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Glucose prediction, iatrogenic hypoglycemia and medical intervention: the role of the Diabetes Data Centre

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Abstract

Background: Glycemic control is fundamental to the management of diabetes and maintenance of health. Popular measures of performance in glycemic control include A1c and self-monitoring of blood glucose (SMBG). As measures of performance, A1c has perspective but fails to recognize hypoglycemia while SMBG lacks overall perspective but finds use mainly by patients to self evaluate their glycemic status and current response to therapy. Predictions of future glycemia and the risks of hypoglycemia are now available to assist providers with interventions that avert iatrogenic hypoglycemia.

Methods and results: A diabetes data centre has been created. It incorporates the customary hardware and, besides the usual database services, provides an engine for glycemic prediction that can utilize SMBG data captured remotely. Clinical use of the engine's glucose predictions support interventions that avert iatrogenic hypoglycemia while allowing providers to optimize glycemic control. Other centre resources include distribution of supporting software and user instruction.

Conclusions: Use of the resources of a shared diabetes data centre can empower providers to identify problems in glycemic control, take proactive action, adopt beneficial strategies, evaluate outcomes and, most importantly, avoid interventions that engender hypoglycemia. In this light, glycemic predictions appear crucial to better diabetes care.

Keywords: Glycemic control; Diabetes therapy; Diabetes self management; Telemedicine; Decision support system

Contents

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1. Introduction

Glycemic control is fundamental to the management of diabetes [1]. Prospective randomized clinical trials such as the Diabetes Control and Complications Trial [2] and the U.K. Prospective Diabetes Study [3,4] have shown that improved glycemic control is associated with sustained decreased rates of retinopathy, nephropathy, and neuropathy. In these trials, treatment regimens that reduced average A1C to ∼1% above the upper limits of normal were associated with fewer long-term microvascular complications. However, intensive control was found to increase the risk of hypoglycemia and weight gain [5,6]. For glycemic control, several measures of performance are common, including A1C and the self-monitoring of blood glucose (SMBG). Both have limitations which may in part account for the failure to meet the DCCT/UKPDS goals in clinical practice.

Although A1C is the providers' gold standard for overall glycemic control, it fails to identify both the polyglycemia (wide fluctuations in blood glucose levels) and the hypoglycemia that frequently accompanies aggressive control. This failure is a direct consequence of the averaging nature of the chemical glycosylation process [7].

SMBG [8] is widely used by patients to evaluate their current response to therapy, identify hypoglycemia and assess if glycemic targets are being achieved. Additionally, archived SMBG values in logbooks and meter memories contain valuable information about both patient [9] and provider [10] performance in glycemic control. Attempts have been made to present these data using computers to construct "ambulatory glucose profiles" and "modal days" [11,12]. Though deemed to be useful [13] to the providers and patients, these methods have not been widely accepted, especially since early reports suggested a lack of benefit [14–16]. Even contemporary systems for this purpose have rather complex graphical user interfaces [17]. Thus, in spite of the personal effort in SMBG and the significant costs of the materials and supplies, SMBG data are not providing real value, especially in guiding interventions.

In light of the above, we suggest full use of patient data from diabetes self management is needed. For providers, use of such treatment outcomes would be valuable in deciding among various clinical courses of action. Most importantly, glycemic predictions would afford clear guidance in optimizing glycemic control while averting hypoglycemia through alterations in therapy whether educational, nutritional, pharmacological, device mediated, or any combination thereof. Accordingly, we here describe the crucial role of the diabetes data centre as a universal resource.

2. Methods

2.1. Supporting hardware

The Diabetes Data Cnter (DDC) is secured, protected [18] and meets privacy requirements. A dynamic relational database (Microsoft Access 2000) is deployed on a server (Hewlett-Packard, NetServer LC3 running Microsoft Windows NT version 4, SP 6). The server supports a local area network (LAN) in the DDC and includes an interface (WesTell Wirespeed 2200B, Duluth, GA) to the WWW via a high speed data connection to the local internet service provider (BellSouth, Hollywood, FL). For additional security, the server includes an integral firewall (Microsoft Proxy Server Version 2.0). It also supports a hardware telephony interface (Dialogic Corporation, D/41ESC) through custom IVR software.

2.2. Supporting software

The software supporting the GUI and the telephone interface is written in Visual Basic (Microsoft Visual Basic Pro) for the 32 bit environment. The software is available either on CD or for direct download from an ftp site hosted on the server in the DDC and can be installed on any of the PCs running any version of Windows 95+.

2.3. User instructions

User instructions can be given by the staff of the DDC both for the providers and initially for the patients. These are rarely face-to-face and usually either over the telephone or over the WWW. In most cases, an initial working familiarity can be created in about 15 minutes with subsequent follow-up as needed for providers to explore other features in depth.

3. Results

3.1. DDC resources for data capture: patient interfaces

Patients can be instructed to contribute their daily self management data to the remote database using the resources provided by the DDC. In this manner, the contents of the patient's SMBG diary and their notebook lifestyle annotations (diet, exercise, stress)

can be captured into their personal database in a standardized way. It is possible for remote patients to do this using only a touch-tone telephone to dial into the DDC's interactive voice response interface. Alternately, patients can connect to the DDC via the WWW from their home PC. Except for the daily effort amounting to less than 10 minutes, there are no costs to the patient to acquire these data.

3.2. DDC resources for data review: provider interface

Providers can access the central database using a custom GUI available from the DDC. According to their workgroup credentials (username and password), providers have full access to the server in the DDC but are restricted only to the data from their cohort of registered patients.

The main window of the GUI used by the providers is shown in Fig. 1. It presents the patient's name and the current date. The patient's body weight is shown along with the result of an analysis of its trend. A tabulation of the real risks of hypoglycemia and hyperglycemia are shown. These are calculated over the antecedent 30 days of data in the patient's database. The provider must select whether the patient has been instructed to use estimates of absolute or differential carbohydrate counting in their self management. A framed grouping includes the medication prescriptions arrange by meal period, by type and by dosage. Dosing decision support is facilitated with pairs of up-down buttons which the provider can simply click to increment or decrement each specific dosage. The bar graphs in the frame to the right display the forecasts generated by the glucose prediction engine. These are shown at each meal period and can include predictions of pre- and post-prandial glycemia. Each range highlights a circled, predicted value along with a graded, shaded area which by extent shows the risks of both hyper- and hypo-glycemia. Hovering the mouse pointer over the lower extent of the shading indicates the risks of hypoglycemia. In this case, the risks are 3% after Breakfast, 7% before Lunch, and 5% after Dinner. A banner at the top right announces when there are risks of hypoglycemia. The glycemic predictions are automated. Thus, if the provider elects to decrease the Regular insulin at Breakfast, the prediction engine is re-invoked and the effects of such a change are reflected in the predicted readings across the day. Each shaded range changes as appropriate to indicate whether the proposed intervention will increase or decrease the predicted value and the pending risks of future hyper- and hypo-glycemia. Medications at other times of the day can be shown by selecting other meal periods, also with a click of the user's mouse. In this way, several interventions can be done in a single session in order to optimize the medication dosages and improve

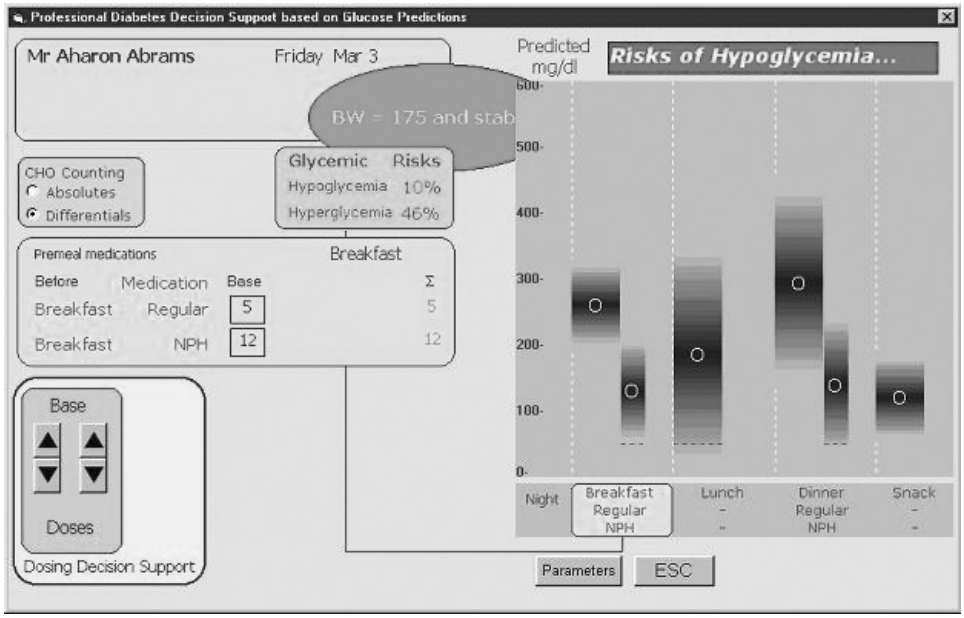

Fig. 1. Computer screen-shot from the GUI used by the provider to review outcomes and intervene as required. The display supports interventions with predictions of future glycemia together with the future risks of hypoglycemia. Data supporting the display that guide such interventions include patient SMBG and life-style factors which are captured by telephone or WWW and then stored in a central server in the remote diabetes data center.

metabolic control while minimizing the risks of future hypoglycemia. A Parameters button invokes a modal display to allow the provider to customize the settings for each patient's carbohydrate sensitivities, their glucose sensitivity to stress, their specific glycemic thresholds for hyper- and hypo-glycemia, and their target for post prandial blood glucose levels. The GUI has been described elsewhere [19]. A following screen (not shown) allows the provider to explore the effects of their prescriptions for carbohydrate counting, exercise and stress. Also not shown are the collection of free text comments which are generated automatically to help in documenting each of the provider's interventions. A notebook display (also not shown) is available that excludes the foregoing glycemic predictions and decision support automation but, in column format, presents the daily pre meal blood glucose concentrations, medications (prescribed and taken), carbohydrate counts, and other life-style events as annotated by the patient.

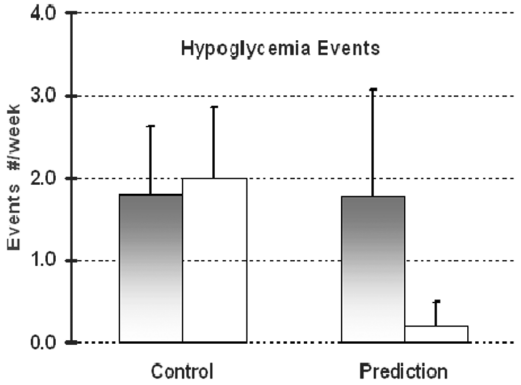

Fig. 2. Iatrogenic hypoglycemia is averted when interventions are supported by glycemic predictions (Prediction group, right) but not when similar interventions are done without benefit of glycemic predictions (Control group, left). Interventions were done weekly using data from a remote diabetes data center charged to collect daily self management data electronically from patients. Shaded bar, frequency at baseline; clear bar, frequency after interventions for 2 months.

3.3. DDC resources for glycemic prediction

Glycemic predictions are generated by an engine that dynamically accesses medical, personal and SMBG data contained in the database on the server in the DDC. Only current data are used to form such predictions. Glycemic predictions generated in this way have been validated [20]. The safety and efficacy of using these predictions in diabetes management have also been demonstrated [21].

3.4. DDC resources for support of medical interventions

As shown in Fig. 2, with the help of glycemic predictions, interventions by the providers readily succeeded in reducing rates of hypoglycemia 9-fold, from averages of 1.8 ± 1.3 (1 to 5) at baseline dropping to just 0.2 ± 0.3 (0 to 1) episodes/week at follow up. Hypoglycemia declined in all subjects in the Prediction group. In 5/11 subjects, it virtually disappeared while in another 5/11 it dropped to just once a month. In 1/11, it fell from 20/month to 1/month. On average, the elapsed time to achieve these results was 46 ± 16 (17 to 67) days.

Without the help of glycemic predictions in the Control group, the interventions by the providers failed to change the observed rates of hypoglycemia from baseline with 1.8 ± 0.8 (1 to 3) to follow up with 2.0 ± 0.9 (1 to 3) episodes/week after a full elapsed time of days.

The changes in rates of hypoglycemia in the Prediction group were accomplished through provider mediated interventions which included changes in the doses of medications. In the Prediction group, daily insulin doses were reduced by an average of −9 Units/day ($P < 0.01$). In the Control group, the total insulin doses barely changed from baseline to follow up. The ranges of changes in daily insulin dosages made by the providers were −4 to 16 U/d in the Control group and −27 to 0U/d in the Prediction group. Mean pre meal glycemia and overall mean glycemia (not shown) demonstarted no discernable changes attributable to the interventions (or the dosing changes) by the providers. Glycated hemoglobin A1c levels (also not shown) were similar in both groups at baseline and showed minor reductions which did not reach statistical significance after the 2 month period of the study.

4. Discussion

Any diabetes data centre that will meet all clinical and administrative requirements is both expensive to create initially and costly to maintain subsequently. Yet, without such a resource charged with remotely capturing patient data, providers are denied basic information to support either their monitoring and/or medical interventions.

A shared resource (The Diabetes Data Centre) is now available that specializes in automated data capture from remote patients. The information is secured in user databases that can be accessed by the providers.

All tasks are supported by software available from the centre. Instructions are provided on its use.

Uniquely, an engine that utilizes the SMBG and individual patient data can form glycemic predictions [20,21] supporting medical interventions. In this way, providers can not only optimize glycemic control but also avert hypoglycemia. Rigorous outcomes measures of glycemic control can also be provided [22]. This work builds on previous efforts [23–25].

Insofar as a reduction in observed rates of hypoglycemia might follow downward changes in insulin doses, the Prediction group revealed a significant drop in insulin of 9 Units/day. Clearly, this may account in large part for the observed reduction in the rates of hypoglycemia in this group, especially since there were no such changes in the Control Group. Most importantly, this reduction in daily insulin dosages in the Prediction group did not result in any changes whatever in mean pre meal glycemia or glycated hemoglobin A1c levels. This suggests that the desirable reductions in rates of hypoglycemia realized by the providers were not accompanied by an undesirable deterioration in glycemic control.

Possibly, the observed reductions also occurred for other reasons. In this regard, adjustments upward and downward in the pre meal insulin doses may balance and not change the total daily dose. Clearly, such fine changes could have had a significant impact on reducing the rates of hypoglycemia. The observed ranges of changes in daily insulin doses suggest that interventions were frequent and effective, most likely facilitated by the glucose predictions which were being exploited by the providers during their weekly review of their patients' data.

With similar relative effort, the failure of the providers' frequent interventions to reduce rates of hypoglycemia in the Control group suggest that standard methods are not effective. Ostensibly, lacking the insights afforded by glycemic predictions may be a serious handicap in managing diabetes. A continuing review (data not shown) of the outcomes in the Control group reveals that their hypoglycemia persists relentlessly. For the subjects in the Prediction group, the reduction in hypoglycemia was provisional. Hypoglycemia returns specifically when decision support is withheld or if decision support is no longer based on glycemic predictions. However, in those cases where the procedure is repeated by re-applying interventions based on glycemic predictions, a reduction in the rates of hypoglycemia is again achievable, even with different regimens. In retrospect, it seems that transference of skills gained by providers using the glycemic predictions does not occur. This suggests that glycemic prediction, especially in regards to the future risks of hypoglycemia, is neither intuitive nor an acquirable skill but seemingly must be based on rigorous, repeated, on going analysis of SMBG data using the numerical methods of the glucose prediction engine.

Our findings indicate that providers, given direct evidence of a real risk of hypoglycemia, will tend to this first and not to optimizing glycemia. However it is important to note that in reviewing a patient's predicted glycemic profile, there may be opportunities to avert hypoglycemia as well as to optimize glycemia. With all the glycemic predictions displayed on-screen, it is possible to do multiple interventions in one review session. Thus, averting hypoglycemia is best done while optimizing glycemia.

Finally, use of the WWW to connect providers and their designated patients to the data centre implies that a single centre can serve virtually all users regardless of their location. For patients without access to the WWW, a telephone interface can be substituted using the alternative interactive voice response channel for patient data capture and provider intervention. Further studies will be needed to refine the service and explore its clinical potential in diabetes disease management.

References

[1] American Diabetes Association. Standards of Medical Care for Patients With Diabetes Mellitus. Diabetes Care 26 Suppl 1 (2003).
[2] Diabetes Control and Complications Trial Research Group, The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329 (1993) 977–986.
[3] UK Prospective Diabetes Study Group, Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352 (1998) 837–853.
[4] UK Prospective Diabetes Study Group, Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34), Lancet 352 (1998) 854–865.
[5] The Diabetes Control and Complications Trial Research Group, Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial, Am J Medicine, 90 (1991) 450–459.
[6] The DCCT Research Group, Diabetes Control and Complications Trial (DCCT): results of feasibility study, Diabetes Care 10 (1987) 1–19.
[7] H.F. Bunn, D.N. Haney, S. Kamin, K.H. Gabbay, P.M. Gallop, The biosynthesis of human hemoglobin A1c. Slow glycosylation of hemoglobin in vivo, J Clin Invest 57 (1976) 1652–1659.
[8] American Diabetes Association, Self-monitoring of blood glucose (Consensus Statement), Diabetes Care 17 (1994) 81–86.

[9] S.M. Strowig, P. Raskin, Improved glycemic control in intensively treated type 1 diabetic patients using blood glucose meters with storage capability and computer-assisted analyses, Diabetes Care 21 (1998) 1694–1698.
[10] M.P. Berger, R.A. Gelfand, P.L. Miller, Combining statistical, rule-based, and physiologic model-based methods to assist in the management of diabetes mellitus, Comput Biomed Res 23 (1990) 346–357.
[11] D. Rodbard, Potential role of computers in clinical investigation and management of diabetes mellitus, Diabetes Care 11 Suppl 1 (1988) 54–61.
[12] R.S. Mazze, Computers and diabetes therapy: key variables and quality of data for clinical decision-making, Horm Metab Res Suppl 24 (1990) 97–103.
[13] P. Zimmet, A. Lang, R.S. Mazze, R. Endersbee, Computer-based patient monitoring systems. Use in research and clinical practice, Diabetes Care 11 Suppl 1 (1988) 62–66.
[14] N.J. Morrish, D.L. Cohen, B. Hicks, H. Keen, A controlled study of the effect of computer-aided analysis of home blood glucose monitoring on blood glucose control, Diabet Med 6 (1989) 591–594.
[15] D.G. Marrero, K.K. Kronz, M.P. Golden, J.C. Wright, D.P. Orr, N.S. Fineberg, Clinical evaluation of computer-assisted self-monitoring of blood glucose system, Diabetes Care 12 (1989) 345–350.
[16] C. Meyerhoff, F.Bischof, E.F. Pfeiffer, Long-term experiences with a computerized diabetes management and glucose monitoring system in insulin-dependent diabetic patients, Diabetes Res Clin Pract 24 (1994) 1–7.
[17] T. Bailey, Diabetes software can help you gain insights into your blood sugar patterns, http://www.bddiabetes.com/us/stayingontarget/issue2/testingtips.asp. Accessed Nov, 2004
[18] A.M. Albisser, J.B. Albisser, L. Parker, Patient confidentiality, data security, and provider liabilities in diabetes management, Diabetes Technol Ther 5 (2003) 631–640.
[19] A.M. Albisser, A graphical user interface for diabetes management that integrates glucose prediction and decision support, Diabetes Technol Ther 7 (2005) 264–273.
[20] A.M. Albisser, D. Baidal, R. Alejandro, C. Ricordi, Home blood glucose prediction: clinical feasibility and validation in islet cell transplantation candidates, Diabetologia 48 (2005) 1273–1279.
[21] A.M. Albisser, S. Sakkal, C. Wright, Home blood glucose prediction: validation, efficacy and safety testing in Diabetes, Diabetes Technol Ther 7 (2005) 487–496.
[22] A.M. Albisser, R. Alejandro, L.F. Meneghini, C. Ricordi, How Good is your Glucose Control? Diabetes Technol Ther 7 (2005) 863–875.
[23] C.D. Williams, I.N. Scobie, S. Till, R. Crane, C. Lowy, P.H. Sonksen, Use of memory meters to measure reliability of self blood glucose monitoring, Diabet Med 5 (1988) 459–462.
[24] R.S. Mazze, H. Shamoon, R. Pasmantier, D. Lucido, J. Murphy, K. Hartmann, et al, Reliability of blood glucose monitoring by patients with diabetes mellitus, Am J Med. 77 (1984) 211–217.
[25] R.S. Mazze, R. Pasmantier, J.A. Murphy, H. Shamoon, Self-monitoring of capillary blood glucose: changing the performance of individuals with diabetes, Diabetes Care 8 (1985) 207–213.