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Predictive Low Glucose Suspend: An Option for Routine Outpatient Care

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Abstract

In type 1 diabetes, severe hypoglycemia is a barrier to optimal metabolic control. The combination of a continuous glucose sensor and an insulin pump with a mechanism of automatic shut-off in the presence of low glucose values [low glucose suspend (LGS)] can be used to reduce the risk of hypoglycemia. In a prospective study, we investigated the effect of the LGS algorithm on the frequency of hypoglycemic episodes in children and adolescents with type 1 diabetes under real-life conditions. We found that 2-hour insulin shut-off increased glucose levels by approximately 35 mg/dl/h and significantly decreased the number of hypoglycemic episodes. Reactive ketoacidosis was not detected, even in the presence of serious patient errors (e.g. calibration-associated errors). The ASPIRE (Automation to Simulate Pancreatic Insulin Response) study showed that these conclusions can be extended to adult patients. As children are at greatest risk for hypoglycemia, it is important to study the safety and efficacy of predictive LGS in this population.

Hypoglycemia, besides being frightening, is a major obstacle in the achievement of euglycemia and the prevention of long-term complications. The Diabetes Control and Complications Trial (DCCT) convincingly established a link between tight glucose control and avoidance of long-term complications, but also underscored the between link aggressive management of diabetes and an increase in the number of hypoglycemic episodes. Indeed, the DCCT reported a threefold increase in severe hypoglycemia in intensively treated patients. Hypoglycemia is also reported to be the cause of death in 2–4% of type 1 diabetic patients. In addition to type 1 diabetes, hypoglycemia is also relatively common in type 2 diabetes, with prevalence rates of 70–80% in patients using insulin to achieve good metabolic control [1].

The use of real-time or personal continuous glucose monitoring (CGM) provides data on hypoglycemia that may otherwise go unnoticed to the patient. Hypoglycemia is particularly challenging because it may occur when the patient is distracted, unaware, or asleep [2, 3]. Hypoglycemia can lead to hyperglycemia and contribute to glucose variabil-

ity due to the release of counterregulatory hormones and to overtreatment with glucose. In rare cases, severe prolonged hypoglycemia remains a considerable risk to the patient and can result in cardiac arrhythmias, neurological sequelae, and even death [4–8].

Rationale for Suspension of Insulin to Prevent Severe Hypoglycemia

Hypoglycemia is frightening to patients and their families. It has been estimated that about 55% of severe hypoglycemic episodes occur during sleep. Acutely, diminished brain function during a hypoglycemic episode is a danger to the patient. In addition, recurrent hypoglycemia may cause long-lasting damage to the brain, resulting in impairment of memory or other cognitive functions.

In addition to the effects on cognition, recurrent hypoglycemia also impairs natural defense mechanisms against hypoglycemia, creating a vicious cycle. Normally, hypoglycemia triggers a series of hormonal and neural responses designed to bring glucose concentration towards normal and maintain brain metabolism. A component of this counterregulatory response is the secretion of epinephrine, which generates 'neurogenic' symptoms (e.g. palpitations, sweating, and anxiety) that warn the patient of the impending threat; however, after severe hypoglycemia the body's natural responses are depressed, impairing the exit from hypoglycemia. Prolonged hypoglycemia is a precursor of seizure activity. In children, CGM tracings have shown that nocturnal seizures are preceded by 2.25–4 h of glucose levels <60 mg/dl [9]. The JDRF study [10] reported an average time spent on hypoglycemia as follows: 62 min at a glucose level <70 mg/dl, 30 min <60 mg/dl, and even 7 min <50 mg/dl.

The integration of an insulin pump with a CGM system [so-called 'sensor-augmented pump therapy' (SAP)] can improve the management of diabetes, as indicated by several randomized controlled trials which found a significant reduction in glycated hemoglobin (HbA_{1c}) levels during SAP with respect to intensive insulin therapy by multiple daily injections or pump alone [10–13].

Real-time CGM offers the possibility of proactively avoiding hypoglycemic episodes through adjustable alert limits [14–16]; however, patients do not always react to the alerts. This is the rationale for developing automated insulin delivery systems where withdrawal of insulin infusion with impending hypoglycemia would be a first clinically relevant step.

General Considerations for Automatic Insulin Delivery

Several physiological considerations need to be taken into account when comparing continuous subcutaneous insulin infusion (CSII) in patients with type 1 diabetes to the nondiabetic situation. Insulin should ideally be released first in high concentrations into the portal circulation (where approx. 50% is extracted for glycogen production and in-

hibition of gluconeogenesis) before it reaches the peripheral circulation. Also, to mimic the secretion pattern of pancreatic β-cells, at mealtime a short insulin peak (hunger-induced in the cephalic phase) should be followed by a sustained (glucose concentration-dependent) secretion, while between meals glucose levels should be regulated by small amounts of insulin released in a pulsatile fashion. Thus, CSII should deliver human insulin into the portal system on the basis of local glucose concentrations to avoid excessive insulin concentrations and hypoglycemia. In addition, rapid changes in insulin sensitivity, as following physical exercise, should be taken into consideration. With current technologies, such an ideal closed loop can only be created under artificial laboratory conditions, while several compromises are made for real-life outpatient conditions.

A physiological insulin infusion into the portal vein is theoretically possible through an umbilical access which is usually not available after the neonatal period. However even the intraperitoneal route from an implanted pump or via an abdominal port is a compromise. This access remains reserved for rare indications such as subcutaneous insulin resistance and presently leaves the subcutaneous route (CSII) as the only option for routine outpatient care.

This results in several consequences for designing algorithms for hypoglycemia prevention and closing the loop. To mimic more closely the β-cell and to compensate for the delay due to subcutaneous absorption, human regular insulin usually has been replaced by rapid-acting insulin analogues, but even these new insulins do not have the quick onset of action and the short period of activity that would be needed for near-physiological regulation and the requirements of closed-loop technologies. In addition, the nonphysiologic subcutaneous route delays the suppression of hepatic glucose output. Thus, the automated response to low or falling glucose levels would require intravenous glucose or a bihormonal pump with simultaneous insulin and glucagon infusion [17]. The latter approach has been tried but needs a complex system with two reservoirs and delivery sites, and faces stability issues regarding glucagon. It also appears that glucagon may not always be effective (e.g. after alcohol consumption).

A minimum requirement for the continuous adjustment of insulin delivery is the presence of a continuous glucose sensor. Ideally, this sensor should measure blood glucose which would necessitate an implanted access. Currently available sensors analyze the glucose concentration in the subcutaneous tissue, which may result in a significant delay in case of rapid changes in the glucose concentration. In general the fine-tuning of glucose via the interstitial glucose values appears feasible due to the close relationship between cerebral and interstitial glucose values.

Architecture of a Closed Loop System

The hardware design for an outpatient system for continuous glucose regulation has to make use of currently available insulin pumps and glucose sensors (fig. 1). While these components are readily available on the market, the crucial link between them

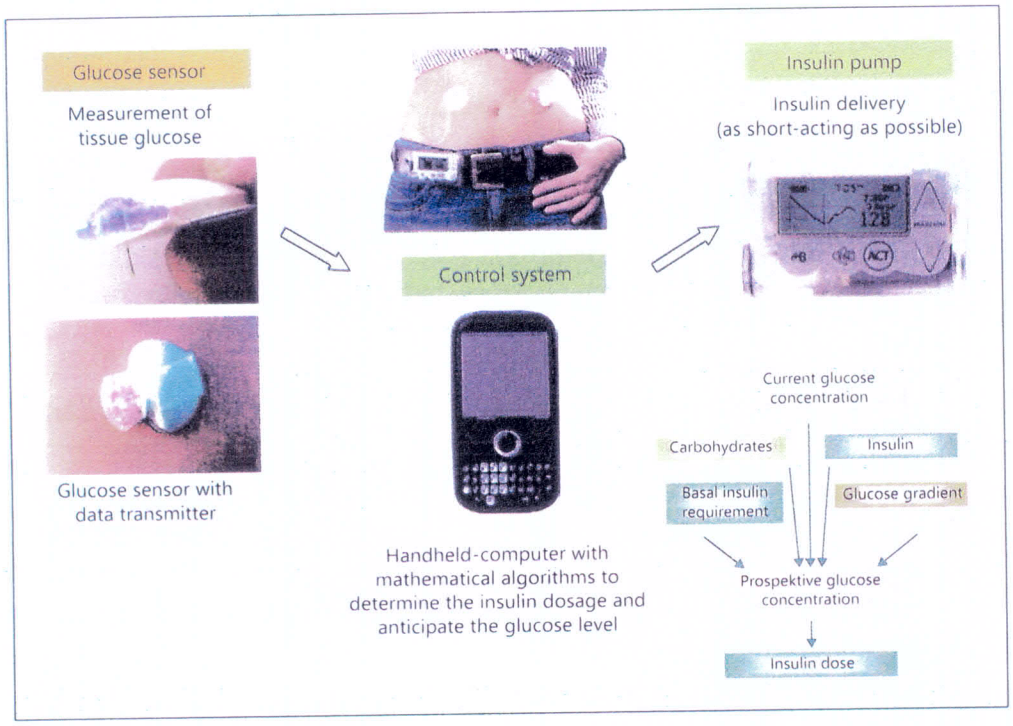

Fig. 1. Components and design of a closed-loop system with an external insulin pump, external glucose sensor, and handheld computer that contains the algorithm for regulation of insulin delivery. The diagram at bottom right shows factors to consider in the calculation of the insulin dose.

is the software that can be preinstalled on one of the devices or an additional handheld computer or smartphone. These software algorithms, which change subcutaneous insulin delivery on the basis of measured glucose, need to consider the compromises and limitations mentioned above. Under inpatient conditions, those algorithms have already been tested in a system called 'Biostator', which infuses glucose or insulin intravenously. In addition to the problems related to the subcutaneous site, the lack of regulating glucagon needs to be figured in as well.

Methodology of Continuous Glucose Monitoring

Current methods of CGM include the use of subcutaneous glucose sensors which convert glucose from the subject's interstitial fluid into an electronic signal, the strength of which is proportional to the amount of glucose concentration. In the electrochemical method, glucose is chemically converted into gluconic acid and hydrogen peroxide with the help of biocatalytical enzymes (e.g. glucose oxidase):

$$\text{Glucose} + O_2 + H_2O \rightarrow \text{Gluconic acid} + H_2O_2 \quad (1)$$

Hydrogen peroxide is then oxidized over a platinum electrode with a voltage between 600 and 900 mV, and the released electrons generate a current that is proportional to the amount of converted glucose:

$$H_2O_2 \rightarrow 2\,H^+ + O_2 + 2\,e^- \quad (2)$$

At the physiological glucose concentration (40–400 mg/dl, 2.2–22.2 mmol/l) such a current is in the nanoampere range. The prerequisite for the electrochemical measurement is a direct access to the glucose-containing compartment. Thus, the glucose sensor (an electrochemical enzyme electrode that is wrapped in an oxygen-containing membrane) needs to be placed in the subcutaneous tissue to have access to the interstitial fluid. A second prerequisite is that there has to be equilibrium between interstitial and blood glucose, as rapid blood glucose changes may otherwise lead to a time lag of 5–25 min. In addition, individual factors such as glucose absorption rates or insulin action need to be taken into consideration when algorithms for predictive glucose management are developed. Due to variable rates of sensor 'drift', the sensor needs to be calibrated and recalibrated in certain intervals with conventional blood glucose measurements. The sensor is attached to a transmitter which sends the interstitial glucose information via radio or blue tooth signals to a screen that provides continuous real-time glucose values, as well as high/low glucose alerts.

Algorithms for Calculating Insulin Delivery in Closed-Loop Systems

While there is agreement that most of the modern pump models fulfil the mechanical and technical prerequisites regarding precision and reliability of insulin delivery, the current generation of glucose sensors still needs improvements both in accuracy and reliability. Meanwhile, a great effort has been made to develop algorithms dictating insulin dosing not only on the basis of the current glucose estimates, but also on the basis of values predicted 2–3 h ahead. This requires the regulation of both glucose concentration (C_{Gluc}) and insulin concentration (C_{Ins}). Basically, glucose homeostasis is regulated by a system of interconnected regulatory circuits. In the nondiabetic human, the pancreatic β- and α-cells are the regulatory units for secreting either insulin or glucagon, targeting glucose levels of 70–140 mg/dl (3.9–7.8 mmol/l). However, these regulatory circuits have a certain time lag. Thus, in addition to glucose concentration, additional factors like the time-dependent absorption of nutrients and variation of insulin action after subcutaneous infusion (as well as type of rapid insulin), amount of physical exercise, or other stress have to be considered when predicting the necessary insulin dose. Moreover, the insulin concentration that still is active in the organism needs to be figured in. Further complexity arises from glucose sensor-related issues such as the physiological difference between measurement in interstitial fluid compared to blood as well as potential bias related to sensor calibration (fig. 2). Therefore, it is necessary to develop a mathematical formula like in the example shown below. This formula de-

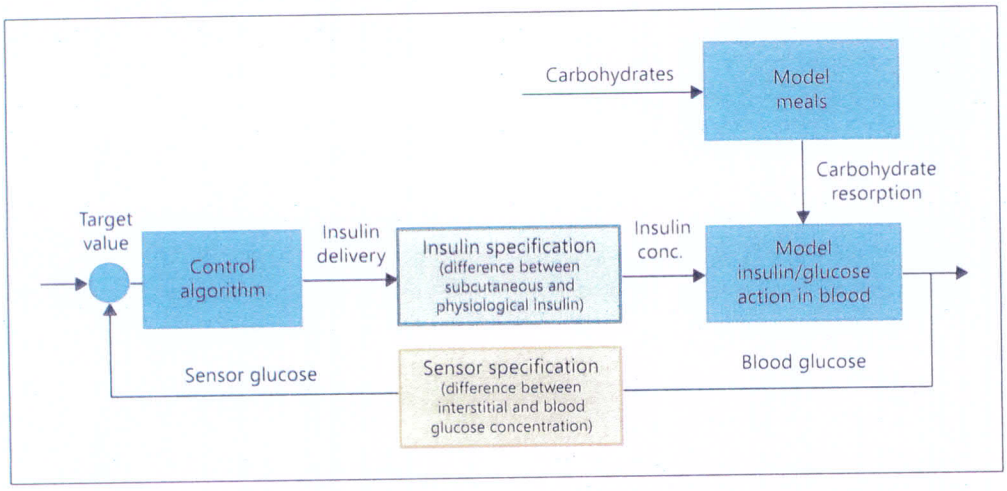

Fig. 2. Control cycle for a closed-loop system, with subcutaneous glucose measurement and insulin delivery in subcutaneous tissue. conc. = Concentration.

scribes the control cycle for a closed-loop system and the physiological glucose regulation (fig. 2–4).

For those readers interested in the mathematical details, one algorithm is explained in detail as an example. One approach for predictive glucose management is the so-called 'PID control' imitating the physiological insulin secretion pattern where 'P' represents the proportional regulation, 'I' the integral regulation, and 'D' derivative regulation [18]. These three phases correspond to the feedback behavior of the β-cell [fig. 3, compare the picture of physiological secretion pattern (top left) with the mathematical reproduction (top right)]. It can be calculated as follows:

- The proportional phase (P) considers the difference between the current glucose value and the target glucose ($C_{sensor} - C_{target}$); the resulting insulin delivery is proportional to the glucose level:

$$P = K_p \times [C_{sensor} - C_{target}] \quad (3)$$

where C_{Sensor} = glucose concentration sensor, C_{target} = target glucose concentration, and K_p = proportionality factor.

- Increment phase I (slow second-phase rise of insulin secreation) is proportional to the difference between the current sensor glucose level and target glucose ($C_{sensor} - C_{target}$):

$$dI/dt = K_p \times [C_{sensor} - C_{target}] / T_I \quad (4)$$

where T_I = time parameter for increment phase.

- Response phase (derivative, rapid first-phase rise of insulin secreation); the resulting insulin delivery is proportional to the rate of glucose change over the time (D):

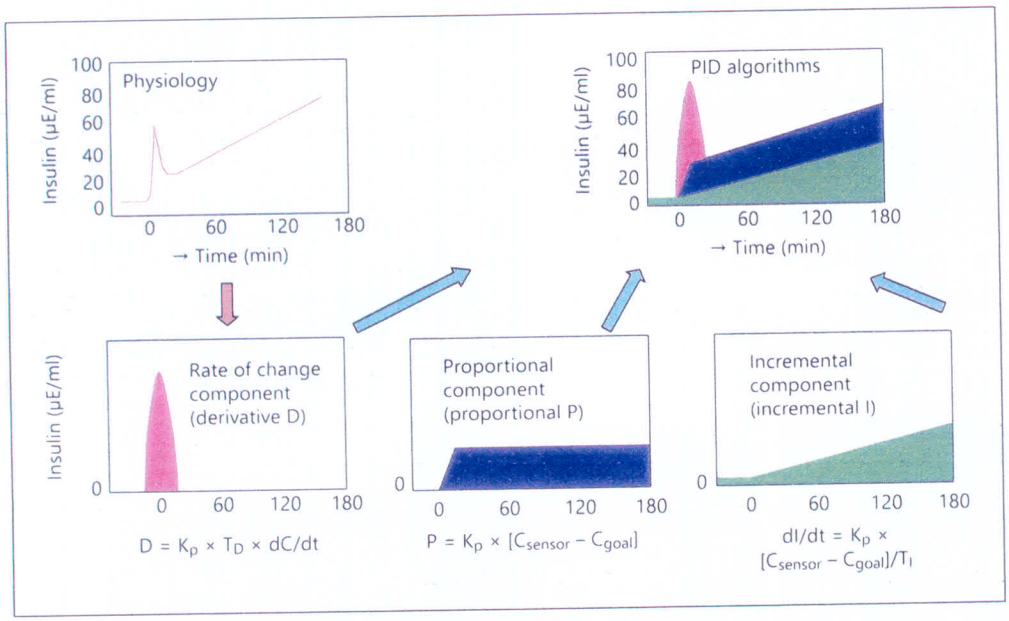

Fig. 3. Model of insulin secretion from the β-cell according to the PID model [18].

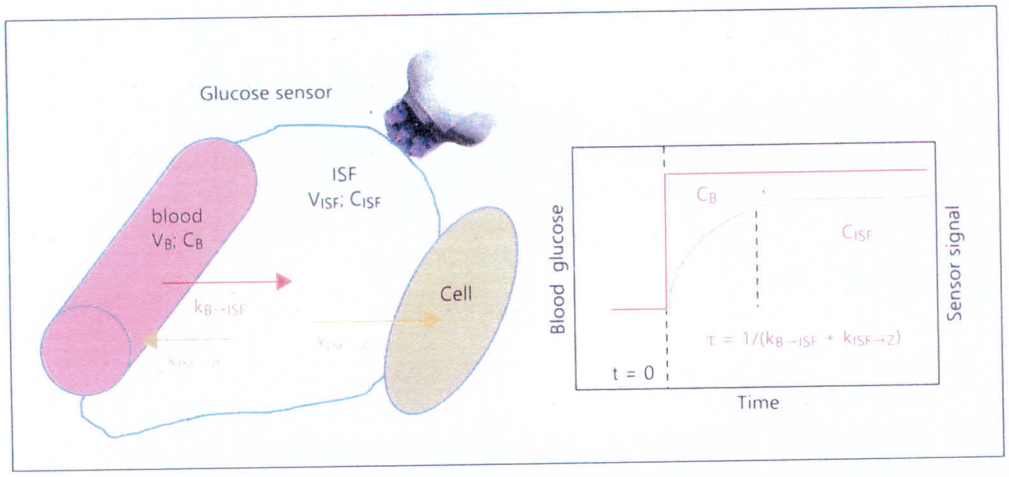

Fig. 4. Continuity model for the exchange of glucose between blood and interstitial fluid.

$$D = K_p \times T_D \times dC / dt \quad (5)$$

where dC/dt = change of glucose concentration/time, and T_D = time parameter for the derivative phase.

The relative amount of insulin delivered in each component is balanced by the three parameters K_p, T_I, and T_D. All three parameters have to be adjusted individually: K_p (in mIU/min/mg/dl, IU = international insulin unit) determines the insulin secretion

rate as a reaction of the basal glucose level, T_I (in min) determines the proportion of the increment phase, and T_D determines the proportion of the derivative phase.

The complete algorithm for delivery is the sum of the three parts (fig. 3):

$$PID = P + I + D \tag{6}$$

Thus, the necessary insulin dose is calculated from the current glucose concentration, the glucose target and the parameters K_p, T_I, and T_D. As mentioned above, the use of glucose sensors placed in the subcutaneous tissue requires an adjustment for the glucose concentration C_{ISF} (ISF = interstitial fluid) being different from the blood glucose concentration C_B (B = blood), when the blood glucose is changing. This can be expressed in a simple model of continuity (fig. 4). The figure shows the physiological flow between blood and interstitial tissue with flow rates k between both compartments. This flow results in a change of the glucose concentration C in the blood or interstitial volume V. Following the time-dependent rate of change in the glucose concentration in the subcutaneous tissue depends on the glucose exchange between blood and interstitial fluid represented by the glucose flow rate $k_{B\rightarrow ISF}$, $k_{ISF\rightarrow B}$, and the drainage of glucose in the body cells (Z) $k_{ISF\rightarrow Z}$ (glucose consumption). An increase of the insulin concentration results in an increase of glucose consumption in the peripheral cells. The ensuing equation is:

$$dC_{ISF} / dt = - (k_{ISF\rightarrow Z} + k_{B\rightarrow ISF}) \times C_{ISF} + k_{ISF\rightarrow B} \times V_B / V_{ISF} \times C_B \tag{7}$$

where C_B = glucose concentration in blood, C_{ISF} = glucose concentration in the interstitial fluid, V_B = blood volume, V_{ISF} = interstitial volume, $k_{B\rightarrow ISF}$ = flow rate blood → interstitial space, $k_{ISF\rightarrow B}$ = flow rate interstitial space → blood, and $k_{ISF\rightarrow Z}$ = glucose consumption in the peripheral cells.

The relationship of glucose concentration in the interstitial fluid to concentration in the blood is the concentration (C_{ISF}/C_B). After reaching glucose homeostasis, the glucose concentration in the interstitial fluid can be calculated as follows:

$$C_{ISF} = C_B \times [k_{ISF\rightarrow B} \times V_B / V_{ISF}] / (k_{ISF\rightarrow Z} + k_{B\rightarrow ISF}) \tag{8}$$

The time lag between blood and interstitial fluid depends on the two flow rates $k_{B\rightarrow ISF}$ and $k_{ISF\rightarrow Z}$, and can be expressed as:

$$\tau_{Sensor} = 1 / (k_{B\rightarrow ISF} + k_{ISF\rightarrow Z}) \tag{9}$$

This time constant is calculated to be the time necessary to reach 63% of the equilibrium. When using an enzymatic electrochemical glucose sensor, the sensor current I_{sig} is proportional to the glucose concentration in the interstitial space:

$$I_{sig} = \alpha \times C_{ISF} \tag{10}$$

Here α is a parameter expressing the sensitivity of the sensor (in nA/mg/dl) which changes over time. As the glucose sensor is calibrated, the measured glucose concentration is calculated, accounting for the calibration factors F_{cal} as follows:

$$C_{sensor\ glucose} = F_{cal} \times I_{sig} \quad (11)$$

Using the PID model, the necessary insulin delivery per time period is calculated as:

$$I_{dose}(t) = K_p \times F_{Err} + 1 / T_I \int F_{Err} \times dt + T_D{}^s \quad (12)$$

F_{Err} is the resulting error due to the deviation from the blood glucose, i.e. the difference between the current glucose level and target glucose level, and K_p, T_I, T_D are the individual adjustable parameters in the PID model. In addition, equation 12 does not account for the subcutaneous insulin delivery, thus the relationship between sensor glucose $C_{sensor\ glucose}$ and blood glucose C_B needs to be adjusted as follows:

$$C_{sensor\ glucose} / C_B = F_{kal} \times K_{sensor} / (\tau_{Sensor}\, s + 1) \quad (13)$$

This results in the following relationship between insulin level in blood (I_{blood}) to insulin dose (I_{dose}):

$$I_{blood} / I_{dose} = K_{Ins} / [(\tau_{blood}\, s + 1) \times (\tau_{ISF}\, s + 1)] \quad (14)$$

This formula allows the prediction of the glucose concentration during closed-loop control as a result of a given insulin dose. Different complex models of glucose metabolism have been developed by various groups on the basis of these equations like the MPC-algorithm (model predictive control [19], or the hypoglycemic predictive algorithms [20]). These different models and algorithms essentially all calculate the same parameters: how to change the insulin infusion rate depending on time and given glucose concentration. Differences in the algorithms result in the degree that parameters such as insulin sensitivity, insulin action, carbohydrate intake, physical exercise, stress, etc., are taken into account and to what degree a prediction horizon is calculated. Mathematical approaches that are used in the algorithms include fuzzy logic [21] and neuronal networks [22].

Trials with Automatic Suspension of Insulin Delivery

Despite the development of real-time glucose sensors with hypoglycemic alarms, many patients sleep through these alarms. Therefore, pilot studies investigated the feasibility of using real-time CGM to discontinue insulin pump therapy when hypoglycemia was predicted [23]. The efficacy of automatic suspension of insulin delivery in induced hypoglycemia among subjects with type 1 diabetes was evaluated in the ASPIRE (Automation to Simulate Pancreatic Insulin Response) study, which tested the experimental design of an exercise provocation by ergometer in adults [24, 25]. In this randomized crossover study, subjects used a sensor-augmented insulin pump system with a low glucose suspend (LGS) feature that automatically stops insulin delivery for 2 h following a sensor glucose value ≤70 mg/dl. Subjects fasted overnight and exercised until their plasma glucose value reached ≤85 mg/dl

on different occasions separated by washout periods lasting 3–10 days. Exercise sessions were done with the LGS feature turned on (LGS-on) or with continued insulin delivery regardless of sensor glucose value (LGS-off). The order of LGS-on and LGS-off sessions was randomly assigned. YSI glucose data were used to compare the duration and severity of hypoglycemia from successful LGS-on and LGS-off sessions, and to estimate the risk of rebound hyperglycemia after pump suspension. Fifty subjects attempted 134 sessions, 98 of which were successful. The length of hypoglycemia was less during LGS-on than during LGS-off (mean ± SD = 138.5 ± 76.68 vs. 170.7 ± 75.91 min, $p = 0.006$). Compared with LGS-off sessions, mean nadir YSI glucose was higher (59.5 ± 5.72 vs. 57.6 ± 5.69 mg/dl, $p = 0.015$) during LGS-on, as was mean end-observation YSI glucose (91.4 ± 41.84 vs. 66.2 ± 13.48 mg/dl, $p < 0.001$). Most (53.2%) end-observation YSI glucose values in the LGS-on sessions were in the 70–180 mg/dl range, and none was >250 mg/dl. This study in adults demonstrated that automatic suspension of insulin delivery significantly reduced duration and severity of induced hypoglycemia without causing rebound hyperglycemia.

The Low Glucose Suspend Approach

The first insulin pump equipped with a number of features to actively manage glucose levels was the Paradigm® Veo™ System (Medtronic Inc.). It is equipped with a LGS feature that leads to an interruption in the supply of insulin for a period of up to 120 min. This occurs when the glucose value falls below an adjustable hypoglycemia threshold (set by the patient and healthcare provider) and the patient does not respond to the alert (e.g. during sleep or in an environment with very loud background noise), and turns off insulin suspension to resume insulin delivery. After LGS is triggered, if the patient fails to respond by resuming insulin delivery, insulin suspension will last for 120 min, after which insulin delivery will be automatically resumed for 4 h, even if the sensor glucose value falls below the set LGS threshold again. However, if at the 4-hour period of time the glucose value reaches the LGS threshold, another cycle of 120-min suspension followed by 4 h of insulin delivery will be resumed. The goal of this algorithm, with insulin delivery cycling on and off, is to prevent the occurrence of diabetic ketoacidosis after LGS events [26].

The Pediatric Low Glucose Suspend Feasibility Study

The aim of our investigation was to determine whether number, duration, and degree of hypoglycemic episodes could be reduced through the use of the LGS feature under real-life conditions, using a hypoglycemia alert level of 75 mg/dl (4.2 mmol/l) and a LGS threshold of 70 mg/dl (3.9 mmol/l), and what effects the use of LGS had on met-

abolic control in pediatric patients. Twenty-one children and youth with type 1 diabetes (1–18 years of age, duration of diabetes ≥12 months, and CSII ≥3 months) from three diabetes centers in Germany with experience in CSII, CGM, and SAP were included in the study [27].

Before starting, patients and parents were trained on the use of the Veo system. Two phases were compared with each other in this prospective study. The first phase (2 weeks) consisted of SAP without the use of LGS, as previous research has shown that such CGM time is sufficient to determine the hypoglycemia rate in terms of statistical safety [28, 29]. The second phase lasted 6 weeks, as no previous experience on the behavior of patients using the LGS algorithm was available. The hypoglycemia alert was set at 75 mg/dl (4.2 mmol/l) and thus slightly higher than commonly defined for hypoglycemia. The rationale was the inherent 'time lag' between blood glucose and sensor glucose (measured in interstitial tissue), and the possibility that during a phase of rapidly decreasing blood glucose concentration, a sensor glucose reading of 75 mg/dl (4.2 mmol/l) may correspond to blood glucose values <70 mg/dl (3.9 mmol/l).

All patients used the glucose sensor >90% of the time over 8 weeks. The baseline HbA_{1c} level was 7.8 ± 1.1% (DCA 2000). A total of 445 LGS activations occurred in which the insulin supply was interrupted or 0.89 ± 0.67 LGS activations per patient per day (LGS/patient/day). When subdivided into day- and nighttime, the results were 0.38 ± 0.32 LGS/patient/day for the time between 10.00 p.m. and 6.00 a.m., and 0.49 ± 0.43 LGS/patient/day for the time between 6.00 a.m. and 10.00 p.m. If all LGS alerts are counted, including those confirmed by patients, and those during which no interruption in insulin delivery occurred, there were 853 events ≤70 mg/dl (3.9 mmol/l). When these alerts are included in the total, the average comes to 2.56 ± 1.86 LGS/patient/day. In contrast to the total number of LGS alerts and the total number of LGS activations, the complete cycle occurred primarily during sleep time (84.4% of the 120-min interruptions).

Comparing the glycemic parameters during the two phases of the investigation, a significant improvement in all parameters of hypoglycemia was observed with LGS, while average glucose or occurrence of hyperglycemia remained unchanged. Using the Device Satisfaction Survey, the majority of patients and their parents evaluated the management of hypoglycemia and the Veo system very positively, although patients with a high number of alerts tended to be a little less content. This study showed that with LGS the risk for hypoglycemia can be reduced without compromising the safety of CSII in children with type 1 diabetes.

The occurrence of severe hypoglycemia has been labeled as the rate limiting step in achieving optimal metabolic control [30]. The LGS algorithm was effective using 70 mg/dl (4.2 mmol/l) as the threshold for the onset of LGS. This value allowed for a reduction in time spent and number of episodes of <70 mg/dl without a concomitant rise in hyperglycemia. Even though not all hypoglycemic episodes were avoided with this LGS threshold, it is possible that setting a higher LGS threshold of 80 mg/dl (4.4

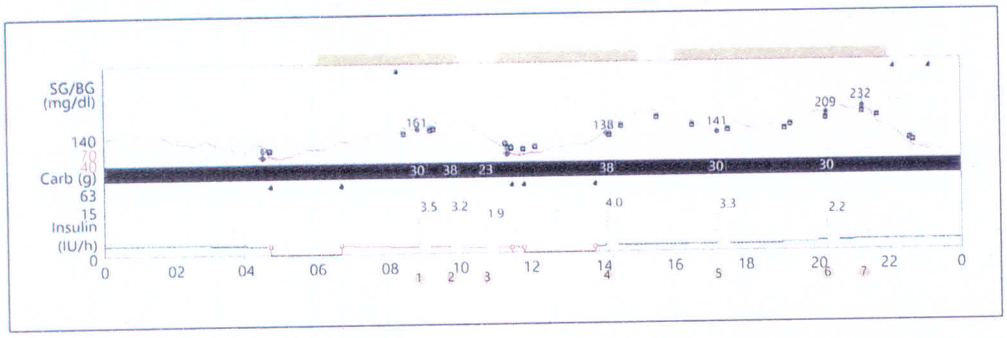

Fig. 5. Example for prevention of a severe hypoglycemic episode by switching off the insulin supply after an LGS alert not noticed by patient. For both cases, an interruption of 2 h occurred at 4:40 a.m. and 11:45 a.m. [27].

mmol/l) or 90 mg/dl (5.0 mmol/l) may be successful in reducing low glycemic excursions even further. This may be desirable for example in patients prone to hypoglycemia or young children at greater risk for neurocognitive consequences. However, potential hypoglycemia reduction by setting the threshold higher has to be balanced with the occurrence of more LGS alerts.

Increasing the overall number of alerts may affect a patient's sensitivity to the alerts and the overall patient acceptance of the device. In a 6-hour cycle, the 2-hour suspended insulin delivery is followed by 4 h of basal insulin delivery. In the absence of intervention, this 6-hour cycle continues indefinitely. For the period of the study, 5 patients cycled twice and 1 patient cycled 3 times. During the LGS time, there was an elevation in glucose concentration of 68.4 ± 13.1 mg/dl (3.8 ± 0.73 mmol/l) after the 2-hour interruption or a rate of approximately 35 mg/dl/h. Reactive ketoacidosis is not to be expected, even in the presence of serious patient errors (e.g. calibration-associated errors). We observed a case of sensor failure due to an extension of the sensor implantation time way beyond the recommended duration. The erroneous low glucose readings due to sensor failure prompted subsequent interruptions in the insulin supply during the night, but did not result in DKA. The elevated morning glucose could be readily corrected in the morning as would have been the case without LGS. The study provided evidence that by using the LGS function in children, severe hypoglycemia may be prevented in many cases (fig. 5). Our data are in line with three other major studies with the LGS that have been published to date: the UK User Evaluation [31], the CareLink Data Mining [32], and the Australian Hypoglycemia Prevention Study [33]. Common findings across studies show that when the LGS is set between 50 and 70 mg/dl, most individuals have an LGS event every day or every other day, but in more than 50% they turn back on the insulin in less than 5 min. While two thirds of LGS events are during the day, LGS events lasting 2 h are mainly at night; however, these make up only 10% of all LGS events. Applying the LGS feature results in an increase of approximately 35 mg/dl/h with suspend and 2 h

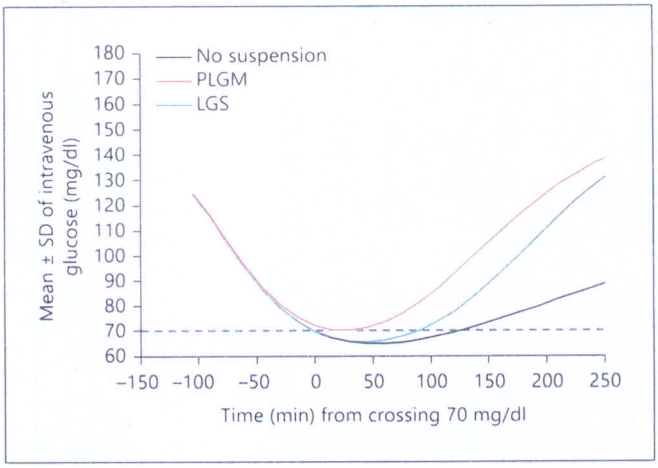

Fig. 6. Reduction of hypoglycemia with LGS and PLGM.

after with no increase in the hyperglycemia region (>180 mg/dl, 10 mmol/l). Thus, the LGS feature in SAP has been the first step towards a semiclosed loop in routine outpatient care.

Predictive Low Glucose Suspend

To further improve hypoglycemia prevention, there is an alternative to raising the LGS threshold. Implementing a predictive LGS when rapidly falling glucose values are predicted to reach the hypoglycemic range would trigger insulin suspension and could be even more effective in preventing low glucose [23]. Data for 50 virtual subjects ('in silico testing') were generated by using the University of Virginia/Padova type 1 diabetes simulator, quantifying the potential benefits of glucose prediction to reduce the number and duration of hypoglycemia epidsodes by using predicted rather than measured continuous glucose values [34]. Indeed, this allowed a 75% reduction of the number of hypoglycemic events and the time spent in hypoglycemic range, supporting the use of preventive hypoglycemic alerts on the basis of glucose prediction methods.

Currently under investigation is the 'Predictive Low Glucose Management (PLGM)' feature as the next iterative step after the success of the LGS system in the Paradigm Veo pump (fig. 6). To use this feature, the user will be required to select a predictive horizon (e.g. 30 min) when a predictive sensor low glucose suspension threshold (e.g. 80 mg/dl) would trigger the PLGM feature. When this feature is selected, if the sensor glucose prediction reaches a level equal to or lower than the programmed threshold, the user receives an alert and the pump suspends. The subject then has the option to continue suspending the pump or resume insulin delivery. Once the prediction horizon is safely above the threshold or after 120 min have elapsed (or if the user does not cancel suspend within 2 h), the pump will automatically resume insulin delivery at the previously programmed basal rate. The intended use of the PLGM system is to work

as a supervisory system that monitors glucose levels and advises when and for how long a suspension of basal delivery is warranted. Initial research of the PILGRIM (Predictive Low Glucose Management in Real-Time Sensing Insulin Pump Therapy) study in adolescents and young adults with type 1 diabetes with exercise-induced hypoglycemia indicates that this approach may be a further stepping stone in the development of a commercially available closed-loop system.

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