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SYMPOSIUM

A Model of Self-Treatment Behavior, Glucose Variability, and Hypoglycemia-Associated Autonomic Failure in Type 1 Diabetes

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Abstract

Background:

Type 1 diabetes patients face a lifelong behaviorally controlled optimization problem: maintaining strict glycemic control without increasing the risk of hypoglycemia. Because internal insulin secretion in type 1 diabetes (T1DM) is practically absent, this optimization is entirely dependent on the interplay among (i) self-treatment behavior, (ii) interaction between exogenous insulin and carbohydrates utilization, and (iii) internal defenses against hypoglycemia. This article presents a mathematical model and a computer simulation of the relationship among self-treatment in T1DM, blood glucose (BG) variability, and hypoglycemia-associated autonomic failure (HAAF).

Method:

A stochastic behavioral self-control process was coupled with a dynamical system simulation of the dampening effect of counterregulation on BG oscillations. The resulting biobehavioral control system was compared to data from a field clinical trial (85 T1DM patients, 21–62 years old, T1DM of at least 2 years duration, and at least two documented severe hypoglycemia episodes during the previous year).

Results:

The mathematical simulation was able to reproduce characteristics of hypoglycemic events observed during a field clinical trial, such as temporal clustering of hypoglycemic episodes associated with HAAF and occurrence of severe hypoglycemia as a result of periods of HAAF augmented by increased BG variability.

Conclusion:

This investigation offers a mathematical model of HAAF—the primary barrier to intensive insulin treatment. This combined modeling/computer simulation/data analysis approach explains the temporal relationship among behaviorally induced hypoglycemia, glucose variability, and autonomic failure in T1DM. This explanation is valuable not only because it indicates that signs of HAAF can be detected in patients' natural environment via self-monitoring or continuous glucose monitoring, but also because it allows for tracking of the risk of severe hypoglycemia over time.

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Abbreviations: (BG) blood glucose, (CR) counterregulation, (HAAF) hypoglycemia-associated autonomic failure, (SH) severe hypoglycemia, (T1DM) type 1 diabetes, (T2DM) type 2 diabetes

Keywords: counterregulation, HAAF, hypoglycemia, modeling, risk of hypoglycemia, simulation

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Introduction

In health, blood glucose (BG) is tightly controlled by a hormonal network that includes gut, liver, pancreas, and brain, ensuring stable fasting BG levels (~4.5–5.5 mmol/liter) and transient postprandial glucose fluctuations. Intensive insulin treatment used to maintain nearly normal levels of glycemia reduces chronic complications in type 1 (T1DM[1]) and type 2 diabetes (T2DM[2]) markedly, but is associated with a potentially life-threatening risk of severe hypoglycemia (SH), a result from insulin overtreatment, which may reduce warning symptoms and hormonal defenses.[3] Consequently, hypoglycemia has been identified as the primary barrier to optimal diabetes management.[4] Thus, people with diabetes face a lifelong behaviorally controlled optimization problem: maintaining strict glycemic control without increasing their risk for hypoglycemia.[5] This struggle for tight glycemic control results in large BG fluctuations over time, a process influenced by many external factors, including the timing and amount of insulin injected, food eaten, and physical activity. In other words, BG fluctuations in diabetes are the measurable result of the action of a complex dynamical system influenced by many internal and external factors. The macro (human)-level optimization of this system depends on self-treatment behavior. Because internal insulin secretion is practically absent in T1DM, this optimization is entirely dependent on the three feedback processes presented in **Figure 1**: (i) self-treatment behavior, (ii) interaction between exogenous insulin and carbohydrate utilization, and (iii) internal hormonal defenses against hypoglycemia known as hypoglycemia counterregulation (CR). The biobehavioral control of T1DM is therefore composed of (i) a process of commonly stable glucose fluctuation interrupted by generally random hypoglycemia-triggering behavioral events (e.g., insulin overtreatment, missed food, or excessive exercise[6,7]), (ii) an internal process of glucose metabolism depending on a person's insulin sensitivity,[8] and (iii) counterregulation that counteracts hypoglycemia, but suffers from an occasional desensitized autonomic system as a consequence of repeated hypoglycemic episodes, known as hypoglycemia-associated autonomic failure (HAAF). HAAF has been observed in both T1DM[9] and T2DM[10] and has been studied extensively since 1992.[5,11–14] Studies also show that HAAF should be reversible and that the replenishment of counterregulatory abilities could be achieved through avoidance of mild hypoglycemia.[15] The recovery process has been estimated to take several days, likely at least 72 hours.[16]

This article proposes a model quantifying the interplay between behavior and physiology via integration of behavioral control of T1DM and HAAF. The model is validated via a computer simulation that reproduces key features of the occurrence of hypoglycemia observed in a clinical study: clustering of hypoglycemic episodes in time[17] and a higher risk of SH within periods of increased glucose variability.[16] The model is descriptive, not discussing in detail the specific physiology of glucose–insulin interaction, which is outside the scope of this article.

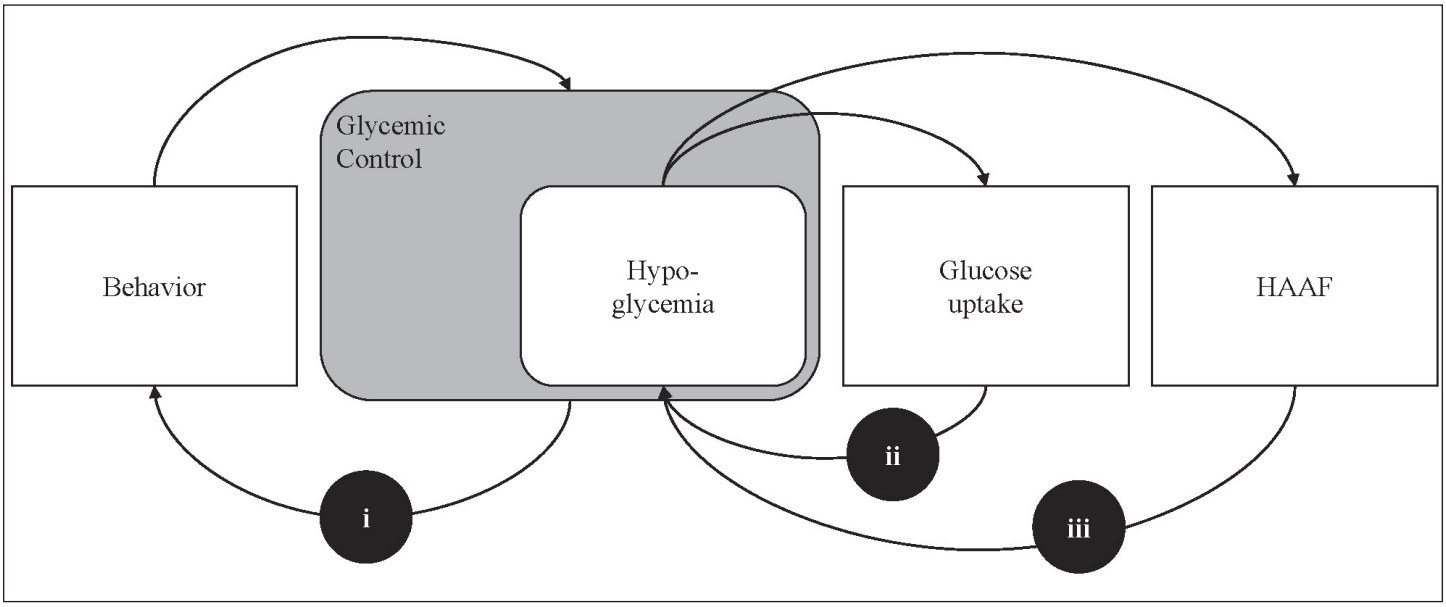

Figure 1. Feedback loops.

Methods

The mathematical model describing the relationships among self-treatment behavior, hypoglycemia, and HAAF is based on the following assumptions: (i) BG fluctuations in T1DM are driven by insulin–glucose interaction and are dampened down by counterregulatory responses that protect against extreme hypoglycemic deviations; (ii) combinations of behavioral events trigger hypoglycemia, which increases the chance of subsequent hypoglycemic episodes because of weakened counterregulatory response; and (iii) avoidance of hypoglycemia restores counter-regulatory ability.

Our study is then composed of two parts: (1) a computer simulation of the interplay between a behavioral random process and a deterministic representation of the insulin–glucose system. From this simulation we extract two qualitative characteristics of blood glucose concentration: variability and timing of occurrence of hypoglycemic events; the latter defined as mild (<4.5 mmol/liter), moderate (<4 mmol/liter), and severe (<3.5 mmol/liter). (2) A field study is then used to demonstrate the soundness of the proposed model.

Computer Simulation

Behavioral Triggers of Hypoglycemia. In order to formally describe the process of behavioral self-treatment we have previously introduced a stochastic model of self-regulation behavior, which gives a probabilistic description of the pattern: internal condition–perception/awareness–appraisal–self-regulation decision.[18] To summarize, internal events, such as low (or high) BG episodes, are followed by self-regulation behavioral sequences that, if inappropriate, could lead the patient to severe hypoglycemia (or extreme hyperglycemia) and, if appropriate, lead to avoidance of these extreme situations.

Because of the recurrent nature of diabetes self-treatment behavior, behavioral self-regulation can be approximated by a generally periodic renewal process with a significant random component, which causes downward and upward BG fluctuations. On rare occasions this process escalates into behaviorally induced hypo/hyperglycemia, which is a result from the superposition of several low-probability events.[17] The timing of such a process can therefore be simulated by a Wiener process: the duration between events is a normal random variable with mean equal to the desired seasonality. The intensity of the perturbations is governed by the combination of two separate perturbations of opposite direction (e.g., a meal and an insulin bolus). The joint probability distribution of event intensity is set so that positive and negative perturbations balance themselves out most of the time.

Glucose Uptake, HAAF, and Counterregulatory Replenishment: The behavioral perturbations described earlier are superimposed upon two underlying components: an

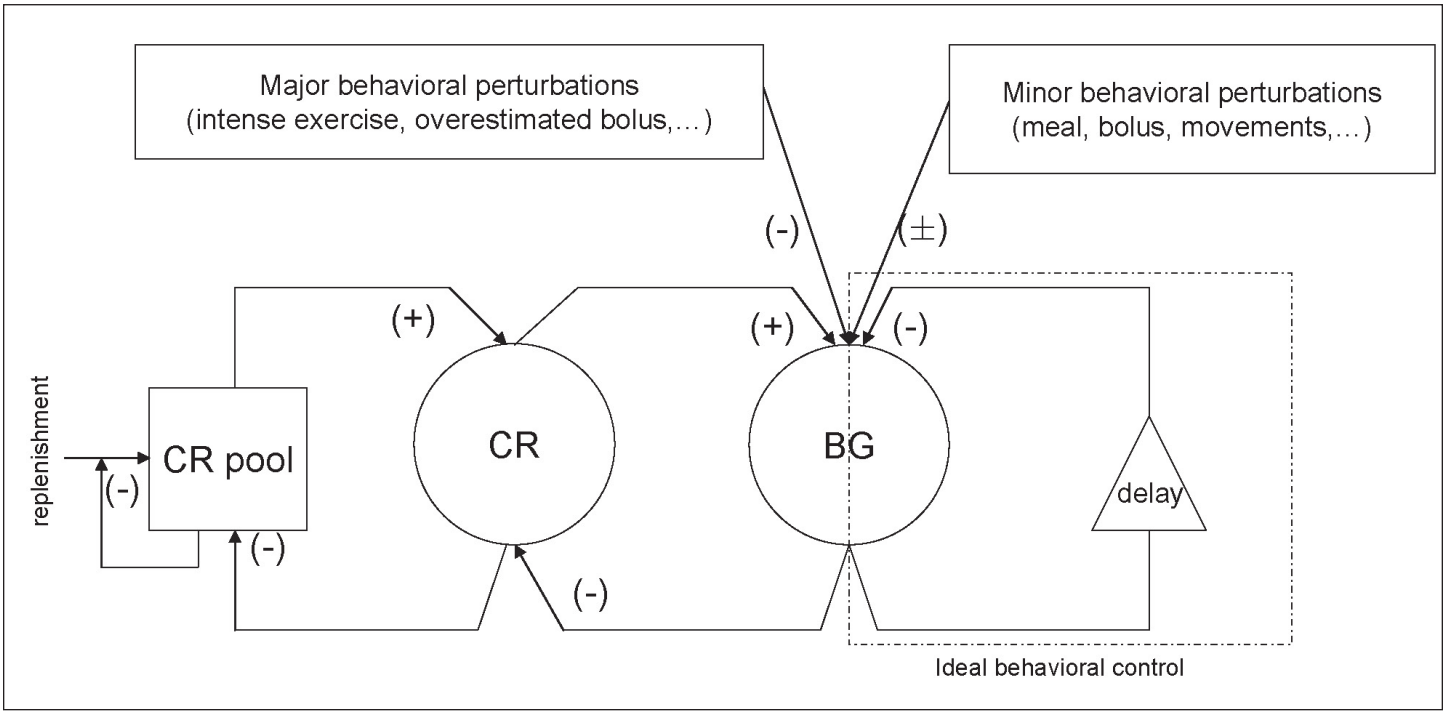

Figure 2. Behaviorally controlled BG system.

optimal behavioral control loop and counterregulation (see **Figure 2**).

The optimal behavioral control corresponds to a high-level representation of perfect self-treatment, which represents optimal behavior of the patient. The optimal behavioral effect is modeled as a negative nonlinear feedback loop with a delay, described in Equation (1).

Counterregulation is modeled as a positive nonlinear feedback loop dependent on blood glucose, as presented in Equation (2). The amount of glucose influx from the CR response depends on both blood glucose and the state of the counterregulatory capacity (CR_{pool}). At constant capacity (HAAF level) CR follows an S curve with an inflexion point at 2.8 mmol/liter, the clinical boundary of hypoglycemia.

As documented previously, recurrent hypoglycemia may weaken the counterregulatory response by weakening a person's counterregulatory capacity $CR_{pool}(t)$. The latter shifts the threshold at which counterregulation occurs to lower blood glucose concentration and blunts the hormonal signal. $CR_{pool}(t)$ is assumed fully restored in 72 hours, with 24 hours for half-restoration. The hormonal signal and counterregulation blood glucose threshold are restored in 2–3 weeks.

We model these phenomena by means of a counterregulatory compartment with limited capacity, on which the counterregulatory response is dependent. The CR compartment regenerates itself via a first-order dynamic [Equation (3)]. The intensity of the CR response is nonlinearly dependent on the state of the CR capacity via Equation (2).

This combination of processes is summarized in **Figure 2**.

The following equations comprise the biobehavioral model of HAAF:

$$\left(\frac{\partial BG}{\partial t}\right)_t = -\alpha \frac{\left(\frac{BG(t-\delta)}{\tau_1}\right)^{v_1}}{1+\left(\frac{BG(t-\delta)}{\tau_1}\right)^{v_1}} \left(BG(t) - BG_{fasting}\right) + perturbations(t) + \beta CR(t) \quad (1)$$

$$CR(t) = \frac{\left(\frac{2CR_{pool}(t)}{CR_{pool_{max}}}\right)^{v_2}}{1+\left(\frac{2CR_{pool}(t)}{CR_{pool_{max}}}\right)^{v_2}} \times \frac{1}{1+\left(\frac{BG(t)}{\tau_3}\right)^{v_3}} \quad (2)$$

$$\left(\frac{\partial CR_{pool}}{\partial t}\right)_t = r\left(CR_{pool_{max}} - CR_{pool}(t)\right) - CR(t) \quad (3)$$

For the purposes of computer simulation, the parameters of this system were set to reflect

- a blood glucose average of 6.11 mmol/liter in perfect control steady state,
- variations of blood glucose between 2 and 17 mmol/liter,
- CR response triggered at 3.9 mmol/liter when CR capacity is optimum, and
- replenishment of CR capacity in 72 hours, in absence of hypoglycemic events.

The simulation was run twice for 160 hours; blood glucose levels and state of the CR capacity were recorded. On the first simulation the CR pool was set so that it would deplete itself at about one to two hypoglycemic episodes per day; the second simulation was run with a much larger CR capacity in order to observe the behavior of the model without CR capacity depletion. Both simulations used the exact same perturbation set (although initially chosen randomly, see earlier discussion) in order to make the glucose curves comparable.

Clinical Study

Subjects and Data Collection Procedure. Eighty-five individuals were recruited through advertisement in newsletters and diabetes clinics and by direct referrals. All participants attended introductory meetings in groups of 6–10, were informed about the study, and signed consent forms. The initial screening included a collection of background data and a determination of HbA1c. Inclusion criteria were (1) age of 21–60 years, (2) T1DM of at least 2 years duration and insulin use since the time of diagnosis, (3) at least two documented SH episodes in the past year, and (4) routine use of SMBG devices for diabetes monitoring. **Table 1** presents the demographic characteristics of the participants.

The participants' usual BG meters were replaced by LifeScan OneTouch Profile memory meters (LifeScan Inc., Milpitas, CA), which can store up to 250 BG readings together with the date and time of each reading. The participants were instructed to use the meter three to five times a day and to record any SH episodes in monthly diaries, with the exact date and time. SH was defined as severe neuroglycopenia that results in stupor or unconsciousness and precludes self-treatment. The occurrence of SH was confirmed by the research team in telephone interviews after SH episodes. For each subject

Table 1.
Demographics Table of Field Study

Characteristic (at the time of recruitment)	Mean ± SD
Age (yr)	44.3 ± 10
Gender (female/male)	41/44
Duration of diabetes (yr)	26.4 ± 10.7
Daily insulin dose (U/kg)	0.6 ± 0.2
No. of insulin injections/day (for nonpump users)	2.7 ± 0.9
HbA1c (%; nondiabetic range for this laboratory, 6.9%)	
At the beginning of the study	7.6 ± 1.1
At the end of the study	7.4 ± 1.0
No. of SH episodes during the previous year	9.4 ± 6.3

the study continued 6–8 months; every month his/her meter was downloaded and the SH diary was collected.

Results

Recurrent Hypoglycemia, HAAF, and Increased Glucose Variability

Figure 3 presents the results of our simulation: In T1DM the natural feedback loop from BG to insulin is disrupted because there is practically no endogenous insulin (and exogenous insulin is not dependent on internal feedback). Thus, the only dampening of the system is exerted by its counterregulatory loop, which contributes to recovery from hypoglycemia. A hypoglycemic episode depletes the counterregulatory response, which, if not fully recovered, increases the risk of subsequent hypoglycemia and results in a general increase of the magnitude of BG fluctuations. By comparing the two curves in **Figure 3** we observe that a depleted counterregulatory pool (dotted line) results in increased glucose variability, if compared to a normal pool. In turn, increased variability leads to an SH episode at hour 47. The model-derived time course of increasing BG amplitude is close to the time course observed in previous animal studies, suggesting that this model explains realistically the effects of recurrent hypoglycemia.[19]

Clustering of SH Episodes

Figure 4 shows that recurrent mild hypoglycemia (bottom) leads to more frequent moderate hypoglycemia (middle) and eventually to SH episodes. In our model this effect results solely from the dampened counterregulatory response, i.e., HAAF. This model-predicted pattern of clustering of hypoglycemic episodes in time has been reported previously.[16,21]

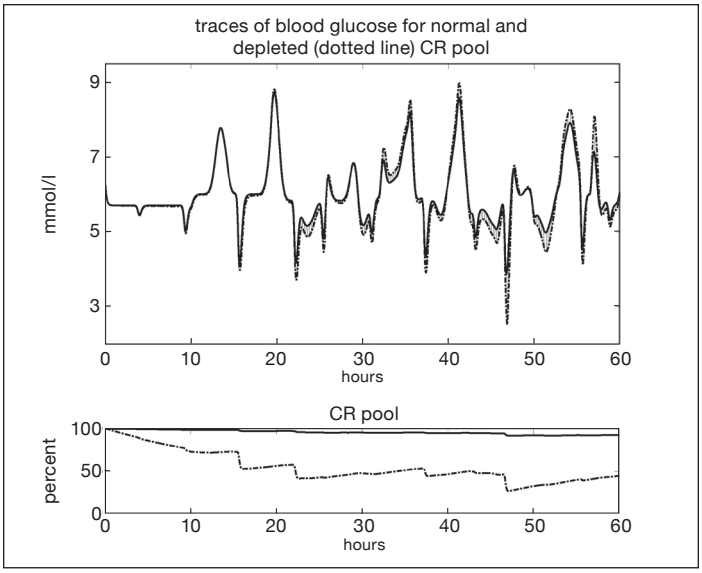

Figure 3. Effect of decreased CR pool on glucose variability and hypoglycemia.

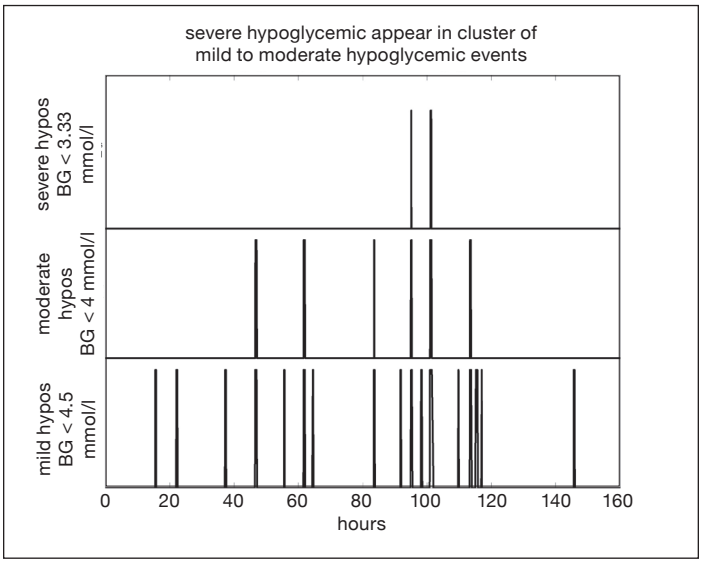

Figure 4. Clustering of hypoglycemic events during simulation.

BG Patterns Preceding SH Episodes

The modeling and simulation results were validated by data from a field study that identified a specific glycemic pattern of increased glucose variability and a series of mild hypoglycemic episodes occurring prior to SH (see **Figure 5**). A clear indicator of an upcoming SH episode was a highly significant ($p < 0.001$) increase in glucose variability, quantified by an index of the relative risk for hypoglycemia,[20] thus linking the concept of glucose variability to the occurrence of a severe hypoglycemic event. Once SH occurred, it took ~3 days for the BG level to become normalized, which concurs with the

concept of replenishment in our simulation. Thus, in the computer simulation and in the field study, we observed an increased glucose variability prior to a SH episode and a return to a normal glucose pattern within 3 days after an SH episode.

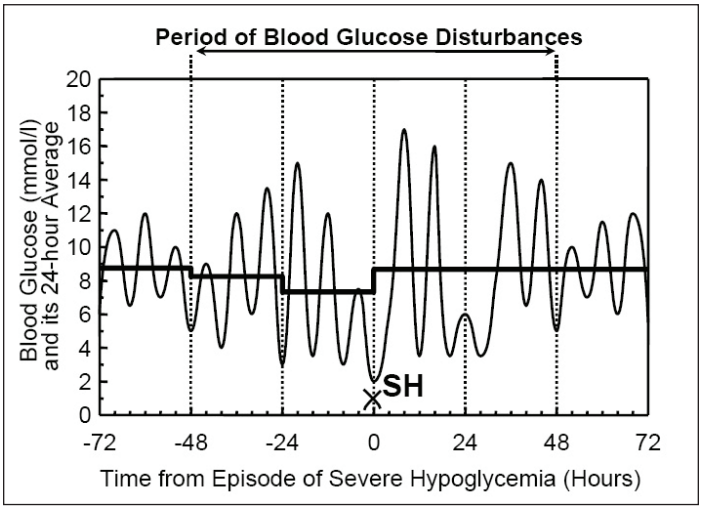

Figure 5. Clustering of hypoglycemic events in the field.

Discussion

This investigation offers a mathematical model of HAAF—the primary barrier to intensive insulin treatment.[4] In general, there are two mathematical approaches to that problem. The first approach would be to build a deterministic model of insulin–glucose–counterregulation dynamics and evaluate individual parameters with the goal of assessing a person's ability to process glucose, counterregulate, and avoid SH. Such an approach requires detailed understanding of the physiology of the insulin–glucose interaction, as well as a formal description of the network of hormonal interaction determining the response to hypoglycemia. While the first of these tasks is accomplished by the classic minimal model of glucose dynamics and numerous subsequent investigations, the counterregulatory network is not described in sufficient mathematical detail. Thus, in order to formally approximate the counterregulatory process and be able to link this process to self-treatment behavior, we adopted an alternative approach using stochastic modeling based on the observation of subjects' metabolic system at a "macro level," without detailed reference to specific underlying dynamics. The assumption behind this second approach is that SH is an extreme manifestation of BG irregularity, driven by an infrequently occurring combination of behavioral and biological factors. This approach includes a combination of formal descriptions of human behavior, glucose metabolism, and counterregulatory depletion. To describe self-treatment behavior we relied on a certain degree of periodicity, a reasonable assumption, given the approximately repeated patterns of daily activities. To this basic periodicity, we added random disturbances, which assert unusual stress on the system, simulating out-of-ordinary situations, typically regarded to as precursors to hypoglycemia.[6] A person's counterregulatory ability is modeled as a finite compartment that becomes partially depleted by behaviorally induced disturbances and recovers if sufficient time without disturbances is allowed. In turn, a depleted counterregulatory ability increases the risk of severe hypoglycemia, which corresponds to the concept of HAAF. This system of behavioral and biologic interactions is formally described by differential equations, which allow its real-time computer simulation. The patterns predicted by the simulation model reproduce characteristics of HAAF observed in clinical trials, including a higher likelihood of recurrent hypoglycemia following an initial episode[9] and an increased likelihood of SH within periods of higher glucose variability.[16] To confirm these similarities, we used data from a previously reported clinical trial investigating recurrent hypoglycemia,[16] which allow drawing not only phenomenological parallels, but also a comparison of the timescales of the observed events. In summary, a combined modeling/computer simulation/data analysis approach explains the temporal relationship among behaviorally induced hypoglycemia, glucose variability, and autonomic failure in T1DM. This explanation is valuable not only because it indicates that signs of HAAF can be detected in patients' natural environment via self-monitoring or continuous glucose monitoring, but also because it allows for tracking of the risk of SH over time.

Acknowledgements:

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References:

1. The 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. 1993 Sep 30;329(14):977-86.
2. UK Prospective Diabetes Study Group (UKPDS). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet. 1998 Sep 12;352(9131):837-53.
3. Gold AE, Deary IJ, Frier BM. Recurrent severe hypoglycemia and cognitive function in type 1 diabetes. Diabet Med. 1993 Jul;10(6):503-8.
4. Cryer PE. Hypoglycemia: the limiting factor in the glycaemic management of Type I and Type II diabetes. Diabetologia. 2002 Jul;45(7):937-48.

5. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care. 2003 Jun;26(6):1902-12.

6. Clarke WL, Cox, DJ, Goncer-Frederick LA, Julian DM, Kovatchev BP, Young-Hyman D. Biopsychobehavioral model of risk of severe hypoglycemia. Self-management behaviors. Diabetes Care. 1999 Apr;22(4):580-4.

7. Gonder-Frederick L, Cox D, Kovatchev B, Schlundt D, Clarke W. A biopsychobehavioral model of risk of severe hypoglycemia. Diabetes Care. 1997 Apr;20(4):661-9.

8. Bergman, RN, Ider YZ, Bowden CR, Cobelli C. Quantitative estimation of insulin sensitivity. Am J Physiol. 1979 Jun;236(6): E667-77.

9. Cryer PE. Iatrogenic hypoglycemia as a cause of hypoglycemia-associated autonomic failure IDDM. A vicious cycle. Diabetes. 1992 Mar;41(3):255-60.

10. Segel SA, Paramore DS, Cryer PE. Hypoglycemia-associated autonomic failure in advanced type 2 diabetes. Diabetes. 2002 Mar;51(3):724-33.

11. Cryer PE. Hypoglycemia-associated autonomic failure in diabetes. Am J Physiol Endocrinol Metab. 2001 Dec;281(6):E1115-21.

12. Galassetti P, Tate D, Neill RA, Richardson A, Leu SY, Davis SN. Effect of differing antecedent hypoglycemia on counterregulatory responses to exercise in type 1 diabetes. Am J Physiol Endocrinol Metab. 2006 Jun;290(6):E1109-17.

13. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. Diabetes. 2005 Dec;54(12):3592-601.

14. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med. 2004 May 27;350(22):2272-9.

15. Cranston I, Lomas J, Maran A, Macdonald I, Amiel S. Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes. Lancet. 1994 Jul 30;344(8918):283-7.

16. Kovatchev BP, Cox DJ, Farhy LS, Straume M, Gonder-Frederick L, Clarke WL. Episodes of severe hypoglycemia in type 1 diabetes are preceded and followed within 48 hours by measurable disturbances in blood glucose. J Clin Endocrinol Metab. 2000 Nov;85(11):4287-92.

17. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Clarke WL. Recurrent hypoglycemia and severe hypoglycemia (SH) in T1DM patients with history of multiple SH. Diabetes. 2002;51(2):A446.

18. Kovatchev B, Cox D, Gonder-Frederick L, Schlundt D, Clarke W. Stochastic model of self regulation decision making exemplified by decisions concerning hypoglycemia. Health Psychol. 1998 May;17(3):277-84.

19. Inouye K, Shum K, Chan O, Mathoo J, Matthews SG, Vranic M. Effects of recurrent hyperinsulinemia with and without hypoglycemia on counterregulation in diabetic rats. Am J Physiol Endocrinol Metab. 2002 Jun;282(6):E1369-79.

20. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Young-Hyman D, Schlundt D, Clarke W. Assessment of risk for severe hypoglycemia among adults with IDDM: validation of the low blood glucose index. Diabetes Care. 1998 Nov;21(11):1870-5.

21. Farhy LS, McCall A, Kovatchev BP. Putative impairment in counterregulatory mechanisms explains elevated variability in circulating blood glucose. Diabetes Technol Ther. 2003;5(1):A40.