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Home blood glucose prediction: clinical feasibility and validation in islet cell transplantation candidates

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Abstract *Aims/hypothesis:* Diabetic subjects do home monitoring to substantiate their success (or failure) in meeting blood glucose targets set by their providers. To succeed, patients require decision support, which, until now, has not included knowledge of future blood glucose levels or of hypoglycaemia. To remedy this, we devised a glucose prediction engine. This study validates its predictions. *Methods:* The prediction engine is a computer program that accesses a central database in which daily records of self-monitored blood glucose data and life-style parameters are stored. New data are captured by an interactive voice response server on-line 24 h a day, 7 days a week. Study subjects included 24 patients with debilitating hypoglycaemia (unawareness), which qualified them for islet cell transplantation. Comparison of each prediction with the actually observed data was done using a Clarke Error Grid (CEG). Patients and providers were blinded as to the predictions. *Results:* Prior to transplantation, a total of 31,878 blood glucose levels were reported by the study subjects. Some 31,353 blood glucose predictions were made by the engine on a total of 8,733 days-used. Of these, 79.4% were in the clinically acceptable Zones of the CEG. Of 728 observed episodes of hypoglycaemia, 384 were

predicted. After transplantation, a total of 45,529 glucose measurements were reported on a total of 12,906 days-used. Some 42,316 glucose predictions were made, of which 97.5% were in the acceptable CEG Zones A and B. Successful transplantation eliminated hypoglycaemia, improved glycaemic control, lowered HbA_{1c} and freed 10 of 24 patients from daily insulin therapy. *Conclusions/interpretation:* It is clinically feasible to generate valid predictions of future blood glucose levels. Prediction accuracy is related to glycaemic stability. Risk of hypoglycaemia can be predicted. Such knowledge may be useful in self-management.

Keywords Algorithms · Diabetes control · Disease management · Glucose forecasting · Glucose monitoring · Intervention · Models

Abbreviations CEG: Clarke Error Grid · SMBG: self-monitored blood glucose

Introduction

All patients with type 1 diabetes are required to make daily decisions in regard to self-management. Both short- and long-term disease state outcomes depend resolutely on these decisions [1, 2]. For these patients, self-monitored blood glucose (SMBG) provides information as to the success (or failure) of recent decisions, particularly in respect to diet, exercise, stress and medication dosing.

Modern, intensified insulin regimens practiced by such patients must always be supported by frequent SMBG. To these ends, many providers are asking patients to measure not only before meals but also after meals. In spite of these efforts and the wealth of information generated, certain patients cannot reach the targets set by their providers and some suffer frequent episodes of chemical hypoglycaemia, hypoglycaemia symptoms, or hypoglycaemia unawareness. Often these episodes are unpredictable. Where they become debilitating, patients are seeking relief through islet cell transplantation [3, 4].

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Notwithstanding the anticipated elimination of their diabetes problems, we asked whether such patients might benefit from a prediction of future blood glucose levels to manage better their own diabetes, particularly while awaiting islet cell transplantation. For example at breakfast, a glucose prediction resource can provide information about the pre-meal glucose values to be expected later that day. This prediction may then be utilised at that moment by the patient to decide on regimen alterations, with changes in medication dosing and/or life-style (including behaviour, diet, exercise and stress). As a first step to approaching this common diabetes problem, a blood glucose prediction engine was developed by one of us (A. M. Albisser). The engine processes current and previous blood glucose data and then generates a prediction of the glucose levels that the patient can expect at the next meals. It superimposes this information on a prediction of the pending risks of hypoglycaemia. We here offer evidence of the clinical feasibility and validity of predicting future blood glucose levels using data from a carefully selected population of patients with diabetes so complex as to qualify them for islet cell transplantation. Clinical safety and metabolic efficacy issues are addressed elsewhere [5]. To eliminate bias in these validation studies, both patients and their providers were blinded as to the predictions for the entire course of the study.

Subjects, materials and methods

Glucose prediction engine The various computational procedures needed for glucose prediction are incorporated into an engine that is deployed in software. When the engine is invoked, it makes use of a registry database that contains specific information about each patient. These data include the user's anonymous identifier, body weight and height as well as an archive of all home-monitored blood glucose and other life-style/self-management data. The methods used by the prediction engine involve adaptation of random walk techniques [6], mathematical models [7, 8] and simulation procedures [9, 10]. Together these overcome some of the necessary restrictions of modelling approaches [11]. In general, the methods are similar to the dynamic systems used in weather research and forecasting [12].

At the very outset for any given patient, the engine chooses the starting points that are specific for each patient-user. In other words, the engine begins with a default set of internal parameters. External variables that impact on blood glucose, such as diet, activity, stress, carbohydrate intakes, and so on, are all set to nominal values generally considered typical for a person of such anthropomorphic dimensions. However, the similarity at the start is short lived. As data accumulate, these default internal parameters are continually tuned so that a set of model parameters fit the specific patient's previous and current data. Concordance of these models to the data is generally within the expected error limits of the patient's methods of

SMBG. Over time, ranges of the internal parameters and external variables are developed by the engine for each patient and stored in the database. This follows suggested methods [13, 14]. In effect, each patient has his or her own customised engine, awaiting the next opportunity to generate a glucose prediction. When this occurs, the engine is invoked and may re-tune itself according to recent data from the database. This may alter the ranges of the internal parameters. These and the custom ranges of the external variables are then used by the engine to generate projections of all glucose values that may be expected. In this way, at each pre-meal measurement point, all possible blood glucose levels at the next meals are predicted by the engine. Superimposed on the resulting range are the most likely blood glucose values. The underlying predicted ranges give information about the risks of pending hyper- and hypoglycaemia. Notably, these predictions are specific for each meal and for each patient. The software program to do this was coded in Microsoft Visual Basic Pro and runs on any personal computer with a Microsoft 32-bit operating system.

Patients studied Diabetic subjects in the islet cell transplantation programme at the Diabetes Research Institute at the University of Miami were studied. All are under the care of three of us (D. Baidal, R. Alejandro, C. Ricordi). Each patient recruited into the programme participates in a carefully designed protocol and has given informed consent granting permission for all the research procedures as well as the use for scientific purposes of the data collected in their daily self-management. All investigations were approved by the University of Miami Institutional Review Board.

Participation criteria No selection criteria were applied for this study. However, the cohort of patients conformed to the selection criteria for islet cell transplantation [4]. All were insulin treated. All measured blood glucose three or more times a day and managed their own diabetes according to varied, intensified methods specified by their providers.

Validation data set For the purposes of this validation study, SMBG data were collected at the point of self-management. Each value was transmitted to the clinic via an interactive voice response telephone connection, confirmed and then stored in a secure database on a server also accessible via the Internet. These data, along with medication doses taken, were submitted every day. The stored data pairs from each patient include the pre-meal glucose readings with the dates and times of ascertainment. While pre-meal readings were taken on a daily basis, postprandial blood glucose concentrations [15] were also measured, but less frequently.

Analytical methods Since blood glucose testing is the cornerstone of all blood glucose predictions, accuracy in testing is paramount to reduce errors in the predicted

Table 1 Characteristics of the patients at recruitment, at baseline just before transplantation (TX) and at latest follow-up after TX

Characteristic	Recruitment (pre-TX)	Baseline (pre-TX)	Follow-up (post-TX)
Males/females (<i>n</i>)	11/13	11/13	11/13
Follow-up duration (days)	0	755±359 (94–1,462)	434±372 (8–1,288)
Age (years)	43±8 (26–62)	45±8 (28–62)	46±8 (29–63)
Height (cm)	167.0±9.6 (154–185)	–	–
BMI (kg/m ²)	23.9±1.9 (20.7–27.0)	23.7±2.0 (19.8–27.0)	22.9±2.1 (18.6–26.7)
HbA _{1c} (%)	7.6±0.9 (6.4–10.8)	7.2±1.1 (4.8–9.4) ^a	6.1±0.9 (4.8–8.1) ^b
Total insulin (U/day)	35±16 (14–78)	33±11 (6.0–57.2)	11±9 (2–30) ^b
Treated with insulin	24/24	24/24	14/24 ^b
Hypoglycaemia unawareness (rate [%])	24/24 (2.6±2.5)	24/24 (2.6±2.6)	2/24 ^b (0.1±0.1 ^b)

^a*p*<0.05 vs recruitment^b*p*<0.001 vs baseline

values [16, 17]. Accordingly, patients contributing to the validation data set were fully trained before starting and their accuracy was reviewed at follow-up clinic visits.

As the ultimate goal of glucose prediction is to provide decision support for the patient practising self-management, the Clarke Error Grid (CEG) (Clarke et al. [18]) was chosen as the tool with which to determine the clinical validity of the glucose predictions. The CEG specifies five Zones, A–E. Depending on the Zone in which a specific forecast falls, it may be classified as clinically accurate and useful (Zones A and B), or not (Zones C–E).

Analysis of the data followed a day-by-day step-and-repeat procedure whereby the engine accessed the data in the database beginning at the first record following recruitment for each patient. At each step the engine tried to form a prediction. Where none was possible, it advanced to the next step. When a prediction was made the resulting expected value was then associated with the actual value observed by plotting a single point on the CEG. The engine then advanced to the next record thereby including the current (actual) observations and the process was ready to be repeated. Accumulators kept track of the number of patients, the number of days for each patient (days-used), the number of glucose readings, the number of episodes of hypoglycaemia, the number of predictions and the number of entries falling in each Zone. The entire process was automated. All raw data in the database were used. No pre-filtering was applied.

Rates of hypoglycaemia were calculated as the percentage of SMBG less than 2.7 mmol/l over 1 month at recruitment, over 1 month at baseline just before transplantation (in order to discern changes in the pretransplantation phase), and finally over the entire post-transplantation follow-up period. Statistical comparisons of clinical outcomes were done using as appropriate the Fisher *F*-test for variances or a one-tailed Student's *t*-test for paired data. Summary data are shown as means±SD; significance is at *p*<0.05, or as otherwise indicated.

Results

Twenty-four islet cell transplantation candidates were studied. The group included 11 males and 13 females. Their characteristics at recruitment, at baseline just prior to transplantation and at the most recent follow-up (after transplantation) are shown in Table 1. At recruitment their BMI averaged 23.9±1.9 kg/m² (range 20.7–27.0), their HbA_{1c} averaged 7.6±0.9% (range 6.4–10.8) and they were managed on a total of 35±16 U/day (range 14–78). Hypoglycaemia was documented to occur on average at a rate 2.6±2.5% and all 24 suffered from hypoglycaemia (unawareness). The duration of the baseline phase was 755±359 days and that of the follow-up phase after transplantation was 434±372 days. During the pretransplantation

Table 2 Outcomes from application of the glucose prediction engine to the data set from islet cell transplantation candidates classified according to pre- and post-transplantation (TX) status

Phase	<i>n</i>	Actual Bgs	Patient-days	Predictions	SMBG efficiency (%)	Plotted (<i>n</i>)	Pre-meal hypoglycaemia (no. observed)	Pre-meal hypoglycaemia (no. predicted)	Mean absolute error (%)	Mean error (mmol/l)
Pre-TX	24	31,878	8,733	31,353	98	20	728	384	47±55	0.1±4
Post-TX with insulin	14	30,256	8,652	28,762	95	20	52	29	17±20	0±1.6
Post-TX without insulin	10	15,273	4,254	13,544	89	10	5	2	13±13	0±1.2

Post-TX patients are grouped by insulin treated, or not
SMBG Self-monitored blood glucose

Fig. 1 Pretransplantation phase. Clarke Error Grid showing predicted and actual pre-meal blood glucose levels in islet cell transplantation (TX) candidates

phase only HbA_{1c} changed, dropping to $7.2 \pm 1.1\%$ (range 4.8–9.4), $p < 0.05$.

As shown in Table 2, all 24 patients contributed SMBG results for these validation studies. In the pretransplantation phase the patients entered a total of 31,878 self-measured pre-meal blood glucose concentrations over a period of 8,733 patient-days, spanning a range of 94–1,462 days. On average, patients in this phase measured ~ 3.7 times a day. On these data, the engine generated a total of almost 32,000 glucose predictions. Each predicted datum was paired with the actual value subsequently observed and the resulting data pair was plotted on a CEG as shown in Fig. 1. Of the 31,353 predictions, 10,781 (34%) fell in Zone A and 14,125 (45%) fell in Zone B, as shown in Table 3. Thus, for this phase, 79.4% of forecasts were in the clinically acceptable ranges (Zones A and B). The remainder were in Zone C (3.4%), in Zone D (15%), or in Zone E (2%). In the pretransplantation phase, 98% of the glucose readings supported predictions. Of 728 reported pre-meal episodes of hypoglycaemia, 384 (53%) were also predicted by the engine. In this phase the mean absolute percentage error was $47 \pm 55\%$ and the mean error of prediction was 0.1 ± 4 mmol/l.

Fig. 2 Post-transplantation phase. Clarke Error Grid showing predicted and actual pre-meal blood glucose levels in islet cell transplantation (TX) recipients still treated, but with reduced amounts of insulin

Following islet cell transplantation, all 24 patients continued to contribute SMBG results for periods ranging from 8 to 1,288 days. Compared with pretransplantation baseline values, at the most recent follow-up, there was no change in BMI but HbA_{1c} dropped to $6.1 \pm 0.9\%$ (range 4.8–8.1), $p = 0.0007$, settling at the upper limit of normal. Total daily insulin dropped threefold ($p < 0.0001$) to an average of just 11 ± 9 U/day (range 2–30), $p < 0.001$ and $n = 14$. Thus, of the 24 patients, ten injected no insulin at all. The tendency to improved glycaemic control is evident, comparing the range of scatter in Fig. 1 with that in Figs. 2 and 3.

For the group receiving reduced insulin therapy, over a follow-up period of 8,652 patient-days, some 30,256 SMBG levels were reported (Table 2). With these, the engine made a total of 28,762 blood glucose predictions. When plotted on the CEG as shown in Fig. 2, 20,339 (71%) fell into Zone A and 7,599 (26%) were in Zone B (Table 3). Thus, following transplantation, 97.1% of the predicted blood glucose values were in the clinically acceptable ranges (Zones A and B). Of the remainder, 0.1% were in Zones C and E, and 3% were in Zone D. In this group and

Table 3 Glucose prediction: outcomes analysis by zone in the Clarke Error Grid in the data set from islet cell transplantation candidates classified according to pre- and post-transplantation (TX) status

Phase	Zones A+B (%)	Zone A (n)	Zone B (n)	Zone C (n)	Zone D (n)	Zone E (n)
Pre-TX	79.4	10,781 (34%)	14,125 (45%)	1,079 (3.4%)	4,843 (15%)	525 (2%)
Post-TX with insulin	97.1	20,339 (71%)	7,599 (26%)	42 (0.1%)	767 (3%)	15 (0.1%)
Post-TX without insulin	98.2	10,632 (78%)	2,672 (20%)	1 (0%)	239 (2%)	0 (0%)

Post-TX patients are grouped by insulin treated, or not

Fig. 3 Post-transplantation phase. Clarke Error Grid showing predicted and actual pre-meal blood glucose levels in islet cell transplantation (TX) recipients not treated with any insulin at all

phase, 95% of the glucose readings supported predictions. Of just 52 pre-meal episodes of hypoglycaemia observed, 29 (54%) were concordant with predictions. In this phase the mean absolute percentage error fell to $17 \pm 20\%$ ($p < 0.001$) and the mean error of prediction was 0 ± 1.6 mmol/l.

For the group receiving no insulin therapy, over the follow-up period of 4,254 patient-days, some 15,273 SMBG levels were reported (Table 2). With these, the engine made a total of 13,544 blood glucose predictions. When plotted on the CEG as shown in Fig. 3, 10,632 (78%) fell into Zone A and 2,672 (20%) were in Zone B (Table 3). Thus, following transplantation, 98.2% of the predicted blood glucose values were in the clinically acceptable ranges (Zones A and B). Of the remainder, essentially none were in Zones C and E, and 239 (2%) were in Zone D. In this group and phase, 89% of the glucose readings supported predictions. Of just five pre-meal episodes of hypoglycaemia observed, two (40%) were concordant with predictions. In this phase the mean absolute percentage error fell to $13 \pm 13\%$ ($p < 0.0001$) and the mean error of prediction was 0 ± 1.2 mmol/l.

Due to the large number of predicted values in each phase, not all data pairs plotted on the CEGs are shown in Figs. 1, 2, 3. Thus for clarity, only every 20th or 10th data point in each phase is shown. No selection criteria were applied to the data shown.

Discussion

Based on the evidence presented, it appears clinically feasible to predict blood glucose levels in diabetes. Further-

more, these predictions are valid much of the time. In the present study, patients measured pre-meal blood glucose readings on average 3.5 times/day. The resulting flow of information was rich but most importantly it was consistent and timely. With access to these data, the prediction engine demonstrated a high efficiency, meaning that 89–98% of the SMBG readings made by the patients could be utilised in predictions. Clearly, the value or cost/benefit of home blood glucose monitoring may be undeniable if, in the future, patients have such predicted data available for decision support, especially since it has recently been shown to improve outcomes [5].

The results of the present study suggest that the glucose values predicted by the engine are valid almost 80% of the time in pretransplantation and over 95% of the time in post-transplantation patients, an increase that corresponds to the decrease in glycaemic fluctuations. Regardless, when coupled with an indication of pending hypoglycaemia (to moderate self-management decisions), we believe that the information afforded by the prediction engine is crucial for decision support. In this light, further clinical trials are in order certainly in hypoglycaemia-prone populations as studied here and in different patient-care settings, e.g. private practice, health maintenance organisations or academia. In such clinical studies crucial outcome measures would simply be the standard clinical measures in diabetes care: glycated haemoglobin, body weight, medication dosing and incidence of hypoglycaemia, although extended indicators of metabolic state such as lipid profiles and blood pressure may also be affected. We suggest that such studies will demonstrate added impact on outcomes, including costs [19].

Notably, in the research patients studied here before transplantation, a large number of the observed values (15%) fell in Zone D near the vertical axis, as also shown in Fig. 1. In this Zone, the actual values observed were below 3.9 mmol/l. While the engine erroneously predicted blood glucose levels higher than 3.9 mmol/l in these situations, it also consistently predicted the risks of hypoglycaemia. Since the present group of patients were blinded to these predictions, they could not act on them and their rates of hypoglycaemia did not change. These findings confirm that this group of patients had diabetes complicated with frequent hypoglycaemia and that these events were, for them, systematically unpredictable, although the prediction engine was often able to discern pending hypoglycaemia. It is noteworthy that most of these patients were candidates for islet cell transplantation precisely because of hypoglycaemia unawareness [3].

Following islet cell transplantation, the frequency of unpredictable hypoglycaemia (unawareness) dropped as evident in Figs. 2 and 3, and the proportion of forecasts in Zone D fell 6.5-fold from 15 to just 3% or less. Furthermore, the proportion of predicted values in the clinically accurate Zone A and clinically acceptable Zone B of the CEG rose to over 97%. Clearly, the element of unpredictability had been removed by islet cell transplantation whether or not the patients were independent of insulin therapy.

Since islet cell transplantation does not always result in uniform euglycaemia or independence from insulin, all patients still needed to monitor their blood glucose values. Some 14 of 24 injected token amounts of insulin, in all cases much less than used prior to transplantation. For such patients, the availability of a predicted blood glucose level may prove valuable in self-management. Where anti-rejection drugs affect insulin requirements, such predictions may also assist the patients in tracking changes in their daily dosing requirements, especially after changes in anti-rejection medications are prescribed.

It is noteworthy that HbA_{1c} dropped during the baseline period preceding transplantation. This improvement in overall glycaemic control occurred without significant changes in either daily insulin doses or rates of hypoglycaemia. Since no feedback whatever (acknowledgement, encouragement, intervention, education) was returned to the patient using the system, we suggest that this favourable drop may be attributed to a Hawthorne (placebo) effect caused by merely requiring patients to report their blood glucose values on a daily basis to a passive call centre. Young et al. [20] achieved identical improvements in HbA_{1c} in type 2 diabetes but using a personalised telephone care centre support system, known as the Pro-Active Call Center Treatment Support, which featured two telecarers supported by a diabetes nurse specialist. It is encouraging that when the predictions afforded by the engine are acted upon [5], large and significant reductions in the rates of hypoglycaemia and major improvements in glycaemic control can be realised. To these ends, the prediction software affords a unique user interface [21]. It displays not only the expected glucose value but also the pending risks of hypoglycaemia. Having an indication of the risk of hypoglycaemia may prove to be a useful adjunct to diabetes management [19, 21]. Clearly, randomised, controlled, clinical trials will be appropriate to verify both these preliminary observations and the benefit of using predicted blood glucose levels in support of diabetes management in this and other less complicated populations of patients with diabetes.

Historically, the concept of computer-based glucose prediction was first suggested by Deutsch et al. [22]. They devised a logical model that defines the relationships between changes in insulin dosing (site and timing of injections) and glycaemic response. Their device provided advice concerning insulin therapy by making qualitative predictions of patient blood glucose profiles resulting from alternative insulin regimens. Subsequently, others [23] developed a computer simulator program that allows patients to practice dose and dietary adjustment on a day of planned exercise. The blood glucose changes predicted by the program were determined from values predicted by specialists presented with hypothetical scenarios involving exercise with or without dietary or insulin dose adjustments. Both these early prediction tools played more of a role in education than in actual treatment in diabetes self-care.

Lehmann and Deutsch [24] designed a number of computer-based prototypes for the provision of therapeutic

advice and the generation of glucose predictions in type 1 diabetes. Preliminary retrospective validation work performed with this model revealed a mean predictive accuracy for blood glucose simulations of ~2.0 mmol/l. They concluded that, although such methodologies may not be suitable for safe and effective application in routine clinical practice, the evolution of such a system for demonstration/educational purposes could have widespread clinical utility as an interactive teaching tool. They also reviewed and critically appraised the application of compartmental models for generating glycaemic predictions and offering clinical decision support in diabetes care. Comparisons were drawn with algorithm-based approaches. They concluded that model-based approaches, while not offering much benefit for clinical, therapeutic decision support, would have a role in research and in education, but that algorithm-based approaches, especially in conjunction with telemedicine and Internet applications, would probably see growing use for day-to-day therapeutic decision support. We believe that, coupled with a prediction of the risks of pending hypoglycaemia, the prediction engine described in this paper may serve these latter purposes.

Salzsieder et al. [25] devised a model-based simulator of diabetes to assist patients and their providers in choosing the diabetes management regimen which would be most appropriate. Another group [26] also developed an educational tool which was Internet-based. Others have looked upon glycaemia as a time series [27, 28] and constructed glucose prediction algorithms that are in the process of being clinically validated.

Finally, the results of the present studies suggest that it is clinically feasible to generate valid predictions of future blood glucose levels. Prediction accuracy is related to glycaemic stability. Risk of hypoglycaemia can be predicted. Such combined knowledge may be useful in diabetes management.

Duality of interest statement

A. M. Albisser is employed by Better Control Medical Computers (BCMC), Hollywood Beach, FL, USA. He directs the National and International Diabetes Monitoring and Decision Support Service (NIDM) and is appointed Adjunct Professor of Bioengineering at the University of California in San Diego (UCSD). D. Baidal, R. Alejandro and C. Ricordi are employed by the University of Miami and the Diabetes Research Institute. They have no connection to or financial involvement with BCMC, NIDM or UCSD.

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