Journal of Diabetes Science and Technology
Volume 3, Issue 3, May 2009

ORIGINAL ARTICLES

Prescription Checking Device Promises to Resolve Intractable Hypoglycemia

A. Michael Albisser, Ph.D.,[1] Rodolfo Alejandro, M.D.,[2] Marianne Sperlich, B.Ed.,[1] and Camillo Ricordi, M.D.[2]

Abstract

Background:

Satisfactory glycemic control, meeting American Diabetes Association recommendations, is often accompanied by unsatisfactory hypoglycemia. The converse is also true. We hypothesize that this diabetes treatment dilemma may be resolved by repeated, objective, prescription checks. To do this, a new, two-part device has been developed. It includes a personal diabetes database for the patient and a built-in diabetes prescription checker for the provider. Its goals are to enhance diabetes education and improve patient care.

Research Design and Methods:

The device includes a database and supporting software, all contained in a standard USB flash drive. Using the medical prescription, body weight, and recent self-monitored blood glucose (SMBG) data, prescription checks can be done at any time. To demonstrate the device's capabilities, an observational study was performed using data from 11 patients with type 1 diabetes mellitus, on intensified therapy, with a mean glycated hemoglobin A1c <7%, and who all suffered intractable hypoglycemia. Patients had performed SMBG contours on successive days at monthly intervals. Each contour included pre- and postmeal as well as bedtime measurements. The replicated contours were used to predict the patient's glycemic profile each month. Applying a built-in simulator to each profile, changes in the prescription were explored that were consistent with reducing the recalcitrant hypoglycemia.

Results:

A total of 110 glycemic profiles containing 822 profile points were explored. Of these profile points, 351 (43%) showed risks of hypoglycemia, whereas 385 (47%) fell outside desired ranges. With the simulated changes in the prescription, the predicted risks of hypoglycemia were reduced 2.5-fold with insignificant increases predicted in hemoglobin A1c levels of +0.6 ± 0.9%.

continued →

Author Affiliations: [1]Diabetes Control and Complications Treatment Initiative, Hollywood, Florida; and [2]The Diabetes Research Institute, University of Miami, Miami, Florida

Abbreviations: (ACCORD) Action to Control Cardiovascular Risk in Diabetes, (A1C) glycated hemoglobin A1c, (Rx) prescription, (SMBG) self-monitored blood glucose

Keywords: algorithms, blood glucose control, disease management, evidence-based medicine, glucose monitoring, glycated hemoglobin, hypoglycemia, insulin resistance, intervention, outcome measures, remote monitoring, simulation, telemedicine

Corresponding Author: A. Michael Albisser, Ph.D., DCCTreatment Initiative, 1400 South Ocean Drive, Unit 604, Hollywood Beach, FL 33019; email address albisser@nidm.org

Abstract cont.

Conclusions:

A novel support tool for diabetes promises to resolve the diabetes treatment dilemma. Supporting the patient, it improves self-management. Supporting the provider, it reviews the medical prescription in light of objective outcomes and formalizes interventions for maximum safety and efficacy.

J Diabetes Sci Technol 2009;3(3):524-532

Introduction

The control of blood glucose often presents an irreconcilable dilemma to both care providers and their patients with diabetes. Strongly encouraged by the American Diabetes Association,[1] providers must strive for glycated hemoglobin A1c (A1C) values less than 7% in the majority of their patients. While this is now being achieved in roughly half of the patients in the United States,[2] this wonderful success frequently has an adverse consequence, most notably, treatment-related *hypoglycemia*.

Such hypoglycemia is often difficult to avoid in the subpopulation that meets recommended A1C goals whether treated with insulin[3] or antidiabetic oral agents. In fact, on February 6, 2008, the National Heart, Lung, and Blood Institute, which sponsored the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, announced that it had stopped the intensive blood glucose control substudy due to safety concerns.[4] The trial randomized patients with diabetes and vascular disease or multiple cardiovascular risk factors either to an intensive treatment program targeting normal blood glucose values and an A1C less than 6% or to a standard treatment program with an A1C between 7 and 7.9%. The intensively treated participants in ACCORD were switched to the standard treatment program. There was an increased incidence of hypoglycemia in the intensively treated arm. Exploratory analyses have not been able to conclude a link between hypoglycemia and death, but analyses are ongoing. Again, the irreconcilable dilemma in diabetes suggests that satisfactory glycemic control seemingly may only be achieved with unsatisfactory hypoglycemia. The converse is also true. Other studies of intensified therapy have risked severe hypoglycemia as well.[5]

In this light, we asked whether repeated, objective reviews of a person's diabetes prescription could serve to trigger not only timely interventions, but also offer suggestions as to what issues most need attention. We hypothesized that such "prescription checks" would result in improved diabetes care in general and better (safer) glycemic control in particular. Among other benefits, such triggered interventions would serve to correct details of a medical prescription that may no longer be appropriate. If this prescription check concurrently were to teach the provider the effects (on their patient's glycemic control) of *simulated* changes in their prescription, it would be a valuable extension to their diabetes practice. Furthermore, the knowledge so gained would offer substance for discussion at each encounter. We further hypothesized that closing the circle of care in this way may help untangle the aforementioned irreconcilable dilemma.

Accordingly, this article explores a new educational support tool for diabetes care. The device includes a diabetes database that takes in both personal information and medical information, executes a pertinent prescription check, and then allows the provider to predict the consequences of potential prescription changes. It then overlays all these in such a way as to highlight where the patient may need crucial medical attention. An observational study using archived clinical data is presented.

Materials

Educational Firmware

The device is called MyDiaBase+RxChecker. As the name implies, it includes a personal diabetes database and supporting software that can also perform a diabetes

prescription check. The combination is distributed in a standard, USB flash memory drive.[6] The drive can be inserted into any USB port on any computer running any contemporary Microsoft Windows operating system. Macintosh users must have Intel OS-X and a PC emulator.

Developer and Availability

The MyDiaBase+RxChecker technology was developed by a group directed by one us (AMA). Access to the device is provided through professional user training courses. See http://www.nidm.org for device and course details. A pragmatic description of the device is provided elsewhere in this issue.

Installation and Personalization

Each flash drive includes all the resources with which to install the MyDiaBase+RxChecker software. Installation must be done once on each computer where the user will be running the program in the future. Once installed, the patient's MyDiaBase+RxChecker flash drive can be personalized with their own demographics, their providers' demographics, and their diabetes prescription. These are stored internally in a database that is secured, private, and password protected in case the flash drive is lost or stolen. At any time, the patient can insert their current or previous SMBG and related self-management data, which are then all similarly stored.

Procedure for Doing a Diabetes Prescription Check

A prescription (Rx) check can be done at any time. It requires (i) current diabetes medications prescription, (ii) current body weight, and (iii) recent, antecedent SMBG data. These data should be collected by the patient at home, as instructed by their provider, over the previous week. Depending on the regimen, type 1 patients doing carbohydrate counting may enter pre- and postmeal measurements, whereas type 2 patients may enter only premeal measurements. A valid glycemic profile can be formed with the equivalent of at least 2 days of data gathered over the previous week. More data are believed better.

Each prescription check then addresses the following eight elements sequentially.

i. An automatic calculation of the patient's current body mass index.

ii. A graphical display of the patient's body weight history.

iii. A regression analysis of the patient's body weight history to show the trend over time.

iv. If applicable, a check on the current tablet dosing rates that identifies whether any oral medication is exceeding the recommended meal or daily limits.

v. If applicable, a check on the patient's sensitivity to injected insulin or their apparent resistance to insulin.

vi. A visual display of the patient's glycemic profiles derived from SMBG data showing the expected ranges of glycemia and the risks of both hyper- and hypoglycemia at each measurement time (profile point).

vii. A visual superposition on each profile point of the glycemic target ranges specified by the provider.

viii. A dynamic interaction with a built-in simulator that predicts the possible effects of ±changes in the nominal or base dosing of any one or all of the prescribed diabetes medications. The simulator includes the pharmacokinetics of all the oral hypoglycemic agents and all the different insulin formulations.

Each element of the prescription check (that is out of limits or not) results in a text comment that is appended to the database and subsequently appears in the SMBG diary. At any time, the diary can be viewed, printed, or even faxed to remote providers directly, if the user's computer is equipped with a fax modem.

Methods

Study Design and Data Source

In order to demonstrate one of the merits of the MyDiaBase+RxChecker device, a simple observational study was undertaken. Another one of us (RA) supplied clinical data, which were drawn from the electronic databases used in the Clinical Islet Transplant Program of the Diabetes Research Institute at the University of Miami, Miami, Florida, directed by another of us (CR). Permission to use these data for research purposes had been granted previously by each patient as part of their participation in the research program.

Study Subjects

The patients included six males and five females. Their ages ranged from 26 to 66 years. They all had type 1 diabetes of more than 3 years' duration. They were all

on intensified insulin therapy with basal bolus regimens that included fast and either intermediate or long-acting insulin. Accordingly, insulin was either pumped continuously or injected at least four times a day. Each patient had received diet and nutrition counseling that followed ADA recommendations specific to his or her insulin regimen. As part of their comprehensive diabetes education experiences, each had been taught how to adjust their bolus doses according to meal size and exercise, even their preprandial glycemia, as well as to take into account previously injected insulin that may yet remain onboard. They all performed SMBG at least four times a day. Most had reached the recommended[1] glycemic targets with A1C levels below 7%. However, all suffered from frequent episodes of hypoglycemia (defined as SMBG <50 mg/dl). The hypoglycemia was chronic, debilitating, and, in most cases, the primary reason for their candidacy for islet cell transplantation.

Glycemic Targets

The providers specified target glycemic ranges. They followed accepted guidelines, asking patients to achieve a premeal glycemia in the range of 80 < SMBG < 140 mg/dl and after meals of <180 mg/dl.

Data Collection

As part of a research project unrelated to the present study, patients had been instructed to complete a full seven to eight SMBG contour on 2 successive days each month. Accordingly, a contour included SMBG done before and after the main meals and before bedtime with an overnight reading in many cases. These contour data were extracted from the database along with the diabetes medication prescription and then used in the present series of tests.

Data Reduction

Duplicate contour readings were used by the simulator to predict the patient's glycemic profile. Each profile thus included up to eight profile points. Results of each prescription check were summarized as follows: the total number of profile points, the number that were outside the physician's target ranges, and the number that risked hypoglycemia. Ideal glycemic control resulted when the SMBG average at each profile point was within the specified target range. The statistical distributions of data were displayed as dithered areas extending upward and downward from the SMBG average value. Target ranges could be superimposed on data so that it would be obvious when a profile point was outside the target range.

Exploring Potential Interventions

The final item in the prescription check explored the potential impact of medication dosing changes using a built-in simulation method that has been described previously.[7,8] The goal of the exercise was to decide whether each dose was nominally correct, too high, or too low. Changes in any one, of course, had an impact on the appropriateness of all the others, according to its predicted impact on the entire glycemic profile. Often several doses needed to be altered in order to eliminate hypoglycemia without unduly causing hyperglycemia. Another one of us (MS), using the simulator and the displayed profiles, performed this task. The procedure usually resulted in an improved profile and a text summary in the database indicating which doses needed to be changed either upward or downward. The simulation did not specify the actual dose change numerically, only whether more or less was needed. In this way, the RxChecker only guides providers as to whether it is the base dose, the carbohydrate ratio, or the sliding scale that most needs changing. In all cases, the actual therapeutic decision would reside with the doctor. In effect the provider is supported in decoding where changes, usually small changes, in the prescription may be most beneficial to the glycemic profile. In practice, these changes are typically in the range of 0.5 to 2 units of insulin.

Again, the total number of profile points that day, the resulting number outside the physician's targets, and the resulting number that risked hypoglycemia were all summarized.

Outcome Measures

Hemoglobin A1c values were used to estimate the impact of predicted changes on the glycemic profiles. The effects of possible regimen changes were not explored.

Analyses

Estimates of A1C were derived from mean SMBG, as defined previously.[9] Standard descriptive statistical methods were used.[10] Although profile data seemed amenable to a formal repeated measures analysis of variance, the use of ranges as criteria would complicate both the analysis and the interpretation of its results. Therefore, we elected to use simple measures that parallel clinical practice, that are visually informative on computer displays, and that reinforce the clinical value of glycemic profiles. Accordingly, the χ^2 test for paired proportions was used for testing whether the proportion of profile points risking hypoglycemia was the same before and

after simulated intervention. The same test was used for deciding whether the proportion of profile points outside the target ranges was the same before and after simulated intervention. Simple regression was applied to determine the relationship between estimated A1C and the number of profile points that risked hypoglycemia. Significance levels are as stated. All results are shown as mean ± SD.

Results

Figure 1 is an example of how each study was done. It shows the results from the use of SMBG contours #113 and #114 done on 12/21/00 and 12/22/00 by subject #689. The pair was selected at random from the set of all contours studied. The predicted glycemic profiles are both shown with the physician's target ranges superimposed. In the upper part of **Figure 1**, before applying the simulation, estimated A1C is 7.7%. Three of the seven profile points are outside the set target ranges (respectively, before lunch, after dinner, and before bedtime). There is also a risk of hypoglycemia at the before-dinner profile point. After the simulation is applied (bottom half of **Figure 1**), the profile is predicted to improve with minor changes in the existing medication prescription. To these ends, the simulator suggests that the provider considers an increase in intermediate-acting insulin at breakfast and at dinner, an equivalent reduction at lunch, and a small increase at bedtime. Notably, a drop in A1C from 7.7 to 6.8% is predicted. The risk of hypoglycemia before dinner is eliminated, and the number of profile points outside target ranges is reduced from 3 to 2.

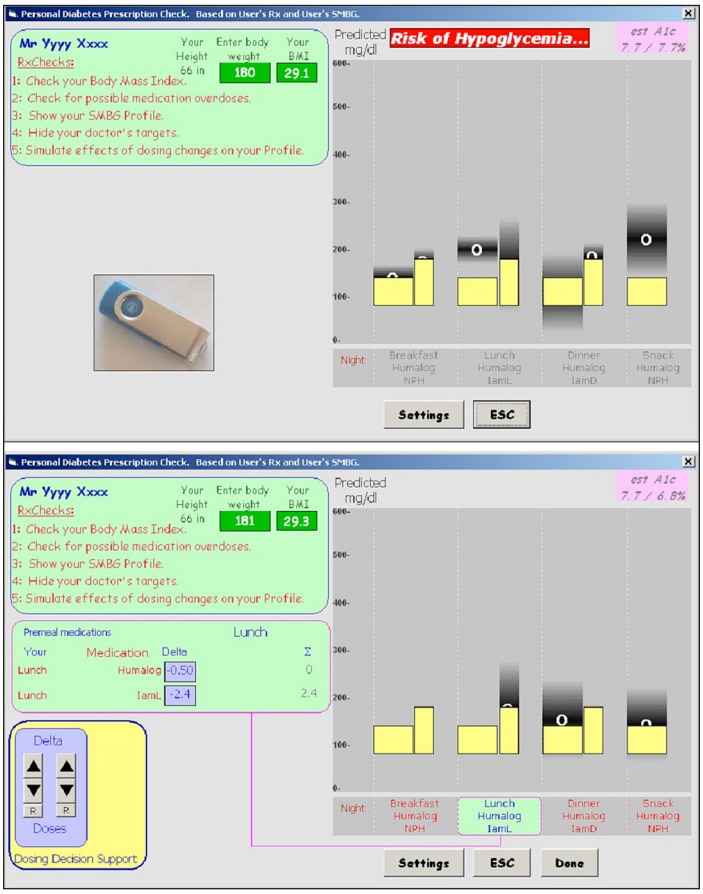

Figure 1. (Top) Example of one patient's predicted SMBG profile with physician targets superimposed. Predicted A1C is 7.7%. Three profile points are outside target ranges (before lunch, after dinner, and before bedtime). There is a risk of hypoglycemia before dinner. **(Bottom)** Simulation suggests that minor changes in existing medications can improve A1C by 0.9%, eliminate the risk of hypoglycemia, and reduce the number of profile points outside target ranges from 3 to 2.

Similarly, the 11 patients had provided repeated SMBG contours, done on 2 successive days monthly for ~10 months. Each contour included seven to eight points, respectively, overnight, premeal, and postmeal readings. These resulted in 110 predicted glycemic profiles that included 822 profile points. Of these profile points, 351 (43%) showed risks of hypoglycemia and 385 (47%) were outside the desired ranges. The latter risked hypoglycemia, hyperglycemia, or both.

As shown in **Figure 2** on the left, on average, 3.2 profile points out of each 8-point profile risked hypoglycemia. Simulated interventions suggested that the risks of hypoglycemia could be reduced almost 2.5-fold to an average of just 1.4 profile points in the same 8-point profile. This promised reduction was significant ($P < 0.0001$).

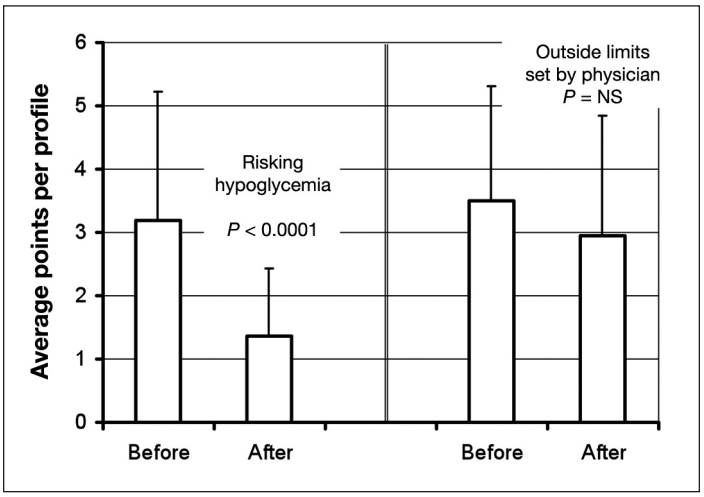

Figure 2. (Left) Before: Mean ± SD profile points risking hypoglycemia at baseline. After: Mean ± SD profile points risking hypoglycemia are reduced following a simulation that allows the provider to explore potential changes in their diabetes medication prescription ($P < 0.0001$). **(Right)** Before: Mean ± SD profile points falling outside the limits set by the physician at baseline. After: Mean ± SD profile points falling outside set limits following simulated changes that reduced the risks of hypoglycemia shown at the left (P = NS).

At the same time, as shown in **Figure 2** on the right, the average number of profile points in each 8-point profile outside the limits set by the physician was 3.5 before the simulation. These were suggested to drop to an average of 3.0 after simulation, reflecting the effort to reduce the risks of hypoglycemia, although it must be emphasized that the number of points risking **hyper**glycemia may sometimes be increased temporarily at the expense of the reduction in those risking **hypo**glycemia.

Interestingly, the simulated interventions by and large did not change the predicted average glycemia (P = NS). Thus, based on the glycemic profiles and as illustrated in **Figure 3**, the mean A1C level was 6.7 ± 0.8% before simulated interventions. In the unlikely absence of any subsequent interventions, this A1C value was projected to rise to 7.3 ± 1.0% (P = NS) after the simulated interventions that emphasized reducing hypoglycemia in the first instance.

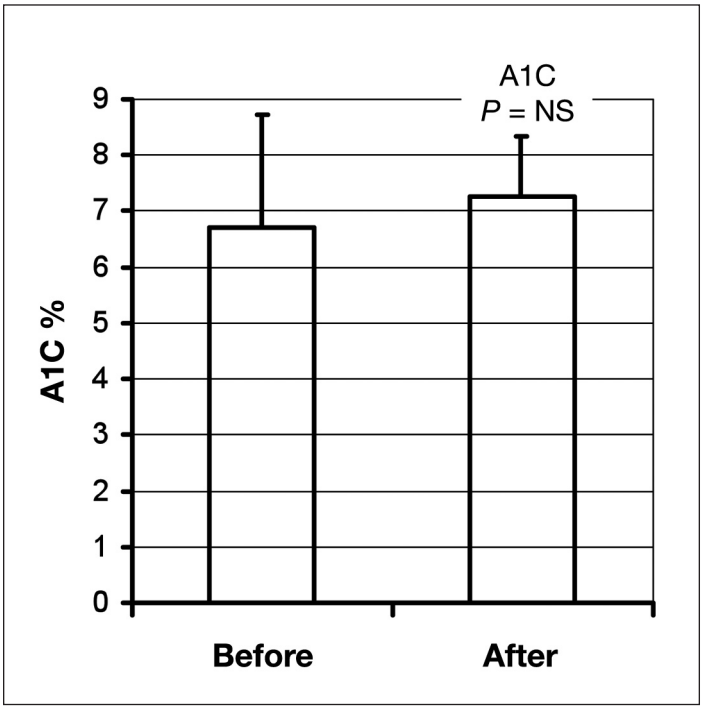

Figure 3. Before: Estimated glycated hemoglobin A1c at baseline. After: Estimated A1C after the provider explores simulated changes that reduce the risks of hypoglycemia, as shown in **Figure 2**.

Figure 4 shows the inverse relationship between A1C and the number of profile points risking hypoglycemia. The overall significant (P < 0.001) downward slope constitutes the essence of the diabetes treatment dilemma.

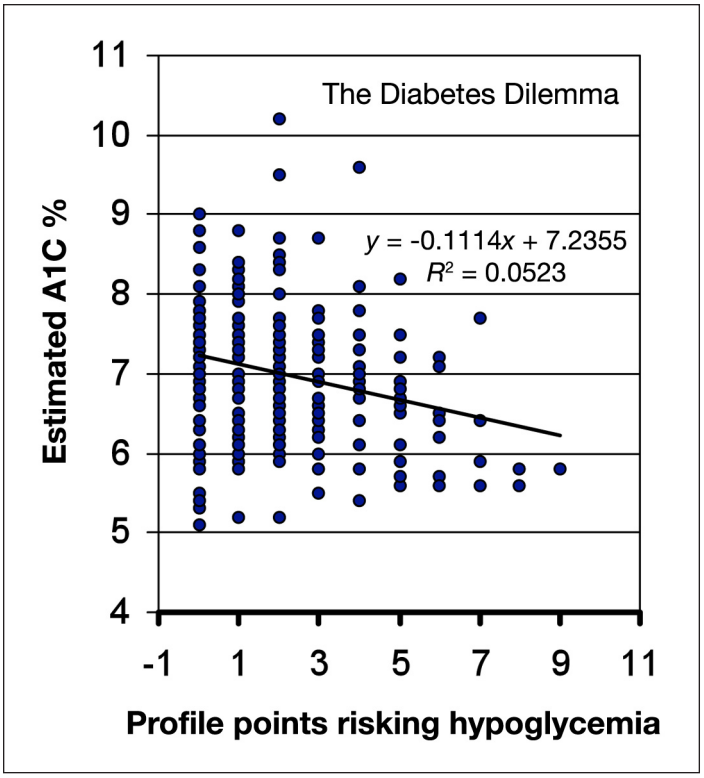

Figure 4. The diabetes dilemma suggests that satisfactory glycemic control, as recommended by the ADA, is most likely accompanied by unsatisfactory risks of hypoglycemia.

Conclusions

A new device has been developed for diabetes care that enhances diabetes education by helping providers objectively review their medical prescription for safety and efficacy. The present observational study focused on data from patients who succeeded in meeting the recommended[1] goals for blood glucose control with a mean A1C less than 7%. Notwithstanding this achievement, each patient suffered chronic episodes of hypoglycemia that had not been corrected by repeated medical interventions and review of their SMBG data. In all cases, the hypoglycemia was so severe that it qualified them, inter alia, for islet cell transplantation. We suggest that this occurred because neither they nor their providers had the crucial outcomes data presented in such a way as to teach them which potential combinations of changes in the prescriptions might end the recalcitrant, iatrogenic hypoglycemia. Clearly, in these subjects the hypoglycemia suggests a treatment-related etiology.

Although the changes suggested in the simulation were usually minor, it was rare that only one dosing change

would suffice in this population. Several potential changes were suggested that were oftentimes counterbalancing in terms of total daily medication dosages. Not shown in summary data presented here are the numerous, antecedent prescription changes, repeated education, and supplementary counseling sessions that had all proved futile. In all patients, hypoglycemia had persisted until islet transplantation.

In contrast, using the simulator interactively, it seemed easy (almost intuitive) for the provider to eliminate the displayed risks of hypoglycemia and to do so without unduly compromising overall glycemic control. To facilitate this, the simulator dynamically estimated glycemic control, which it then summarized simply as A1C. In this way, providers could witness the predicted effects on glycemic control of any potential changes they wished to prescribe.

Since the major clinical complaint of these subjects was intractable **hypo**glycemia, the goal of simulated changes was primarily to reduce the number of profile points that risked **hypo**glycemia with only secondary emphasis on eliminating existing or consequential **hyper**glycemia. Because this was a retrospective, observational study, the actual effects are unknown of the potential prescription changes that the RxChecker suggested. However, subsequent work[11] has shown that knowledge of future glycemia and future risks of hypoglycemia can indeed guide providers to modify their prescriptions to avert hypoglycemia in actual clinical practice. Of the many reasons why providers may fail to reduce hypoglycemia, results from the control group in the cited study[11] suggest that compliance in using the tool may be most significant.

It is important to note that the prospective treatment strategy, implicit in these prescription checks, should be to resolve major complaints first. For hypoglycemia, this may be done even if the simulator predicts a near-term rise in A1C, as a subsequent prescription check will be done, not in 3 months but usually in just a week or two. If this subsequent check confirms that the risks of **hypo**glycemia have been eliminated, it would then be wise to pursue correcting gently those profile points that now suggest **hyper**glycemia. Educating the provider how to do this without risking **hypo**glycemia is what the RxChecker tool and its training course are designed to support. We suggest that repetition of this cycle may help providers close the circle of care with their patients and thereby meet recommended guidelines[1] more safely.[3–5]

In the present observational study, we showed that while it may be possible to eliminate hypoglycemia in the first instance, doing so may be at the expense of a rise in one or more profile points in the glycemic profile. Obviously, single use of the RxChecker device does not resolve all metabolic control issues. In this light, repeated use of the RxChecker is indicated at intervals best specified by the providers. These intervals may range from weekly in cases of pregnancy or labile diabetes, to monthly for stable type 1 diabetes, and to quarterly just before follow-up visits for stable type 2 diabetes.

Collaboration in beta clinical studies will be welcomed to show how this personal diabetes database and prescription checker may be extended to support diabetes education[12] in diverse populations.

Pragmatically, there must be considerations as to the validity, safety, and efficacy of such devices. In the context of Food and Drug Administration regulations, the patient is indeed intended to carry the device and is responsible for inserting their SMBG and related data. In this respect, it is fully like an electronic version of the notebook diary they all use. Using the tool to check the Rx may be valuable in teaching patients when to trigger an encounter with their providers in order to obtain timely changes to the prescription. At present, the provider can configure the device for any of these scenarios.

Often, physicians encourage type 1 patients on intensive basal-bolus regimens to slavishly follow their insulin prescriptions. For those not so inclined, we have used our modeling expertise to help patients adjust each meal's dose automatically according to the actual meal, current blood glucose, previously injected insulin, exercise, stress, and so on, starting from the basic, prescribed amount.[25] This alternative is not usually accepted. In its place many doctors have been persuaded that patients would be better served if the adjustment process started with the basal dose, using a continuous monitor while fasting to really get it right, before moving on to focus on bolus doses. We suggest that this is true with manual methods. However, now with RxChecker and adequate profile data, this can be achieved routinely on the run, as it were. Predicted profiles are fundamental to solving all the equations simultaneously instead of seriatim. Furthermore, the process of prescription checking can be repeated ad nauseam. In fact, it can even be the provider's decision to enable the process for selected patients and thereby take herself essentially out of the loop between follow-up visits. In this way, the MyDiaBase+RxChecker

device can provide ongoing second opinions, as it were, for the patient to tune their dosing repeatedly in order to meet the targets preset by the provider.

The present study included ~10 profiles/patient collected over a 12-month period. This allowed the investigators to repeat the exercise in each patient while observing that concurrent clinical interventions by providers (blinded to the predictions) were remarkably incapable of resolving their patients' hypoglycemia. In part, this failure fortified the decision to include these patients as candidates for islet cell transplantation. It also suggests that a screening procedure may be implemented to rule out future candidates whose difficulties with diabetes can be corrected by objective prescription checks using the RxChecker device.

Here the simulation model assumes that all variables and factors contributing to the variance observed remain similar (diet, lifestyle, exercise, stress, metabolic parameters, etc.) and that only changes in insulin affect the model's glycemic predictions. In the long run, this assumption cannot hold but it does in the short (2-day) term. Therefore we can use the predicted consequences of small changes to adjust insulin doses before administering them. This is the power of glycemic prediction.

With the simulator inside RxChecker, providers need not commit to the same, old-fashioned approach of the past, "do exactly the same thing every day so we can adapt a fixed prescription to it." Instead, patients on basal-bolus regimens are able to exercise, eat different meals at different times, and take lifestyle events such as stress and preprandial glucose into account when deciding on a bolus dose. Even in this complex diabetes management environment, RxChecker can clearly suggest when any bolus or basal dose, or the way in which it was determined, needs to be changed. This is the benefit of ongoing prescription checks that the RxChecker device supports. It is also the rationale for the present study in a homogeneous population of complex-to-manage type 1 diabetic patients all suffering from intractable hypoglycemia.

Fundamental to every prescription check are data from current SMBG contours. SMBG, along with diabetes education, forms two of the cornerstones of contemporary diabetes care and self-management. SMBG is promoted heavily,[13] producing reliable data,[14] the acceptability of which depend on recurrent practice.[15] It is ideally suited to supporting this novel application in the MyDiaBase+RxChecker device.

Severe hypoglycemia is likely to occur with a multiple injection regimen, particularly in children.[3,5] Cryer[16] has focused much effort on hypoglycemia in contemporary diabetes management and recognized it as the limiting factor in the management of type 1 diabetes mellitus.[17] We suggest that the concept of a *diabetes dilemma* takes treatment-related hypoglycemia one step further by linking it inversely with A1C outcomes. For most populations this is an unsatisfactory risk, although some clinicians find it an acceptable risk for certain patients.

MyDiaBase+RxChecker is a remote monitoring device but it differs in complexity from other telemedicine technologies in diabetes. Since the early 1990s,[18] blood glucose monitors have been able to store SMBG in internal memory. Some can communicate the resulting array of numbers to the user visually or to computers in the providers' clinics and offices.[19] Because these devices do not capture either the medication prescription or identify the meal period or allow annotating lifestyle details, they are not really suited for supporting diabetes prescription checks.

Over the last 2½ decades,[20,21] a potential role of computers in the management of diabetes has been resurrected many times, more recently for decision support.[22–24] Some devices can run locally in the patients' personal computers but link to a remote database in the clinic.[25,26] Such links are expensive and may risk personal data privacy and security, requiring added layers of complexity. The hope has been that providers would welcome the flood of data, but this has generally not been the case.[27]

In contrast, the MyDiaBase+RxChecker device is inexpensive, robust, and small enough to be carried in a pocket or purse, on a key chain, or attached to a lanyard about the neck. It is provider-friendly in that it obviates the need to study the patient's daily diary. The internal database is secure and can be backed up automatically so that it can be restored should the device be damaged, lost, or stolen. However, like all software, it is a work in progress. We expect its capabilities to expand with beta testing and future clinical experience.

Funding:

Sources of funding are Diabetes Control and Complications Treatment Initiative; National Institutes of Diabetes and Digestive and Kidney Diseases of the U.S. National Institutes of Health; and Juvenile Diabetes Foundation.

Disclosure:

Dr. Albisser is employed by Diabetes Control & Complications Treatment Initiative.

References:

1. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care. 2005(28):S4-36.
2. Ford ES, Li C, Little RR, Mokdad AH. Trends in A1C concentrations among U.S. adults with diagnosed diabetes from 1999 to 2004. Diabetes Care. 2008;31(1):102-4.
3. Verrotti A, Chiarelli F, Blasetti A, Bruni E, Morgese G. Severe hypoglycemia in insulin-dependent diabetic children treated by multiple injection insulin regimen. Acta Diabetol. 1996;33(1):53-7.
4. U.S. Department of Health and Human Services. National Heart Lung and Blood Institute. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [cited 2008 Feb]. Available from: http://www.nhlbi.nih.gov/health/prof/heart/other/accord/.
5. The Diabetes Control and Complications Trial Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. The DCCT Research Group. Am J Med. 1991;90(4):450-9.
6. USB flash drives [cited 2008 Feb]. Available from: http://en.wikipedia.org/wiki/USB_flash_drive.
7. Albisser AM, Sakkal S, Wright C. Home blood glucose prediction: validation, efficacy and safety testing in diabetes. Diabetes Technol Ther. 2005;7(3):487-96.
8. Albisser AM. A graphical user interface for diabetes management that integrates glucose prediction and decision support. Diabetes Technol Ther. 2005;3(2):264-73.
9. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. Diabetes Care. 2002;25(2):275-8.
10. Web pages that perform statistical calculations [cited 2008 Feb]. Available from: http://statpages.org/#Comparisons.
11. Albisser AM, Wright CE, Sakkal S. Averting iatrogenic hypoglycemia through glucose prediction in clinical practice: progress towards a new procedure in diabetes. Diabetes Res Clin Pract. 2007;76(2):207-14.
12. Mensing C, Boucher J, Cypress M, Weinger K, Mulcahy K, Barta P, Hosey G, Kopher W, Lasichak A, Lamb B, Mangan M, Norman J, Tanja J, Yauk L, Wisdom K, Adams C. National standards for diabetes self-management education. Diabetes Care. 2005;28 Suppl 1:S72-9.
13. American Diabetes Association. Self-monitoring of blood glucose. Diabetes Care. 1994;17(1):81-6.
14. Ziegler O, Kolopp M, Got I, Genton P, Debry G, Drouin P. Reliability of self-monitoring of blood glucose by CSII-treated patients with type I diabetes. Diabetes Care. 1989;12(3):184-8.
15. Kabadi UM, O'Connell KM, Johnson J, Kabadi M. The effect of recurrent practice at home on the acceptability of capillary blood glucose readings. Accuracy of self blood glucose testing. Diabetes Care. 1994;17(10):1110-23.
16. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care. 2003;26(6):1902-12.
17. Cryer PE. Banting lecture. Hypoglycemia: the limiting factor in the management of IDDM. Diabetes. 1994;43(11):1378-89.
18. Williams CD, Scobie IN, Till S, Crane R, Lowy C, Sonksen PH. Use of memory meters to measure reliability of self blood glucose monitoring. Diabet Med. 1988;5(5):459-62.
19. Strowig SM, Raskin P. Improved glycemic control in intensively treated type 1 diabetic patients using blood glucose meters with storage capability and computer-assisted analyses. Diabetes Care. 1998;21(10):1694-8.
20. Rodbard D. Potential role of computers in clinical investigation and management of diabetes mellitus. Diabetes Care. 1988;11 Suppl 1:54-61.
21. Zimmet P, Lang A, Mazze RS, Endersbee R. Computer-based patient monitoring systems. Use in research and clinical practice. Diabetes Care. 1988;11 Suppl 1:62-6.
22. Berger MP, Gelfand RA, Miller PL. Combining statistical, rule-based, and physiologic model-based methods to assist in the management of diabetes mellitus. Comput Biomed Res. 1990;23(4):346-57.
23. Mazze RS. Computers and diabetes therapy: key variables and quality of data for clinical decision-making. Horm Metab Res Suppl. 1990;24:97-103.
24. Morrish NJ, Cohen DL, Hicks B, Keen H. A controlled study of the effect of computer-aided analysis of home blood glucose monitoring on blood glucose control. Diabet Med. 1989;6(7):591-4.
25. Albisser AM, Harris RI, Albisser JB, Sperlich M. The impact of initiatives in education, self-management training, and computer-assisted self-care on outcomes in diabetes disease management. Diabetes Technol Ther. 2001;3(4):571-9.
26. Marrero DG, Kronz KK, Golden MP, Wright JC, Orr DP, Fineberg NS. Clinical evaluation of computer-assisted self-monitoring of blood glucose system. Diabetes Care. 1989;12(5):345-50.
27. Meyerhoff C, Bischof F, Pfeiffer EF. Long-term experiences with a computerized diabetes management and glucose monitoring system in insulin-dependent diabetic patients. Diabetes Res Clin Pract. 1994;24(1):1-7.