pilot test a study in which a smartphone was used to obtain these data. Data from one female was obtained over a period of two days. CGM and continuous physical activity accelerometry data were collected with minimum and no dropouts, respectively. The collection of diet, insulin and blood glucose data, also, proceeded without problems. These results indicate that it is possible to collect glucose, diet, insulin and physical activity data of high quality. These data will facilitate further development of models for the detection and prediction of low blood glucose.

Keywords: *Hypoglycaemia, detection, prediction, continuous glucose monitoring, study design.*

Introduction

Persons with Type 1 diabetes (T1D) lack the ability to produce the glucose-regulating hormone insulin due to a partly unknown autoimmune destruction of the pancreatic beta-cells. The result is an abnormal high blood glucose that typically leads to severe late-diabetic complications, such as neuropathy, nephropathy, retinopathy, micro- and macroangiopathy. Late-diabetic complications are not only very disabling for the patient, but they also place a significant economical burden on society: the annual estimated cost of late-diabetic complications in the USA is $58 billion. [1]

Abnormally high blood glucose is most often treated with an individually-tailored regimen of either exogenous insulin as boluses or continuous insulin from a pump. The Diabetes Control and Complication Trial demonstrated that intensive insulin therapy delays the onset and slows the progression of late-diabetic complications in people with T1D. [2] This finding was subsequently confirmed by the UK Prospective Diabetes Study Group. [3] Unfortunately, the intensive insulin therapy results in a 2-3-fold increase in the prevalence of hypoglycaemia. Hypoglycaemia (plasma glucose ≤ 70 mg/dl [4]) is potentially fatal and is a constant concern for those with T1D and their care providers. [5]

Adolescents with T1D, previously thought to be protected from early development of microvascular complications, are at significant risk of these complications, [6] making optimal glycemic control an important goal in their diabetes management. However, the metabolic demands combined with an unpredictable lifestyle make adolescents vulnerable to both repeated and severe hypoglycaemia. Consequently, detection of imminent hypoglycaemic events followed by recommendations to prevent further hypoglycaemic development may help adolescents identify a personally optimal diabetes therapy. Continuous glucose monitoring (CGM), which measures interstitial glucose and produces a reading typically every 5 minutes, offers a much higher temporal resolution than conventional glucose monitoring and is, therefore, a promising technology for hypoglycaemia detection in adolescents. Unfortunately, CGM is inaccurate, especially in the hypoglycaemic range primarily due to an interstitial-blood glucose delay and a filter delay. [7] On 71 adults with T1D, Bode et al. [8] demonstrated a significant reduction in hypoglycaemia by using hypoglycaemic threshold alerts, but they also revealed 67% sensitivity, 90% specificity, and 47% false alerts. Although, the study of Bode et al. provides some insight into the the potential for CGM devices in diabetes managment, the evidence of hypoglycaemia detection is sparse. [9] A study by Jensen et al. [10] has shown that it is possible to develop a model that processes CGM and insulin data and improves the retrospective detection of insulin-induced hypoglycaemic events. Another study by Jensen et al. [11] showed that with similar information and processing, it was possible to improve real-time detection of these events. However, during the process from retrospective to real-time, it was evident that the detection rate decreased. Apparently, this was due to the reduced amount of information to discriminate between hypoglycaemia and non-hypoglycaemia periods for the real-time algorithm. Plausible, spontaneous hypoglycaemic events occurring in real-life data from people with T1D will cause an even lower detection rate because they do not exhibit such pronounced characteristics as insulin-induced events. Moreover, ideally *predicting*, as opposed to only detecting these

events, places further demands for real-time data. Information that may help in discriminating between hypoglycaemia and non-hypoglycaemia periods besides the CGM signal itself are the three primary glucose-regulating factors, insulin, diet and physical activity. Studies have dealt with collection of these data but the reliability of especially diet and physical activity data has been an ongoing problem, which hampers the results. [12] [13]

The aim of this research was to present and pilot test a study design for collecting accurate data on insulin, diet, physical activity and glucose using modern smartphone technologies that are already prevalent and are increasingly used amongst adolescent populations. We present data from one of our pilot test subjects with the goal of illustrating the qualities of information from integrated monitoring, and furthermore, to present our intended data analysis methodology.

Protocol presentation

Population

The population of interest for our study met the following criteria.

Inclusion:

- $10 \leq$ Age ≤ 18 years.
- Type 1 diabetes.
- Diabetes duration ≥ 6 months (to avoid subjects with honey moon periods)
- $6.5\% \leq$ HbA1c $\leq 11\%$.
- Insulin pump users.
- CGM device users.
- Blood glucose meter with memory function and connection to CGM.
- English proficiency of 3rd grade or above.

Exclusion:

- Non-English speaking.
- Pregnancy.

The adolescents should already be CGM and insulin pump users to ensure elimination of user-related measuring errors. Furthermore, an inclusion requirement is the use of a blood glucose meter, which can wirelessly transmit self-monitoring of blood glucose (SMBG) measurements to the CGM. Hereby, human errors occurring on typing in data are reduced. The remaining criteria represent accepted typical standard for diabetes studies.

Information recorded

The subjects should as part of their diabetes-related routines measure interstitial glucose, blood glucose, physical activity and register insulin injections and carbohydrate intake.

Glucose and insulin recording

The interstitial glucose, blood glucose and insulin injections were recorded with the Paradigm® REAL-Time Revel™ System (MiniMed Inc., USA) or similar, which together with a blood glucose meter like the CONTOUR® LINK (Bayer, USA) is capable of transmitting data to the MiniMed system wirelessly, eliminating most user interaction and, thus, reducing the probability of human errors. Furthermore, the transferred blood glucose values were automatically used to calibrate the CGM.

Diet recording

Carbohydrate intake has previously been estimated based on patient self-reporting. But this approach has been linked to both inter- and intrapatient variability, [12] [14] which makes the use of the unreliable data in detection/prediction models difficult. Because most subjects in the age group already have smartphones, carbohydrate intake was recorded by capturing a photo of each carbohydrate-containing intake. This simple photo-taking approach, as opposed to completing detailed food diaries, reduced the burden on patients. Thereafter, three blinded dieticians estimated the carbohydrate content of each picture and the median of the three estimates was used. This ensured homogeneous estimates, reducing inter- and intrapatient variability.

Physical activity recording

Also, recording of physical activity has been performed manually in the past but with varying reliability due to many reasons, one of which may be that subjects do not want to appear sedentary. [13] To ensure increased reliability, physical activity was estimated with CalFit. [15] CalFit is a non-commercial application developed for Android smartphones. Continuously, it records the subject's time-location patterns and energy expenditure associated with physical activity using the phone's integrated GPS and accelerometer, respectively. Since the application works on the smartphone, which the subjects already use for diet photo recording, they just have to carry the smartphone around in their pocket or purse to monitor physical activity.

Number of subjects

To train models of pattern classification, both glucose readings in hypoglycaemia and otherwise are necessary. With at least 100 paired PCGM-SMBG readings in hypoglycaemia, it is possible to train a model. People with T1D are in hypoglycaemia 10% of the time, [16] and the total number is, thus, 1000 paired PCGM-SMBG readings Assuming that T1D people are capable of measuring SMBG 3 times per day and the monitoring period is 7 days, the number of subjects needs to be at least

$$N = \frac{1000 \text{ PCGM-SMBG readings}}{7 \text{ days } x \text{ 3 SMBG pr. day}} \approx 50$$

A monitoring period of 7 days is deemed acceptable in light of the inconvenience of the diet registration

Data analysis and model development

The obtained data are in a sense, raw. For example, the carbohydrate intake of the diet recording does not directly specify the absorbed amounts from the gut. However, several models for this purpose exist. For example, the absorption from the gut can be found as a non-linear function of the carbohydrate in the content in the gastrointestinal tract. [17] Data on insulin injections also need post-processing. One way is estimating insulin-on-board, which can be derived from the model of Berger and Rodbard [18] that via superposition also works for multiple injections. With these post-processing approaches, there will exist continuous data for diet, insulin, physical activity and CGM. Systematic feature extraction and reduction methods previously demonstrated in Jensen et al. [10] [11] can be performed on these data and discriminative features iden-

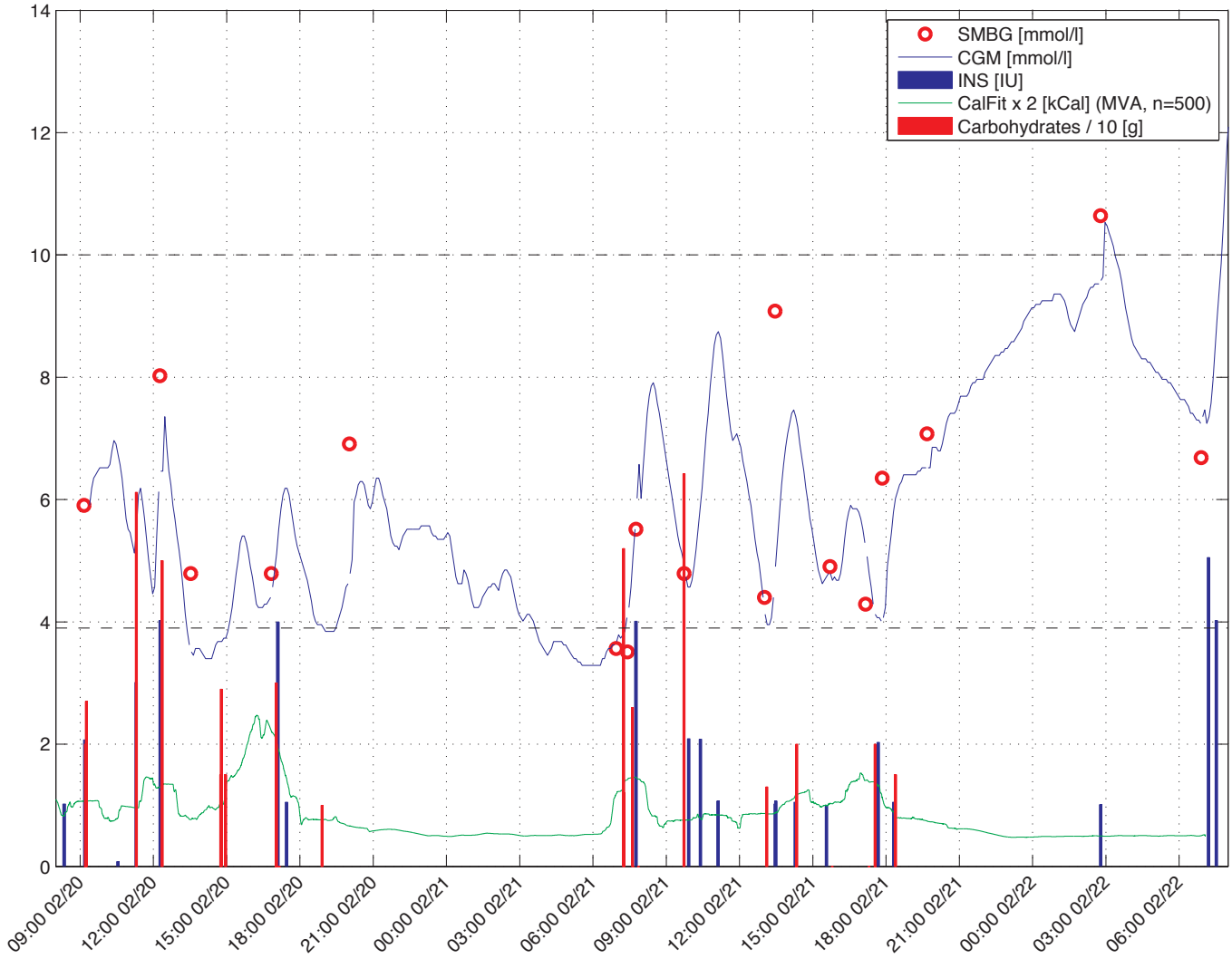

Figure 1 – Obtained data from the pilot study. The subject was monitored from 9 AM 20th Feb 2013 to 6 AM 22th Feb. 2013. The CalFit signal was filtered with a moving average filter (MVA) using a delay of 500 readings. For visual aid, carbohydrate readings were divided by 10 and CalFit readings were multiplied by 2.

tified. Applying models, such as, Support Vector Machines on the remaining features can determine how well the different glucose-regulating parameters classify CGM readings in hypoglycaemia and in non-hypoglycaemia as defined by the SMBG readings.

Pilot study

Materials and methods

To illustrate how an integrated set of monitoring data may be useful for modelling, we present data from one female subject aged 18 years with Type 1 diabetes who participated in the pilot study, which preceded our main study. During a period of two days she was monitored with the Paradigm® REAL-Time Revel™ System (MiniMed Inc., USA) and a CONTOUR® LINK (Bayer, USA) blood glucose meter. Furthermore, she used a Galaxy Y (Samung, USA) for diet and activity recording. A Registered Dietician performed estimation of carbohydrates from the diet pictures. To assess the quality of the study design, the pilot study is presented with a plot of raw data and with a table of daily sum of insulin injection, calorie burn and carbohydrate consumption. Furthermore, a Clarke Error Grid Analysis (EGA) is presented. The EGA is presented to elaborate on the CGM accuracy in the pilot study. Presentations of the obtained pilot study data were created in MATLAB® (version R2011b; MathWorks, Natick, MA, USA).

Results

The obtained two-days monitoring pilot test data from the one female can be seen in Figure 1. In Table 1, daily sum of injected insulin, burned kilocalories and consumed carbohydrates is seen.

There was a CGM dropout of 3.3% with a maximum gap of 15 minutes (2 readings). A Clarke Error Grid analysis of the CGM can be seen in figure 2. 62.5% CGM readings fall in zone A and 37.5% in zone B. It took two hours for the dietician to decode the pictures and estimate carbohydrate contents.

Table 1 – Average of daily insulin injections, calorie burn and carbohydrate intake for the pilot study subject.

Parameter	Average daily sum
Insulin (U)	21
Physical activity (kCal)	3405
Carbohydrates (g)	250

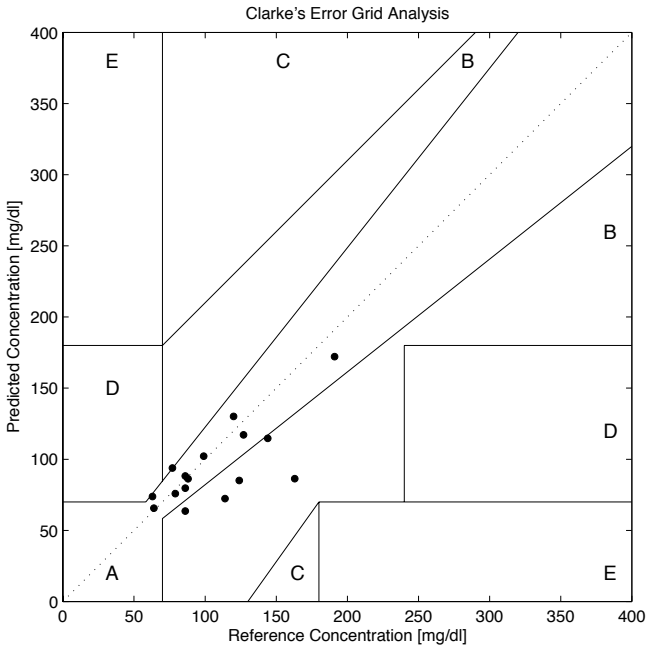

Figure 2 – Clarke Error Grid analysis of obtained pilot data

Discussion

In this study, we have presented and pilot tested a study design that can be used to optimize the CGM detection/prediction of hypoglycaemia in adolescents with Type 1 diabetes.

To our knowledge, no prior study has investigated optimization of CGM hypoglycaemia detection/prediction with such rich information about glucose-regulating factors using novel smartphone physical activity and photo-based diet assessments. In a study by Pappada et al., [19] Neural Network combined information from CGM, SMBG, insulin, diet, lifestyle and emotional factors were used to predict hypoglycaemic events. In the study, they used CGM to characterize hypoglycaemia and non-hypoglycaemia periods, which is misleading due to the significant inaccuracy especially in hypoglycaemia. In the study by Jensen et al., [11] only 71% of the hypoglycaemic events were confirmed by CGM. Training a prediction model to not produce alerts during these 29% events will result in an erroneous model. Other researchers only use CGM as input in their models to optimize the CGM prediction of hypoglycaemia but the varying results might suggest that this is not enough. [20] [21] [22]

Our pilot study has shown that it is possible to continuously collect these rich data of very high quality in community daily living situation. From Figure 1 it is possible to see that there is very few data gaps. Only the CGM has dropouts. But they do not exceed 15 minutes, and are acceptable in relation to other observed dropouts. [20] [23] It is impossible to know if the pilot subject took pictures of every carbohydrate intake, but from the density of the recordings only a few could have been missed and the amount of consumed carbohydrates is consistent with the literature. [12] Also, it is difficult to know whether the subject wore the smartphone, and thereby whether CalFit recorded accurate accelerometry. However, from the signal, it can be concluded that the smartphone was in motion all the time except at night-time.

The Registered Dietician's estimation of carbohydrates is naturally linked to some degree of inaccuracy and the use of only one dietician is dangerous. However, in our main study we will use three blinded dieticians. From a detection/prediction model's point-of-view inaccuracy is acceptable because features from the carbohydrate intake will only be used to discriminate between hypoglycaemia and non-hypoglycaemia periods and the absolute carbohydrate values are therefore less important.

From the EGA, it appears that the CGM-SMBG consistency is clinically acceptable (Zone A and B). Zone D represent dangerous failure to detect either hypoglycaemia (left D zone) or hyperglycaemia (right D zone). [24] Typically, left D zone would contain a lot of readings due to the CGM hypoglycaemia inaccuracy. However, from Figure 1 it can be observed that the pilot subject only measured hypoglycaemic blood glucose two times during the pilot study. Both are measured during a spontaneous hypoglycaemic event developed during the first night. Due to the slow development of this event the interstitial-blood delay and filter delay do not have significant influence on the interstitial measurement and the CGM readings are, thus, accurate. Furthermore, this subject did measure blood glucose more than usual. The typical regimen is 3-4 times per Day. An increased regimen results in a more accurate CGM model.

In conclusion, our pilot study indicates that it is possible to obtain CGM data from adolescents with Type 1 diabetes, as well as quality information about insulin, diet and physical activity. With such data, and appropriate modelling it may be possible to determine the added value of these additional behavioural data in the processing of CGM to obtain clinical acceptable hypoglycaemia detection and prediction rates.

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