Abstracts

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Reliable Glycemic Control Can Be Achieved Safely with Enhanced Model Predictive Control in Medical Intensive Care Unit Patients

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Objective:
The goal of this study was to investigate the performance of the enhanced model predictive control (eMPC) algorithm for glycemic control in mechanically ventilated, critically ill patients for the whole intensive care unit (ICU) stay. The primary end point was the time within target range (4.4–6.1 mmol/liter).

Method:
The method used was a single-center, open, noncontrolled trial. Patients with an expected ICU stay >5 days were treated with a laptop-based bedside version of the eMPC.

Result:
For a period of 7.8 ± 4.1 (minimum 3, maximum 22) days, 20 patients (age 69 ± 11, body mass index 27.4 ± 4.5, Acute Physiology and Chronic Health Evaluation II 25.5 ± 5.2, 16 males, 6 diabetes subjects) were included in the study. The time within target range (4.4–6.1 mmol/liter; primary end point) was 58.12 ± 10.05% (mean ± standard deviation). The percentage of time spent within other glucose level ranges was as follows: <2.2 mmol/liter: 0.02 ± 0.08; 2.2–3.3 mmol/liter: 0.79 ± 0.66; 3.3–4.4 mmol/liter: 11.39 ± 3.50; 6.1–8.3 mmol/liter: 23.09 ± 7.00; and >8.3 mmol/liter: 6.59 ± 7.15. Mean arterial blood glucose was 5.8 ± 0.5 mmol/liter, insulin requirement was 101.3 ± 50.7 IU/day, and mean carbohydrate intake (enteral and parenteral nutrition) was 176.4 ± 61.9 g/day. Three hypoglycemic episodes occurred in three subjects, corresponding to a rate of 0.018 per treatment day. No malfunctions of the eMPC algorithm were observed. Glycemic control was superior during treatment with the eMPC algorithm when compared to time before and after study treatment.

Conclusion:
The performance of the eMPC algorithm was excellent from a clinical point of view. The eMPC algorithm is a safe and reliable method to control blood glucose in critically ill patients in the medical ICU.

Benchmarking Glucose Data through Automation

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Objective:
While inpatient hyperglycemia is considered important, the best means of management remains a topic of continued investigation. Currently, limited data are available to benchmark inpatient glycemic control nationally. The objective of this analysis was to use the Medical Automation Systems (MAS) Remote Automated Laboratory System (RALS) database to compare individual hospital metrics for reporting glycemic control data.

Methods:
For participating hospitals, a continuous automated extraction of deidentified patient blood glucose data from the MAS RALS-Plus data management system was performed through a proprietary software application. These data were transferred automatically via a secured internet connection to MAS where reports were created and returned to the subscribers electronically. Metrics included mean and median blood glucose results for all inpatients, intensive care unit (ICU) patients, and non-ICU patients for each hospital and a comparison to the aggregate of all hospitals. Rates of hyperglycemia and hypoglycemia were analyzed.

Results:
A cumulative total of more than 90 million blood glucose results from over 300 hospitals were extracted in 2006, 2007, and 2008, of which more than 25% were from the ICU. Mean blood glucose results were obtained for all 3 years for the patient populations in ICU and non-ICU inpatient units. The range of mean hospital level glucose for all inpatients in 2006, 2007, and 2008 was 142.2–201.9, 145.6–201.2, and 140.6–205.7 mg/dl, respectively. The range for ICU patients was 128–226.5, 119.5–219.8, and 121.6–226.0 mg/dl, respectively. The range for non-ICU patients was 143.4–195.5, 148.6-199.8, and 145.2–201.9 mg/dl, respectively.

Conclusion:
These data have implications for glucose management interest groups involved in the state of glycemic control in U.S. hospitals.

Minimizing the Causality Effect of the Response to Meals of the MD-Logic Artificial Pancreas System

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Objective:
We developed the MD-Logic Artificial Pancreas (MDLAP) system, which is based on a model that imitates the logic of diabetes care givers. The system, based on continuous subcutaneous glucose sensing and insulin delivery, allows automatic individual glucose regulation. As a casual system, its response to meals is challenging. New algorithms that minimize the causality effect were developed to address this issue.

Method:
The MDLAP system was tested prospectively in clinical studies with a group of seven type 1 diabetes mellitus (T1DM) patients. The trials prolonged 8 and 24 hours at rest state. Following these trials, new meal detection and treatment algorithms were developed and the control parameters of the system were adjusted. Today, ongoing closed-loop sessions are conducted to evaluate the improved system postmeal response.

Result:
Results of the prospective trials (8 and 24 hours) showed that the MDLAP system managed to return glucose levels postmeal to below 180 mg/dl within an average of 2.6 ± 0.6 hours. Postmeal glucose levels remained stable within the normal range for a satisfactory time of at least 1 hour. However, stabilization after meal consumption took quite long (4 ± 1 hours). In the 24-hour sessions, the percentage of time kept in the normal range was slightly higher than in home open-loop control. In addition, time spent in the hypoglycemic range was zero during closed-loop control compared to 15.3% during home open-loop control. Additional results from our ongoing clinical trials with the improved MDLAP system will be presented.

Conclusion:
The MDLAP system is a promising tool for individualized glucose control of T1DM patients with the ultimate aim of minimizing high glucose peaks while preventing hypoglycemia.

A New Hypoglycemia Alarm Based on Continuous Electroencephalogram Recording by an Implanted Device

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Objective:
Twenty-five percent of patients with type 1 diabetes suffer from impaired hypoglycemia awareness, leading to an increased risk for severe hypoglycemia. Neuroglycopenia is associated with characteristic changes in the electroencephalogram (EEG). We have demonstrated that EEG changes occurring during insulin-induced hypoglycemia can be recorded from subcutaneously placed electrodes after depletion of noisy signals and detected by an automated mathematical algorithm with high specificity and sensitivity.

Method:
Subcutaneous electrodes were inserted on the scalp of type 1 diabetes patients for continuous EEG recordings. Patients were observed during everyday activity and during insulin-induced hypoglycemia.

Results:
This presentation showed the following: (1) the alarm can be released before loss of cognitive functions (corresponding to 20 minutes before); (2) patients receiving an acoustic alarm at the time of EEG abnormalities were able to correct impending hypoglycemia by the ingestion of carbohydrates; (3) EEG recorded during everyday activities showed detectable EEG changes at the time of both clinical and biochemical hypoglycemia and that these changes disappeared concomitantly with the reinstatement of euglycemia; and (4) initial results from studies of insulin-induced hypoglycemia during sleep demonstrated the ability of the algorithm to distinguish hypoglycemia-associated EEG changes from normal sleep patterns. The design of our portable EEG device will be presented together with nonpatent-protected information concerning the algorithm.

Conclusion:
Through continuous EEG recording by subcutaneous electrodes, we concluded that it is possible to obtain EEG patterns, which, during hypoglycemia, develop specific characteristics as a basis for a hypoglycemia alarm. The device may be used specifically by diabetes patients experiencing hypoglycemia unawareness and also as a safety guard during treatment with a closed-loop system.

Glucose Clamp Algorithms and Insulin Time-Action Profiles

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Background:
Most current insulin pumps include an insulin-on-board feature to help subjects avoid problems associated with "insulin stacking." In addition, many control algorithms proposed for a closed-loop artificial pancreas make use of insulin on board to reduce the probability of hypoglycemic events that often occur due to the integral action of the controller. The insulin-on-board curves are generated from the pharmacodynamic (time-activity profiles) action of subcutaneous insulin, which are obtained from glycemic clamp studies.

Methods:
Glycemic clamp algorithms were reviewed and *in silico* studies were performed to analyze the effect of glucose measurement bias and noise on glycemic control and the manipulated glucose infusion rates. The glucose infusion rates were used to obtain insulin time-activity profiles, which were then used to generate insulin-on-board curves.

Results:
A model-based, three-step-ahead controller was shown to be equivalent to a proportional-integral control algorithm with time-delay compensation. A systematic glucose meter bias of +6 mg/dl resulted in a decrease in the glucose area under the curve of 3%, but no change in the insulin-on-board profiles.

Conclusions:
A substantial amount of glucose meter bias and noise during a glycemic clamp can be tolerated with little net effect on insulin-on-board curves. Handheld glucose meters can therefore be used in clamp studies if the measurements are filtered (averaged) before processing by the control algorithm.

Miniaturization of Raman Spectroscopic Apparatus for Wearable Noninvasive Glucose Monitoring

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Objective:
Laboratory apparatus based on Raman spectroscopy has been used to generate promising glucose signal calibration. The intent of this work was to show that the apparatus can be miniaturized to the extent that it is practical to wear.

Method:
Optical design rules were derived such that the total signal-to-noise ratio of the Raman signal from glucose was optimized within specified size constraints. In particular, the field of view and collection numerical aperture were maximized within the constraint that resolution of the associated spectrometer met acceptable requirements. Prototypes were fabricated and initial *in vivo* measurements were used to confirm the potential efficacy.

Result:
The footprint of the prototype device is 120 × 60 mm and the thickness is 28 mm. The resolution of the spectrographic apparatus is 1.5 nm, the numerical aperture is 0.35 (f/1.4), and the field of view is approximately 0.6 mm in diameter. The apparatus incorporates 830- and 685-nm lasers for measuring Raman spectra of glucose and water, respectively, with the latter being used for signal normalization. Other features ensure thermal, optical, and mechanical stability of the measurement. The unit is sufficiently efficient in collecting glucose signals while being approximately 400 times smaller in volume than the laboratory apparatus. The current prototype size is constrained by the footprint of readily obtained detector arrays, with the choice being predicated on the timely availability of prototypes as a prelude to product qualification.

Conclusion:
Requirements for noninvasive measurement of glucose by Raman spectroscopy are completely consistent with optical design constraints for a device in a size considered practical to be worn. Prototype devices have functionality comparable to laboratory equipment that had been used to demonstrate the efficacy of the measurement technique. The size of the device is subject to straightforward reduction through the procurement of customized components.

Optimizing the Heating Process to Increase Local Blood Perfusion and Improve Insulin Pharmacokinetic and Pharmacodynamic Profiles Using the InsuPatch Device

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Objective:
The pharmacodynamic (PD) and pharmacokinetic (PK) profiles of current insulin analogs are still slow compared to normal physiology. Among other effects, this results in large postprandial blood glucose excursions in insulin-dependent diabetes subjects. The InsuPatch is a novel device intended to accelerate insulin delivery when used with insulin pumps by warming the infusion site locally without heating the insulin itself. Previous clinical studies found that the main benefits of using the device were a reduction of 42% in the time to peak action of insulin, an increase of 45% in available insulin in the blood during the first hour postinjection, and a reduction of 33% in the average glucose level during the first 2 hours postmeal. In this study the effects of the InsuPatch device on local blood perfusion and consequently on insulin PK and PD profiles were explored further. Specifically, we investigated the effect of the size of the heated skin on analog insulin PK and local blood perfusion. Additionally, we tested the effects of specific spatial and temporal heating profiles on local blood perfusion measured using a laser Doppler flowmeter and the heat washout method.

Methods:
The effect of the device on insulin PK was tested by comparing insulin concentration in the blood with and without the device in a meal tolerance test protocol for two different heating pads with different heating areas. The effect of different heating profiles on local blood perfusion was tested by heating the skin with different heating profiles and measuring tissue temperature and local blood perfusion under those conditions.

Bitton cont. ⟶

Bitton cont. ⟶

Results:
Increasing the heating area from 8.2 to 17.5 cm^2 was found to increase the effect of the InsuPatch device on the PK profile. The small heating element improved the area under the curve of insulin delivery during the first hour (AUC1hr) by 30%, whereas the larger heating element improved the AUC1hr by 45%. Changes in heating element size, temporal heating profile, and spatial heating profile were found to affect local blood perfusion.

Conclusions:
The aforementioned results suggest that the effect of the InsuPatch device may be further tuned to optimize its effect on analog insulin PK and PD profiles while reducing power requirements.

Application of a Multisensor Device for Noninvasive Continuous Glucose Monitoring under Home-Use Conditions

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Objective:
We reported earlier about the findings of the application of a novel multisensor device under development for continuous noninvasive glucose monitoring. The multisensor yields signals from skin surface sensors for dielectric, optical, temperature, blood perfusion, and hydration measurements. Under controlled conditions, the multisensor yielded a R^2 of 0.68 and a mean absolute relative difference (MARD) of 27.3% compared to capillary self-monitoring of blood glucose (SMBG) reference blood glucose values. Here we report about the application of the multisensor under home-use conditions.

Method:
Sixteen type 1 diabetes mellitus (T1DM) patients (age 39 ± 12 years; body mass index 23.8 ± 2.7 kg/m^2, duration of diabetes 20 ± 13 years; hemoglobin A1c 6.8 ± 0.8%) wore the multisensor, attached to the upper arm with an elasticized arm band, on average 9 hours per day. Fifteen patients performed a total of 24 study days; one patient performed a total of only 20 study days over a period of 4 months under regular life conditions. A total of 380 study days were collected. On average, patients collected 11 SMBG measurements during each study day. The study was split into two blocks, of overall 160 nonconsecutive and 220 preferably consecutive days, respectively. The multisensor and SMBG measurements from the first block were used for selecting and training a linear regression model. The model was then applied prospectively on the second block of data.

Results:
The model yielded a MARD of 39.7% and a mean absolute difference of 44.8 mg/dl when comparing the multisensor to SMBG values. Data were collected during daily life and across climatic conditions, ranging from a hot summer to a colder autumn (average environmental temperature 20 ± 10°C).

Conclusion:
Using a purely statistical model, application of the multisensor in T1DM patients under daily life conditions applied prospectively demonstrates that glucose variations can be tracked per se. Further developments are under way to increase precision of the glucose variation estimation.

Closed-Loop Control by Hypoglycemia Risk Management

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Objective:
Blood glucose (BG) controllers experience significant uncertainty in BG dynamics, meal, exercise, and sensor noise. Furthermore, BG control is challenged by the asymmetric risk of low vs high BG levels and the one-sided insulin action. As such, aggressive control may be necessary but can overadminister insulin and induce hypoglycemia. We propose a control strategy that explicitly considers uncertainty and regulates the risk of hypoglycemia.

Method:
The controller lowers the BG levels as far as possible without raising the projected hypoglycemia risk above a preset level. Assessing risk requires blood glucose level predictions and certainty estimates. The certainties can be calculated either analytically or empirically. The certainties allow us to construct lower bound blood glucose predictions. The control law then selects the maximum insulin bolus such that the lower bound of the prediction does not drop below the hypoglycemic threshold.

Result:
We compared manual (bolus and basal) and automatic control performance on the Food and Drug Administration-approved University of Virginia type 1 diabetes simulator. The scenario included 100 adults and 100 adolescents and lasted for 43 hours, with daily 40-, 50-, 20-, and 80-gram carbohydrate meal challenges. Automatic control began after 7 hours and lasted for 36 hours. The manual/automatic control had a mean glucose of 183/179 on adolescents and 179/131 on adults. Similarly, the percent time within 70–180 mg/dl was 57/83 and 53/91%. Also, the number of minutes spent below 60 mg/dl per day was 0/7.2 and 0/0 minutes.

Conclusion:
This novel, probabilistic control law successfully achieved significant improvements in overall glucose control when compared to manual control, with a minimal increase in hypoglycemia in a few of the simulated adolescents. The control law is portable and can use any glucose prediction algorithm easily.

Probabilistic, Evolving Meal Detection

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Objective:
Automatic blood glucose control in type 1 diabetes patients benefits from meal detection using continuous glucose monitor (CGM) readings. To support control, our detector estimates future glucose appearance (FGA). Our estimates are fundamentally uncertain due to the variability in glucose dynamics, as well as the lag and noise associated with CGM sensors. We therefore evolved our FGA estimate and provided both a certainty of FGA assuming meal presence and a probability of meal presence.

Method:
The method is unique in continually evolving estimates and simultaneously providing certainty measures. The algorithm operates in three phases: (1) it compares the CGM signal to no-meal predictions made by a simplistic model of insulin dynamics, (2) it fits any residuals to potential, assumed meal shapes, and (3) it compares and combines these fits to estimate meal probability, FGA, and FGA certainty.

Result:
We verified detection on DirecNet clinical research center data. We detected 37 of 38 isolated meals. Exercise masked the missed meal. We examined the sensitivity of detection for 200 compensated 40-gram carbohydrate meals on the Food and Drug Administration-approved University of Virginia type 1 diabetes simulator. After a glucose rise of 10, 20, and 30 mg/dl, the meal probabilities averaged 3, 80, and 100%, respectively. We assessed the accuracy of FGA estimates on simulated meals with sensor noise. After 30, 60, and 90 minutes the errors in FGA estimates dropped to 73, 49, and 33% of the actual meal size. The corresponding certainty estimates were 52, 37, and 28%.

Conclusion:
This novel, extensible meal detection method shows the feasibility, relevance, and performance of evolving estimates with explicit certainty measures for closed-loop control of type 1 diabetes. This method is extendable to exercise and other disturbances.

A Proactive Telemonitoring Platform for Managing Complications of Diabetes Exchanging Data and Short Message Service

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Objective:
Chronic diseases suffer from a high level of incompliance, especially concerning their complications. To reduce incompliance, we improved the modular architecture of our telemedicine platform, adding rules for monitoring events and sending out suggestions proactively.

Method:
Incompliance is being addressed, anticipating it through reminder alarms and correcting any occurrence by notifications. Reminders represent a mandatory schedule for any physiological measurement or medication event that must be obeyed to comply with the protocol. Notifications instead alert about missed or out-of-bound measures. Those proactive actions can be created and configured by the physician for each patient and for each monitored variable.

Result:
The architecture encompasses a mobile phone for the patient and Web tools accessed by the physician. While the patient still has the freedom of autonomously acquiring measures and notifying events through a mobile device, the patient will receive an alarm in terms of a virtual call to be answered when approaching a scheduled event. Alarms listed in a calendar screen may be answered, denied, or snoozed and have a validity period during which some action is expected to be taken. They are set by the physician and may be tagged with a set of incompliancy rules, classified as missed action, action beyond time frame, value out of bound, or critical trend. Every matched rule triggers notification concerning incompliancy either by a short message service or by email to patients and physicians.

Conclusion:
Our proactive telemedicine architecture is presently being validated against four patients affected by renal failure as a complication of diabetes undergoing peritoneal dialysis in a major hospital located in northern Italy. Proactive behavior has been hailed by the clinical staff as an effective solution against incompliance events, especially for elder patients who are prone to forget to take measures altogether or do so at incorrect times, thereby biasing the outcomes negatively.

Pharmacokinetic Characterization of the Technosphere® Inhalation Platform

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Objective:
Technosphere® [fumaryl diketopiperazine (FDKP)] microparticles, an integral component of the Technosphere oral inhalation system, deliver drugs to the deep lung, with an ultrarapid absorption profile (t_{max} of 14 and 3 minutes for insulin and glucagon-like peptide-1) without changes in *in vitro* or *in vivo* (histology after chronic exposure) flux. We evaluated FDKP disposition as part of an integrated clinical safety assessment.

Method:
For the absorption, distribution, metabolism, and excretion (ADME) study, a ^{14}C-labeled FDKP solution was administered via an intravenous or oral bolus. Biological samples were assayed via high-performance liquid chromatography, with radio detection for assessing possible metabolites. For renal and hepatic disease, Technosphere particles were administered by oral inhalation with the MedTone inhaler. Serum/urine pharmacokinetic analyses were performed with validated liquid chromatography tandem mass spectrometry.

Result:
A human ADME study of single intravenous and oral administrations of FDKP in normal healthy subjects (NHS; n = 6) showed >95% elimination unchanged via urine and <3.5% oral bioavailability, indicating that inhalation pharmacokinetics is not confounded by secondary oral absorption. In patients with mild (n = 15) and moderate (n = 9) renal impairment, C_{max} was 184 and 126 ng/ml vs 147 ng/ml in NHS (n = 12); t_{max} was 15 and 30 minutes vs 12 minutes in NHS; and area under the curve $(AUC)_{0\text{-}480}$ was 36,090 and 32,700 min•ng/ml vs 30,474 min•ng/ml in NHS. In patients with mild (n = 15) and moderate (n = 6) hepatic impairment, C_{max} was 162 and 157 ng/ml vs 143 ng/ml in NHS (n = 12); t_{max} was 6 minutes vs 7.5 minutes in NHS; and $AUC_{0\text{-}480}$ was 31,001 and 32,700 min•ng/ml vs 26,710 min•ng/ml in NHS.

Conclusion:
Fumaryl diketopiperazine is absorbed readily from the lungs and excreted unchanged in urine. There is no need to modify doses in patients with chronic renal or liver disease based on FDKP removal from the systemic bloodstream.

Amperometric Glucose Sensors: Are Two Better Than One?

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Objective:
The effectiveness and safety of closed-loop systems are limited by suboptimal sensor accuracy, which is due in part to sensor drift. We hypothesized that using two sensors, and selecting the one with better accuracy, would improve accuracy compared to using a single sensor.

Method:
Each of 10 subjects with type 1 diabetes wore two amperometric glucose sensors (Medtronic® or DexCom®) for a total of 13 closed-loop studies (duration 18.3 ± 2.6 hours). Sensors were calibrated at the start of the study and again at the end of a 4-hour initial comparison period. Venous glucose, drawn every 10 minutes, was used to determine accuracy. We compared the accuracy of the following three sensing methods. (1) Compare-select method: The more accurate of the two sensors was used after the 4-hour initial comparison period. (2) Averaging method: The average of the two sensors was used after the comparison period. (3) Single sensor method: Data for each single sensor were used after the comparison period.

Result:
The compare-select method demonstrated the best accuracy and was superior to averaging (mean absolute percentage difference, 12.3 ± 2.9% vs 13.5 ± 3.0%, $p = 0.03$). The compare-select method was also superior to sensor 1 (14.4 ± 3.5%, $p = 0.05$) and demonstrated a trend toward better accuracy than sensor 2 (13.8 ± 3.3%, p = not significant).

Conclusion:
Sensor accuracy is improved with the use of dual sensors. Selecting the more accurate of the two sensors after an initial observation period is superior to the use of a single sensor and superior to the use of the average of two sensors.

Glucose-Dependent Nonlinearity of Insulin Action in Patients with Type 1 Diabetes Mellitus

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Objective:
Increased insulin resistance at high blood glucose (BG) levels and increased insulin sensitivity at low BG levels have been suspected clinically. We now demonstrate experimentally and analytically the nonlinearity of insulin action at low and high BG levels.

Method:
Data from two studies were used to demonstrate these effects. Study 1: A hyperinsulinemic hypoglycemic clamp was performed in 19 patients with type 1 diabetes mellitus (T1DM) [age: 40 ± 10 years, body weight (BW): 82 ± 12 kg, hemoglobin A1c: 7.7 ± 1.9%]. Glucose consumption and insulin action were estimated during the steady descent into hypoglycemia. Study 2: The Biostator™ was used to first lower BG levels from 100 to 45 mg/dl and subsequently from 200 to 45mg/dl 4.5 hours later in 15 patients with T1DM (age: 27 ± 6 years, BW: 76 ± 13 kg), which allowed comparison of insulin action at normal vs high glucose levels.

Result:
Study 1 demonstrated the nonlinearity of glucose consumption at low BG levels. The degree of nonlinearity as defined by the deviation of glucose consumption from linearity was significant below 70 mg/dl ($p < 0.0001$), and the nonlinear model fit was significantly better than the linear fit for all but one subject. Insulin sensitivity increased significantly at low BG levels ($p = 0.0015$). In study 2, insulin resistance was significantly higher at 200 mg/dl compared to 100 mg/dl ($p = 0.0012$).

Conclusion:
In T1DM, insulin sensitivity increases at low BG levels and decreases at high BG levels, indicating nonlinear dependence of insulin action on BG level. This has important consequences for the prevention of hypoglycemia, open- and closed-loop glucose control: the same amount of insulin would cause substantially larger BG lowering at normal than at hyperglycemic levels.

Hemoglobin A1c (HbA1c) Prediction Model Using Self-Monitoring of Blood Glucose Data in Real Practice for Subjects with Type 2 Diabetes: The Catholic–Ajou HbA1c Predictor

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Objective:
Hemoglobin A1c (HbA1c), expressed as a percentage of glycated hemoglobin, is the most widely used measurement of chronic glycemia. However, daily adjustment of diabetes therapy depends on capillary glucose levels. We developed a model that predicts HbA1c levels by analyzing self-monitoring of blood glucose (SMBG) data collected from type 2 diabetes patients for 30 days.

Methods:
We collected SMBG data of 78 patients, which were recorded from their online Web chart (www.biodang.com) from 2002 to 2005. We determined the relationship between HbA1c level and SMBG data. SMBG data of 78 patients were recorded from 60 to 30 days before measurement of the HbA1c.

Results:
We found 215 HbA1c levels, which had previous 30-day SMBG data sets. We used 115 of the total 215 SMBG data sets to build a model and the other 100 sets to test the model. In order to generate the prediction model, we utilized three parameters: mean value of preprandial blood glucose (MpreBG), postprandial blood glucose (MptBG), and nighttime blood glucose (MnBG). The predicted HbA1c based on the mean blood glucose level was calculated to derive the regression equation. A statistical significant relationship between the mean blood glucose level and HbA1c was observed, and the following regression equation reflects such a relationship:

$$\text{HbA1c} = 0.219 \times \text{MptBG (mmol/liter)} + 0.407 \times \text{MpreBG (mmol/liter)} - 0.111 \times \text{MnBG (mmol/liter)} + 3.075 \quad (r = 0.778,\ p < 0.0001)$$

Conclusion:
We developed a new HbA1c prediction model for type 2 diabetes patients by analyzing a 30-day SMBG data set. With this new prediction model, we could accurately predict an HbA1c level after 1 month.

Using Telemedicine to Provide Diabetes Care to Rural Patients in Montana

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Objective:
The goal of this study was to evaluate the effectiveness of a nurse practitioner (NP)-led interdisciplinary team approach to diabetes self-management using telemedicine technology on achieving established American Diabetes Association (ADA) guidelines for diabetes disease care, patient satisfaction, and patient self-management in rural primary care clinics.

Method:
A randomized control design was utilized to evaluate a patient-centered team approach to diabetes management provided via telemedicine. Intervention and control patients were compared on adherence to ADA-recommended guidelines, patient satisfaction with the intervention and the telemedicine technology, and patient diabetes self-management.

Results:
One-year postintervention, receipt of a dilated eye examination increased 47% among intervention patients compared to no change among controls ($p = 0.05$). Patient diabetes care satisfaction rates increased 211% among intervention patients compared to a 45% increase among controls ($p = 0.03$). Intervention patients reported feeling good to excellent about managing their diabetes ($p < 0.05$). Self-reported correct blood glucose monitoring and frequent vigorous exercise were greater among intervention patients compared with controls ($p = 0.05$). All patients surveyed reported satisfaction with, and comfort in, learning health information via telemedicine. Staff satisfaction with use of the technology was also high. Control of vascular risk factors (hemoglobin A1c <7%, blood pressure <130/80 mm Hg, and low-density lipoprotein cholesterol <100 mg/dl) was greater in intervention patients and trending toward statistical significance.

Conclusions:
A NP-led interdisciplinary team approach to diabetes management had a positive impact on improved diabetes preventive care, patient satisfaction, and patient self-management among rural patients with diabetes. Telemedicine proved to be an effective means of communication for the provision of diabetes care to rural patients. This model of care is a possible alternative to traditional one-on-one patient–provider encounters and may be a viable strategy for addressing the unique challenges faced by patients living in rural communities.

Southern Arizona Limb Salvage Alliance Patient Database: Clinical Tool for Management of Lower Extremity Complications of Diabetes

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Objective:
Management of the diabetes population is both challenging and complex. Neuropathic foot ulcer is one of the most common complications of diabetes and the most common reason for hospitalization when infected. The Southern Arizona Limb Salvage Alliance (SALSA) patient database (SALSAbase Footware) was created in an attempt to examine key variables that can be followed over time, manage patient care, and monitor outcomes over time in order to increase understanding of the lower extremity disease process.

Methods:
A chart review of 203 patients with lower extremity wounds admitted to the University of Arizona's SALSA service from July 2008 through June 2009 was performed. Patient vital and laboratory data were examined, as well as several key variables, including age, sex, presence of vascular disease, lower extremity ulcer location, type of surgical intervention, presence or absence of infection, occurrence of readmission, and date of death, if applicable. Data were analyzed using SPSS.

Results:
Of the 203 patients, 59.1% were male, average patient age was 58.85 ± 15.38 years, average hemoglobin A1c was 8.54 ± 2.24%, and 75.9% demonstrated peripheral vascular disease. Additionally, the most common ulcer location was the forefoot (38.4%), and the most common infecting organism was methicillin-susceptible *Staphylococcus aureus* (23.39%).

Conclusion:
These interim results demonstrate the value of using technology to track the diabetes patient population as it will allow better management of the disease and identification of risk factors associated with poorer outcomes. It is hoped that the SALSAbase Footware can be used as a model for other diabetic lower extremity database software so that the complications of this disease can be prevented in the future.

In Vitro/Vivo Evaluation of Medtronic's Interference Rejection Membrane

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Objective:
A common problem found in most electrochemical sensors is interference caused by the oxidation/reduction of an outside species, resulting in an unwanted offset in signal. While not every compound that causes interference is known, acetaminophen (i.e., Tylenol®) has been cited as the most common. To reduce the offset caused by interferents, Medtronic Diabetes has developed a proprietary interference rejection membrane (IRM) that is biocompatible and labeled for permanent subcutaneous implant.

Method:
To determine the effectiveness of the IRM, a series of *in vitro/vivo* experiments were conducted. Glucose sensors with (test) and without (control) IRM were exposed to 29 different medications in a buffer solution. Both the control and the test groups were subjected to the following types of possible interferents *in vitro*: antibiotics, immunosuppressants, steroids, antivirals, laxatives, antidepressants, enzymes, antinauseas, insulins, statins, sleep aids, narcotics, hormones, and nonsteroidal anti-inflammatory drugs. Response to an interferent is defined as an increase of ≥0.4 nA in signal offset, which equates to approximately 3 mg/dl offset for typical sensors. To determine if the IRM would affect sensor performance *in vivo*, the canine and human model was chosen. None of the aforementioned interferents, other than insulin, were tested on canines or humans.

Results:
The *in vitro* experiment resulted in the control group showing a positive response to 10 of the interferents, whereas the test group showed response to 0 of the interferents. *In vivo* human/canine experiments resulted in the control and test groups performing with excellent linearity and sensor response to glucose changes.

Conclusion:
Results of the *in vitro* experiment suggest that use of the IRM is effective in reducing the offset caused by common prescription and over-the-counter medications, without sacrificing sensor performance.

Institutional Subcutaneous Insulin Protocol Utilizing Computerized Prescriber Order Entry Eliminates Sliding Scale Orders

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Objective:
Computerized prescriber order entry (CPOE) was instituted at New York Hospital Queens in November 2007 utilizing the Eclipsys Sunrise Clinical Manager™ platform. Prior to and immediately after implementing CPOE, the majority of insulin regimens prescribed were based on a sliding scale approach. In an effort to improve inpatient glycemic control, decrease the use of sliding scales, and decrease the use of 50% dextrose in hypoglycemic patients able to be treated with oral glucose, a multidisciplinary team was formed to utilize information technology to augment prescribing behavior and encourage the appropriate use of subcutaneous insulin.

Method:
Subcutaneous insulin protocols were developed in CPOE and limited to display multiple dose insulin regimens using either basal-bolus or twice-daily premixed insulin. The CPOE insulin protocols included orders for capillary glucose timing, insulin administration, and staged treatment of hypoglycemia and were implemented in January 2008. Point-of-service glucose results, parenteral hypoglycemia treatment, and adherence to the protocol for patients who were prescribed subcutaneous insulin regimens prior to the CPOE protocol (July 2007–December 2007) were compared to after the protocol (July 2008–December 2008) for patients on the general medical/surgery units. Subjects were identified through retrospective chart review.

Result:
Elimination of sliding scale regimens, increased utilization of basal-bolus insulin therapy, and a significant impact upon distribution of glucose levels without an increase in rates of hypoglycemia were observed. A decreased use of 50% dextrose for hypoglycemia treatment was also seen.

Conclusion:
Utilization of information technology to implement a computerized subcutaneous insulin protocol resulted in the elimination of sliding scale regimens while encouraging the use of basal insulin. Target blood glucose goals were achieved more often for patients prescribed CPOE subcutaneous insulin therapy.

Computerized Treatment of Hyperglycemia in a Neurosurgical Intensive Care Unit

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Objective:
The presence of hyperglycemia and hypoglycemia in the critically ill patient has been shown to increase morbidity and mortality. Many methods of glycemic control have been utilized in an attempt to maintain a normal blood glucose level in the critically ill patient with neurological disorders. The purpose of this study was to determine the effectiveness of utilizing a computerized software program for intravenous insulin dosing to control blood glucose levels in neurosurgical patients. The computerized protocol should provide relatively quick, but safe, reductions in blood sugar with reduced blood glucose fluctuations and minimal risk of severe hypoglycemia.

Method:
A retrospective chart review of 46 patients enrolled in the software program from June 1, 2008 to June 1, 2009. A systematic review of the clinical parameters of critical care and the blood glucose level responses were reviewed in these 46 patients.

Results:
The total number of neurosurgical/neurological patients initiated on the software program during the review period was 46. Demographics: mean age was 61.7 years (19, 84); reviewed patients with a diagnosis of type 1 or type 2 diabetes mellitus was 29; average time to blood glucose level <140 mg/dl was 176.69 minutes; hypoglycemia <50 mg/dl was 2.

Conclusion:
Use of this computerized program for calculating blood glucose correction measures in neurosurgical patients provides relatively quick and safe reductions in blood sugar with a minimal risk of severe hypoglycemia.

Hyperglycemia Implications in Stroke

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Objective:
The American Stroke Association recommends treatment of hyperglycemia in patients with blood glucose greater than >140 mg/dl as a standard protocol of care. Treatment for hyperglycemia is important in those patients receiving thrombolytics due to the risk of intracranial hemorrhage. Because glucose is an important fuel for brain cells, it must be maintained at a sufficient level but yet is known to promote thrombosis when elevated. The purpose of this study was to examine the role of the nurse in the recommended treatment to normalize blood glucose levels in patients with acute ischemic stroke while avoiding hypoglycemia. This was done in a setting of full nutritional support and required the use of intravenous insulin and accurate insulin dosing regimens.

Method:
A literature review was completed to determine the best evidence for treatment of hyperglycemia in acute ischemic stroke patients and best evidence for nutritional support of those patients in the setting of acute stroke and hyperglycemia.

Results:
The American Stroke Association recommends treatment of hyperglycemia in patients with blood glucose greater that >140 mg/dl as a standard protocol of care. The Scientific Statement for Nursing and Interdisciplinary Care reinforces this recommendation through the continuum of care from prehospital identification to emergency department and during the acute care stay.

Conclusion:
Treatment to normalize blood glucose levels in patients with acute ischemic stroke is recommended if the initial blood glucose is greater than 140 mg/dl. Nurses have a unique role in identifying blood glucose abnormalities in these patients on initial presentation of symptoms prehospital to the acute care facility as well as ongoing monitoring via a point-of-care device and by routine laboratory work.

A Pre- and Type 2 Diabetes Simulator for *in Silico* Trials

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Objective:
Realistic computer simulation could provide useful information about the efficacy of diabetes treatments, as it can be used for *in silico* testing of drug pharmacodynamics before performing *in vivo* experiments in humans. The objective of this study was to develop a simulator of prediabetes (PD) and type 2 diabetes mellitus (T2DM), which, at variance with the existing ones, is able to realistically describe not only population averages, but also intersubject variability observed during clinical trials.

Method:
The *in silico* model consists of 12 ordinary differential equations and 26 parameters, describing glucose and insulin kinetics, endogenous glucose production, meal rate of appearance, insulin secretion, and renal excretion. The database used for model identification consisted of 35 PD subjects and 23 T2DM patients, who underwent a triple tracer meal protocol, thus providing virtually model-independent estimates of all relevant glucose and insulin fluxes. The model was identified in each subject via subsystem decomposition and forcing function strategy. Then, from individual parameter estimates, the joint parameter distribution was reconstructed in each population. Incorporating pharmacokinetics/pharmacodynamics of major drugs, e.g., metformin, DDP4 inhibitors, and insulin, various treatment strategies can be assessed *in silico*.

Result:
The model generates PD and T2DM virtual subjects. The simulated range of glucose concentration is similar to that observed in both PD and T2DM populations. Examples of use of the simulator to assess the efficacy of various diabetes treatments are presented.

Conclusion:
An *in silico* model of prediabetes and type 2 diabetes has been developed from gold standard data. The simulator can be used to perform rapid and cost-effective *in silico* experiments.

In Silico Comparative Assessment of Three Different Closed-Loop Control Strategies for Type 1 Diabetes Patients

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Objective:
The aim of the present study was the design, development, *in silico* evaluation, and comparative assessment of three different control algorithms used for the implementation of the closed-loop artificial pancreas.

Method:
The three algorithms were (1) a proportional-integral-derivative (PID) controller, (2) a fuzzy logic (FL) controller, and (3) their parallel combination, in order to take advantages of each separate controller. The ability of each algorithm to regulate the glucose profile using the subcutaneous–subcutaneous (s.c.–s.c.) route was evaluated *in silico* under different disturbances (meals) and delays. The following scenarios were applied to each control algorithm: (i) one meal and stepwise increase of delays starting from 0 to 20 minutes with a time step of 5 minutes and (ii) four meals of different sizes and stepwise increase of delays starting from 0 to 20 minutes with a time step of 5 minutes. The performance of each controller was assessed from the ability to keep the glucose profile in normoglycemia (90–140 mg/dl) for a time period of 24 hours.

Results:
Even for the most difficult scenario (four meals and delay equal to 20 minutes), the controller based on parallel combination of the PID and FL controllers achieved the best performance, keeping the s.c. glucose concentration in normoglycemia 95.2% of the time, followed by the FL controller (87.5% of the time in normoglycemia) and the PID controller (82.3% of the time in normoglycemia).

Conclusions:
The parallel architecture seems to be more appropriate used in an artificial pancreas. Prior to clinical trials, further evaluation is needed, while comparative assessment with model predictive controllers is in progress.

Use of Telemedicine in Development of an Artificial Pancreatic β Cell

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Objective:
The quest toward an artificial pancreatic β cell (AP) that will regulate insulin delivery through a computer algorithm requires engineering expertise and clinical validation. Telemedicine allows for real-time clinical evaluation at remote locations.

Method:
A fully automated AP system (APS) was developed at the University of California, Santa Barbara, and the Sansum Diabetes Research Institute. The APS can use different control algorithms and communicate with either the FreeStyle Navigator® (ADC, Alameda, CA) or the STS7® (DexCom, San Diego, CA) continuous glucose monitor and the OmniPod® (Insulet, Bedford, MA) insulin infusion pump. The APS and devices were delivered to Schneider Children's Medical Center of Israel (SCMCI). Clinical data were collected at SCMCI and sent to the Santa Barbara team for development of a personalized controller. This controller was sent to SCMCI before the clinical day. Trials were observed online via a secure internet connection with an audio/video link.

Result:
Ten fully automated closed-loop clinical trials were conducted at SCMCI with a mean duration of 6 hours. Clinical work was conducted in Israel, the algorithmic development was performed in Santa Barbara, and telemedicine allowed the developers to participate remotely in the clinical trials and to provide technical support in troubleshooting sensor-related problems and/or overriding controller delivery.

Conclusion:
The use of APS and telemedicine tools will expedite development of an AP. Engineering centers can develop control algorithms, and multiple clinical sites can perform clinical validation. The use of an internet connection and the APS will allow remote support by the developing team across time zones and borders. This type of distributed approach will allow for faster development of a functional system.

Performance of a Fuzzy Logic-Based Multiple Input Multiple Output Controller as an Artificial Pancreas

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Objective:
Hyperglycemia in the intensive care unit (ICU) setting has been shown to increase morbidity/mortality rates. Tight glucose control can normalize blood glucose values and decrease glucose variability. The pancreas releases insulin in Gaussian-shaped pulses with a cycle interval of 5 minutes. Current software-based insulin management tools adjust the insulin dose with a maximal frequency of every 1 hour and use a square wave dosing pattern; they also fail to account for glycogenolysis/gluconeogenesis. A novel fuzzy logic (FL)-based artificial pancreas has been created in an attempt to duplicate the native glucoregulatory system.

Method:
A multiple input multiple output (MIMO) FL controller with a built-in secondary controller has been created using the input variables of absolute glucose, rate of glucose change, weight-based insulin dose, and weight-based dextrose dose. Output variables are weight-based insulin dose and weight-based dextrose dose. The primary controller has over 200 discrete algorithms, and the secondary controller has 20 separate modifying rules. A simplified theoretical model was used to compare the MIMO controller to the Amarillo protocol, which is based on the work of Dr. Bruce Bode.

Result:
Over a 20-hour ICU scenario, the Amarillo protocol versus MIMO FL controller showed the following: time to target (100–140 mg/dl), 4 hours vs 1.5 hours; % glucose <100 mg/dl, 36% vs 5%; % glucose <60 mg/dl, 5% vs 0%; and % glucose in the range 100–140 mg/dl, 32% vs 88%.

Conclusion:
A MIMO FL controller using a standard cycle interval of 10 minutes with secondary modification rules performed better than the Amarillo protocol in a theoretical model. A proof-of-concept clinical trial is warranted.

Effect of the Insertion Method on the Continuous Glucose Sensor Response

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Objective:
A significant drawback of currently available continuous glucose sensors is the slow attainment of stable sensing conditions following insertion (run-in period of several hours). The aim of this study was to investigate the effect of the insertion procedure on the early sensor response in humans.

Method:
Four needle-type, amperometric enzyme-tipped sensors were inserted into subcutaneous adipose tissue of 15 healthy volunteers, two using the provided automated inserter with a V-shaped needle and a side length of 1 mm (AUTO-sensors) and two manually after puncturing the skin with a 0.6-mm lancet (MAN-sensors). The system was calibrated 30 minutes after insertion using capillary blood readings. Sensor glucose signals were recorded continuously and blood glucose (reference) at half-hourly intervals over an 11-hour period.

Result:
During the first 3 hours after insertion, the glucose concentration measured with AUTO-sensors declined more rapidly than that measured with MAN-sensors. At 3 hours, concentrations were 27.0 ± 4.8 and 12.9 ± 2.8% lower than the plasma glucose concentration, respectively. During the remainder of the study (hour 3 to 11), glucose signals of AUTO- and MAN-sensors followed a moderate and comparable decline. By the end of the experiment, glucose concentrations measured with the AUTO- and MAN-sensors were 37.2 ± 5.2 and 25.4 ± 3.1% lower than plasma glucose ($p < 0.01$), whereby MAN-sensor glucose levels were still significantly higher than AUTO-sensor glucose levels ($p < 0.05$).

Conclusion:
Results obtained from these experiments indicate that the less invasive manual insertion method results in a significantly smaller reduction in sensor sensitivity over an 11-hour period after sensor insertion. Thus, by applying this method, the duration of the run-in period after sensor insertion may be shortened, thereby helping improve the performance of continuous glucose monitoring systems.

Evaluation of Hemoglobin A1c Results in Renal Disease Using the Bio-Rad VARIANT™ II Hemoglobin A1c Program Reorder Pack

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Background:
Elevation of plasma urea in diabetes patients with renal disease results in the formation of carbamylated hemoglobin (CHb), which can interfere with hemoglobin A1c (HbA1c) measurements. The purpose of this study was to evaluate the accuracy of HbA1c results using the new VARIANT™ II HbA1c program reorder pack assay in patients with a wide range of creatinine concentrations and glomerular filtration rate (GFR) estimates representing all stages of renal insufficiency. It was shown that CHb does not interfere with HbA1c quantitation using this improved HbA1c assay.

Method:
Samples with varying concentrations of creatinine and a wide range of HbA1c values (5–12%) were identified. Samples were run using the VARIANT II HbA1c assay (test method) and were analyzed at the National Glycohemoglobin Standardization Program (NGSP) Secondary Reference Laboratory (SRL) by boronate affinity chromatography (reference method). Differences between methods were correlated with creatinine concentration and GFR to assess CHb interference indirectly in patients with varying stages of renal insufficiency.

Results:
The regression equation of the VARIANT II HbA1c program compared with the boronate affinity method was $y = 1.054x - 0.174$, with $R^2 = 0.986$. The correlation slope between creatinine concentrations and the difference in percent HbA1c between methods was 0.0047, with a 95% confidence interval for the slope that included zero (-0.019–0.020). Estimated GFRs were calculated from creatinine concentrations using the Modification of Diet in Renal Disease study equation to provide a means of assessing the severity of chronic kidney disease.

Conclusion:
In patients with creatinine and GFR estimates consistent with level 5 kidney disease, there was no apparent interference in the new VARIANT II hemoglobin A1c assay compared to a NGSP SRL boronate affinity reference method.

Amperometric Glucose Sensors: Mathematical Concepts for Optimization of Accuracy

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Objective:
We hypothesized that real-time sensor accuracy could be improved by using three procedures: (1) correction for sensor lag, (2) correction for background current, and (3) increasing calibration frequency.

Method:
We examined six consecutive 28-hour data sets in which the Medtronic sensor was used in a closed-loop control study in subjects with type 1 diabetes. Reference venous blood glucose values were obtained every 10 minutes. Data were examined for accuracy with and without lag correction, with and without background current correction, and according to frequency of calibration (every 4, 8, or 12 hours). For rising (or falling) glucose values, it is assumed that the sensor reads falsely low (or high). The background current was determined for this population by comparing sensor current to reference glucose.

Results:
Correction for a sensor lag of 8 minutes vs 0 minute resulted in an improvement in mean absolute percent difference [MAPD, 12.2% vs 13.6%, calibration every 8 hours, background current (BC) = 3 nA, $p = 0.005$]. Correction for a BC of 3 nA vs 0 nA also resulted in a significant improvement in MAPD, 12.2% vs 15.7%, each with an optimized time lag correction, with calibration every 8 hours. Increasing calibration frequency from every 12 hours to every 8 hours also resulted in a significant improvement in MAPD when matched for time delay: 12.2% vs 13.4% with a lag correction of 8 minutes and a BC of 3 nA ($p < 0.0001$).

Conclusion:
Corrections for sensor lag and background current, accompanied by increased calibration frequency, increase the accuracy of amperometric glucose sensors in persons with type 1 diabetes. These procedures are all suitable for real-time use.

Fully Automated Overnight Closed-Loop Glucose Control in Young Children with Type 1 Diabetes

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Objective:
We evaluated fully automated overnight closed-loop (FAOCL) insulin delivery in young children with type 1 diabetes (T1DM).

Methods:
Seven children with T1DM [four males; age 8.9 ± 2.4 years; body mass index 17.6 ± 1.4 kg/m^2; duration of diabetes 4.0 ± 2.7 years; total daily dose 0.7 ± 0.1 U/kg/day; hemoglobin A1c 7.8 ± 1.0%; mean ± standard deviation (SD)] were studied in a clinical research facility on two occasions. Subjects had a meal at 1800 [76.7 ± 8.6 grams carbohydrate (CHO)] and a snack at 21:00 (20.8 ± 6.5 grams CHO) accompanied by a prandial insulin bolus. In random order, FAOCL started at 18:00 or 21:00 and ran until 08:00 the next day. Subcutaneous (sc) continuous glucose monitoring (CGM) data were fed automatically into a model predictive control algorithm, which calculated sc insulin infusion rates sent wirelessly to an insulin pump.

Results:
No rescue carbohydrates were administered. Time spent in the target glucose range 3.9–8.0 mmol/liter [46 (7, 75)% vs 60 (23, 67)%; median CGM (interquartile range), p = not significant (NS), Wilcoxon test] and time above 8.0 mmol/liter [36 (25, 93)% vs 40 (33, 77)%, p = NS] did not differ between the two occasions. Time below 3.9 mmol/liter was 0 (0, 0)% on both occasions. A low BG index (1.2 ± 3.0 vs 0.4 ± 0.5, mean ± SD, p = NS), glucose at the start of FAOCL (12.9 ± 3.1 mmol/liter vs 13.5 ± 2.5 mmol/liter, p = NS), and mean overnight glucose (9.0 ± 2.1 mmol/liter vs 9.0 ± 2.0 mmol/liter) were also similar. Insulin infusion rates during FAOCL were higher than preprogrammed basal rates on both occasions (0.58 ± 0.25 U/hr vs 0.41 ± 0.16 U/hr, p = 0.03, and 0.57 ± 0.21 U/hr vs 0.42 ± 0.16 U/hr, p = 0.01).

Conclusions:
A fully automated overnight closed-loop is feasible in young children with T1DM. Comparable results were obtained when closed-loop was initiated at 18:00 or 21:00.

Predicting Future Glucose Concentrations Using Continuous Glucose Monitoring and Physiological Measurement Data

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Objective:
Many patients with diabetes experience high variability in glucose concentrations that includes prolonged hyperglycemia or hypoglycemia. Models predicting a subject's future glucose concentrations can be used for preventing such conditions by providing early alarms. We have previously developed subject-specific models that utilize *only* recent glucose history from a continuous glucose monitoring (CGM) device, with 3–5% error for 30-minutes ahead prediction. Continuous metabolic, physical activity, and lifestyle information from a multisensor body sensor may supplement the CGM information to enhance the predictions. The objective of this work was to develop subject-specific glucose prediction models using both CGM data and physiological measurements from a multisensor body monitor.

Method:
Multivariate time-series analyses were utilized to develop low-order linear glucose prediction models. Model parameters were identified online at each sampling step using the weighted recursive least-squares (RLS) method. A change detection strategy that monitors variation in model parameters was also included. The proposed algorithm was validated on CGM (CGMS System Gold, Medtronic MiniMed) and armband (SenseWear Pro3, BodyMedia Inc.) data collected at 5-minute intervals from patients conducting normal daily life.

Result:
Models developed are linear low-order and easy to identify. The RLS and the change detection methods enable dynamic adaptation of the models to inter/intrasubject variation and glycemic disturbances. Errors in predictions are reduced significantly with additional measurements from the armband when compared to predictions done solely on glucose measurements.

Conclusion:
A subject-specific glucose prediction strategy that uses measurements from a CGM device and an armband has been developed. The proposed algorithm with a small number of parameters is a good candidate for early hyper/hypoglycemic alarms and closing the glucose regulation loop with an insulin pump.

Usability Assessment of a Novel Diabetes Risk Stratification Tool

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Objective:
Blood glucose (BG) variability, a measure of glycemic excursions over time, was identified by the Diabetes Control and Complications Trial as a good predictor of diabetes complications. Average daily risk range (ADRR), an algorithm developed by Kovatchev and colleagues from the University of Virginia, is one of the few methods used to measure BG variability that is sensitive to both hypo- and hyperglycemic events and computes a risk group from self-monitoring of blood glucose (SMBG) data that is highly correlated with diabetes complications. This study assessed the usability of the ADRR glycemic variability calculator (ADRR-GVC), a software implementation of ADRR that allows physicians to observe BG variability trends in a diabetes clinic.

Methods:
Twenty-eight participants (patients with diabetes) attended three monthly visits, during which physicians (three endocrinologists) used ADRR-GVC to compute and graphically display the ADRR index and risk group from the participant's SMBG data and then completed a usability questionnaire with 24 Likert questions in eight categories plus five free-text questions. The Likert questions were scored as usable or not usable and aggregated by category. The free-text questions were analyzed for meaningful trends.

Results:
Seven out of the eight categories were scored as "usable." "Content" was scored as "not usable" as a result of two low-scored questions on system completeness by one physician who wanted additional functions on the software. Features most appreciated included bar charts comparing results over time and use of ADRR as a quantitative risk estimator. Suggested additions were most recent hemoglobin A1c and number of SMBG readings used.

Conclusion:
Average daily risk range offers meaningful risk stratification information to clinicians treating patients with diabetes and can be implemented as a graphic-rich software application with high usability by physicians who want to see ADRR included in other diabetes management service tools.

Accuracy of Continuous Glucose Monitoring Sensors Improved in Real Time by Exploiting Short-Time Prediction

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Objective:
Even if the possibility of improving diabetes management by using continuous glucose monitoring (CGM) systems is rather consolidate, the accuracy of CGM devices is still suboptimal. This work presents a stochastically based, short-time prediction algorithm that is able to improve, in real time, the accuracy of CGM devices. In particular, short-term prediction is used to compensate the well-known 10- to 20-minute delay due to the blood-to-interstitium kinetics.

Method:
The data set consisted of 13 type 1 diabetes patients. Each subject file contained 3-day FreeStyle Navigator™ CGM data monitoring and blood glucose (BG) references measured in parallel every 15 minutes. An online Kalman filter-based prediction algorithm was developed and applied, exploiting three different short-time prediction horizons (PH = 10, 15, and 20 minutes). The root mean square error (RMSE) between BG references and original and predicted CGM data and the continuous glucose–error grid analysis (CG-EGA) were chosen as performance indexes.

Result:
By using short-time predicted CGM data, the RMSE was reduced on average of 10.1, 12.1, and 10.5% with PH equal to 10, 15, and 20 minutes, respectively. Concerning the CG-EGA, the number of couples in accurate and benign zones (A+B) during hypoglycemia increased significantly from 60 to 80% for each PH value, while the percentages in euglycemia and hyperglycemia remained similar.

Conclusion:
Short-time prediction can be exploited to improve the accuracy of CGM output. In particular, by compensating part of the distortion introduced by the blood-to-interstitium kinetics, the prediction with PH of 15 minutes allows increasing the RMSE of 12% and A+B reading in CG-EGA of 20%.

Real-Time Detection of Continuous Glucose Monitoring Sensor Failure

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Objective:
Failures in continuous glucose monitoring (CGM) devices due to loss of sensitivity of the skin sensor are critical events that can last for several minutes and need to be detected in a timely manner in order for the patient to take correct actions. This work presents a methodology, based on short-time prediction, which, in its application to simulated data, is able to detect most CGM failure episodes in real time.

Method:
The database consisted of 10 *in silico* CGM time series (3 days of monitoring), created by using GIM, the type 1 diabetic simulator of Dalla Man and colleagues. Two sensor failure events per day were simulated by rapidly increasing/decreasing the measured CGM reading up to 30% of the correct value. Gaussian noise was added to simulate measurement error. Online 15 minutes ahead-of-time prediction was calculated using a self-tuning Kalman filtering approach. Failures were then detected by a statistically based decision strategy.

Result:
More than 70% of the simulated failure episodes were identified correctly within 10 minutes after the failure event began. False positives were less than 10%.

Conclusion:
The combination of a short-time prediction algorithm and a statistically based decision strategy is able to identify, in real time, most sensor failures. Further investigation will concern optimization of the parameters of both the prediction algorithm and the decision strategy, and the extension of the study to real data.

Autofeedback Control of Glucagon Counterregulation

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Objective:
Glucagon counterregulation (GCR) is a key protection against hypoglycemia compromised in insulinopenic diabetes patients by an unknown mechanism. Recent experimental and theoretical work suggests that α-cell autofeedback plays a role in GCR regulation, and here we test *in silico* the hypothesis that a minimal control network (MCN) in which α cells are suppressed by blood glucose (BG), β-cell activity, and autofeedback can replicate the normal GCR control mechanism and explain its impairment in diabetes.

Method:
The MCN was described by a mathematical model. The model parameters were set such that α-cell autofeedback drives glucagon pulsatility and hypoglycemia triggers pulsatile GCR by switching off the BG and β-cell suppression of α cells. The parameters were further adjusted to allow the model to approximate key experimental findings.

Result:
The model predicted the *in vivo* GCR response to hypoglycemia of the normal pancreas and enhancement of defective pulsatile GCR by switch-off of intrapancreatic α-cell-suppressing signals in insulin deficiency. The model also predicted that reduced insulin secretion elevates basal glucagon and decreases and delays the GCR. Another key prediction is that defective GCR can be repaired by reducing hyperglucagonemia.

Conclusion:
We have developed and validated a model of normal GCR control mechanisms and their dysregulation in insulin-deficient diabetes. All model components are clinically measurable, thereby permitting its transfer, validation, and application to the study of GCR abnormalities of the human endocrine pancreas *in vivo*. The model prediction that reducing hyperglucagonemia may repair defective GCR suggests exciting strategies for manipulation of the glucagon axis that could protect against hypoglycemia as part of an artificial pancreas design.

First Report from Argentina of Three First Years Follow-Up of Autologous Stem Cells Implanted in Type 2 Diabetes

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Objective:
The goal of this study was to evaluate the long-time performance of stem cells implanted in the pancreas of type 2 diabetes patients. Adult stem cells CD34(+)CD38(-) have demonstrated the capacity to differentiate in functional cells on the endocrine pancreas.

Method:
After 3 years on cell therapy for diabetes patients, the conclusions are optimistic. This study observed the evolution of 58 type 2 diabetes patients (37 males, 21 females, 29–71 years old). Twenty-nine patients were under insulin therapy, and 20 patients were using sulfonylureas + biguanides. For transplantation, bone marrow was harvested from the iliac crest by aspiration, after which the sample was processed using a density gradient separation method; 120 ml (±95) of CD34(+)CD38(-) solution was obtained. Catheterization through the splenic artery was used for implantation. No complications or further events were observed during or after the procedure.

Results:
Patients were followed clinically with blood sample analysis during the next 36 months after the implant. C-peptide (ng/ml): before implant, 1.18; at 6 months, 1.17; at 36 months, 2.19; increment 48.42%. C-peptide after meal (ng/ml): before implant, 2.22; at 6 months, 2.95; at 36 months, 4.40; increment 95.52% ($P = 0.0036$). Hemoglobin A1c: basal, 9.14; at 6 months, 8.25; at 36 months, 6.35; decrement 21.25% ($P = 0.003$). Insulin (mU/ml): basal, 12.33; at 6 months, 15.27; at 36 months, 15.02; increment 25.26%. Insulin after meal (mU/ml): basal, 19.11; at 6 months, 15.27; at 36 months, 34.7; increment: 58.75% ($P = 0.016$). Pills per day: 2.25 prior to implant, 0.33 after 36 months, decrement of use 44.36% ($P = 0.0007$). Insulin dose (IU/day): basal, 50.59; after 36 months, 9.55; decrement 89.03% ($P = 0.037$).

Conclusions:
The implant of mononuclear CD34(+)CD38(-)(stem cells) from autologous bone marrow improves pancreatic function in patients with type 2 diabetes and is maintained after at least 3 years.

Glucose Modeling and Prediction Using Physical Activity Variables

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Objective:
Conceptualization of a model-based controller for an artificial pancreas necessarily includes continuous, online measurements of glucose concentration and insulin infusion rates. The inclusion of other factors that influence glucose concentration—namely, physical activity—has the potential to increase the accuracy of the models and thus improve the performance of the controller. This study investigated the improvement obtained in model prediction accuracy when physical activity variables were modeled.

Method:
Ten type 1 diabetes patients using continuous glucose monitoring in conjunction with continuous subcutaneous insulin infusion were outfitted with a small Actiheart (Cambridge Neurotechnology Ltd.) device that measures activity and heart rate continuously. From these measurements and patient-specific parameters, the device also calculated estimated energy expenditure. For a period of 1 week in ambulatory conditions, each of the 10 participants wore the Actiheart and recorded all carbohydrate consumption manually. Empirical models were then developed from these data and their prediction accuracy was evaluated.

Result:
Data from the participants were analyzed statistically to determine the degree of correlation of activity, heart rate, and energy expenditure relative to the rate-of-change of glucose. Using multiple linear regression, heart rate was found to be the variable with the greatest degree of correlation to the rate-of-change of glucose (p values ranged from 6.9×10^{-6} to 0.11). For all data sets, multiple linear regression was found to be statistically significant.

Conclusion:
From a modeling perspective, the inclusion of physical activity variables has the potential to improve the model accuracy greatly; from a medical device perspective, their inclusion is readily achievable. These factors suggest that physical activity variables should be incorporated into the control algorithm for an artificial pancreas.

Intact Proinsulin as a Marker to Evaluate β Cell Protective Effects of Basal Insulin Supplementation in Type 2 Diabetes Patients

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Background and Aims:
Postprandial (pp) release of intact proinsulin is a marker of β-cell dysfunction in patients with type 2 diabetes (T2DM). This parallel, two-arm, pilot study compared the β-cell-relieving effect of a basal insulin-supported treatment by combining metformin plus neutral protamine Hagedorn (MET+NPH) or glargine (GLA).

Patients and Methods:
Twenty-eight insulin-naïve T2DM patients [mean ± standard deviation (SD) age, 61.5 ± 6.7 years; T2DM duration, 9.8 ± 6.5 years; hemoglobin A1c, 7.1 ± 0.5%; body mass index, 30.7 ± 4.3 kg/m^2] were randomized to receive either MET+NPH or GLA at bedtime [both titrated to fasting (BG) <100 mg/dl]. At baseline (BL) and after 3 months of treatment, patients received a standardized breakfast, lunch, and dinner, with subsequent preprandial and pp blood sampling (60 and 120 minutes) for the measurement of intact proinsulin, total insulin, and BG values.

Results:
The insulin dose after 3 months was comparable in both treatment groups (NPH 23.3 ± 12.7 IU vs GLA 23.6 ± 13.4 IU; p = not significant). Both treatments reduced fasting glucose levels (NPH BL 157 ± 34, 3 month 119 ± 29 mg/dl*; GLA BL 158 ± 19, 3 month 121 ± 22 mg/dl*; *$p < 0.01$ vs baseline). No difference was observed in fasting or pp glucose levels between treatment groups. A powerful reduction of overall intact proinsulin levels was observed in both treatment arms [area under curve $(AUC)_{breakfast}$: NPH BL 4080 ± 2310, 3 month 1715 ± 1129*; GLA BL 3469 ± 993, 3 month 1630 ± 695*; AUC_{lunch}: NPH BL 6358 ± 3544, 3 month 2933 ± 1703*; GLA BL 5813 ± 1702, 3 month 2356 ± 943*,†; AUC_{dinner}: NPH BL 4960 ± 2789, 3 month 2123 ± 1426*; GLA BL 3865 ± 1295, 3 month 1503 ± 665*,‡; mean ± SD; *p < 0.05 vs BL; †$p = 0.08$ vs NPH; ‡$p < 0.05$ vs NPH). While no difference in β-cell-relieving effects could be observed at breakfast, GLA led to a stronger reduction in pp intact proinsulin release after lunch and dinner. In contrast, total plasma insulin levels, representing endogenous and exogenous insulin resources, did not differ between treatment groups.

Conclusions:
Basal insulin supplementation, in addition to MET treatment, effectively reduces pp β-cell load. Postprandial intact proinsulin levels might serve as a marker to assess the β-cell-relieving effects of basal insulin supplementation.

Laboratory Investigation for the Assessment of Hematocrit Interference on Handheld Blood Glucose Meters for Patient Self-Blood Glucose Testing

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Background:
Recent reports have indicated that the majority of hospital-based, point-of-care blood glucose meters show pronounced interference with hematocrit (HCT) variations. The purpose of this laboratory investigation was to explore to what extent handheld glucose meters for patient self-monitoring (SBGM) may also be affected by this phenomenon.

Method:
Seven SBGMs (Accu-Chek® Aviva, Ascensia Contour+, Ascensia Breeze 2, Precision Xceed, FreeStyle Freedom, OneTouch Ultra 2, and FineTouch) were tested with laboratory samples with different hematocrit values (20, 30, 40, 50, and 60 %) and at three different glucose concentrations (50, 170, and 370 mg/dl). Each individual sample was tested six times with each meter. In addition, two point-of-care devices and one reference method were tested (HemoCue, StatStrip, and Cobas). For interference analysis, the value determined with 40% hematocrit was used as the reference value. Mean deviations were calculated for all meters over all three blood glucose ranges. No analysis of precision or accuracy was undertaken, as the study was performed with artificially modified laboratory samples and not with capillary whole blood, the natural specimen for these devices.

Results:
Different degrees of interference were observed for many of the SBGMs at either low or high hematocrit values [or both; deviation at hematocrit of 20/30/40/50/60%: AccuCheck Aviva: 2.7/2.2/0/–12.4/–24.1%; Ascensia Contour+: 6.4/2.2/0/–9.1/–9.4%; Ascensia Breeze 2: 38.9/20.3/0/–17.3/–34.7%; Precision Xceed: 12.8/8.7/0/–15.3/–31.2%; FreeStyle Freedom: 20.5/2.3/0/–7.1/–8.5%; OneTouch Ultra 2: 10.3/6.6/0/–22.3/–35.2%; FineTouch: –1.7/–8.1/0/3.5/2.7%; StatStrip: 0.4/1.7/0/–3.1/–5.0%; HemoCue: 4.8/7.6/0/–10.7/–19.1%; Cobas (laboratory reference: –3.6/0/0/–1.8/2.4%)]. Only the FineTouch device showed a stable measurement performance together with one point-of-care device (StatStrip) and the reference method (Cobas).

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Conclusions:
Small hematocrit variations (especially increases) showed pronounced effects with some meters. Although this study was not performed in capillary blood samples, appropriate education and clear labeling appear to be strongly recommended for these meters. Only one point-of-care meter (StatStrip, Nova Biomedical) and one handheld SBGM (FineTouch, Terumo) were not influenced substantially by hematocrit interference. As variation in hematocrit can occur in daily life (e.g., in patients with dehydration or during hemodialysis), a possible translation of these results into real-life measurements can be considered to be an advantage of these meters in practical routine use.

Diabeo: An Innovative Telemedicine System for the Follow-Up of Type 1 Diabetes Patients

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Objective:
Telemedicine has become of great interest in the diabetes field. The PDA-FIT, a personal digital assistant phone coupled with a secure Web site, has been developed with three main functionalities: a decision support system for insulin dose adjustments, an electronic diary program, and a data transfer system that allows phone consultations. The aim of our study was to assess the interest of this system in the follow-up of type 1 diabetes (T1DM) patients.

Method:
A 4-month observational study was conducted in 35 T1DM patients treated with functional insulin therapy (FIT) for at least 6 months. FIT parameters had been entered in the system previously for each patient.

Result:
The study showed good control of the postprandial state: whatever the number of carbohydrate portions, mean 2-hour postprandial blood glucose value (PPBG) levels remained close to the target of 7.8 mmol/liter. The algorithm for compensation allowed the preservation of 2-hour PPBG in the objectives whatever the premeal blood glucose value. A significant 0.51% hemoglobin A1c reduction was observed with a trend toward a decrease in the incidence of hypoglycemic events. The mean filling rate of premeal daily data was 90%, without any decrease in electronic diary use throughout the study; 20 patients accepted the machine proposal more than 9 times out of 10.

Conclusion:
The PDA phone, coupled with the Internet, proved to be a useful tool in facilitating the caretaking of T1DM patients. A multicenter study has been conducted to confirm these results. This PDA phone system, called Diabeo, is henceforth in current use in France for all T1DM patients in centers of the multicenter study. These patients could benefit from a "telemedecine"-fixed package for their ambulatory follow-up.

Assessment of Glucose Variability in Type 2 Diabetes Patients on Diet and Metformin Therapy: Comparison of Seven-Point Blood Glucose Profile and Continuous Glucose Monitoring

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Objective:
The goals of this study were to evaluate glucose variability (GV) in type 2 diabetes patients on diet and under therapy with metformin and to compare the GV obtained from seven-point self-monitoring blood glucose (7pSMBG) and continuous glucose monitoring (CGM) profiles.

Method:
Persons with type 2 diabetes [5 females, 14 males; age 58.9 ± 11.0 years; body mass index 30.0 ± 4.9 kg/m², hemoglobin A1c 7.6 ± 1.9 % (mean ± standard deviation)] participated in two 3.5-day visits with identical procedures. At the first visit, patients were on a diet. Metformin intake (2× 850 mg) started 4–6 weeks before the second visit. Two microdialysis subcutaneous CGM (SCGM1) devices were applied during the visits. Glucose traces of the two devices were merged into one curve; 7pSMBG profiles were performed as follows: before and 2 hours after breakfast, lunch, and dinner and before bedtime. GV was calculated for each day based on 7pSMBG and CGM profiles by low and high blood glucose indices (LBGI/HBGI and standard deviation (SD) in relation to mean blood glucose (mBG). The categories for low, moderate, and high risk were set for LBGI as <2.5, 2.5–5, and >5 and for HBGI as <10, 10–15, and >15, respectively.

Result:
Under diet 53 days in 18 subjects and under metformin therapy 57 days in 19 subjects could be compared. The distribution of days to risk categories under diet and metformin was similar for LBGI-CGM (96.2, 3.8, and 0% and 98.2, 1.8, and 0% for low, moderate, and high risk, respectively) and LBGI-7pSMBG (100% in low-risk category) and identical for HBGI-CGM and HBGI-7pSMBG (diet: 73.6, 11.3, and 15.1%, respectively; metformin: 100% in low-risk category). Mean BG ± SD under the diet was 168.7 ± 34.1 (CGM) and 170.8 ± 20.3 (7pSMBG) and under metformin therapy was 131.8 ± 28.5 and 132.3 ± 17.0, respectively.

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Conclusion:
Using LBGI/HBGI classification and SD to express GV, these data demonstrate that 7pSMBG provides comparable information to CGM profiles in type 2 diabetes patients under diet and metformin therapy. Reduction of hyperglycemia and mean blood glucose by metformin was reflected similarly by both glucose monitoring methods.

Combination of Multitechnologies and Multisensors for Noninvasive Spot Glucose Measurement

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Objective:
Previous publications suggest a unique method for noninvasive glucose measurement, combining three independent technologies: ultrasonic, electromagnetic, and thermal. Each channel contains information of glucose and accompanying disturbances. A multidimensional signal processing produces a glucose value with a smaller impact of interferences, leading to more accurate, real-time spot reading.

Methods:
Measurements were performed externally on the earlobe. The sensor was adjusted individually (directed by the device, according to personal earlobe) for optimal fitness prior to calibration. Calibration was performed individually against invasive basal and postprandial blood glucose references, producing an individual calibration model for each measurement channel. The procedure was easy, took about 1.5 hours, and, more importantly, was valid for over a month. Glucose spot measurements were then performed by clipping the sensor to the earlobe. After sensor position verification (by the device), each channel produced several outputs upon which three-stage signal processing was applied: signal validation and recognition of outliers, temperature compensation, and temperature correction. By using data from different sensors, the algorithm also accounts for parameters such as position on the earlobe, contact quality, and ambient and skin temperatures. A weighted combination of the three technologies' multiple outputs produces a more sensitive and accurate glucose reading.

Results:
Clarke error grid analysis of 456 points from 23 patients showed 98% of points in the clinically accepted zones A+B, of which 60% were in zone A. Mean absolute relative difference $(MARD)_{mean}$ was 21.8% and $MARD_{median}$ was 16.2%.

Conclusions:
Combining several (noninvasive) technologies and a multisensor data collection improves the validity of glucose measurement. The suggested approach provides a way to increase the accuracy of glucose measurements and encourages high frequency testing, thus improving control of the disease and quality of life.

Insulin Therapy Controller Based on High-Order Sliding Mode Control

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Objective:
This work proposed a high-order sliding mode controller (HOSMC) to drive an insulin pump for tight management of diabetes. HOSMC is based on the relative degree of the system and not on any model or parameters, which means that is possible to design a universal insulin delivery controller suitable for every patient.

Method:
The Sorensen model and the Hovorka model are two of the most complete models of the literature, and the relative degree of them is 5; even when patient's parameters vary, the relative degree remains constant. The HOSMC has blood glucose (BG) from a sensor as the only input. The success of this therapy depends on sensor accuracy but it also reduces the risk of hypoglycemia.

Result:
A test of the controller was conducted with Hovorka and Sorensen models to generate *in silico* patients (SP); for each model, three different SP were simulated with an insulin resistance of 5.5 ± 4.5 minutes^{-1} per mU/liter. This study simulation lasted 400 minutes, with initial conditions for BG of 150 mg/dl. At minute 100, meal ingestion was simulated, and postprandial BG was 180 ± 25 mg/dl. BG for every patient was under 110 mg/dl at minute 300; after minute 350, all SP reached the BG target of 90 mg/dl.

Conclusion:
The same controller was able to regulate the BG in all SP even though the model is different. This type of designed controller can be used for any patient because it is not designed for any specific parameter set or mathematical model. In the simulations, pump dynamics and sample rate of commercial sensors are considered in order to have an implementable system for a trial in a clinical setting.

Toward a Robust Artificial Pancreas Based on Intelligent Controllers

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Introduction:
Type 1 diabetes mellitus is characterized by the inability of the pancreas to produce and secrete insulin; exogenous insulin must be administered throughout the day. In order to improve glycemia, blood glucose determinations must be done several times per day, which is a burdensome task. These glucose determinations are then used by the subject or specialist to decide on insulin dosing, but these determinations are not enough. Ideally, multiple input/ multiple output systems with other inputs (such as carbohydrate intake, frame or state of mind, diseases, and fitness), capable of continuous feedback, would be available to optimize insulin administration; in such a scenario, closed-loop control would be the ultimate goal. An analysis technique is necessary in order to analyze the stability of an intelligent controller based over nonlinear plants as an artificial pancreas.

Methods:
Recent advances in insulin pump and glucose sensing technology suggest that a closed-loop artificial pancreatic β cell could soon be achieved with suitable control algorithms. With fuzzy logic, genetic algorithms, and artificial neural network modeling and identifying patients through clinical data monitoring for each patient, it is possible to obtain an *in silico* and "ad hoc" insulin model and the control algorithms required for communication between pump and sensor. A robust stability analysis based on harmonic balance was presented and applied to a complete system with unstructured or parametric uncertainty. We analyzed the robustness of controller-based multivariable control systems with uncertainty. For this purpose we made use of the generalized Nyquist stability criterion applied to analyze nominal stability and robustness. The pilot artificial pancreas consisted of a minimally invasive subcutaneous glucose system, a personal portable meal calculator, an accelerometer, a computer control system, and an insulin pump delivering insulin lispro/neutral protamine Hagedorn subcutaneously.

González-Pérez cont. ⟶

González-Pérez cont. ⟶

Results:
Results were quantified *in silico* using graph methods. In this work, a robust stability analysis based on harmonic balance was presented and applied to an intelligent structure-based control of a multivariable nonlinear system with structural norm-bounded uncertainty. We developed ways to describe uncertainty, both in the form of neglected nonlinear dynamics due to plant linearization and high harmonics effects for the controller, respectively. Finally, results obtained versus real clinical data were discussed, comparing an accurate "ad hoc" *in silico* model with real measurements of patients using the Nyquist stability margin, together with structured singular values of the uncertainty as a robustness measure.

Conclusions:
We analyzed the robustness of neural-based multivariable control systems with uncertainty, provided that both the intelligent controller and the plant were represented by its sinusoid input describing function approximation and inverse identified patient model, respectively. Future works are directed toward development of a design method for training the intelligent controller in order to satisfy not only performance requirements but robustness conditions.

Automated Modeling Approach for Closed-Loop Control of an Artificial Pancreatic β Cell

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Objective:
A typical dynamic model used in glucose regulation as part of an advanced control algorithm describes the connection between exogenous insulin and meal inputs to blood glucose. Ambulatory clinical data pose an identification challenge because meals and insulin boluses are delivered at the same time in most cases. This results in an identifiability problem because the inputs have opposing effects on the output. We have developed an input filter and a clinical protocol that overcome this challenge.

Method:
In order to improve the resolution between the meal and the insulin effects, a new clinical protocol was formulated. Under medical supervision the meal and the insulin bolus were separated up to 2 hours. Data were prefiltered in order to improve system identification. Filtered data were used to identify a range of autoregressive exogenous input (ARX) models that have been evaluated based on predictive ability.

Result:
Autoregressive exogenous input model identification using this approach has shown a significant improvement in model gain sign resolution. Without input filtering, more than 66% out of 3600 ARX models identified by data collected from 10 *in silico* subjects and one clinical data set had opposite insulin gain compared with only 1% when the ARX models were identified with the suggested approach. On three other clinical trials, an improvement of 26 to 44% in the number of ARX models with the correct gain sign was achieved using input filtering without implementing the new protocol.

Conclusion:
The use of filtered inputs and predictive testing accompanied with a new data collection protocol generated a promising ARX selection methodology that describes blood glucose concentration dynamics correctly.

Identifying Dynamic of Glycemia by Genetic Programming

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Objective:
Glycemia has been modeled over the years by various techniques, with models ranging from physiologically driven to purely empirical. The detailed physiological models are suitable for simulation, but are too complicated to be used as part of a control algorithm. However, empirical models such as autoregressive exogenous input (ARX) are simplified linear models that aim to capture the nonlinear glycemia dynamic. We suggest different types of empirical models created by genetic programming (GP) that can capture the insulin glucose dynamic from clinical data and be suitable for closed-loop control.

Method:
Genetic programming is an evolutional computational method that can be used to optimize the structure of models. The GP algorithm was provided with meal and insulin data that had been filtered to ensure data richness and produce nonlinear models that identify glycemia dynamics.

Result:
Genetic programming models were generated based on 10 *in silico* subjects following a 5-day data collection protocol. The nonlinear models identified by the GP showed superior prediction capabilities over ARX models that were identified upon the same data. The R^2 value of the GP model prediction over 36 steps ahead was 0.8054 compared to 0.7145 of the best ARX out of 3600 models.

Conclusion:
Genetic programming seems to be a promising technique suitable for modeling diabetic dynamics. This can expand prediction capabilities to be used in hypoglycemia prediction as well as the ability to improve closed-loop control.

The Importance of Performing a Human Factors Trial When Developing a Wireless Remote Monitoring Device for Diabetes Management

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Objective:
A clinical trial to test the ease of use, labeling comprehension, and end user value of a newly developed wireless diabetes monitoring program is critical for understanding user preferences.

Methods:
A human factors study was conducted with patients (15) diagnosed with diabetes along with their health care providers (HCPs)(6). Each patient was provided with a blood glucose (BG) meter, a wireless device, cell phone, and an account to a secure diabetes program Web site. Patients collected BG data for a week and attended three visits. The patients could view BG in relation to their meals, insulin, and activity and had access to a library of diabetes-related articles. The patient and HCP had an opportunity to review information together. At the end of the 7 days (± 3), patients and HCPs completed a comprehension questionnaire, human factors testing ability of the system, and a satisfaction survey.

Results:
All patients demonstrated being able to use the mobile phone application, the Web site during first use, and familiarity of site navigation. An ease-of-use score was reported by patients as a minimum of 92.8% and a maximum of 100%. One hundred percent of the HCPs rated the system as one that could help them provide effective care by improving communication to their patients. HCP's noted tools that were helpful were a library of educational articles that could be assigned and seeing BG readings in relation to meals, insulin, and activity.

Conclusion:
One hundred percent of study participants—patients and HCPs who completed all three visits—thought the system would improve their diabetes care. This information in a clinical trial setting allows better understanding and validation of user preferences.

Comparison of Four Methods for Online Calibration of Continuous Glucose Monitoring Data

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Objective:
Continuous glucose monitoring (CGM) sensors provide an estimate of glucose concentration into the interstitium by transforming a current value into a glucose concentration level on the base of a preliminary calibration step. This transformation can often become suboptimal, and recalibration should be performed. In this contribution, we compared the performance of four different recalibration methods (including two unpublished algorithms) with different degrees of sophistication and numerical complexity.

Methods:
We considered 36 CGM recordings, collected in 11 type 1 diabetes patients in 4-hour intervals (including a meal) by using the FreeStyle Navigator™ device. In parallel to CGM, blood glucose references were assessed every 15 minutes. Four recalibration methods were applied: a two-point linear regression, an extended Kalman filter-based method (EKF), a deterministic method exploiting polynomial functions (POL)(new method), and a stochastic deconvolution-based method (DEC) (new method). Performance was assessed via root mean square error (RMSE) analysis.

Results:
The RMSE between reference blood glucose concentration and recalibrated vs raw CGM recordings was evaluated. All methods led to an overall improvement in CGM signal quality, with the EKF being the best but also the most numerically complex method. Despite their simplicity, the performance of DEC and POL methods is quite similar to EKF, with some improvements of RMSE up to 50%.

Conclusion:
Online recalibration of CGM signals is crucial in several practical applications, e.g., artificial pancreas. An EFK method can address the problem satisfactorily, but the DEC and POL exhibit a similar performance and can be implemented much more simply. Further studies will comprise the test on a broader database and an optimization of the algorithm parameters.

A Pan European and Canadian Prospective Survey to Evaluate Patient Satisfaction with the SoloSTAR® Insulin Injection Device in Type 1 and 2 Diabetes: An Interim Analysis

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Objective:
This study evaluated patient satisfaction with SoloSTAR® (sanofi-aventis), a disposable insulin pen device for injection of insulin glargine (glargine) or insulin glulisine (glulisine).

Method:
This was a 6–8-week multicenter (n = 652), noninterventional, observational, prospective Pan European and Canadian registry study (Austria, Canada, Denmark, Greece, Hungary, Latvia, The Netherlands, Poland, Romania, Slovenia, Slovakia, Sweden, United Kingdom) in diabetes mellitus patients (n = 6559) recently switched to glargine and/or glulisine using SoloSTAR. At the baseline visit, patients were given a questionnaire and, if applicable, asked to evaluate their satisfaction with their previous device. After 6–8 weeks of SoloSTAR use, patients were asked to rate their satisfaction.

Result:
Of the 3722/6559 patients included in this interim analysis, the mean age was 53 years, 47% were male, and 70% had type 2 diabetes. Of the patients, 721 and 2359 had used disposable or reusable pens previously, respectively; 106 patients were using a vial/syringe and 655 were insulin naïve. SoloSTAR was used to administer glargine and glulisine in 98 and 46% of patients, respectively. Ninety-eight percent of patients rated SoloSTAR as "excellent/good" in ease of use, learning to use and selecting dose, and 95% in reading the dose. At follow-up, the mean ± standard deviation daily dose of glargine/glulisine was 27.6 ± 15/32.4 ± 15 IU; patients administered an average of three glulisine injections/day. Most patients rated ease of use and injecting a dose with SoloSTAR "excellent/good" versus their previous pen (84–90%) and 98% planned to continue using SoloSTAR. No safety concerns were reported.

Conclusion:
This European and Canadian survey showed that SoloSTAR was well accepted in this large patient population, with the majority rating SoloSTAR as "excellent/good" for ease of use/learning. The majority also preferred SoloSTAR to their previous pen and planned to continue SoloSTAR use.

Nitric Oxide in Diabetic Rats: Possible Role of *Lactobacillus acidophilus* and α-Glucosidase Inhibitor

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Objective:
The objective of this study was to investigate the effect of administration of *Lactobacillus acidophilus* (LA) alone or in combination with the α-glucosidase inhibitor acarbose (AC) on the plasma nitric oxide (NO) level and some oxidative stress parameters in diabetic rats.

Method:
Diabetes was induced in rats by an intraperitoneal injection of streptozotocin. Rats were divided into control, diabetic, diabetic received AC, diabetic received LA, and diabetic received AC plus LA groups. Fasting blood sugar (FBS), glycosylated hemoglobin (HbA1c %), triacylglycerol (TAG) level, activity of paraoxonase (PON1) enzyme, malondialdehyde (MDA), and plasma nitrate were measured. Spectrophotometric methods were used in the analysis procedures.

Result:
Results obtained from this study revealed that treatment with LA alone or in combination with AC significantly decreased the elevated FBS level, HbA1c %, plasma TAG, and MDA compared to diabetic rats. The same treatment elevated the PON1 activity compared to that of the diabetic group. Administration of LA alone or with AC showed a significant elevation in the plasma nitrate level compared with that of the diabetic group.

Conclusion:
It was concluded that LA and AC supplementation exerts hypoglycemic, hypotriglyceridemic, and antioxidant effects. These effects are responsible for restoration of the NO level.

Evaluation of the Impact of Blood Glucose Sampling Frequency on an Algorithm for Hypoglycemic Alarming

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Objective:
An alarm is an important safety mechanism used to alert people with type 1 diabetes mellitus (T1DM) to impending hypoglycemic events. Continuous glucose sensors currently provide glucose values in 1-, 5-, and 10-minute intervals. We therefore tested the effectiveness of our alarm using these various sampling frequencies.

Method:
An algorithm was developed to predict impending hypoglycemia events. The algorithm calculates the rate of change of blood glucose (BG) with the ability to overcome data gaps. The time of crossing a BG threshold (70, 80, or 90 mg/dl) was predicted, and an alarm was raised if two successive points were within a prediction horizon (35, 45, or 55 minutes). The algorithm was tested on data from a study on 18 people with T1DM (mean age of 20 years). Hypoglycemia was induced by increasing the basal infusion rate by an average of 180%, and BG data were taken from the Abbott FreeStyle Navigator® (ADC, Alameda, CA) calibrated with finger-stick measurements. To evaluate the viability of alarming using longer delays in sampling frequency, calculations were made at steps of 1, 5, and 10 minutes.

Result:
Using longer intervals, fewer hypoglycemia events were alarmed: 67, 47, and 43% of hypoglycemia events were alarmed within 60 minutes of the event for 1-, 5-, and 10-minute intervals, respectively. Conversely, more alarms were within the prediction horizon of the threshold for longer intervals: 78, 88, and 95%.

Conclusion:
This algorithm effectively predicts pending hypoglycemia with a minimum of false alarms with up to 10-minute sampling times. However, the decrease in the number of events alarmed indicates that longer sampling times may not be sufficient to alarm patients to hypoglycemia events.

Impact of Pharmaceuticals on Continuous Infrared Spectrometric Glucose Assay for Body Fluid Dialysates

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Objective:
As part of the previous European Commission project "Closed-Loop Insulin Infusion for Critically Ill Patients" (CLINICIP), we developed an infrared spectroscopic device to monitor glucose concentrations continuously in the dialysates of body fluids. The reagent-free assay must be safe with regard to cross-sensitivities from administered drugs, which have not been included systematically in previous calibration work. Therefore, we studied the infrared spectra of many water-soluble pharmaceuticals and their impact on glucose concentration predictions.

Method:
The developed system includes microfluidic technology for harvesting submicroliter samples from subcutaneous interstitial fluid using a microdialysis catheter CMA60 as a body interface. Alternatively, whole blood diluted by a heparin solution was dialyzed by a custom-made microdialysis unit containing a planar membrane. Experiments were carried out on healthy and type 1 diabetes subjects. In parallel, blood glucose concentrations in venous blood, collected under arterialized conditions, were determined. Multivariate calibration models based on dialysate spectra using classical least squares and partial least squares were required for glucose quantification and drug cross-sensitivity estimation.

Result:
Clarke error grid plots with pure dialysate samples either from interstitial fluid or from whole blood have shown excellent agreement between spectrometrically predicted values and reference blood glucose concentrations. In addition, cross-sensitivities from pharmaceuticals from various categories such as analgesics, antibiotics, lipid-lowering agents, vasoactive drugs, and others at therapeutic concentration levels are reported for their impact on sensor readings.

Conclusion:
Clinical investigations indicated that the developed spectroscopic technology enables us to realize long-term glucose and metabolite monitoring in the intensive care unit with lowest calibration effort and negligible effect from administered drugs.

Safeguarding Bedside Monitoring of Blood Glucose Using a Vascular Interface with Microdialysis and Infrared Spectrometry

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Objective:
Implementing strict glycemic control can reduce the risk of serious complications in intensive care unit (ICU) patients. For this purpose, many different blood glucose monitoring techniques and insulin infusion strategies have been tested toward the realization of an artificial pancreas under closed-loop control. In contrast to competing subcutaneously implanted biosensors or microdialysis-based systems with *ex vivo* electrochemical detection, a vascular body interface in combination with a long-term stable spectrometric glucose sensor was developed.

Method:
The device consists of two main components: a double-lumen venous catheter in combination with an *ex vivo* μ-dialysis system and a mini-infrared spectrometer. Continuous measurements can be carried out by sampling whole blood diluted with heparin solution. The blood dialysate is transported steadily to the flow-through spectrometer cell by computer-controlled fluidics. Using this setup, *ex vivo* experiments were conducted on several diabetes subjects lasting up to 28 hours.

Result:
Clinical experiments have shown excellent agreement between sensor readout and reference blood glucose concentration values. The simultaneous assessment of dialysis recovery rates renders a reliable quantification of whole blood concentrations after taking the blood dilution into account. The method also enables the simultaneous determination of important metabolites (lactate, bicarbonate, pCO_2, and others) in the ICU. The separation of macromolecular substances such as heparin or hydroxylethyl starch from blood can also be established by microdialysis for removing cross-sensitivities for glucose.

Conclusion:
Clinical experiments indicated that the developed vascular body interface–spectroscopic monitoring technology is very promising. The performance of the system under closed-loop control with an insulin pump will also be reported.

Feasibility Study of a Technological Platform for the Prevention of Diabetes Mellitus and Cardiometabolic Risk

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Objective:
PREDIRCAM is an innovative technological platform whose aim is to provide a comprehensive tool to improve the efficacy of behavior modification by means of intensive utilization of new technologies to both patients and health care professionals. A pilot study was carried out in order to evaluate the feasibility of the platform envisaging a midterm clinical study.

Method:
The PREDIRCAM platform covers two main components: (1) a Web-based user interface, which provides a communication interface with monitoring devices; an innovative application to facilitate the laborious task of monitoring dietary intake; an ad hoc electronic clinical record; a bidirectional communication system; and intelligent alarms, and (2) a set of wearable physical activity monitors [e.g., heart rate (HR)], which enables automated monitoring of physical activity. Fifteen volunteers were recruited for a period of 15 days. Volunteers were asked to record their dietary food intake, upload HR monitor data, register body weight, use an internal communication system, and fill out a satisfaction questionnaire.

Results:
The Web site received an average of one visit/volunteer/day with an average time of 18 minutes per visit. Two dietary intakes/volunteer/day were registered. One and a half HR uploads/volunteer were carried out, and 0.8 weight records/volunteer were sent. Forty-three topics were discussed through a forum system. Of the volunteers that filled out the satisfaction questionnaire, 71% would strongly recommend utilization of the platform to people who desire to improve healthy habits. The same percentage of volunteers found utilization of the platform for a prolonged period of time feasible.

Conclusion:
The PREDIRCAM platform is technically ready for being evaluated clinically in a midterm study. Intensive training is required before using the platform.

Hemoglobin A1c Is Not a Good Screening Test for Diabetes

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Objective:
The goal of this study was to evaluate if the hemoglobin A1c (HbA1c) test can be used as a screening test for diabetes.

Method:
Results for a 2-hour oral glucose tolerance test (OGGT) with an accompanying HbA1c test for a 3-year period were extracted from the MiSys LIS system. In total, 3163 data pairs were collected [1537 males, average age = 55.4 ± 14.7 years (standard deviation) and 1626 females, 55.6 ± 15.2 years]. Of the OGGT tests, 279 were positive for diabetes using 2008 Canadian Diabetes Association criteria for diagnosis of diabetes using a 2-hour OGGT. Receiver operating characteristic curves were plotted to determine the HbA1c value with optimal sensitivity and specificity using the OGGT diagnosis as the reference standard.

Result:
An HbA1c value of 5.7% gave a sensitivity of 91.8% with a specificity of 35.3%, whereas a value of 6.0% gave a sensitivity of 78.9% and a specificity of 67.2%. For a diabetes prevalence of 0.1, positive predictive values of 0.136 and 0.211 for HbA1c values of 5.7 and 6.0% were obtained with negative predictive values of 0.975 and 0.966.

Conclusion:
The upper limit of the HbA1c reference range recommended by the National Academy of Clinical Biochemistry (6.0%) did not give optimal sensitivity for the diagnosis of diabetes. A screening test for diabetes should provide both good sensitivity and specificity. An HbA1c value of 5.7% yielded a very low positive predictive value. Our analysis shows sensitivity and specificity for HbA1c in screening for diabetes comparable to those of other groups. However, based on its low positive predictive value, we recommend that HbA1c not be used for screening for diabetes mellitus.

Development of an *in Silico* Model to Extrapolate Whole Body Glucose–Insulin Homeostasis by Altering Tissue-Specific Effects: Simulation of Sodium–Glucose Cotransporter-2 Inhibition in Type 2 Diabetes

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Aim:
Sodium–glucose cotransporter-2 (SGLT-2) inhibitors acutely induce renal glucose excretion. We have developed an interactive homeostatic model of assessment (iHOMA) that can be used for *in silico* calculations of the specific effects drugs may have on glucose metabolism. The aim was to use iHOMA to model the effect of an SGLT-2 inhibitor in patients with type 2 diabetes (T2DM).

Methods:
A total of 428 patients (239 male) with T2DM were analyzed retrospectively. They had a mean body mass index of 30.4 (±5.6) kg/m^2, mean age of 62 (±11) years, mean hemoglobin A1c of 7.9 (±1.6), mean fasting plasma glucose (FPG) of 9.6 (±3.1) mmol/liter, and geometric mean fasting plasma insulin (FPI) of 112.0 (range 65.8–190.5) pmol/liter. β-cell function and insulin resistance were calculated for each subject using HOMA and used as inputs into the interactive model. The iHOMA program was developed by the authors at the University of Oxford and has been validated against the original HOMA algorithms. iHOMA modeled the effect of an SGLT-2 inhibitor decreasing the renal glucose excretion threshold by 50%; FPG and FPI were then calculated.

Results:
The simulated whole body effect by altering renal excretion of glucose was moderate. A paired-sample *t* test revealed a significant difference in the mean FPG (9.6 vs 8.9, $p < 0.01$) mmol/liter, a decrease of 0.7 mmol/liter accompanied by a change in the geometric mean FPI (112.0 vs 99.3, $p < 0.01$) pmol/liter, a decrease of 12.7 pmol/liter.

Conclusion:
Development of the iHOMA program enables the investigation of pharmacological effects of a novel therapy on glucose metabolism *in silico*. The model suggests that SGLT-2 inhibitors have the potential to affect a moderate change in glucose in people with T2DM.

Evaluation of the CGMS Gold® Using a Standardized Test

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Objective:
We investigated the accuracy of the Medtronic CGMS Gold® under a standardized glycemic pattern.

Method:
Paired reference/sensor data were collected in 12 subjects. In each subject, the blood glucose was manipulated in a predefined manner using intravenous infusions of insulin and dextrose. Each reference value was the average of two plasma glucose concentrations measured simultaneously on both channels of the YSI 2300 Stat Plus (Yellow Springs, OH) using a single venous blood sample. Blood samples were obtained at alternating intervals of 2 and 5 minutes. The output current of the sensor from the CGMS Gold (Medtronic Diabetes, Northridge, CA) was recorded every 5 minutes. Spline interpolation was used to pair each reference value in time to a corresponding sensor value using MATLAB (MathWorks, Natick, MA). Any data pairs recorded in the 60 minutes after sensor insertion were not analyzed. The correlation coefficient was computed for each subject.

Result:
The minimum, maximum, and mean numbers of paired values per subject were 86, 131, and 108. The average maximum and minimum blood glucose concentrations were 183 ± 0.24 and 41 ± 0.4 mg/dl, and the average range was 142 ± 21 mg/dl. The minimum, maximum, median, mean, and standard deviations of the correlation coefficients were 0.3251, 0.9597, 0.7422, 0.7386, and 0.1831.

Conclusion:
The correlation coefficient has not been widely used as a measure to assess continuous glucose monitoring accuracy because it is sensitive to the glycemic range under which continuous glucose monitoring is evaluated. However, if the test is standardized, any continuous glucose monitor can be evaluated and compared.

Evaluation of Performance of a Continuous Glucose Measurement Device in Subjects with Type 1 and Type 2 Diabetes by Means of a Glucose Clamp (Hypoglycemia Performance Feasibility)

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Objective:
Continuous glucose monitoring (CGM) technology with a high level of accuracy in the hypoglycemic range may enable intensive control with limited hypoglycemia. The aim of this study was to evaluate the performance of a new CGM device.

Method:
Fourteen subjects with type 1 or 2 diabetes underwent glucose clamp procedures with euglycemic (target 90 mg/dl), hyperglycemic (target 250 mg/dl), and hypoglycemic (target 50 mg/dl) plateaus. The investigational devices provided raw current results, which were converted to sensor (ISF) glucose after the study using an algorithm provided prestudy. Plasma venous glucose measured on a Yellow Springs Instrument was used for calibration. Plasma venous results in comparison to CGM results were measured at 5-minute intervals, and mean absolute percent difference (MAPD) was determined.

Results:
The smallest MAPD, 12.8%, occurred during the hypoglycemic plateau [95% confidence interval (CI), 11.7–13.8]; the largest, 18.5%, occurred during the euglycemic plateau (95% CI, 15.7–21.3). MAPD during the hyperglycemic plateau was 17.2% (95% CI, 15.4–18.9) and 16.8% for all clamp and nonclamp data points combined (95% CI 16.2– 17.4). Parkes error grid analyses (n = 873 paired data sets) yielded 86.8% of results in zone A, 12.2% in zone B, and 1% in zone C. Continuous error grid results were 98 and 100% in the accurate or benign zones for the hypoglycemic and euglycemic ranges, respectively. In hyperglycemia, 81.0% were classified as accurate or benign and 19.0% were erroneous.

Conclusion:
A new CGM device under development has a high degree of accuracy and reliability during euglycemic, hypoglycemic, and hyperglycemic plateaus. Future studies will explore clinical application of this device.

Miniaturized Affinity Sensors with Capacitive Detection for Continuous Glucose Monitoring

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Objective:
We present miniaturized glucose sensors based on affinity binding between glucose and a biocompatible, synthetic polymer. The miniaturized sensors use capacitive transduction and are amenable to full implantation in subcutaneous tissue for long-term, stable continuous glucose monitoring (CGM).

Method:
The sensors were constructed using microelectromechanical systems technology and exploited poly(acrylamide-*ran*-3-acrylamidophenylboronic acid), a biocompatible glucose-binding polymer with excellent specificity, reversibility, and stability. Two devices were investigated, which respectively measure changes in viscosity and dielectric properties due to glucose–polymer binding. The viscometric device features a magnetically driven vibrational diaphragm whose characteristics (e.g., amplitude and phase) depend on viscous damping (and hence viscosity) of the polymer solution, whereas the dielectric device consists of a pair of electrodes whose capacitance depends on the polarization behavior of the polymer. The diaphragm or electrodes are situated in a polymer-filled microchamber equipped with a semipermeable membrane. Both devices measure capacitance changes detectable in a wireless manner.

Result:
At physiologically relevant glucose concentrations (30 to 360 mg/dl), the output of the viscometric sensor varied by 11%, whereas that of the dielectric device varied by 14%. The viscometric sensor demonstrated a time response of approximately 1.5 minutes with respect to glucose concentration changes and was highly repeatable (94 ppm variation) and reversible (60 ppm deviation) as the glucose concentration values of the sample were repeated or reversed. Such characteristics for the dielectric sensor are currently being measured. Both viscometric and dielectric devices demonstrated excellent stability, with drift rates as small as 1.6 and 4.2 ppm/hr, respectively.

Conclusion:
The miniaturized devices exploit capacitive measurements of affinity glucose recognition. Because of excellent sensitivity, repeatability, reversibility, and stability, they hold the potential to enable long-term and reliable CGM applications.

Information from Insulin Pump Improves Continuous Glucose Monitoring-Based Detection and Prevention of Hypoglycemia

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Objective:
Future continuous glucose monitor (CGM)/pump systems will allow automated transmission of hypoglycemia risk data from the sensor to the pump for real-time intervention. Contemporary proposals involve unidirectional information flow: from CGM to pump, ignoring the opportunity to improve signal processing with insulin data. We present a method in which the CGM uses pump data to improve hypoglycemia detection and prevention.

Method:
Our algorithm continuously retrieves information from both the CGM and the insulin pump and has three levels of action, best described using a "stoplight" analogy: green light—there is no detectable risk of hypoglycemia; yellow light—a risk of hypoglycemia is detected and a gradual attenuation of insulin delivery rate is applied, e.g., insulin pump "brakes"; and red light—braking action is insufficient to prevent hypoglycemia and rescue action should be taken. We use insulin injection history from the pump to inform two methods for sensor alerts: without and with forecast of glucose concentration, with the latter employing a model of glucose–insulin kinetics and Kalman filter state estimation. We compared these methods against current techniques that do not employ insulin injection information using computer simulation experiments with an elevated basal rate to "induce" hypoglycemia in $N = 100$ simulated "patients" with type 1 diabetes mellitus.

Result:
The algorithmic "brakes" prevented hypoglycemia in 84 and 96% of cases (without and with prediction) compared to 60% of cases when insulin information was not used. During the control condition (no brakes), hypoglycemia did not occur in only 20% of the simulated patients.

Conclusion:
The use of insulin injection information can greatly improve the accuracy of detection and the prevention of hypoglycemic events, while also providing a longer time frame between alerts for imminent hypoglycemia and its onset.

Pain Sensation at Fingertips and Palm Using Different Blood Glucose Monitoring Systems

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Objective:
Self-monitoring of blood glucose (SMBG) is an integral part of diabetes management. Pain caused by SMBG at fingertips or palm was studied with different blood glucose monitoring systems (meter plus lancing device).

Method:
Sixty-two diabetes patients (19 type 1, 43 type 2) experienced in SMBG participated in the study. Four different systems with their corresponding lancing device were tested in randomized order: Accu-Chek® Mobile, OneTouch Ultra2, FreeStyle Lite, and Ascensia Contour. Each patient measured blood glucose with each system in a block of 3 days and three times per day on fingertips and palm, respectively (nine pricks per site and device). After each prick the patient had to rate the pain using a seven-point Likert scale: 1 indicating painless to 7 meaning painful. Likert scale ratings of the pricks on fingertips and palm were evaluated for each patient and compared with the signed rank test.

Result:
Pain sensation after pricks at fingertips or palm was categorized with a seven-point Likert scale (1: painless, 7: painful). Results are given as mean ± standard deviation (62 patients): Accu-Chek Mobile 1.7 ± 0.7/2.4 ± 1.2 (fingertip/palm), FreeStyle Lite 2.0 ± 0.7/2.6 ± 1.0, Ascensia Contour 2.0 ± 0.8/2.7 ± 1.1, and OneTouch Ultra2 2.1 ± 0.8/2.8 ± 1.1. Most patients rated pricks on the fingertips as practically painless (Likert scale 1 or 2), whereas pricks on the palm seemed to be somewhat more painful, probably due to the higher penetration depth needed. On both sites, the lowest average pain sensation was observed with the Accu-Chek Mobile blood glucose monitoring system ($p < 0.03$ to $p < 0.001$).

Conclusion:
These results demonstrated that in most cases pain sensation at fingertips is very low when blood glucose measurements are performed with modern devices and optimal adaptation of the penetration depth of lancing devices. The use of practically painless devices might improve patient's adherence to testing and thus might also result in better glycemic control.

The Injectable Continuous Osmotic Glucose Sensor

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Objective:
The injectable osmotic glucose sensor represents a revolutionary new concept in the treatment of diabetes mellitus. The implementation of micro- and nanofabrication technologies has enabled a size reduction that permits subcutaneous implantation without the need of surgery. This discontinuous technology will realize a long-term continuous *in vivo* glucose sensor that will replace current state of the art.

Method:
A reversible competitive affinity assay performs the glucose-specific recognition in which an absolute change in particle concentration across a nanoporous semipermeable membrane generates a pressure that is proportional to the glucose concentration. This pressure change is detected by a 2 × 2-mm^2 large integrated pressure transducer, with data recorded by a 1 × 1-mm^2 large integrated circuit module. The sensor package measures only 3 × 7 mm^2 and consumes less than 2 μW of power. The sensor is powered from an externally coupled inductive link through which continuous wireless transmission of glucose data is relayed and recorded on an external receiver.

Results:
Results conducted over periods of 1 week have demonstrated reproducible osmotic pressures that exhibit an absolute change of 20 mbar in response to test solutions ranging from 2 to 40 m*M* glucose. Nanoporous membranes of 5000 Da molecular mass cutoff were used to permit confluence of glucose yet retaining the assay components inside the 0.5-μl large sensor lumen. The glucose-specific recognition of the assay will filter out unwanted signals arising from other dissolved components in blood of comparable molecular weight to that of glucose.

Conclusion:
Current investigations will determine reactions from the immune system on capsule materials and the semipermeable membrane, as well as long-term exposure *in vivo*.

Comparative Accuracy of Continuous Glucose Monitoring Using Glucose-Binding Protein in a 12-Hour Feasibility Study

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Objective:
The goal of this study was to evaluate new technology that continuously monitors glucose utilizing a genetically engineered glucose-binding protein (GBP) in a clinical study by means of a 6-hour glucose clamp as well as a 6-hour meal challenge in 40 patients with type 1 or type 2 diabetes.

Method:
A fluorescent dye-labeled GBP was immobilized in a hydrogel matrix and chemically affixed to the face of a 100-µm-diameter optical fiber within a 31-gauge cannula. Each patient had three Becton Dickinson (BD) sensors placed subcutaneously (>3 mm = BDSC) and three sensors placed intradermally (<1.0 mm = BDID). One MiniMed Guardian® sensor (MM) was used as a control. A predetermined profile of glucose excursions, including a hypoglycemic period, was obtained in the first 6 hours by means of an automated glucose clamp. A nonclamp meal challenge comprised the next 6 hours. BD sensor readings were taken every 3 minutes, and reference arterialized venous blood glucose values were measured by a Yellow Springs Instrument (YSI) every 5–10 minutes throughout. Blood glucose was estimated from a two-compartment diffusion model using rate constants for each sensor type derived from a five-subject training set.

Result:
Median absolute percent errors: for glucose <75 mg/dl BDID 7.7*, BDSC 10.7*, and MM 20.6; for glucose 75–180 mg/dl BDID 7.6*, BDSC 9.0*, and MM 11.2; and for glucose >180 mg/dl BDID 7.2*, BDSC 8.9, and MM 10.0 (*statistically significant vs MM).

Conclusion:
In this 12-hour feasibility study, investigational BD GBP sensors placed in both intradermal and subcutaneous spaces demonstrated competitive accuracies relative to a glucose oxidase sensor vs a YSI blood standard. Prolonged warm-up of the glucose oxidase device cannot be ruled out as the cause of its relatively poor observed performance in the hypoglycemic range.

Performance Analysis of the DexCom™ SEVEN® PLUS Trend Arrow

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Objective:
The DexCom™ SEVEN® PLUS continuous glucose monitoring (CGM) system displays a glucose trend arrow in addition to trend graphs. Trend graphs show glucose values and rates of change; trend arrows indicate one of seven rate zones. For example, when the arrow is horizontal, the rate is between –1 and +1 mg/dl/min. Effective interpretation of the trend arrow requires awareness of its performance and limitations.

Method:
Sensor and reference blood glucose (SBG and RBG) data were collected from 53 subjects with insulin-dependent diabetes. An 8-hour in-clinic study was performed on sensor day 1, 4, or 7 during which RBG was measured every 15 minutes with a laboratory analyzer. The RBG rate was computed as $[RBG(t_2) - RBG(t_1)]/(t_2 - t_1)$. The SBG rate was computed using a 20-minute window of sensor trend data. The SBG rate within 1 mg/dl/min of RBG was considered accurate. Using the trend arrow rate zones, arrow agreement occurred if SBG and RBG rates were in the same zone (arrows in same direction).

Result:
The mean SBG – RBG rate difference was 0.0 ± 0.9 mg/dl/min (N = 1506). The SBG rate was 83.9% accurate across all glucose levels, and at glucose levels <70 mg/dl (N = 142) was 88.7% accurate. However, trend arrow agreement was 65.7% overall, and 76.1% at glucose levels <70 mg/dl. In 17.7% of instances, the SBG rate was within 1 mg/dl/min of RBG, but was on the opposite side of a rate zone boundary.

Conclusion:
The SEVEN PLUS provides rate-of-change information with 83.9% accuracy, 88.7% at hypoglycemic levels. At rate zone boundaries, similar rates (e.g, 0.9 mg/dl/min vs 1.1 mg/dl/min) can appear as different trend arrows. It is important for CGM use that the trend graph is always available and is the primary source of rate information.

Independent *in Silico* Validation of Fully Automated Closed-Loop versus Semiautomated Hybrid Control of Insulin Delivery in Patients with Type 1 Diabetes

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Objective:
Automated closed-loop (CL) insulin delivery for individuals with type 1 diabetes requires an algorithm whereby the infusion rate of insulin is derived from real-time continuous glucose sensor data. A metabolic mathematical model capable of reproducing clinical data obtained independent from that used to identify it should be able to facilitate the design process.

Method:
Parameters of a virtual patient model composed of five equations were identified in 10 subjects using data from a preliminary CL study. The 10 virtual patients identified from the preliminary CL clinical study were then used to simulate a second CL clinical study performed on an independent set of patients. The second clinical study compared a fully closed-loop (FCL) algorithm to a hybrid closed-loop (HCL) algorithm where a premeal insulin bolus, half the amount given under open-loop, was given manually 15 minutes in advance of meals. Both the FCL and the HCL algorithms were simulated on the 10 virtual patients identified in the first clinical study and *in silico* results were compared with the second clinical study.

Result:
The second clinical study showed peak postprandial glucose levels of 226 ± 51 mg/dl (± standard deviation) with the FCL group and 194 ± 47 mg/dl with the HCL group. *In silico* the 10 virtual patients had peak postprandial glucose of 226 ± 47 mg/dl in the FCL group and 202 ± 41 mg/dl in the HCL group (clinical vs *in silico* results not different; $p < 0.05$).

Conclusion:
Agreement between the postprandial glucose excursions of the *in silico* study and those of the independent clinical study provide validation that the virtual patient model can be used to aid closed-loop algorithm development.

Web 2.0–Twitter and Diabetes: Usage and Impressions

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Objective:
For this project, we conducted a review of how people with diabetes use the popular Web 2.0 service Twitter. Twitter is a microblogging service that allows people to post short messages. These public posts can then be read by anyone. We were interested in what information people freely reveal about themselves and their diabetes from a clinical and personal perspective. We conclude with our impressions and thoughts on how Twitter is currently being used and how its use can be expanded to provide better diabetes care.

Method:
Subjects were identified using Twitter's search feature, Google, and various Twitter group services, such as TwittGroup and Twibes. For each subject we captured the last 100 posts. Subjects were defined as those who post information about their diabetes regularly (several times a day). The resulting posts were categorized manually according to the content of the post, i.e., blood glucose readings, laboratory data, personal experience, and/or emotions.

Result:
Identifying patients through a Twitter-based search was not productive in finding people who post regularly about their diabetes. Most people found using this methodology post an occasional message mentioning their diabetes and did not reveal too much information about their diabetes. However, the Google and Twitter group services revealed a number of people that post regularly about their condition.

Conclusion:
Twitter is a powerful communication tool. Many people post regular information about their diabetes, including blood glucose readings, personal information about their experiences, and how they are feeling. It could be used as an effective tool in learning more about a person's experience with diabetes in their daily life and should be explored as a means of patient–provider communication.

User-Centered Design of an Electronic Health Record for Patients with Diabetes Mellitus Type 2 to Support Self-Management

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Objective:
Supporting patients with diabetes mellitus type 2 in taking control of their own condition promises advantages as increased treatment adherence and improved quality of life. Information about one's own health can be seen as a critical condition to achieve such control. In The Netherlands, regional networks exist that enable care providers to share patient information. Until now, this information has not been available to patients themselves. The objective of this research was to develop a user-friendly and tailored electronic health record (EHR) that supports patients in controlling their own care.

Method:
A step-wise, user-centered approach was used. First, semistructured interviews with stakeholders (care providers, patient organizations, care organizations; $n = 7$) were conducted. Results were translated into requirements for functionalities and content, which were transformed into nonworking prototypes. Finally, focus groups with patients ($n = 9$) were held to get user input on content and layout of the prototype EHR.

Result:
The interviews characterized expected problems as "information overload" (too much for the patient) and "interpretation issues" (understanding and giving meaning). Perceived changes were personalization and automatically creating action-plans based on care plans. The created prototype included six topic blocks with information and actions, a wizard for first use, and tools to personalize the application. The focus groups confirmed the interview results and yielded useful content and layout recommendations. Layout and personalization especially were regarded as positive aspects of the prototype. Respondents felt we were "on the right track."

Conclusion:
The used methodology seems to enable us to create an EHR for patients with diabetes mellitus type 2 to support self-management. Still, many questions remain, especially about how patients will use the application and how user-friendly it will be. Future research will include usability testing and usage analyses.

A Novel Glucagon-like Peptide-1 Analog Delivered Orally Reduces Postprandial Glucose Excursion in a Porcine Model

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Objectives:
This study sought to examine whether a novel, enterically delivered glucagon-like peptide-1 (GLP-1) analog (ORMD-0901) retains its pharmacodynamic effect of reducing postprandial glucose excursions.

Background:
Glucagon-like peptide-1 bears insulinomimetic and insulinotropic properties, rendering it a useful drug for the management of type 2 diabetes. However, GLP-1 analogs are only available in parenteral dosage forms. A novel, enterically delivered GLP-1 analog with a prolonged half-life has been designed and is being studied.

Methods:
We tested the capacity of various formulations of the enterically delivered, single-dose ORMD 0901 to reduce postprandial glucose excursions in a porcine model. Each formulation was tested on three pigs (average weight: 40 kg), whereby ORMD-0901 was administered directly through an indwelling jejunal cannula. Animals were then challenged with an oral glucose load (3 or 5 g/kg), delivered 30 minutes after ORMD-0901 dosing. Postload glucose excursions were compared to those of a control session, where equal amounts of glucose were administered without pretreatment with ORMD-0901. Tolerance and adverse effects were also assessed.

Results:
Enteric instillation of the ORMD-0901 drug was well tolerated by all animals and no adverse reactions were noted. Additionally, glucose excursions were reduced significantly in pigs receiving formulation RG3 and AG2 of ORMD-0901 prior to a 5-g/kg glucose challenge (p = 0.004 and 0.0.041, respectively). Mean area under the curve values of pigs pretreated with ORMD-0901 were up to 34% lower than control animals treated with glucose alone.

Conclusion:
Enteric administration of ORMD-0901 prior to a glucose load demonstrates a potent curbing effect on postprandial glucose excursions, replicating the effects of parenterally delivered GLP-1.

How Many Basal Rate Changes Are Needed for Normal Glucose Control in Pump-Treated Type 2 Diabetes Mellitus?

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Objective:
There is minimal information available concerning dosing of continuous subcutaneous insulin infusion pump therapy in type 2 diabetes mellitus (T2DM).

Method:
An open label, uncontrolled, single center pilot study was designed to determine the number of rate changes needed to maintain basal glucose control defined as 70–130 mg/dl during omitted meal periods and overnight. Daily dosing adjustments were made from continuous glucose monitoring (CGMS-Gold, Medtronic, Northridge, CA) downloads. All pump-treated subjects ate an isocaloric diet (50% carbohydrate, 30% fat, 20% protein) and were started on a singe basal rate.

Results:
Eleven pump-naive patients (six female), five insulin naive and six on basal insulin therapy, were enrolled (mean ± SE) with a mean age of 55 ± 4 years, diabetes mellitus duration of 11 ± 3 years, hemoglobin A1c of 7.6 ± 0.3%, body mass index of 35.8 ± 1.9 kg/m^2, C-peptide of 2.55 ± 0.58 ng/ml, and all were glutamic acid decarboxylase antibody negative. All basal insulin and noninsulin treatment was discontinued upon starting pump insulin except for metformin (n = 8) and thiazolidinedione (n = 6). The basal glucose achieved was 95.5 ± 5.0 mg/dl, and the postmeal glucose was returned to within 8.3% of the premeal glucose. One subject required two basal rate changes while all others required only one. The average total daily dose was 0.51 ± 0.05 U/kg.

Conclusions:
This study supports one basal rate as adequate for near-normal basal glucose control in most T2DM patients.

Patency Evaluation of an Automated *Ex Vivo* Whole Blood Glucose Analyzer

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Objective:
The purpose of this study was to evaluate patency of a blood line connected from a subject's peripheral vein to an *ex vivo* point-of-care whole blood glucose analyzer.

Method:
The OPTIMUS® system (IntelliDx, Santa Clara, CA) automates the blood draw and measurement process by the sterile transfer of 80 µl of blood from the subject to an electrochemical blood glucose sensor. This was the first of multiple studies to identify adjustments to the system that will lead to improved performance. Ten volunteer subjects (six type 1 and four type 2, ages 50–66 years) were enrolled and each was connected to the analyzer using a catheter (18–22 gauge) inserted into the vein. The system continuously monitored and adjusted pressure and flow rates to achieve blood draw and reinfusion. Patency was maintained using flushes and keep-vein-open infusion with sterile saline; no anticoagulant was required. Over a 7- to 8-hour period, the analyzer cycled every 15 minutes to pull whole blood for glucose measurements (n = 27–32 per subject). A cycle consisted of consecutive multiple blood draws if recoverable errors occurred.

Result:
The study produced 301 cycles resulting in 288 glucose results (96%). Glucose results not obtained (4%) were due to system errors. No adverse events were observed, and no cycles resulted in loss of patency of the system to the subject.

Conclusion:
This study demonstrated patency of the intravenous line over a 7- to 8-hour period with multiple sampling. Adequate phlebotomy was confirmed—catheter size and positioning on the arm were well tolerated. Further studies will be performed to demonstrate glucose measurement accuracy and increased reliability in obtaining a successful glucose reading.

Mast Cells, Macrophages, and Continuous Glucose Monitoring *in Vivo*

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Objective:
Mast cells (MCs)–macrophages (MQs) are known to play critical roles in a variety of human diseases but their roles/interactions in the loss of glucose sensor function (GSF) *in vivo* are unknown. The objective of these studies was to determine the roles of mast cells and macrophages in limiting glucose sensor function *in vivo*.

Method:
Using immunohistochemical techniques, we evaluated the presence and distribution of MCs and MQs at sites of glucose sensor implantation in our mouse model and correlated these results with continuous glucose monitoring. Using various mutant/pharmacologic agents in mouse MC/MQ models, we determined the role of MCs and MQs in limiting sensor function *in vivo* over a 28-day time period. We also investigated the ability of direct injections of MCs and MQs at the site of glucose sensor implantation. Finally, we determined the ability of MCs and MQs, as well as their products, to interfere directly with GSF *in vitro*.

Result:
Immunohistochemical studies demonstrated that MCs and MQs were closely associated with each other at the tissue–sensor interface throughout the 28 days. MC deficiency or blockade of MC function extended GSF *in vivo*. Direct injections of MCs at the site of glucose sensor implantation decreased GSF dramatically. *In vitro* studies demonstrated that MCs and MQs directly suppressed GSF. A similar loss of GSF was seen *in vivo* using MQ depletion and direct injections.

Conclusion:
These studies not only demonstrate the association and importance of MCs and MQs in GSF *in vivo*, but suggest that there is likely synergistic interactions between these two cell populations that likely control not only inflammation and wound healing at sites of sensor implantation, but GSF and life span *in vivo*.

Audiovisual Touch Screen Knowledge Assessment Tool for Low-Literacy Hispanic Patients with Diabetes

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Objective:
The goal of this study was to develop an audiovisual touch screen knowledge assessment tool for low-literacy Hispanic patients with diabetes. The University of Southern California-affiliated Roybal Diabetes Management Clinic offers ~450 patients/year 6-months comprehensive diabetes care, including diabetes self-management education (DSME). In order to assess each patient's needs, and for quality improvement of the educational program, each patient's knowledge on entry and on leaving the program needs to be assessed. Furthermore, the clinic is applying for recognition by the American Diabetes Association (ADA) as a center for DSME. This also requires an individual knowledge assessment pre- and posteducation of 10 curricular content areas. Test results need to be kept in the patient's permanent educational record. Most patients have low-literacy levels and are Spanish speaking. They are unable to complete a written questionnaire without assistance. Staffing is insufficient to adequately meet this need. Currently available tools do not meet the need for a self-administered test suitable for low-literacy Hispanic patients.

Method:
Using Digivey Suite touch screen survey software (CREOSO; Phoenix, AZ), clinic staff with experience in diabetes education in this population designed a 40-item audiovisual touch screen questionnaire covering the 10 content areas of the ADA curriculum. The questionnaire can be self-administered by most low-literacy patients. Instructions and questions are presented verbally in Spanish, and answering requires touching a picture or a color-coded box. After the patient has completed the questionnaire, the results are converted immediately and automatically into a printable educational record. Summated data are also stored for program quality improvement.

Results:
By conducting individual item analyses and evaluating the program for reliability with Cronbach's α, we were able to assess the questions against 23 criteria addressing literacy demand as used by Hill-Briggs and colleagues. Finally, validity will be assessed by comparison with previously validated knowledge assessment methods.

Konersman cont. ⟶

Konersman cont. ⟶

Conclusion:
Ongoing efforts will be made to improve ease of use and validity of the questionnaire. The system lends itself to easy alteration of the questions and translation into different languages. There is the potential to develop tests individualized for age, gender, type of diabetes, and literacy level. The system has the potential to be generalizable to low-literacy populations with diabetes and other illnesses worldwide. As it is designed to cover the ADA DSME content area, it may be of particular interest to groups applying for this certification.

A Mobile Phone Application for Enhancement of Diabetes Mellitus Management

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Objective:
Mobile phones promise a portable, user-friendly, and accepted way for self-management of diabetes mellitus (DM). The purpose of the study was to design and develop a mobile phone application for better management of people with DM.

Method:
The application was designed following the requirements provided by people with DM and dialectologists. The requirements have been selected using questionnaires and having face-to-face contact with both sides. In summary, the major requirements were user-friendly interfaces, large-screen buttons, and attractive colors, especially for children with type 1 DM. The developed application runs on the patient's 3G mobile phone and keeps a log file that includes data of blood glucose measurements, blood pressure measurements, insulin pump dosage, food/drink intake, and physical activity. Data can be provided either manually by the user or automatically through appropriate communication interfaces. Furthermore, the user has the following abilities: (i) to keep notes and (ii) in case of an emergency press a button in order to transmit immediately his/her position to both an emergency call center and the attendant physician. The latest capability is provided only if the mobile phone is equipped with a global positioning system receiver. All the aforementioned data are stored locally to the mobile phone and transmitted regularly via the GPRS/3G mobile network to a dedicated hospital Web server.

Results:
Diabetes mellitus patients can use the application anytime and anywhere. From a technical point of view, data transmission failures and delays between mobile phones and hospital server are minimal.

Conclusion:
Preliminary results indicate that the design and development of a patient-oriented mobile phone application can enhance the self-management of people with DM.

Modular Architecture for Closed-Loop Control of Diabetes

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Objective:
The goal of this study was to define the architecture and functional parameters of a modular control system using algorithmic observers of patients' behavior and metabolic state and an array of control modules to maintain glycemic control in diabetes via insulin delivery.

Method:
The principal engineering concept is formulated as follows: external closed-loop glucose control should have separate interacting components responsible for safety supervision and prevention of hypoglycemia, real-time control of insulin delivery, and tailoring of the control to the metabolic and behavioral specifics of each person. These modules receive information from biosystem observers that are responsible for tracking glucose fluctuations, amount of active insulin, and behavioral challenges such as meals and physical activity. Standard hardware components—continuous glucose monitor (CGM) and insulin pump—are utilized.

Result:
The modular architecture is represented by a 3 × 3 matrix decomposing the closed-loop control actions into three timescale layers and three classes of algorithmic functions. The three classes of functions are signal management, biosystem observation/state estimation, and control actuation. The algorithmic processes within each class run at time layers defined as follows: (1) continuous—the fastest rate at which CGM data are obtained (e.g., 1-minute samples), which is dedicated to safety supervision; (2) real time—defined by the rate at which glucose control updates are computed (e.g., 15–60 minutes), and (3) episodic—referring to one-time or periodic (e.g., every 24 hours) identification of patient metabolic and behavioral parameters.

Conclusion:
Modular architecture is dictated by the natural timescale and functional separation of the algorithmic elements of a closed-loop system. We believe that a modular system design would provide the best chances for incremental development, regulatory approval, industrial deployment, and clinical acceptance of system elements.

Design and Optimization of a Disposable, Noninvasive Tear Glucose Sensor

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Objective:
Current invasive technology is often cited as a barrier to self-monitoring of blood glucose. Tear fluid has been proposed as a possible noninvasive method of estimating blood glucose (BG) values. A systems approach to the design, optimization, and testing of an integrated, disposable tear glucose sensor to establish the relationship of tear glucose (TG) to BG is reported.

Method:
A chronoamperometric prototype using glucose dehydrogenase was created using commercial screen-printed sensors integrated with a silicone fluidics system and absorbent polyurethane foam. The prototype was tested for both reproducibility and dynamic range of glucose at physiological levels. Optimization and reduction of a potential interferent and sampling of reservoir volumes were also evaluated. Interferent reduction was attempted using various potentials (0.35, 0.375, 0.4, 0.425, and 0.45 volt) as well as a polymer coating.

Result:
From the integrated device replicated runs, 15.8% variation was calculated at 200 μ*M* (predicted 14.9% variation), and a lower limit of detection was calculated at 43.4 μ*M*. A linear dynamic range was demonstrated from 0 to 1000 μ*M* with a R^2 of 99.56%.

Conclusion:
With the newly designed fluidics component, an integrated tear glucose sensor system was assembled and tested with a model eye surface. Testing demonstrated a reproducible and satisfactory lower limit of detection for measuring TG concentrations across reported levels. The next step in the device design will be to miniaturize the fluidics components further to reduce the dilution factor and evaluate the reduction of other possible interferents. Animal studies are in the planning phase to evaluate the prototype for factors such as irritation and ease of use, as well as developing new techniques for TG capture.

Fear of Hypoglycemia and Satisfaction with Continuous Glucose Monitoring: Comparisons of Youths with Type 1 Diabetes (T1DM), Their Parents, and Adults with T1DM

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Objective:
Recent studies demonstrate improved glycemic control and less hypoglycemia in persons with type 1 diabetes (T1DM) who use continuous glucose monitoring (CGM) consistently. In the Juvenile Diabetes Research Foundation CGM trial, CGM use was less consistent in youths than in adults. We compared fear of hypoglycemia (FOH) and CGM satisfaction in youths with T1DM, their parents, and adults with T1DM.

Method:
Two hundred twenty-eight adults with T1DM for 20.7 ± 12.6 years and 223 youths aged <18 with T1DM for 6.3 ± 3.4 years, along with their parents, completed the FOH survey at baseline, 6 months, and 12 months. CGM satisfaction was assessed after 6 and 12 months in the CGM group and after 12 months in the blood glucose monitoring group (following 6 months of crossover CGM use).

Result:
Parents reported significantly more FOH than either youths or adults with T1DM at baseline, 6 months, and 12 months ($p < 0.001$). Adults with T1DM reported more FOH than youths at baseline ($p = 0.006$); similarly at 6 and 12 months. Attenuation of FOH over time was comparable in youths and adults with T1DM and significantly greater than in parents ($p < 0.001$). CGM satisfaction was higher in adults with T1DM than youths ($p < 0.001$) or parents ($p = 0.08$) after 6 months and was sustained after 12 months in adults versus youths ($p = 0.02$).

Conclusion:
Parents of youths with T1DM reported the greatest FOH while youths acknowledged the least. This substantial FOH among parents did not appear sufficient to encourage consistent CGM use in youths. Adults with T1DM noted the greatest satisfaction with CGM, possibly accounting for their more consistent CGM use. Improvements in CGM systems and providing realistic expectations to youths with T1DM and their parents regarding current barriers/dissatisfaction with CGM implementation may increase CGM uptake and consistent use.

Use of a Novel Web-Based Application for Documenting Diabetes Patient Encounters for Use with Multiple Different Electronic Health Record Systems

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Objective:
The BHM EHR Enhancer for Diabetes (BHMED) is a novel Web-based program for documenting the diabetes patient encounter (DPE) rapidly and efficiently. A pilot study was conducted to assess improvement in documenting the DPE with BHMED compared to the user's native electronic health record (EHR). As background, numerous barriers exist to the adoption and use of proprietary EHRs in clinical practice such as the complexity of the user interface. Additionally, many EHR templating systems for documenting encounters require IT knowledge to setup and have inadequate output. Many clinicians copy and paste previous progress notes to save time, but this can compound errors and be difficult to read.

Method:
BHMED was created with the Ruby on Rails open source Web framework. DPE data are entered by clinicians into a Web-based form. Pressing submit translates data into a human-readable, narrative-based format, which is then copied to the user's system clipboard for pasting into the native EHR. American Diabetes Association clinical practice guidelines are incorporated into the form's output. BHMED was tested in an observational study for use in conjunction with several EHR systems, including Affinity, SOAPware, and Allscripts. Questionnaires were distributed to clinicians to assess ease of use, time spent on documentation, accuracy, and likeliness to use the program again.

Result:
Clinicians were able to successfully create DPE notes with BHMED and incorporate them into all three native EHR systems. They reported as benefits: ease of use, fewer errors, and time saved compared to their standard EHR progress note.

Conclusion:
The BHMED allows creation of a well-documented diabetes patient encounter that is rapid, readable, reusable, and less error-prone, allowing the clinician more time for direct diabetes patient care.

Glycemic Variability and Quality of Life in Type 1 Diabetes Subjects Undergoing Continuous Glucose Monitoring

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Objective:
Previous studies have examined the relationship between hemoglobin A1c (HbA1c) and quality of life in diabetes and produced conflicting data. HbA1c fails to capture temporal changes in glucose levels and, as yet, the relationship between glycemic variability and quality of life has not been investigated. The aim of this study was to determine whether increased glycemic variability is associated with a reduction in quality of life in adults with type 1 diabetes.

Method:
Eighteen adults with type 1 diabetes on multiple daily injection (MDI) or continuous subcutaneous insulin infusion (CSII) therapy underwent continuous glucose monitoring (CGM) for a minimum period of 72 hours. Glycemic variability was analyzed using standard deviation (SD), "J" index, M-value, mean of daily differences, and mean amplitude of glycemic excursions (MAGE). Quality of life was assessed using two diabetes-specific instruments: The Diabetes Quality of Life (DQoL) questionnaire and a novel questionnaire designed to assess quality of life benefits of MDI compared to CSII therapy.

Results:
The mean age of subjects was 43.6 ± 14.17 years, mean duration of diabetes was 20.6 ± 14.93 years, and mean HbA1c was 7.30 ± 0.82. MAGE correlated significantly and negatively with the total DQoL score ($r = -0.48$, $p = 0.046$). SD correlated significantly and negatively with the impact subscale of DQoL ($r = -0.49$, $p = 0.037$). MAGE correlated significantly and negatively with the social and vocational worry subscale of DQoL ($r = -0.83$, $p = 0.012$). No other measure of glycemic variability correlated significantly with DQoL and novel questionnaire total and subsection scores.

Conclusion:
This is the first study to show that increased glycemic variability is significantly associated with a reduced quality of life in adult subjects with type 1 diabetes.

Model-Based Targeted Control with Stochastic Forecasting for Regulation of Glycemia in Extremely Low Birth Weight Neonates

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Objective:
Hyperglycemia occurs in 40–80% of premature, low birth weight infants due to the immaturity of endogenous regulatory systems and the stress of their condition. Increased sepsis, hospital stay, and further negative outcomes, including increased mortality, have been linked to elevated neonatal glucose levels. The emerging use of insulin in neonates carries a significant risk of hypoglycemia due to patient response variations to insulin over time.

Method:
A metabolic computer system model was used to provide tight glycemic control in extremely low birth weight neonates. Stochastic forecasts provided a quantified risk of predicted blood glucose less than 4 mmol/liter in simulation and clinical trials, and influenced insulin dosage selection. Insulin infusions were modulated to hit a predetermined target based on measurements every 2–3 hours. Simulation studies on 25 retrospective insulin episodes and 8 clinical trials up to 24 hours each were conducted. The median trial birth weight was 745 grams (range: 540–995 grams). The median gestational age was 25.4 weeks (range: 24.4–27 weeks). Ethics approval was granted by the South Island Regional Ethics Committee.

Result:
Normoglycemia in a 4- to 7-mmol/liter band was achieved in all cases. Median initial blood glucose was 11.1 mmol/liter (range: 7.4–14.4 mmol/liter). Over all trials, median blood glucose was 6.9 mmol/liter [interquartile range (IQR): 5.6–7.8, 90% confidence interval (CI): 4.7–10.6] over 86 measurements. Minimum blood glucose was 3.8 mmol/liter. Predicted glucose levels had a median error of 8.0% (IQR: 4.8–12.5, 90% CI: 0.7–30.0) compared to the resulting measurement.

Conclusion:
Hyperglycemia affects a large proportion of premature infants and is linked to worsened outcomes. A model that accurately captures and forecasts dynamics of neonatal metabolism provided safe and effective real-time blood glucose control in 24-hour pilot clinical trials.

Real-Time Glucose Estimation Algorithm for Continuous Glucose Monitoring Using Autoregressive Models

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Objective:
The goal of this study was to develop and validate a new algorithm to estimate blood glucose (BG) in real time from continuous glucose monitor readings using autoregressive models in order to improve measurement accuracy and hypoglycemia detection.

Method:
Eighteen patients with type 1 diabetes were monitored for 3 days (one at the hospital and two at home) using the CGMS® (Medtronic, MiniMed). For these patients, BG samples were taken every 15 minutes for 2 hours after meals and every half hour otherwise during the first day. The relationship between the current measured by the CGMS and BG was learned by an autoregressive model. New capillary glucose measurements were used to correct the model BG estimations.

Result:
Some 2260 paired data were obtained (360 below 70 mg/dl, 1093 between 70 and 180 mg/dl, and 753 above 180 mg/dl) from BG and monitor readings. Of the paired points, 95.2% fell in zones A+B of the Clarke error grid analysis (EGA) with the proposed algorithm. Consensus EGA indicated that 98.2% of paired data were in zones A+B. The mean and median absolute relative differences (RAD) were 13.2 and 7.7%, respectively. Measurements meeting International Organization for Standardization (ISO) criteria were 82.6%. Retrospective CGMS and proposed real-time algorithm values were compared against BG, and an increase of data in zone A with the proposed algorithm was achieved (10.5% in the Clarke EGA and 10.7% in the consensus EGA). In the hypoglycemic range, mean and median RAD were reduced by 30.4 and 51.6%, respectively, and measurements meeting ISO criteria were increased by 19.2%.

Conclusion:
The performance as measured with clinical and numerical accuracy metrics illustrates the improved accuracy of the proposed algorithm. A significant improvement in hypoglycemia detection was also observed.

A Closed-Loop Artificial Pancreas Using Model Predictive Control and Sliding Meal Size Estimation

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Objective:
A comprehensive, fully closed-loop artificial pancreas system incorporating insulin-on-board constraints, model predictive control (MPC), and a meal size estimation (MSE) algorithm was evaluated using 200 *in silico* subjects.

Methods:
A pharmacodynamic model of insulin action was used to provide insulin-on-board constraints to explicitly include the effect of past and currently delivered insulin. In addition, a supervisory pump shut off was incorporated to decrease the risk of hypoglycemia. A MSE algorithm provided insulin automatically. A MPC algorithm incorporating these components was developed based on a study of 20 subjects and was tested in a hypothetical clinical trial of 100 adolescent and 100 adult *in silico* subjects using the Food and Drug Administration-approved University of Virginia simulator. For 36 hours of closed-loop, a protocol that included 40 grams of carbohydrates (CHO) for breakfast at 7 am, 50 grams of CHO for lunch at noon, 20 grams of CHO for a snack at 4 pm, and 80 grams of CHO for dinner at 6 pm was used.

Results:
Adolescents had a mean glucose of 159 mg/dl with 72% of the time in the 70- to 180-mg/dl range using MPC only and a mean glucose of 137 mg/dl with 82% of the time in the 70- to 180-mg/dl range using MPC-MSE. Adults had a mean glucose of 145 mg/dl and spent 83% of the time in the 70- to 180-mg/dl range using MPC only with a mean glucose of 131 mg/dl and 90% of the time within the 70- to 180-mg/dl range using MPC-MSE.

Conclusions:
The newly developed meal size estimation detects and compensates for meals in closed-loop without the need for subject input. The integrated system results in robust glucose control, with a calculated hemoglobin A1c less than 7% and a reduction in hyperglycemia risk with a minimal increase in hypoglycemia risk.

A Comparison of Glycemic Strategies under Uncertain Meal Sizes and Timings: A 1-Week *in Silico* Study Involving 20 Subjects

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Objective:
The goal of this study was to assess the impact of varying meal times and estimates of meal size in open-loop control and varying actual meal sizes in closed-loop control through 1 week of simulation. In addition, the insulin bolus was omitted for three meals each week.

Methods:
A test scenario for 1 week was used with the Food and Drug Administration-approved University of Virginia simulator on 10 adolescents and 10 adults. The protocol considered 40 grams of carbohydrates (CHO) for breakfast at 7 am, 50 grams of CHO for lunch at noon, 20 grams of CHO for a snack at 4 pm, and 80 grams of CHO for dinner at 6 pm. The time of each meal was delayed randomly for 0–60 minutes, and each meal insulin bolus reflected a random error in the estimate of meal CHO content (±30%). Three meal boluses per week were omitted randomly to study the effect of missing boluses on mean glucose. Four case studies were considered: open-loop (OL), open-loop with three missing boluses (OL+3MB), closed-loop (CL)(no user input), and hybrid closed-loop with manual bolusing and three missing boluses (hybrid+3MB) (which were compensated by the meal size estimator).

Results:
Adolescents had a mean glucose of 186 mg/dl for OL, 197 mg/dl for OL+3MB, 156 mg/dl for CL, and 155 mg/dl for hybrid+3MB. Adults had a mean glucose of 192 mg/dl for OL, 202 mg/dl for OL+3MB, 145 mg/dl for CL, and 146 mg/dl for hybrid+3MB.

Conclusions:
The closed-loop system with a meal size estimator provides virtually identical results to closed-loop with manual meal bolusing, illustrating the good performance of the meal size estimator. The closed-loop system can maintain a mean glucose near 150 mg/dl, despite randomness, uncertainty, and three missing boluses per week.

Differing Body Color of the SoloSTAR® Pen Enhances the Ability of Patients to Distinguish between Long- and Short-Acting Insulin Compared with the Label Color Used on Other Pen Devices

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Objective:
Successful differentiation between insulin injection pens is critical for diabetes mellitus (DM) patients receiving both long- and short-acting insulins. Available pen devices can be distinguished between long- and short-acting insulins by label color and wording. SoloSTAR® is currently the only pen with an entirely different pen body color according to insulin type.

Method:
Comparable studies using individual patient interviews characterized the ability to distinguish long- from short-acting insulin versions of three pen types: SoloSTAR, FlexPen®, and KwikPen®. Participants were shown the pens, which were each described verbally as once-daily (twice-daily for the KwikPen) for long-acting insulins or thrice-daily with meals for short-acting insulins. The interviewer presented the pens side by side and asked the participant to identify the pen they would use (A) at lunch (short-acting) (B) once-daily (twice-daily for the KwikPen; long-acting), and (C) at breakfast (short-acting), mixing up the pens out of sight before each question. Participants were asked each time how they differentiated among pens. The short-acting insulin pen was then presented and the interviewer asked if this was the correct pen to administer once or three times daily (each participant was asked one of the two questions).

Result:
Considerably more patients identified the correct SoloSTAR pen across the tests (96–98%) vs the FlexPen (84%) or KwikPen (76–78%), with a strikingly lower error rate (2.7% vs 16.3 and 23.3%, respectively). The most common reason for correct responses was color.

Conclusion:
This study suggests that the full body color on SoloSTAR pens enhances patients' ability to differentiate long- from short-acting insulin and is a notable improvement over the standard label-only approach.

A Capillary Polymer Tube with On-Wall Microsensor for Direct Sampling and Measurement of Salivary Glucose

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Objective:
This work aims to develop a capillary polymer tube with on-wall electrochemical glucose biosensors to measure blood glucose noninvasively using saliva. Based on its tiny diameter (500 μm) and hydrophilic surface property (silica nanoparticle), the capillary polymer tube can directly sip saliva samples into the sensing area, thus avoiding the need to drive the samples for current lab-on-a-chip systems.

Method:
First, the silica nanoparticle solution was spin coated on the 15-μm-thick flexible Kapton film with glucose sensor patterns. Then, the working electrode of glucose biosensors was electrodeposited with platinum nanoparticles and further modified with glucose oxidase immobilized by chitosan matrix. Finally, the film was rolled spirally into a 500-μm-diameter polymer tube with the glucose sensors on the inside wall.

Result:
For the 500-μm-diameter spirally rolled polymer tube, the saliva solution can rise at least the height of 13 mm. A potential of +0.6 volt vs Ag/AgCl reference electrode was applied on the working electrode. The detection limit was around 3 μM (S/N = 3), and the response time was 16 seconds. It has the sensitivity of 172 nA/mM in the range of 3 to 350 μM with a linear coefficient of R^2 = 0.9993.

Conclusion:
A simple and smart capillary polymer tube with sensitivity in the micromolar range was demonstrated for a direct measurement of saliva glucose concentration. The developed device can also be used for the measurement of multiple metabolic parameters and other body fluids such as tears, sweat, and urine.

Postprandial Glucose Monitoring Improved Overall Health in Patients with Type 2 Diabetes Mellitus

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Objective:
Postprandial hyperglycemia contributes to poor glucose control and is associated with increased cardiovascular risk in type 2 diabetes mellitus (DM). The objective of this study was to determine the effect of postprandial self blood-glucose monitoring (pp-sbgm) on glucose control, lipids, and body weight and on cardiovascular events.

Method:
Subjects with type 2 diabetes and a hemoglobin A1c level between 6.5 and 7.0 were randomized into the study group (at least two pp-sbgm a day and dietary modification based on glucose readings) and control group (no mandatory pp-sbgm) for a 6-month observational study. The anti-DM drug or insulin regimen was unchanged in either group if the hemoglobin A1c level remained less than 7.0 during the study. End points included hemoglobin A1c, lipids, and weight.

Results:
One hundred sixty-nine subjects, mean age 63 years, and body weight 194 pounds were recruited. Hemoglobin A1c, weight, and triglycerides (TGs) were similar in the groups at baseline. By the end of 6 months, hemoglobin A1c (6.7 ± 0.1 to 6.4 ± 0.1, $p < 0.05$), body weight (195 ± 17 to 188 ± 14, $p < 0.002$), and TGs (141 ± 21 to 96 ± 17, $p < 0.05$) decreased in the study group, but did not change in the control group. No cardiovascular events were observed in either group during the 6-month study period.

Conclusions:
In type 2 DM patients who had already reached the hemoglobin A1c goal, pp-sbgm at least twice a day was associated with a further improvement in glycemia, lipids, and weight. We assume that lifestyle modification promoted by postprandial hyperglycemia awareness may underlie these findings. These results substantiate the importance of implementing pp-sbgm into lifestyle modification and emphasize that pp-sbgm is critical in the control of type 2 DM.

Sensor Response in Continuous Glucose Monitoring Systems

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Objective:
The application of filtering to a sampled, discrete-time signal allows for a reduction in noise and an enhancement of signal-specific patterns. In continuous glucose monitoring (CGM), a monitoring system must reduce signal noise (physiological or systemic) while providing accurate and up-to-date information. While filtering may remove or reduce the occurrence of unwanted artifacts, it also adds a degree of delay into the signal. Sensor lag can be a nuisance, as reference (BG) and sensor (SG) values may diverge. Delay was analyzed between BG and SG using the Medtronic Guardian® REAL-Time (GRT) CGM system. The effects of delay on sensor performance and responsiveness were quantified.

Method:
Data were obtained from 764 sensors worn by a mix of 116 diabetic and nondiabetic subjects over a period of up to 6 days. Various causal filters were applied to data, and the resulting information was run through a calibration algorithm whose pairing time was modified based on calculated system delay. SG output was collected and analyzed for overall system accuracy and performance. System-induced delay was estimated by maximizing the cross-correlation between filtered and raw data. Overall system delay was characterized by sensor response: the amount of time after a BG entry for SG to read within 10% of the instantaneous difference, normalized by bias (SRN, min * $[mg/dl]^{-1}$).

Results:
Baseline statistics were generated using the GRT system [15.31% mean absolute relative difference (MARD), 4.025 SRN]. Postmodification analysis showed that optimization of both filtering and calibration timing resulted in improvements to sensor responsiveness (3.568 SRN) and overall system performance (14.50% MARD).

Conclusion:
Results of this analysis suggest that this novel filtering scheme, coupled with the modification of pairing time, results in increased accuracy and faster sensor response.

Standardization of C-Peptide Measurements: Ongoing Efforts

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Objective:
The C-peptide is a useful marker of endogenous insulin secretion in patients with diabetes. We assessed within and between laboratory variability of C-peptide results and evaluated the impact of harmonizing results using both single-donor and pooled serum calibrators.

Method:
Fifty-two serum samples were sent to 16 laboratories/manufacturers in six countries using 13 different C-peptide assay methods. Twelve of these samples were analyzed in duplicate on each of 4 days by each laboratory for analysis of within and between day variability. The same 12 samples were also used as calibrators: 6 were single-donor calibrators and were assigned values by mass spectrometry and 6 were pooled serum calibrators and were assigned values based on the mean of all laboratories/methods. Statistical analyses were performed using SAS.

Result:
Within and between run coefficients of variations ranged from 1.2 to 9.5% and 2.2 to 30%, respectively. Not surprisingly, before normalization, there were significant differences between laboratory means ($p < 0.0001$); least squares means ranged from 0.92 to 1.35. After normalization with single donor or pooled samples, there were no significant differences in the mean responses among laboratories ($p = 0.86$, $p = 0.44$, respectively); least squares means ranged only from 0.80 to 0.83 (1.07 to 1.13 for pooled calibrators).

Conclusion:
There is a large amount of variability in C-peptide measurements, both within and between laboratories. Normalization of results using serum samples (from either single or pooled donors) significantly improved comparability among laboratories and methods. These data show that C-peptide measurements can be calibrated to improve comparability between laboratories. The next step will be to supply pooled serum calibrators with MS-assigned values to each manufacturer for "recalibration" followed by comparison of results from unknown samples to those of the reference method.

Which Signal Frequency Components Are Needed for Accurate Glucose Predictions?

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Objective:
This study investigated the importance of the various frequency components (or bands) of subcutaneous glucose signals in the prediction of glucose concentrations in type 1 diabetes patients with data-driven, autoregressive (AR) models.

Method:
Employing time-series data collected with a subcutaneous continuous glucose monitoring (CGM) device, we identified four key frequency bands of the glucose signal [band I: rapid pulsatile insulin secretion (5 to 15 minutes), band II: intrinsic responses (60 to 120 minutes), band III: schedule of exogenous inputs (150 to 500 minutes), and band IV: circadian rhythms (>700 minutes)]. We developed filters that eliminated all but one of the frequency bands and constructed corresponding AR models based on each frequency band, pair-wise combinations of frequency bands, and all frequency bands, which was used as a reference model. We used the first 2000 minutes of patient's data to train the models and the second 2000 minutes to test the predictions.

Results:
For this investigation, we employed CGM data collected for approximately 5 days on a minute-by-minute basis from an independent study of nine type 1 diabetes patients. We found that frequency bands II–IV are associated with glucose regulation, whereas band I only captures the noise content in the glucose signal. When compared with the reference model constructed using band II+III+IV, we found that (1) single-band models based on band II or band III alone yield accurate predictions for prediction horizons up to 30 minutes; (2) models based on pair-wise combinations, including band II+III or II+IV, are as predictive as the reference model; and (3) reference models trained on 300 minutes of data are as predictive as those trained on 2000 minutes.

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Conclusions:
Our analyses indicate that the frequency content of bands II, III, and IV fully captures the dynamics of glucose regulation of type 1 diabetes patients, obviating the need to explicitly model exogenous inputs. Moreover, results highlight the importance of band II (60 to 120 minutes) in the predictive power of AR models. Models based on the combination of band II and either band III or band IV are as predictive as the reference model including all bands. Finally, we conclude that the training time series can be shortened to 300 minutes, i.e., it may exclude circadian rhythm information, without any detriment in prediction accuracy.

Disclaimer:
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One-Year Continuous Implanted Glucose Sensor Performance Following Diabetes Induction in the Pig

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Objective:
GlySens has developed an implantable glucose sensor with battery-operated telemetry for >1-year implantation in subcutaneous tissues. The sensor is based on immobilized glucose oxidase and catalase, coupled to a potentiostatic electrochemical oxygen sensor, and includes a reference oxygen sensor without the enzymes. The difference signal, which indicates tissue glucose concentration, is transmitted to an external receiver. In a series of implants in pigs, sensor performance was evaluated before, during, and after diabetes induction to assess the influence of metabolic state and experimental protocol on sensor performance assessments.

Method:
The sensor system was implanted in a 20-kg Yucatan minipig, and it reported tissue glucose concentration continuously for over 1 year; diabetes was then induced by treatment with streptozotocin, and continuous tissue glucose recording continued for several months. The procedure was repeated in a second animal with diabetes induction 1 month following sensor implantation. Sensor outputs were correlated with central venous plasma glucose concentrations, which were manipulated by intravenous glucose and insulin infusions.

Result:
Raw oxygen signals decayed in parallel during the first few weeks after implantation during the wound healing process and thereafter remained acceptably nonzero for the duration of the experiment, whereas the difference signal reflected tissue glucose concentration with occasional (in certain cases weekly to monthly) calibration adjustment. Following diabetes induction, (1) glycemic variability, as reflected by the sensor, increased up to fivefold and (2) mean absolute relative difference (MARD) between sensor output and laboratory plasma analyses improved (decreased from 21 to 18%).

Conclusion:
The sensor performance is unaffected by diabetic induction in the pig. MARD assessments can be influenced, especially in nondiabetic animals, by experimental techniques that employ rapid-rate blood glucose changes.

Continuous Subcutaneous Delivery of Exenatide via ITCA 650 Lowers Plasma Glucose and Hemoglobin A1c and Reduces Weight in a 28-Day Phase 1b Study in Type 2 Diabetes

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Objective:
Exenatide is an effective therapy for type 2 diabetes that improves glucose control and reduces weight; however, twice-daily injections and persistent nausea and vomiting limit its use. ITCA 650 is a small, implantable osmotic pump containing a stabilized formulation of exenatide for long-term treatment of type 2 diabetes that offers the opportunity to enhance efficacy, decrease side effects, and ensure 100% compliance.

Method:
A 28-day study was conducted to evaluate the safety and effectiveness of exenatide delivered via ITCA 650. Subjects with type 2 diabetes with hemoglobin A1c ≥6.5% and ≤10% were enrolled in the study. Subjects were randomized to treatment with ITCA 650 at doses of 10, 20, 40, or 80 μg/day.

Result:
Significant decreases in both fasting and 2-hour postprandial plasma glucose were noted at doses of 20, 40, and 80 μg/day. Fasting glucose decreased by 5.6, 31.2, 42.0, and 28.8 mg/dl, and postprandial glucose decreased by 16.3, 34.7, 47.1, and 69.6 mg/dl with increasing doses. Although treatment was only 28 days, significant decreases in hemoglobin A1c were also observed, as well as a dose-dependent weight loss. Treatment with ITCA 650 was well tolerated. A dose-dependent increase in nausea was noted, although it was mild, transient, and noted primarily during the first week of treatment.

Conclusion:
ITCA 650 can be a safe and efficacious treatment of type 2 diabetes. Substantial beneficial effects on glucose and weight were noted following 28 days of treatment. Gastrointestinal side effects were minimized and allowed higher daily doses of exenatide to be administered. The use of an implanted subcutaneous pump eliminates the need for twice-a-day self-injection and ensures 100% patient compliance to therapy.

Significant Reductions in Hemoglobin A1c with Continuous Subcutaneous Insulin Infusion in Patients with Type 2 Diabetes

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Objective:
Randomized controlled trials demonstrating outcomes with the use of continuous subcutaneous insulin infusion (CSII or insulin pump therapy) in persons with uncontrolled type 2 diabetes are limited in scope and number. This study provides a real-world (retrospective) evaluation of the impact of CSII on 973 patients with type 2 diabetes who initiated CSII therapy between 1/2005 and 10/2007 (mean age 48 years, 47% male, mean duration of follow-up 17 months).

Method:
Administrative claims with integrated hemoglobin A1c (HbA1c) values from a large, geographically diverse, U.S. health plan were used. Prior to CSII initiation, over 50% of patients were using combination insulin analog therapy that included both long- and rapid-acting insulins. Mean baseline HbA1c (prior to CSII initiation) was 9.1%.

Result:
Statistically significant HbA1c reductions (from baseline to follow-up) were achieved with CSII. Among all previous combination insulin users, HbA1c levels decreased –0.86% ($p < 0.001$) vs mean follow-up HbA1c and –1.25% ($p < 0.001$) vs minimum follow-up HbA1c after CSII initiation. Among the subset of subjects using combination insulin analog therapy (long- + short-acting insulin combination) prior to CSII, HbA1c decreased –0.77% ($p < 0.001$) vs mean and –1.19% ($p < 0.001$) vs minimum HbA1c. Hypoglycemic events leading to office, emergency room, or hospital visits decreased slightly after CSII initiation (without CSII 0.0236 vs with CSII 0.0240 events per subject per month, p = not significant). However, this decrease was not clinically or statistically significant, and the technique of capturing these events has not been validated.

Conclusion:
Continuous subcutaneous insulin infusion therapy was associated with significant reductions in HbA1c in type 2 diabetes patients previously using multiple insulins, including combination insulin analog therapy (long- and rapid-acting insulins). HbA1c reductions from CSII did not lead to an increase in hypoglycemic events.

Impact of Patient Hematocrit on Glucose Meter Performance

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Objective:
The objective of this study was to determine if the impact of patient hematocrit on glucose meter performance could be predicted using a multiple regression model: meter glucose = laboratory glucose + laboratory hematocrit + laboratory glucose * laboratory hematocrit.

Method:
Patient-heparinized blood gas specimens (N = 151) were used to compare the performance of the LifeScan SureStep® Flexx® glucose meter and the Nova StatStrip® glucose meter with glucose results obtained from the Radiometer 725 blood gas instrument. Patient hematocrit results were also obtained from the blood gas analysis. Multiple regression analysis was conducted to determine the extent that patient hematocrit and reference method glucose concentration contributed to the performance of the glucose meters. The regression coefficients for each glucose meter were used to predict glucose meter results using 1 month of data (hematocrit and concomitant glucose results, N = 17,925) extracted from the clinical laboratory's database of four adult acute care hospitals.

Results:
Multiple regression analysis indicated that glucose concentration and patient hematocrit were significant contributors to the measured glucose using the LifeScan meter and that the extent of the hematocrit effect was dependent on the glucose concentration. In contrast, only the glucose concentration predicted the outcome of the measured glucose using the Nova meter. Regression analysis of the predicted glucose meter results versus the actual measured glucose concentration (from the 1-month data extract) revealed the following equations: (1) predicted LifeScan result = 1.379 (laboratory glucose) – 1.002 (R^2 = 0.999) and (2) predicted Nova result = 1.019 (laboratory glucose) – 0.257 (R^2= 1.00).

Conclusions:
Patient glucose concentration and hematocrit results significantly impact the performance of the LifeScan SureStep Flexx meter, whereas only glucose concentration influenced the performance of the Nova meter.

Definition of Hypoglycemia for Patients in the Intensive Care Unit

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Objective:
Hypoglycemia is one of the major risks when establishing glycemic control in critically ill patients and may contribute to increased mortality rates. Until today, no comparable measure of hypoglycemia frequency has been suggested. Current measures depend either on treatment period or on number of glucose measurements performed per patient. In the following, we suggest an alternative method to present hypoglycemia incidence by number of episodes per patient normalized for a 24-hour treatment period.

Method:
Two major studies performing glycemic control in critically ill patients were chosen for comparison: 1200 patients at a medical intensive care unit (ICU)[605 standard care (STD), 595 tight glycemic control (TGC); Van den Berghe (VDB) 2006] and 6030 patients in a mixed ICU [3014 STD, 3016 TGC; National Institute for Health and Clinical Excellence (NICE) 2009]. For both studies, rates of hypoglycemia (%) per patient per 24 hours were calculated based on published data.

Result:
Mean duration of treatment was 12.5 days for VDB and 4.2 days for NICE. Acute Physiology and Chronic Health Evaluation scores were 23 for VDB and 21 for NICE, respectively. Numbers of hypoglycemic events per study population were reported as follow: 19 (3.1%) for STD and 111 (18.7%) for TGC in the VDB study and 15 (0.5%) for STD and 206 (6.8%) for TGC in the NICE study. Rates of hypoglycemia per patient per 24 hours were 0.25% (STD) vs 1.49% (TGC) for VDB and 0.12% (STD) vs 1.63% (TGC) for NICE, respectively.

Conclusion:
Applying this novel method revealed that despite the clearly lower frequency of hypoglycemic episodes reported for the NICE study, even a slightly higher rate would have to be reported due to the substantially shorter treatment period. We conclude reporting hypoglycemic episodes in critically ill patients on a per patient and per 24-hour basis may be a more adequate tool to accurately describe hypoglycemia incidence.

Evaluation of Microdialysis-Based Glucose Monitoring in Blood and Subcutaneous Adipose Tissue in Type 1 Diabetes Patients

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Objective:
Glycemic control is beneficial for critically ill patients. In order to achieve glycemic control, a continuous glucose signal could help decrease the workload. Subcutaneous adipose tissue (SAT) has been suggested as an alternative site for continuous glucose monitoring and has been tested extensively in type 1 diabetes patients. In the critically ill patient, vascular access is granted, and thus continuous blood glucose monitoring is feasible. The aim of this study was to test a microdialysis-based technique for peripheral venous glucose monitoring and compare the technique with SAT glucose monitoring in type 1 diabetes patients.

Method:
Thirteen type 1 diabetes patients (age: 31.2 ± 7.3 years; body mass index: 24.8 ± 3.8 kg/m^2) were investigated over a period of 26 hours. For vascular microdialysis (MDv), a conventional double lumen catheter with a planar flow-through microdialysis unit was used. SAT microdialysis (MDs) was performed using a standard CMA60 catheter. Microdialysis samples were collected in 15- to 30-minute intervals and analyzed for glucose with a standard laboratory analyzer. Microdialysis samples were prospectively calibrated to reference applying a one-point calibration. MDv and MDs glucose levels were compared against arterialized-venous reference measurements.

Result:
Mean differences (2 SD) between reference and glucose readings obtained from microdialysis were as follows: MDv 10.8 (36.7)% and MDs 4.2 (37.8)%, respectively. Median absolute relative difference (±SD) was 11.5 (7.7; 26.0)% (MDv) and 10.0 (5.3; 19.1)% (MDs), respectively. Clarke error grid analysis indicated 68.1% in A and 31.9% in B for MDv and 76.6% in A, 22.2% in B, 0.8% in C, and 0.4% in D for MDs, respectively.

Conclusion:
Glucose monitoring from blood and SAT using a microdialysis-based approach indicated similar performance when investigated in type 1 diabetes patients for a period of 26 hours.

Prenatal Continuous Glucose Monitoring as a Motivational Tool

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Objective:
The goal of this study was to incorporate continuous glucose monitoring (CGM) as a motivational intervention for pregnant individuals with diabetes with the goals of increasing individual's change talk, decreasing individual's resistance, and improving opportunity for self-assessment control.

Method:
The MiniMed CGMS® by Medtronic was used to document prenatal glycemic excursions.

Results:
(1) Four gravidas at risk for diabetes refused glucose screening. All four women parturients had hemoglobin A1c <6% and fasting blood sugar <90 mg/dl. A visual review of CGM graphing motivated all to accept glucose challenge test screening and subsequent glucose tolerant testing. (2) CGM was used to confirm that hyperglycemia occurred frequently. The visual discrepancy between what was believed to be infrequent hyperglycemia detected on self-monitoring of blood glucose (SMBG) versus frequent hyperglycemia on CGM motivated self-assessment of medical nutrition therapy (MNT). (3) A 32-year-old type 1 individual continued MNT and basal glargine. Her hemoglobin A1c <6% and mean SMBG ranged from 116 to 120 mg/dl. Clinical signs of hyperglycemia, fetal macrosomia, and polyhydramnios developed. There was a CGM mean glucose of 120 mg/dl but it ranged from 59 to 199 mg/dl. A CGM graph motivated institution of insulin pump therapy. A 35-year-old type 1 at 12 weeks of gestation had a hemoglobin A1c level of 8% and a mean SMBG of 88 mg/dl. The mean glucose by CGM was 90 mg/dl but ranged from 40 to 160 mg/dl. A 34-year-old type 1 managed on MNT and intensive insulin therapy with a mean 104 mg/dl SMBG and hemoglobin A1c <6% had evidence of hyperglycemia suggested by unexplained polyhydramnois. Mean glucose levels were 107 and 102 mg/dl for SMBG and CGM, respectively. CGM documented fasting hypoglycemia and postprandial hyperglycemia. CGM graphs provided visual motivation for use of an insulin pump for these type 1 gravidas.

Conclusion:
Continuous glucose monitoring was used as a motivational tool to decrease resistance, identify discrepancies in glucose goals, and facilitate self-assessment.

Improvement in Bioavailability of Fumaryl Diketopiperazine with a Next Generation Delivery System Device: Implications for Delivery of Pulmonary Insulin

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Objective:
This study was designed to assess the safety and tolerability of various fill weights of Technosphere® inhalation powder, as delivered by the Next Generation Delivery System (NGDSa) compared with MedTone® inhaler model C, and the effect of altering flow rate and inhalation time on the pharmacokinetics (PK) of fumaryl diketopiperazine (FDKP) inhaled as Technosphere inhalation powder through the NGDSa inhaler.

Method:
This was an open label, crossover, two part PK (FDKP) study in volunteers. In the first part, 10 subjects were administered a dose of Technosphere inhalation powder (10 and 15 mg NGDSa and 10 mg model C). In the second part, 10 subjects each were tested on either the effect of flow rate [15 liters per minute (LPM) vs 30 LPM)] or inhalation time (3 seconds vs 6 seconds).

Result:
Ten milligrams of NGDSa delivered approximately twice the blood exposure of FDKP compared with 10 mg of model C (28,523 ± 7375 ng•min/ml vs 15,143 ± 3720 ng•min/ml). Fifteen milligrams of NGDSa on average did not deliver dose-proportional exposure compared with 10 mg NGDSa. This was due to several individuals not having good exposure, as seen in the higher standard deviation. The 10-mg NGDSa results for longer, shorter, harder, or easier inhalation data did not show significant differences in FDKP area under the curve (AUC; 26,960 ± 7788, 27,594 ± 5145, 33,238 ± 11,168, and 34,829 ± 9816 ng•min/ml).

Conclusion:
Ten milligrams of FDKP delivered by NGDSa was more efficient at delivering FDKP by approximately twofold, as measured by FDKP plasma AUC. The delivery of FDKP was independent of inhalation time and effort. NGDSa had an improved bioavailability and efficiency over model C as assessed by FDKP AUC and the effect of altering inhalation parameters on FDKP AUC.

Improvement in Bioavailability of Fumaryl Diketopiperazine and Insulin with a Next Generation Delivery System Device

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Objective:
This study was designed to assess the relative bioavailability of various fill weights of Technosphere® inhalation powder delivered by the Next Generation Delivery System (NGDSb) compared with the MedTone® inhaler (model C) as determined by the pharmacokinetics (PK) of insulin and fumaryl diketopiperazine (FDKP).

Method:
This was an open label, crossover, PK (insulin and FDKP) study in healthy volunteers. C-peptide corrections were used to determine the relative amounts of insulin delivered by inhalation versus insulin of endogenous origin. Twenty-four subjects (12 per arm) were administered a dose of Technosphere inhalation powder (20 or 22 units insulin via NGDSb and 30 units insulin via model C); subsequently, 12 subjects were given 20 units via NGDSb or 30 units via model C in a three-way crossover arm.

Result:
Twenty units of NGDSb or 22 units of insulin delivered similar exposures to insulin and FDKP compared with 30 units of insulin via model C. For insulin, exposures were 3570 ± 1146 μU/ml vs 4370 ± 1719 μU/ml for 20 units of NGDSb and 30 units of model C, respectively, and 5312 ± 2017 μU/ml vs 4176 ± 2579 μU/ml for 22 units of NGDSb and 30 units of model C. For the three-way crossover arm, exposures were 4061 ± 1058 μU/ml and 3583 ± 1338 μU/ml for NGDSb and model C, respectively.

Conclusion:
The NGDSb was more efficient at delivering insulin as measured by insulin plasma exposures than model C. NGDSb delivered similar insulin exposures with 20 units of insulin as that of model C with 30 units of insulin.

Evaluating the Automated Detection of Blood Glucose Control Problems

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Objective:
The Data-Driven Diabetes Decision Support (4 Diabetes Support) system aims to help physicians manage patients with diabetes. It detects 12 types of problems in blood glucose control based on continuous glucose monitoring (CGM), finger stick, insulin, and daily life-event data. This study evaluates the system, comparing results to those of a preliminary study, and considering potential clinical use, where CGM and/or life-event data may be unavailable.

Method:
Twenty-six patients with type 1 diabetes (T1DM) on insulin pump therapy enrolled in the study. Twenty-three patients completed the study, supplying background information and 5 weeks of insulin pump data. Pump data were extracted from Medtronic's CareLink system. Daily life-event data were approximated by a patient's typical schedule for meals, exercise, work, and sleep. CGM data were available only for patients using CGM routinely. Automatically detected problems were reviewed by the patient's physician.

Result:
The software detected a mean of 2.6 (±1.8) problems per patient per week vs 4.9 (±2.7) problems per patient per week in the preliminary study. This was significant ($p = 0.005$), although patient groups did not differ significantly on hemoglobin A1c, age, gender, marital status, work status, years with diabetes, or number of finger sticks. Physicians validated that 98% of automated problem detections were correct. No patients dropped out due to data entry time demands, although this was a problem in the preliminary study.

Conclusion:
The 4 Diabetes Support System automatically detected blood glucose control problems in T1DM patients on insulin pump therapy, even with limited CGM and life-event data. CGM and daily life-event data enabled automated detection of significantly more blood glucose control problems per patient per week. Additional work is needed to provide device/software interfaces allowing patients to provide these data quickly and conveniently.

Continuous Glucose Monitoring with a Microinterferometer

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Objective:
The objective of this study was to build a minimally invasive sensor for continuous glucose monitoring with accuracy required for directing therapy in diabetes patients. The sensor makes accurate measurements at low glucose concentrations and does not generate inflammation-producing by-products.

Method:
The sensor is a miniature differential refractometer consisting of two chambers, each containing a microinterferometer, light source, and detector. The device makes precise measurements of refractive index changes in interstitial fluid that are insensitive to light amplitude variations. One chamber contains the components of a reversible competitive chemistry that is specific to glucose, whereas the second chamber serves as a reference measurement to eliminate common mode factors such as temperature changes. The reversible chemistry is based on the competitive reaction of glucose and dextran with concanavalin A (ConA). The ConA is modified to optimize detection sensitivity and stability.

Results:
Research prototypes made accurate measurements of glucose over a range from 20 to 600 mg/dl. The sensor has negligible sensitivity to temperature variations between 32 and 42°C. The device has been tested in phosphate-buffered saline and serum spiked with contaminants. It is insensitive to fluctuations of both primary interstitial fluid components and assorted other contaminants. The device response time is sufficiently short to provide actionable feedback.

Conclusion:
The microinterferometer-based sensor is a promising optical approach that, combined with ConA chemistry, promises to have the accuracy required for therapeutic action. Because it does not involve a chemical reaction that consumes reagents and creates by-products, the device holds promise for long-term implantation. The next step is to study the device operation *in vivo*.

Factors Predictive of Nocturnal Hypoglycemia with Continuous Glucose Monitoring

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Objective:
The goal of this study was to evaluate factors associated with nocturnal hypoglycemia assessed with continuous glucose monitoring (CGM) in type 1 diabetes (T1DM).

Methods:
In a Juvenile Diabetes Research Foundation-randomized trial on CGM use, we evaluated the frequency of nocturnal hypoglycemia (two consecutive values ≤60 mg/dl) during 51,581 patient nights with at least 4 hours of unblinded CGM data between 12 midnight and 6 am in the 312 subjects who had data available for at least 42 nights. The percentage of nights with hypoglycemia was computed for each subject, and least-squares regression models were used to evaluate the association with various factors, including glycemic indices from blinded CGM use at baseline.

Results:
The median percentage of hypoglycemic nights per subject was 6.6% (interquartile range 3.3 to 11.8%). In a multivariate model, there was significant association (P = 0.002) with baseline hemoglobin A1c (median percentage of hypoglycemic nights 9.1% with hemoglobin A1c <7.0%, 6.3% for hemoglobin A1c 7.0 to <8.0%, and 3.9% for hemoglobin A1c ≥8.0%). A greater amount of time with glucose values ≤60 mg/dl and a lesser amount of time with glucose values >250 mg/dl during baseline-blinded CGM use also were associated with an increased frequency of hypoglycemia (P < 0.001 and 0.004, respectively). Hypoglycemia frequency was similar in children and adults and in pump and multiple daily injection users.

Conclusion:
Nocturnal biochemical hypoglycemia occurs more frequently in individuals with T1DM whose hemoglobin A1c level is in the target range. Blinded CGM use can be helpful in establishing an individual's risk for nocturnal hypoglycemia.

In Silico Testing of the Ability of a Fuzzy Logic Insulin Pump Controller to Address Variable Daily Eating Patterns with Use of Personalization

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Objective:
The primary purpose of this study was to evaluate a fuzzy logic controller (FLC) in three situations: standard day (45/70/80 grams of carbohydrate meals), fasting day, and large meal day (100/100 grams). A secondary goal was to use a personalization factor (PF) to reduce the risk of hypoglycemia and to evaluate the interaction of a PF with other factors.

Methods:
Testing was done using University of Virginia diabetes simulation on 10 adults, 10 adolescents, and 10 children for 24-hour periods. End points included average blood glucose (BG_{avg}, mg/dl), low blood glucose risk index (LBGI), high blood glucose risk index (HBGI), and seven others. Personalization was done by scaling of our original FLC matrix.

Results:
During the standard meal the BG_{avg} was 141, 150, and 141; the LBGI was 0.4, 0.3, and 2.4; and the HBGI was 3.4, 5.2, and 5.5 for adults, adolescents, and children, respectively. During fasting, the BG_{avg} was 112, 109, and 112; the LBGI was 0.5, 0.4, and 0.6; and the HBGI was 0.3, 0.2, and 0.2 for each respective group. During the large meal the BG_{avg} was 140, 154, and 154; the LBGI was 3.5, 1.7, and 11.1; and the HBGI was 5.2, 7.9, and 7.9 for the respective groups. Personalization using five aggressiveness factors (PF1–PF 5) on 10 adults using the standard meal changed BG_{avg} to 119, 131, 141, 151, and 160; LBGI changed to 2.7, 1.1, 0.4, 0.1, and 0.0; and HBGI changed to 1.7, 2.5, 3.4, 4.4, and 5.5, respectively

Conclusion:
The FLC did well in a variety of meal patterns, and the use of personalization allowed customization of dosing to reduce the incidence of hypoglycemia. There were some differences in the response across age.

Effect of Two- and Three-Dimensional Insulinoma Cluster Size on Insulin Secretion: Implications for Cell Encapsulation

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Objective:
The viability of islet transplants for treating type 1 diabetes is decreased for large-diameter islets. For encapsulated islet transplantation, the size of the cell cluster becomes particularly relevant because vascularization can only occur up to the surface of the encapsulating membrane. However, one should take care to not transplant arbitrarily small clusters because previous reports have demonstrated that insulin secretion from β cells is improved significantly by contact with other β cells. Transplanted encapsulated cells should demonstrate maximum insulin secretion while minimizing cell death due to nutrient diffusion limitations. The objective of this study was to better understand the impact that the size of a β-cell cluster has on insulin secretion in both two- and three-dimensional environments.

Method:
The 832/13 insulinoma cell clusters of discreet sizes ranging from 10-μm circles to 120 × 120-μm squares were patterned on glass slides using covalent microcontact printing of laminin surrounded by polyethylene glycol (MW = 5000). The number of cells in each cluster was counted and subjected to a glucose-stimulated insulin secretion (GSIS) assay to evaluate the insulin secretion per cell. The 832/13 insulinoma cells were also embedded within a collagen I gel and grown for varying numbers of days to yield clusters of varying sizes, which were also evaluated using GSIS.

Result:
Insulin secretion per cell from 832/13 insulinoma cells increased with cluster size in both two and three dimensions.

Conclusion:
The results of this study can be used to aid in the selection of appropriately sized islets for transplantation, as well as in the design of discreetly sized cell clusters that will optimally balance nutrient diffusion limitations with optimal insulin secretion behavior to improve the long-term clinical efficacy of islet transplants.

Mobile Phones: Is It a Risk to Develop Diabetes Mellitus?

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Background:
Extensive use of mobile phones has been accompanied with a common public debate about possible adverse effects on human health. No study has been published yet to establish any association between the fastest growing innovation of mobile phone and diabetes mellitus. The aim of this study was to determine the effects of exposure to electromagnetic field radiation generated by mobile phones on fasting blood glucose and serum insulin in Wistar albino rats.

Material and Methods:
Forty male albino rats (Wistar strain) were divided equally into five groups. Group A served as control, group B received mobile phone radiation for less than 15 minutes, group C for 15–30, group D for 31–45, and group E for 46–60 minutes/day for a total period of 3 months. Fasting blood glucose was determined using a spectrophotometer and serum insulin by an enzyme-linked immunosorbent assay. Homeostatic model assessment was applied for the assessment of β-cell function along with homeostasis model assessment of insulin resistance (HOMA-IR).

Results:
Wister albino rats exposed to mobile phone radiation longer than 15 minutes a day for a total period of 3 months had a significantly higher fasting blood glucose ($P < 0.015$) and serum insulin ($P < 0.01$) relative to their control. HOMA-IR was increased significantly ($P < 0.003$) in groups exposed for 15–30 and 46–60 minutes/day compared to their control.

Conclusion:
Long-term exposure to mobile phone radiation causes hyperglycemia associated with insulin resistance in Wistar albino rats. Being the pioneer study in this concern, the same is expected for the human population using mobile phones. Therefore, it is suggested to minimize the exposure of mobile phones to the human body.

Painless Intradermal Delivery of Insulin: The Novel ClickSoft™ Microinjection Device

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Objective:
The goal of this study was to compare the efficacy of a microneedle-based intradermal drug delivery device with a subcutaneous injection dose of human insulin (Humalog) at breakfast time in subjects with type 1 diabetes.

Method:
A randomized, crossover, comparative study of a microneedle device versus a subcutaneous insulin injection was performed on 15 male or female subjects with type 1 diabetes. In treatment 1, subjects were given a dose of 7 units of Humalog (subcutaneous injection) at time 0 minute. In treatment 2, subjects were given a dose of 7 units of Humalog through the microneedle at time 0 minute. Ten minutes after the dose, subjects were asked to consume an Ensure Plus liquid meal (360 calories). Blood samples for glucose and insulin were taken 30 minutes before dosing (–30 minutes), just before dosing (0 minutes), and after dosing (15, 30, 45, 60, 90, 120, 180, 240, and 300 minutes).

Results:
The 30- and 60-minute postprandial glucose levels were lowered significantly with the microneedle device (146 ± 5 mg/dl microneedle device vs 184 ± 7 mg/dl injection at 30 minutes and 192 ± 6 mg/dl microneedle device vs 236 ± 9 mg/dl injection at 60 minutes; $p < 0.003$). Rises in serum insulin levels were significantly higher (C_{max} = 93 ± 6 μU/ml for the microneedle device versus the 78 ± 3 μU/ml subcutaneous injection; 20% higher; $p < 0.001$).

Conclusions:
Insulin delivered through a microneedle device was faster in lowering glucose when compared to a regular subcutaneous insulin injection. This was attributed to the much more rapid absorption of insulin through the skin layers via interstitial fluid. No pain was associated with the microneedle device (intradermal) injection as patients never felt the pricking pain usually associated with subcutaneous injections.

Characterization of Cardiovascular Outcomes in a Glucose Supply-and-Demand Type 2 Diabetes Model

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Objective:
The goal of this study was to construct a pharmacokinetic/pharmacodynamic model that identifies the impact of glucose supply-and-demand dynamics on cardiovascular (CV) outcomes in patients with type 2 diabetes (T2DM).

Method:
We identified quantitative differences between antidiabetic agents on carbohydrate exposure [caloric intake/intestinal absorption (CE)], hepatic glucose uptake (HGU), hepatic gluconeogenesis (GNG), insulin resistance (IR), peripheral glucose uptake (PGU), and peripheral insulin exposure (PIE). Characterized for their respective effects, the impact of the antidiabetic agents on glucose supply (decrease in CE, increase in HGU, decrease in GNG, decrease in IR) and demand (increase in PIE, increase in PGU) was determined, and the ratio of the effect was applied to 50 retrospectively identified patients with 5 years of clinical data preceding a major CV event (myocardial infarction, coronary artery bypass graft, angioplasty) and 50 case-matched controls.

Result:
α-Glucosidase inhibitors (1.25), metformin (2.20), and thiazolidinediones (1.25–1.32) exhibit superior effects on glucose supply-and-demand dynamics (SD ratio) versus secretagogue (0.69–0.81) and insulin-based therapies (0.62–0.79). Patients managed to an average hemoglobin A1c <7% did not demonstrate significantly fewer CV events versus those ≥7% (44% vs 53%; $p = 0.391$). The optimal SD ratio break point predictive of a reduced CV event was determined to be ≥1.25 (43% vs 57%; $p = 0.161$). Combining the parameters, management to an hemoglobin A1c ≥7% and SD ratio <1.25 tended to demonstrate increased CV risk versus those managed ≥7% and <1.25, or <7% ($p = 0.096$).

Conclusion:
This model of glucose supply-and-demand dynamics demonstrates that the combination of higher hemoglobin A1c (≥7%) and lower SD ratio (<1.25) tends to be associated with increased CV risk. Subsequent work should be conducted to hone SD ratio estimates, identify ratios for new antidiabetic agents, and integrate findings into larger, long-term T2DM CV outcome trials.

Impact of Self-Monitoring of Blood Glucose on Cardiovascular Outcomes in Patients with Type 2 Diabetes

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Objective:
A previous retrospective analysis suggested the benefit of self-monitoring of blood glucose (SMBG) on cardiovascular (CV) outcomes. It is our interest to provide supplementary data and additionally provide insight into the relationship between SMBG frequency and CV outcomes in type 2 diabetes (T2DM).

Method:
From a regional managed care database, patients with a known T2DM diagnosis date between 1997 and 2003 were identified retrospectively. Electronic prescription and medical claims were reviewed to identify patients with 5 years of continuous follow-up from T2DM diagnosis. International Statistical Classification of Diseases and Related Health Problems and Current Procedural Terminology codes were cross-referenced to identify CV events (angioplasty, coronary artery bypass graft, myocardial infarction, and stroke). Patients experiencing a CV event within the first year of the 5-year analysis period were excluded. SMBG was evaluated by average percent daily utilization break points (25, 50, 75, 100, 125, and 150%), as determined by prescription claims, where one test strip was equal to 1 day of testing.

Result:
Of patients meeting inclusion criteria, 1355 were eligible to determine CV (N = 145) or non-CV (N = 1210) status and percent daily utilization of SMBG. Patients experiencing a CV event demonstrated a lower frequency of SBMG vs their non-CV counterparts (21.3% vs 32.6%; p = 0.002). Analysis of average percent daily utilization by break point revealed a progressive reduction in the incidence of CV events with increasing frequency of SMBG ($p < 0.001$).

Conclusion:
Consistent with previous results, we identified a beneficial correlation between SMBG and CV events. Patients experiencing a CV event were significantly associated with reduced testing frequency; as the frequency of testing increased, there was a significant reduction in the incidence of the CV event. These results suggest that the general practice of SMBG, along with the frequency of testing, is relevant to CV risk.

Perioperative Hyperglycemia Increases Risk for Deep Wound Infection after Major Orthopedic Surgery

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Objective:
One of the most serious complications after major orthopedic surgery is deep wound infection. Various risk factors for developing infection after hip and knee replacement surgery were described, including patients' comorbidities and surgical technique factors. We investigated whether high blood glucose increases risk for periprosthetic joint infection (PJI) after total hip and knee arthroplasty.

Method:
After obtaining institutional review board approval, we reviewed our computerized database for primary total hip and knee arthroplasty from 2000 to 2008. Demographic information, past medical history of patients, perioperative biochemistry, and postoperative complications were reviewed. Data were analyzed using the *t* test and Fisher's exact test.

Result:
Data from 17960 patients were included in the study. The incidence of PJI was 1.06% (190/17,960 patients, 95% confidence interval 0.91, 1.21). Patients with PJI had mean perioperative blood glucose significantly higher than noninfected patients (130 mg/dl vs 125 mg/dl, $P = 0.012$). Infected patients tended to be male (51% vs 42%, $P = 0.018$), had a higher body mass index (BMI) (33 kg/m^2 vs 30 kg/m^2, $P < 0.001$), had a higher American Society of Anesthesiologists Physical Status (ASA PS)(2.45 vs 2.68, $P < 0.001$), and had a history of (h/o) myocardial infarction (MI)(7.9% vs 4.3%, $P = 0.029$), h/o renal disease (4.2% vs 1.9%, $P = 0.004$), and h/o diabetes mellitus (DM)(20% vs 12%, $P = 0.002$). A longer operative time and knee arthroplasty compared with hip arthroplasty had a significantly higher incidence of PJI ($P < 0.001$).

Conclusion:
Mean blood glucose is a significant risk factor for PJI after total hip and knee arthroplasty. Other risk factors were male sex, BMI, ASA PS, h/o MI, h/o renal disease, h/o DM, longer duration of surgery, and knee arthroplasty. Knowing risk factors associated with PJI could help physicians identify patients who may need more aggressive prophylaxis and postoperative infection surveillance. A prospective, randomized, controlled trial is required to determine whether optimizing blood glucose perioperatively would decrease the incidence of PJI in this clinical setting.

Reduced Variability of Insulin Lispro Injected with Hyaluronidase

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Objective:
The goal of this study was to characterize the pharmacokinetic (PK) and glucodynamic (GD) response and associated variability of insulin lispro coinjected with hyaluronidase (PH20), regular human insulin with PH20, and insulin lispro alone.

Method:
A euglycemic clamp experiment (8 hours at 90% of fasting blood glucose, without basal insulin infusion) was conducted in 20 healthy volunteers, each administered two doses (0.15 U/kg) of regular insulin+PH20, lispro+PH20, and lispro alone in a randomized sequence.

Result:
Median root mean square differences for T_{max} early and late t50% after intrasubject repeat administrations of lispro were reduced from 11 to 0 ($p = 0.003$), 4 to 2 ($p = 0.01$), and 11 to 6 ($p = 0.03$) minutes, respectively, with PH20 coadministration. Neither C_{max} nor total exposure showed meaningfully different variability [coefficient of variation (CV) 10–13%]; however, the percentage of exposure that occurred during the clinically relevant early postprandial window showed reduced intrasubject variability [e.g., median CV fell from 18 to 7% for %area under curve $(AUC)_{0\text{-}1\ hr}$, $p = 0.001$, and from 8 to 4% for $\%AUC_{0\text{-}2\ hr}$, $p = 0.004$]. The intrasubject variability of total glucose infused trended lower from 20 to 11% for median CV ($p = 0.44$) and was reduced for percentage of total glucose infused 0–4 hours from 6 to 2% ($p = 0.03$), while the variability of the glucose infusion $rate_{max}$ was comparable. Intersubject variability, although greater overall, showed similar trends to intrasubject variability differences. PK and GD parameters and associated variability of regular insulin+PH20 were comparable to lispro alone.

Conclusion:
The variability of key PK/GD measures was reduced for lispro+PH20 relative to lispro alone. Coadministration of regular insulin with PH20 accelerated insulin PK/GD profiles to become comparable to lispro.

New Optical Method for Blood Glucose Self-Monitoring

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Objective:
For years, many noninvasive blood glucose monitoring technologies have tried to replace conventional finger sticking. So far all approaches have failed due to insufficient accuracy and/or long-time stability. The new concept of overcoming the drawbacks of other noninvasive measuring technologies is based on a glucose-specific biosensor placed under the conjunctiva of the eye, an ideal place for blood glucose monitoring. Replacement is scheduled once per year. Data are presented proving the feasibility of this new blood glucose self-monitoring approach.

Method:
Small hydrogel disks with an embedded biochemical sensor were inserted below the conjunctiva of 12 insulin-dependent diabetes patients in a minimally invasive procedure under local anesthesia. The disks were interrogated by the patients optically with a small, handheld fluorescence photometer over a period of 20 days. Data were compared against capillary blood glucose (laboratory method).

Result:
A total of 2191 combined data points were registered. An excellent correlation between blood glucose and readout of the photometer was found ($r = 0.93$, $p < 0.001$). Clarke error grid analysis resulted in more than 99.6% of data points in combined zones A and B. Seven data points falling in zone D missed zone A by only 2–3 mg/dl. The mean average relative error was 9.9%. A lag time of 5–15 minutes was observed depending on the dynamics of blood glucose changes. The insertion was perceived painless and simple, and implants were well tolerated during the wearing time.

Conclusion:
Clinical results impressively showed the potential of new technology to replace finger sticking for blood glucose measuring. It conveniently allows frequent, noninvasive measurements after the insert is placed below the conjunctiva.

Quantitative Assessment of Response to Therapy Is Facilitated by Automated Analysis of Structured Self-Monitoring of Blood Glucose Data

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Objective:
As therapy options for type 2 diabetes mellitus (T2DM) expand, the need increases for an objective assessment of a therapeutic response to medication to determine efficacy and cost-effectiveness. This study was designed to illustrate the clinical value of using automated interpretation of structured self-monitoring of blood glucose (SMBG) data to facilitate quantitative evaluation of responses to a DPP-4 inhibitor.

Method:
Fourteen cases, including newly prescribed sitagliptin, were queried from a large, multicenter study containing 271 poorly controlled (hemoglobin A1c ≥7.5%) T2DM subjects. Data were evaluated using automated interpretation tools that calculated differences in glycemic measures after therapy change. Subject response was compared to expected outcomes within sitagliptin prescribing information. A positive response was defined as meeting the manufacturer postprandial glucose goal (–49 mg/dl) and meeting either the hemoglobin A1c goal (–0.5%) or the fasting goal (–13 mg/dl).

Result:
A majority (57.1%) of subjects were not positive responders to sitagliptin. The average seven-point profile of the sample showed mean lowering of blood glucose after sitagliptin addition. However, postmedication, glycemic variability, and postprandial hyperglycemia remained prominent with 100% of values above range. Even among positive responders, 83.3% of subjects showed glycemic measures with ≥75 % of values out of range. Most (83.3%) patients with diabetes for >10 years were negative responders. The majority (83.3%) of positive responders were female, and 75% of negative responders were male. Automated graphs allowed visualization of intrasubject and intersubject variability in response.

Conclusion:
Self-monitoring of blood glucose data analysis promotes quantititative assessment of response to medication. Interpretation allows determination of medication efficacy, characterization of potential responders, and establishment of individualized therapeutic paths. Quantitative data could also play a decisive role in comparative cost analysis, with clear visual evidence of therapy impact potentially augmenting patient and payer support.

Performance of the "Sliver Sensor," a Minimally Invasive Optical Sensor for Glucose Monitoring, after Implantation in Mouse Skin

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Introduction:
The sliver sensor is a micropolymer body that contains sensing capsules sandwiched in between two membranes made of the same polymer. The sensor is meant for implantation in the dermis of the skin. The sensing capsules will change color in the skin in response to changes in the concentration of glucose in the interstitial fluid. This color change can then be recorded externally with a camera.

Methods:
Glucose sensing is achieved through a pH-linked scheme. The glucose-sensing capsule comprises pH-sensitive optode chemistry and the enzyme glucose oxidase. The enzyme oxidizes glucose to produce gluconic acid. The optode beads change color in response to the resulting pH change. This color change is monitored externally with a camera. We present the results of studies carried out in a mouse model to determine how long the sensors remain functional *in vivo*. The pH-sensing optode chemistry was tested alone and after incorporation of enzyme. The sensors were implanted in mice and explanted at three time points: 3 days, 1 week, and 2 weeks. The performance pre- and postimplantation was compared.

Results:
Results of the animal experiments indicate that the sensor remains functional in mouse skin for at least 2 weeks. The sensors retained their ability to respond over the pH range 5–8 and glucose range of 50–200 mg/dl.

Conclusions:
Results indicate that optode-based sensors can be used as a viable glucose monitor for *in vivo* applications. Further efforts are ongoing to test sensor functionality *in vivo* for longer durations of up to 3 months.

Homeostasis Model Assessment of Insulin Resistance Electronic Nomogram

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Objective:
Homeostasis model assessment (HOMA) and HOMA2 models are widely used to assess β-cell function and insulin sensitivity. Because HOMA of insulin resistance (HOMA-IR) and -%beta are expressed as simple equations, this simplicity has contributed to worldwide usage of the HOMA model. The HOMA2 model, however, needs specific computation. Although the freeware of the HOMA2 model is supplied by Oxford Diabetes Trials Unit (http://www.dtu.ox.ac.uk/), usage is limited because of its inconvenience. The aim of this study was to provide the software that makes data input and data comprehension for HOMA-IR computation visual and intuitive and to suggest the possibility that HOMA2 computation could be performed by the same methodology.

Method:
Do action commands as follow on the file of MATLAB (MathWorks, Inc., Natick, MA):

```
[FPG, FPI] = meshgrid(0:0.1:13,0:1:40);
HOMA_R= FPG.*FPI/22.5;
contourf(FPG,FPI,HOMA_R,0:23)
h = datacursormode;
```

Result:
A HOMA-IR electronic nomogram (e-nomogram) of plasma glucose as *x* axis, plasma insulin as *y* axis, and HOMA-IR as contours will be expressed. When any point on the nomogram is clicked on, data of the corresponding plasma glucose level, plasma insulin level, and HOMA-IR will be expressed on the nomogram. Because the HOMA-IR may be obtained by only dragging the mouse to the targeted point, inputting the plasma glucose level or plasma insulin level into the computer as text data is not needed.

Conclusion:
The HOMA-IR electronic nomogram provides a comfortable circumstance for visual and intuitive data input and data comprehension for HOMA-IR computing. Because this concept is also able to be adapted to HOMA-%beta and HOMA2 models, the concept of an e-nomogram would contribute to the spread of the HOMA2 model, which is more preferable than the HOMA model.

Evaluation of Internet-Based Technology for Supporting Self-Care of Patients with Diabetes Mellitus

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Objective:
The goal of this study was to assess the value of a Web-based diabetes support program with functionalities such as online education and monitoring, patient–caregiver e-contact, and online appointment scheduling.

Methods:
Via usability tests and in-depth interviews, we assessed the system's user-friendliness, user experiences, and patient characteristics. Log files were used to register system usage and the content of patient–nurse e-mail communication.

Result:
Six nurses and 50 patients (mean age 62) participated in the pilot. Fifty-six percent of the patients could be described as active users and 44% as inactive. Inactive use was caused by usability problems (unclear navigation, logging-on difficulties, and the lack of reminder functionality). Patients' health-related characteristics were also related to inactive use. Patients stating that they had their diabetes under control had little to report and did not feel the need to use the application. Active users valued the application as a useful supplement on regular diabetes care because of its self-care features: education and continuous feedback by e-mail (personal nutrition and health advice, appointment scheduling, and expression of emotions).

Conclusion:
The Web application was able to support patients in the control of their own care. However, not all patients were motivated to use the system. Our findings illustrate the importance of exploring who suits which technology best and what changes are necessary to reach nonusers or dropouts. Innovations in health care diffuse more rapidly when technology is used that is simple to use, useful (taking into account the needs of end users), and effective (aimed at expression of emotions). Further research is necessary to identify factors that can improve the adoption of e-health applications among different patient groups, especially those who are hard to reach.

Suspended Insulin Infusion during Overnight Closed-Loop Glucose Control in Children and Adolescents with Type 1 Diabetes

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Objective:
We evaluated an extended interruption of subcutaneous insulin delivery during overnight closed-loop glucose control in children and adolescents with type 1 diabetes (T1DM).

Method:
In seven young subjects with T1DM [age 14.2 ± 2.1 years, diabetes duration 6.9 ± 4.0 years, hemoglobin A1c 8.0 ± 1.5 %, body mass index 21.4 ± 4.0 kg/m^2, total daily insulin dose 53.3 ± 24.4 U; mean ± standard deviation (SD)] participating in overnight closed-loop glucose control studies, insulin delivery was interrupted for at least 90 minutes by a model predictive control algorithm on the basis of predicted hypoglycemia, low prevailing glucose levels, or a too steep decline in glucose levels. Plasma glucose and continuous glucose monitoring levels were obtained every 15 minutes and plasma insulin was measured every 30 minutes.

Result:
Insulin delivery was interrupted for 154 ± 57 minutes (mean ± SD). Plasma glucose was 6.2 ± 3.2 mmol/liter at the time of interruption and 5.5 ± 2.0 mmol/liter 105 minutes later (p = 0.15, paired t test). Plasma glucose declined during the first hour of the interruption at a rate of 0.02 ± 0.03 mmol/liter/min and reached a plateau of 5.2 ± 2.7 mmol/liter; 105 minutes after the interruption, plasma glucose increased at a rate of 0.01 ± 0.03 mmol/liter/min. When insulin delivery restarted, plasma glucose was 6.4 ± 2.2 mmol/liter and peaked at 7.9 ± 2.1 mmol/liter in 60 minutes (p = 0.01). Physiological levels of plasma insulin were measured throughout.

Conclusion:
An extended interruption of insulin delivery during closed-loop glucose control to prevent hypoglycemia is not associated with an increased risk of rebound hyperglycemia in young people with T1DM.

Microbiologic and Molecular Studies of Chronic Diabetic Foot Ulcers

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Objective:
The objectives of this study were (1) to characterize the differences between deep wound biopsies after debridement and biopsies of the superficial necrotic material; (2) to determine if pyrosequencing studies and detailed conventional microbiology of deep wound biopsies after debridement of superficial necrotic tissue and debris, and study of biofilms associated with infected bone in patients with osteomyelitis, provide information on infected diabetic foot ulcers so that therapy will be more effective; and (3) to determine the relative importance of underlying and predisposing conditions, such as arterial disease, small vessel disease, neuropathy, and biofilm formation in failure of good response to therapy.

Method:
Superficial necrotic tissue and deep tissue biopsies (300 specimens, 150 patients) and bone biopsies in diabetic foot ulcers with osteomyelitis (50 specimens) are being used in the study. Quantitative aerobic and anaerobic culture utilizing selective and nonselective media, 16S rRNA sequencing, and conventional biochemical tests are being used to identify bacteria in the tissue and bone samples. Using deep tissue biopsies (150 specimens, 150 patients) and bone biopsies in patients with osteomyelitis (50 specimens), microbiology will be identified using pyrosequencing techniques, DNA extraction from wound specimens using the QIAamp DNA extraction kit, and bTEFAP pyrosequencing utilizing the Roche 454 pyrosequencing machine with titanium enhancement. Bone biopsies in patients without osteomyelitis (50 patients) will be used to determine the presence of biofilms by scanning electron microscopy and transmission electron microscopy.

Result:
Results are pending until completion of the proposed study.

Conclusion:
Results of our study will provide direct data for developing and validating guidance for Veterans Affairs and civilian physicians. Data will suggest future treatment trials, including new therapeutic modalities, such as agents that will prevent biofilm formation or break down already established biofilms.

Increased Exercise Adherence in African American Women Using Internet-Based Tools

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Objective:
The goal of this study was to utilize Internet-based technology to engage central guiding principles and spiritual beliefs of African American women to improve adherence to increased physical activity.

Method:
During routine medical visits, 24 African American women (average age 55) who had failed to comply with traditional exercise recommendations listened to an excerpt from YouTube of the gospel song "We Worship You, Hallelujah" on an iPhone. The examiner used 3-pound weights to demonstrate simple chair and walking exercises such as tricep curls and leg lifts. An average duration of 10 minutes and a frequency of two times a day were deemed acceptable and agreed upon by all patients. The patients decided to either bring a tape recorder to church or have a grandchild download the song from iTunes or YouTube. Some patients used the exercise as a component of their daily spiritual regimen.

Result:
On a follow-up medical visit, all 24 patients adhered to their stated agreement to play the song at least once a day for an average of 10 minutes. Patients expressed that this regimen made them feel capable of increasing physical activity and taking control of their health.

Conclusion:
Spirituality can synergize with other interventions to improve the health of many patients. Using the power of the Internet to access a song that has a mantra of faith and thankfulness allowed patients to let go of stress and focus awareness on health and wellness. Health professionals can empower patients to initiate increased physical activity during a routine medical office visit. This practical technique was used to engage and motivate African American women to improve their health by channeling their central guiding principle of spiritual beliefs.

Effects of Bariatric Surgery on Adiposity, Sleep, and Selected Biomarkers in Severely Obese Women

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Objective:
Obesity and central adiposity have been linked to metabolic dysfunction and obstructive sleep apnea. It is suggested that bariatric procedures leading to caloric restriction and substantial weight reduction also alter the secretion of gut hormones that mediate the enteroinsular axis and have an important physiological role in postprandial satiety. We investigated long-term effects of bariatric surgery on adiposity, sleep, and selected biomarkers in severely obese women.

Method:
Twenty women [aged 42.2 ± 9.73 years; body mass index (BMI) 50.3 ± 6.63] recruited from the bariatric surgery clinic were enrolled in this longitudinal study. Overnight polysomnography, anthropometric measurements, and blood tests were performed in all subjects before and after bariatric surgery.

Result:
The average interval between baseline and repeat measurements was 1.03 ± 0.48 years, and average weight loss was 42.3 ± 7.08 kg. Surgical weight loss resulted in a significant decrease in BMI, neck, waist, hip circumference, and sagittal abdominal diameter and was associated with a significant increase in rapid eye movement sleep (13.7 ± 6.55% vs 19.8 ± 6.09%; $p = 0.013$) and reduced time in slow-wave sleep (11.4 ± 8.37% vs 4.9 ± 4.23%; $p = 0.007$). Polysomnography showed a significantly decreased number of disordered breathing events that occurred per hour of sleep (29.4 ± 26.8 vs 13.5 ± 18.2; $p = 0.004$) and improved oxygen saturation parameters significantly. Plasma adiponectin and ghrelin concentrations were elevated significantly after weight loss. Leptin, tumor necrosis factor-α receptor 2, leptin-to-leptin receptor, and leptin-to-adiponectin ratios were decreased significantly compared to baseline levels. The leptin-to-adiponectin ratio showed significant correlations with BMI, waist-to-hip ratio, neck circumference, and sagittal abdominal diameter, thereby better classifying subjects with metabolic syndrome than leptin or adiponectin alone.

Conclusion:
Our findings demonstrated that bariatric surgery was associated with significant weight loss, significant improvement in sleep disordered breathing, and altered secretion of some adipokines in morbidly obese women.

Standardized Test for the Evaluation of Continuous Glucose Monitors

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Objective:
Blood glucose levels were manipulated in a predefined manner to evaluate accuracy and precision of a continuous glucose monitor (CGM).

Method:
Twelve diabetes subjects (six subjects diagnosed with type 1 diabetes mellitus) were consented and studied. Each study was divided into several periods: (1) blood glucose levels of 150 mg/dl were achieved and maintained for 30 minutes, (2) blood glucose levels were decreased from 150 to 50 mg/dl at a rate of 1 mg/dl/min, (3) blood glucose levels were maintained at 50 mg/dl for 30 minutes, (4) blood glucose levels were increased from 50 to 150 mg/dl and maintained for 30 minutes, (5) blood glucose levels were decreased from 150 to 50 mg/dl at a rate of 2 mg/dl/min, (6) same as period 3, and (7) blood glucose levels were normalized. Target glucose levels were achieved by infusing insulin and glucose intravenously. Frequent venous blood samples were assayed for glucose using the Accu-Chek Inform. Blood glucose values were analyzed jointly in a linear mixed effects model, which is suitable to accommodate repeated measures per subject.

Result:
The fitted mixed effect model for periods 2 and 5 indicated significant random subject effects in both slopes and intercepts, as well as significant serial correlation among consecutive repeated over time blood glucose values. Average slopes during periods 2 and 5 were –0.91 and –1.17 mg/dl/min, respectively. During periods 3 and 6, intercepts were 48.3 and 50.6 mg/dl, respectively, and average slopes were not significantly different from 0.

Conclusion:
A standardized test should become an integral part of CGM evaluation. Under these conditions, one CGM device can easily be compared to another.

Contact Heat-Evoked Potential Stimulator Detects Neuropathic Changes Earlier Than Traditional Clinical Measures

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Objective:
Diabetic neuropathy (DN) affects small unmyelinated C-fibers and thinly myelinated Aδ fibers. This study evaluated early small fiber DN using the noninvasive contact heat-evoked potential stimulator (CHEPS) technique, which delivers rapid heat pulses to selectively stimulate Aδ and C-fibers while recording cerebral-evoked potentials.

Methods:
We compared the nerve function of 19 controls and 14 subjects with type 2 diabetes mellitus (T2DM) using sensory examinations and CHEPS. CHEPS testing was performed at 41 and 51°C to the thenar eminence, volar and dorsal aspect of forearm, proximal lower limb, and lower back. Evoked potentials were recorded from the vertex using the 10-20 system with a chin reference. The latency, amplitude, and conduction velocity were determined from an electroencephalogram using Fp1, Fp2, Fz, Cz, and Pz electrodes.

Results:
There was a significant decrease in positive amplitude from the 51°C CHEPS stimulation of the lower back in the group with T2DM (16.55 ± 2.85) compared to controls (24.21 ± 2.17) ($p = 0.04$). There was also a significant difference in total neuropathy scores ($p = 0.027$), with responders having lower scores than nonresponders. Absent CHEPS responses in low scorers could indicate early nerve dysfunction not detected by traditional measures.

Conclusions:
These results suggest that CHEPS is a novel, noninvasive technique used to detect early impairments in nerve function. CHEPS was able to identify abnormalities in controls, people with T2DM but no DN, and those with severe nerve dysfunction. Small fiber nerve dysfunction is thought to be responsible for early symptoms of DN and has been present in prediabetes. Employing CHEPS as a tool for early detection of Aδ and C-fiber dysfunction is central to understanding DN and will lead to better therapies and early prevention.

Safety Supervision Module in Open- and Closed-Loop Control of Diabetes

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Objective:
The quest for optimal glucose control in diabetes may result in hypoglycemia if insulin requirements are occasionally miscalculated. We designed a safety supervision module (SSM) that operates independently from the mode of insulin administration and serves to prevent hypoglycemia by (1) monitoring patient state continuously and (2) reducing or discontinuing insulin delivery when necessary.

Method:
The SSM is based on a combination of constraints using our established risk analysis of blood glucose data and knowledge of active insulin, e.g., using insulin-on-board constraints and "power brakes," making the best possible use of glucose and insulin data. Two software routines are responsible for signal management and continuous-time state estimation. The signal management routine retrieves continuous glucose monitor (CGM) and insulin pump data and performs data cleaning and calibration. The estimation routine, based on Kalman filtering, maintains best estimates of patient states.

Results:
The SSM tracks CGM and insulin pump data and assesses the risk of hypoglycemia in continuous time, meaning that state variables within the SSM are updated as new readings arrive. If the risk of hypoglycemia is high, the SSM intervenes by gradually reducing or discontinuing insulin delivery. When implemented within a closed-loop control architecture, the SSM also informs all relevant modules (e.g., the control algorithm) about the amounts of insulin that are actually administered. Simulation experiments with doubling insulin delivery rate show that power brakes alone prevent over 95% of otherwise imminent hypoglycemic episodes.

Conclusion:
Safety supervision is a natural component of external glucose control. In closed-loop applications, the SSM prevents hypoglycemia by modifying closed-loop control actions independently. More generally, the SSM can act as a supervisor in any sensor-pump system.

Development of a Minimal Model of Carbohydrate and Subcutaneous Insulin Effects on Glycemia

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Objective:
A control algorithm for insulin delivery for people with type 1 diabetes mellitus (T1DM) would require information on the magnitude and duration of effects of orally ingested carbohydrate (CHO) and subcutaneously delivered insulin on blood glucose concentrations. The goal of this study was to quantify these effects in people with T1DM using a simple protocol.

Method:
We designed a protocol to develop meal and insulin models from data. The protocol was first tested in-clinic and then was repeated over 5 days in ambulatory conditions. The in-clinic protocol duration was 8 hours: a 25-gram CHO meal was consumed and a subcutaneous (SC) insulin bolus was delivered 3 hours later based on the insulin-to-carbohydrate ratio. The DexCom™ SEVEN® (San Diego, CA) continuous glucose monitor was used to obtain SC glucose measurements every 5 minutes, and a Yellow Springs Instrument (Yellow Springs, OH) was used to obtain intravenous glucose measurements every 15 minutes. The ambulatory protocol included larger meals with boluses. Data were obtained for the outpatient protocol using continuous subcutaneous insulin infusion pump records, subject-estimated CHO, and SC glucose measurements.

Result:
The in-clinic protocol was tested on eight subjects at Sansum Diabetes Research Institute. Six parameters were identified for the proposed model. The main trends of subject data were characterized using a model with these six parameters. The maximum intersubject variation in parameters was 413%. The coefficient of determination, R^2, for the best personalized model ranged from 93 to 99%.

Conclusion:
Separation of meals and boluses in time was critical to determining model parameters accurately. The wide intersubject variation in parameters supports the notion that insulin delivery algorithms should be personalized.

Intradermal Injection of Regular or Lispro Insulin with Microneedles Provides Faster Insulin Uptake and Postprandial Glycemic Benefit

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Objective:
This study compared the pharmacokinetic (PK) and prandial pharmacodynamic (PD) effects of both insulin lispro (IL) and regular human insulin (RHI) administered using microneedle-based intradermal (ID) or traditional subcutaneous (SC) delivery at two times before a standardized high-carbohydrate (CHO) liquid meal (82 grams CHO).

Method:
After blood glucose stabilization at 120 mg/dl, 29 males with type 1 diabetes (mean body mass index 25.7 kg/m^2, hemoglobin A1c 7.4%) received 0.125 IU/kg of insulin 2 or 17 minutes premeal in a five-period randomized crossover study.

Result:
For PK effects, IL and RHI both showed markedly faster uptake and increased C_{max} when administered ID compared to SC. Although total bioavailability over 4 hours was similar between routes, ID delivery increased early phase absorption by 40–50% during the first 90 minutes postdosing. Likewise, T_{max} was reduced by one-half or greater for each insulin type. For PD effects, postprandial glycemic (PPG) excursion [measured by primary PD end point: blood glucose area under curve (BG-AUC) 0–90 minutes] for ID RHI was reduced vs SC injection at –17 minutes ($p < 0.001$). Time was also a significant factor as ID RHI gave lower PPG 17 minutes premeal vs 2 minutes. At –2 minutes, PPG for ID IL trended lower but the mean difference was not significant (NS) vs SC IL ($P = 0.08$). For immediate premeal application, the 4-hour PPG excursion for ID RHI was NS from SC IL as measured by BG-AUC, although the BG_{max} was slightly higher and later. SC RHI at –17 minutes had the highest BG response; however, ID RHI at –17 minutes had one of the better PD outcomes.

Conclusion:
This study demonstrated that ID insulin application with a 1.5-mm microneedle length may be an attractive means to improve prandial insulin delivery for multiple insulin types.

Influence of VIAject™ Absorption Kinetics on Postreceptor Signal Transduction and Vascular Function of Insulin in Patients with Type 2 Diabetes

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Background:
This pilot study was performed to investigate the impact of prandial insulin formulations with different pharmacokinetic properties on insulin signal transduction pathways indicative for endothelial function [e.g., production of endothelial nitric oxide synthase (eNOS) by circulating monocytes] in patients with type 2 diabetes mellitus (T2DM).

Methods:
Fourteen patients with T2DM (seven male, seven female; age 61.5 ± 1.8 years; disease 6.6 ± 4.6 years; hemoglobin A1c 7.2 ± 0.5%; mean ± SEM) received a single prandial injection of VIAject™ (VJ), regular human insulin (RHI), and insulin lispro in a randomized, crossover study. The mRNA of peripheral circulating monocytes was isolated and subjected to quantitative determination of eNOS and mitogen-activated protein kinase (MAPK)-1 expression in comparison to β-actin as the housekeeping gene by means of LightCycler real-time polymerase chain reaction technology at 0, 30, 60, 90, 120, and 180 minutes. Other observation parameters observed at the same time points were blood glucose and markers of oxidative stress [nitrotyrosine, asymmetric dimethylarginine (ADMA)].

Results:
There was no difference in postprandial glycemic control among the three treatment arms. Treatment with RHI was associated with an increase in nitrotyrosine (30 minutes: +0.25 ± 0.58 mmol/liter) and ADMA secretion (30 minutes: +0.10 ± 0.09 mg/liter), increased expression of MAPK-1 (60 minutes: +40 ± 80%), and a decrease in eNOS expression (60 minutes: –40 ± 110%). In contrast, VJ resulted in opposite results (30 minutes: nitrotyrosine: –0.26 ± 0.64 mg/dl, $p < 0.05$ vs RHI; ADMA: –0.03 ± 0.08 mg/dl, $p < 0.05$; 60 minutes: MAPK-1: –20 ± 40%, $p = 0.11$, eNOS: +40 ± 80%, $p < 0.05$). Results with LP were between these extremes but still significantly different as compared to VJ in some of the observation parameters.

Pfützner cont. ⟶

Pfützner cont. ⟶

Conclusions:
In this pilot experiment, treatment with the ultrafast regular human insulin formulation VIAject resulted in reduced oxidative stress and molecular indications of an improved endothelial function. These results suggest that the pharmacokinetic profile of insulin may have a major impact on the vascular effects of insulin in patients with T2DM, which is independent from glycemic control.

Limitations of the Homeostasis Model Assessment-B Score for Assessment of β-Cell Functionality in Interventional Trials: Results from the Pioglitazone Glimepiride Study

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Background:
The homeostasis model assessment (HOMA)-B score is a commonly used parameter to assess β-cell functionality in clinical studies in patients with type 2 diabetes. However, drugs with unspecific stimulating effects on β-cell secretion, which drive the pathophysiology into an irreversible exhaustion of correct insulin processing, may increase the HOMA-B score, thus wrongly indicating improved β-cell function. The purpose of this analysis was to investigate whether the β-cell protection provided by adding pioglitazone (PIO) to a sulfonylurea drug (glimepiride, GLIM) in comparison to uptitrating the GLIM dose alone is reflected by appropriate changes in a variety of measures of β-cell function, including the HOMA-B score.

Materials and Methods:
This double-blind, parallel prospective study was performed with 82 patients [47 males, 35 females, age: 61 ± 9 years, disease duration: 5.3 ± 4.4 years, body mass index: 32.6 ± 6.0 kg/m^2, hemoglobin A1c (HbA1c) : 7.3 ± 0.7%]. After having been already treated with 1–3 mg of glimepiride monotherapy for at least 3 months, they were randomized to either receive a GLIM+PIO combination (uptitration possibilities: 2 mg + 30 mg, 4 mg + 30 mg, and 4 mg + 45 mg) or remain on GLIM with uptitration (4 to 6 mg) for the next 6 months. Observation parameters determined at baseline and end point were HOMA-B, homeostasis model assessment of insulin resistance (HOMA-IR), HbA1c, glucose, insulin, and intact proinsulin as indicators for insulin resistance and β-cell function.

Pfützner cont. ⟶

Pfützner cont. ⟶

Results:
There was an increase in the HOMA-B score in the GLIM group, which was not seen in the GLIM+PIO arm (baseline/end point: GLIM: 71 ± 48/88 ± 64, PIO+GLIM: 74 ± 56/69 ± 52). In contrast, a clinically relevant improvement in HbA1c, HOMA-IR, and intact proinsulin could only be detected in the PIO treatment group [PIO+GLIM: HbA1c: 7.20 ± 0.61/6.36 ± 0.90%, HOMA-IR: 7.0 ± 4.5/4.1 ± 2.1, intact proinsulin: 12.4 ± 10.3/7.6 ± 4.8 pmol/liter, all $p < 0.05$; GLIM: HbA1c: 7.45 ± 0.69/7.15 ± 0.97%, $p < 0.05$; HOMA-IR: 7.4 ± 4.5/7.5 ± 4.3, not significant (ns); intact proinsulin: 17.3 ± 21.6/16.3 ± 15.5 pmol/liter, ns]. A significant reduction of the number of patients with clinically relevant insulin resistance and late-stage β-cell dysfunction (from 96 to 75%, $p < 0.05$) could also only be observed in the GLIM+PIO arm (GLIM uptitration: 100% at all time points).

Conclusions:
The addition of pioglitazone to glimepiride led to an overall improvement of laboratory biomarkers for insulin resistance, β-cell function, and glycemic control, whereas uptitration of glimepiride had no such effects. However, only glimepiride uptitration did lead to an increase in the HOMA-B score. HOMA-B seems to provide misleading results when used as a diagnostic tool for the assessment of β-cell function in patients treated with sulfonylurea drugs.

Is Insulin Atherogenic or Cardioprotective? Method for the Assessment of Insulin Postreceptor Signal Transduction in Peripheral Monocytes

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Background:
At the cellular level, insulin action is driven by two major signal transduction pathways. In healthy subjects and at low doses, the phosphoinositide-3 kinase (PI3K)-dependent pathways are activated, whereas at high doses (e.g., in insulin-resistant patients), a mitogen-activated protein kinase (MAPK)-dependent pathway may be induced in the endothelium. While PI3K regulates glucose metabolism in lipid and muscle cells and induces nitric oxide (NO) production in the endothelium, activation of MAPK represents the endothelial growth factor action of insulin, leading to cell proliferation and expression of vasoconstrictive endothelin-1, a key protein in the development of atherosclerosis. Because circulating peripheral monocyte/macrophages are in consistent and close cross-talk with the endothelial cells, we hypothesized that they may show a similar pattern of signal transduction after insulin binding to the endothelial cells and that determination of their mRNA expression profile may be a means to identify insulin action in the circulation independent from the glucose-lowering effects.

Methods:
Peripheral monocytes/macrophages were isolated from whole blood using CPT™ tubes (Becton Dickinson, Heidelberg, Germany), further purified by magnetic bead CD14 depletion (Miltenyi Biotec), and the mRNA was transcribed reversely into cDNA by standard methods. Quantification was performed relative to a housekeeping gene (β-actin) by amplification of gene-specific primers for MAPK-1, MAPK-3, and endothelial NO synthetase (eNOS). The final detection reaction was performed using hybridization probes [Universal Probe Library hydrolysis probes #24 (eNOS), #62 (MAPK1), and #16 (MAPK3)] using a real-time polymerase chain reaction (LightCycler 2®, Roche Diagnostics, Mannheim, Germany). Clinical validation of the method was performed with samples derived from two controlled clinical studies that investigated the impact of therapeutic interventions on chronic systemic inflammation and endothelial function, respectively, in patients with type 2 diabetes.

Pfützner cont. ⟶

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Results:
Clinical improvements in endothelial function by short-acting prandial insulins in one of the studies were associated with the expected changes in the relative eNOS and MAPK expression profiles. A faster onset of prandial insulin action reduced MAPK activation and increased eNOS expression independent of glucose control. A decrease in endothelin-1 levels and a reduction in chronic systemic inflammation induced by the peroxisome proliferator-activated receptor γ agonist pioglitazone, which was associated with improved endothelial function, also resulted in the same corresponding mRNA expression changes, whereas the comparator treatments in both trials (regular insulin and placebo, respectively) led to opposite results.

Conclusions:
This method determines insulin response on peripheral circulating monocytes/macrophages, which corresponded to changes in endothelial function in two independent interventional studies. Further experiments are on their way to demonstrate whether our method is suitable to differentiate glucose-independent vasoprotective versus atherogenic effects of insulin in the human vasculature.

E-Cardiology and Academic Education: Experiment of a Remote, Interactive Multimedia Course

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Objective:
The revolution of information and communication technologies (ICT) has also affected the world of health. E-cardiology uses ICT to enhance knowledge and performance on cardiology. Growing health education needs, with the new technologies available, represent an important challenge. We evaluated the "didactic impact" of an interactive multimedia e-learning method in terms of general acceptance, effectiveness, and quality compared with traditional learning methods.

Method:
The interactive multimedia course *Basic echocardiography: Mitral and aortic valvular diseases* was organized for fellows in cardiology attending the 1st Postgraduate School of Cardiology at University of Rome Sapienza. All participants had limited or no experience with online learning courses. The course provided for three teachers, 300 slides, five lecture notes, and hypertext links for a mean overall course duration of 3 hours. All participants underwent 50 pretest multiple-choice questions, 50 post-test multiple-choice questions, and 10 satisfaction questions (scale 1 to 5).

Result:
This interactive multimedia e-learning course showed high quality in terms of lessons and professors, easy accessibility and usage (anytime, anywhere), real-time remote monitoring of the learning process, and a general positive acceptance.

Conclusion:
The experiment held with this interactive multimedia e-learning course showed that it is an effective educational method to support traditional learning methods. All participants demonstrated increased knowledge, with a high percentage of positive acceptance toward this new learning method.

Studies on the Mechanism of Rapid Absorption of VIAject™

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Objective:
VIAject™ is a formulation of ultrafast absorbing recombinant human insulin (UFI). The aim of this study was to elucidate the mechanism of absorption.

Method:
In vitro experiments were designed to study the effect of dilution on the rapidity of hexameric dissociation of insulin formulations: insulin lispro (IL), insulin aspart (IA), regular human insulin (RHI), and UFI. Undiluted insulins were diluted up to 1:20 with extracellular fluid buffer, pH 7. Light scattering and analytical ultracentrifugation were used to assess the mean size distribution and weight average sedimentation coefficient [S(20,w)] of the insulin molecules. Standard hexameric and monomeric insulins were used as references.

Result:
Undiluted insulins show that UFI has a mean size distribution of 5.9 nm, slightly larger than IL (5.25 nm), IA (4.88 nm), and RHI (3.5 nm). However, upon 1:3 dilution, the mean size of UFI was reduced by 2 nm and was further reduced with dilution. Undiluted RHI initially appears smaller but grows in size to greater than 5 nm once diluted 1:1. RHI molecular weight based on the S(w,20) is consistent with a hexamer (35.6 ± 1.6 kDa) over the entire dilution range. Calculations of S(w,20) showed the same trend as the light scattering size distributions.

Conclusion:
Undiluted UFI appears larger than the other insulins studied, possibly due to excipients weakly attracted to the surface, which may serve to increase the rate of absorption from subcutaneous sites by masking the surface charge and further destabilizing the molecule. These data suggest that shortly after subcutaneous administration, UFI has a smaller mean size than rapid-acting insulin analogs and RHI. A higher proportion of monomeric/dimeric particles with UFI is consistent with its more rapid absorption profile.

Harmonic Decomposition of Continuous Glucose Monitoring for the Study of Type 2 Prediabetes

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Objective:
Time series analysis applied to continuous glucose monitoring (CGM) can help us better understand pattern changes in glucose profiles in the transition from normal glucose metabolism to diabetes. The goal of this study was to study CGM records from healthy controls (HC), subjects with impaired fasting glucose (IFG), and recently diagnosed type 2 diabetes patients (DM) using multiple cosinor decomposition parameters.

Method:
Ten HC, 20 IFG, and 10 DM were studied by means of 3-day CGMS®. Preprandial capillary blood glucose of the three allowed meals was used for calibration. Anthropometric parameters, hemoglobin A1c, and homeostatic model assessment, as well as general laboratory determinations, were also studied. Multiple components analysis consisted of fitting to data, by least squares, a function with several fixed anticipated periods. A fundamental period of 24 hours and its five first harmonics (24, 12, 8, 6, and 4.8 hours) was analyzed.

Result:
Mesor, amplitude (overall, 12, 6 hours), and 24-hour acrophase (timing of crest) were different among groups. In the multiple regression analysis, fasting plasma glucose was predicted only by the mesor (R = 0.843; p = 0.000), whereas hemoglobin A1c was predicted by fasting glucose and 6-hour amplitude (R = 0.519; p = 0.001). However, for the subgroup of subjects in which 24-hour acrophase occurred during sleeping hours (N = 13), no correlation between hemoglobin A1c and fasting glucose was observed.

Conclusion:
Continuous glucose monitoring time series analysis based on harmonic decomposition can be of interest in the characterization of prediabetes phases. These preliminary results suggest that a circadian pattern with acrophase at night identifies subjects in which hemoglobin A1c is not predicted by fasting glucose.

Glucocorticoids, Insulin Sensitivity, and Tight Glycemic Control in the Intensive Care Unit

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Objective:
Glucocorticoids reduce insulin sensitivity in healthy individuals by 30–62%. They are used in critical care to treat a variety of inflammatory and allergic disorders, but may inadvertently exacerbate stress hyperglycemia through reduced insulin sensitivity. This research used model-based methods to determine whether this reduction is also true in critically ill patients and how it affects tight glycemic control (TGC).

Method:
A retrospective study used data from patients admitted to the Christchurch Hospital intensive care unit (ICU) between 2005 and 2007 in two matched 40-patient cohorts. Patients in one cohort received glucocorticoid treatment whereas patients in the control cohort received none. All patients were on the Specialized Relative Insulin and Nutrition Table (SPRINT) TGC protocol. A clinically validated glucose–insulin system model was used to identify an insulin sensitivity value every hour. This model-based insulin sensitivity was used to quantify differences between the cohorts. *In silico* virtual patient simulations were performed to determine the clinical impact of these differences on TGC.

Result:
The per-patient median steroid dose was equivalent to 160 mg/day of hydrocortisone. A 7% reduction in median insulin sensitivity was seen between the control cohort and patients receiving glucocorticoids. On a per-patient basis, 8–21% reductions in median insulin sensitivity were observed with higher percentile, with more insulin-sensitive patients having greater suppression. Virtual trial simulations indicate that there is no clinically significant difference in glycemic control achieved under the SPRINT protocol with changes in insulin sensitivity of 10–20%.

Conclusion:
Glucocorticoids cause a much lower reduction in insulin sensitivity for critically ill patients compared to healthy individuals. They therefore have far less impact than suspected on glycemic control in the ICU setting.

Ossulin,™ a Novel Oral Insulin Product: Bioavailability Studies in Rabbits

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Objective:
The goal of this study was to determine insulin absorption after oral administration to healthy rabbits of Ossulin,™ a product containing human insulin and Natsom,™ a delivery agent derived from a natural product with a long history of safe use in humans.

Method:
Ossulin was prepared using human recombinant insulin and Natsom, a drug delivery platform proven with different drug molecules (US Patent No. 6558712B1). Rabbits received Ossulin by gavage at various doses (range 2.5 to 10 IU/kg), whereas control animals received Natsom or insulin solution. As a reference, commercially available insulin was administered subcutaneously (SC) (1 IU/kg). Blood samples were collected up to 6 hours after administration for glucose and insulin determination.

Result:
Ossulin administration gave a dose-related response, with a rapid appearance of insulin in the blood (T_{max}: 30 minutes with Ossulin vs 60 minutes with SC administration) and a consequent and prolonged decrease in glucose levels (maximal effect: 30–90 minutes). With the highest oral dose as well as with SC administration, the effect on blood glucose was still evident 4 hours after administration. Analyzing insulin area under curves, we estimated a bioavailability of about 20% relative to SC administration. Similar results were obtained using three different batches of Ossulin. Natsom and insulin administered orally as discrete entities showed no effect on glucose or insulin levels in blood.

Conclusion:
Oral administration of Ossulin induced a consistent decrease in blood glucose in rabbits, consequent of the appearance of insulin in the blood. These data confirm previous results indicating that Ossulin reduces blood glucose in mice and rats.

Diabetes Mobile Technology: Strategies in Conducting Randomized Clinical Trials in Community Settings

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Objective:
The goal of this study was to discuss methodological issues in conducting randomized clinical trials (RCT) to evaluate mobile diabetes management interventions in community provider practice settings.

Methods:
Forty physicians and 215 of their diabetes patients were enrolled in a RCT to study the impact of a diabetes communication system using mobile phones and physician/patient Web portals. Patients with poor diabetes control at baseline (hemoglobin A1c ≥7.5%) were enrolled in one of four study groups based on physician practice randomized assignment. All study patients received blood glucose meters and a year's supply of testing materials. Patients in three treatment groups selected one of two mobile phone models, received a 1-year unlimited mobile phone data and service plan, registered on the Web patient portal, and received study treatment phone software. Control group patients received usual care from their primary care physician. The primary research outcome is mean change in hemoglobin A1c over a 12-month period. Study patient enrollment is complete.

Results:
Developing and implementing a large RCT in community settings provided "real world" issues in the management of diabetes that impact the conduct of clinical trials. Achieving adequate eligible patient populations for each study group required substantial effort in physician recruitment, institutional review board protocol adjustments, and screening more than 2000 patients to determine eligibility. At baseline, patient characteristics include 9.41 mean hemoglobin A1c, 40% African American, diabetes duration of 8 years, and only 5% of study patients, normal weight. Additional baseline characteristics of interest to behavioral treatment studies include 31% have high school or less education and nearly 20% have moderate or severe depression.

Conclusion:
Methodological approaches identified in this study provide strategies for researchers to evaluate the impact of mobile technology on diabetes outcomes in community settings.

Can the Stat-Strip Glucometer Replace the Beckman Glucose Analyzer as the Instrument of Choice for Clamp Studies?

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Objective:
The Andres hyperinsulinemic–euglycemic clamp is considered state of the art for glucose homeostasis. Accurate and timely determination of plasma glucose levels is essential to running a successful clamp. Therefore, we evaluated the suitability of the Nova StatStrip™ glucose meter in clamp studies. Most investigators use glucose oxidase methodology [Beckman (B) or Yellow Springs Instrument (Y) glucose analyzer], which requires a dedicated operator and preparation of a plasma sample from each whole blood specimen. This plasma preparation and a duplicate measurement requirement add ≥2 minutes to obtain an accurate and reliable glucose result. Both Y and B require instrument maintenance.

Methods:
We evaluated the accuracy, reliability, and near-real time availability of glucose from 1.2-µl venous whole blood specimens in 10 patients who underwent 5.5-hour clamp studies (euglycemic and hyperglycemic). Blood specimens were obtained every 5 minutes and were analyzed simultaneously and immediately upon collection by both instruments.

Results:
The 491 Nova data points ranged in value from 32 to 412, whereas B values ranged from 42 to 444. A regression of B versus Nova values demonstrated a coefficient of 1.02 (r^2 = 0.98). Using error grid analysis, the number and percentage of values for Nova compared to B were 467 (95.1%) in the A zone and 24 (4.9%) in the B zone; none were in the C, D, or E zones. Time required for final reading was 6 seconds for Nova and 120–180 seconds for B. The reproducibility of Nova (N = 93) was 3.1 ± 0.4 mg/dl compared to 1.6 ± 0.2 mg/dl.

Conclusions:
The simplicity of the Nova instrument, together with its reliability, accuracy, and speed, makes it an ideal replacement for B in the conduct of clamp studies.

Glycemic Variability and Oxidized Low Density Lipoprotein in Type 1 Diabetes

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Objective:
Oxidative stress has a role in the development of long-term complications of diabetes. In type 2 diabetes, glycemic variability has been correlated with urinary isoprostane, a marker of oxidative stress. This relationship has not been demonstrated in type 1 diabetes subjects. This study investigated the relationship between glycemic variability and oxidized low density lipoprotein, a marker of oxidative stress, in subjects with type 1 diabetes.

Methods:
Seventeen participants with type 1 diabetes (mean age 44 ± 14.2 years, mean duration of diabetes 20.9 ± 15.3 years, mean hemoglobin A1c 7.28 ± 0.82%) were fitted with a continuous glucose monitor for 72 hours. A blood sample was taken for determination of oxidized low density lipoprotein (oxLDL) using oxLDL ELISA and a diabetes metabolic profile. "J" index, "M" value, mean of daily differences (MODD), mean amplitude of glycemic excursions (MAGE), and postprandial continuous overlapping net glycemic action calculated with 2-hour time intervals (CONGA-2) were calculated as measures of glycemic variability, and correlation with oxLDL was calculated.

Results:
There was a positive association between mean interstitial fluid glucose and three measures of glycemic variability: J index ($p < 0.001$), M value ($p < 0.001$), and MAGE ($p < 0.043$). Triglycerides ($p < 0.007$) and LDL cholesterol ($p < 0.027$) were the strongest predictors of circulating oxLDL levels (mean level 40.70 ± 18.86 U/liter), followed by total cholesterol ($p < 0.037$). Oxidized low density lipoprotein was not significantly associated with any marker of glycemic variability: J index ($p = 0.784$), M value ($p = 0.755$), MODD ($p = 0.262$), MAGE ($p = 0.283$), and CONGA-2 ($p = 0.217$).

Conclusions:
In agreement with previous studies of oxidative stress in type 1 diabetes, no association was found between glycemic variability and levels of circulating oxLDL in subjects in this study.

Hypolipidemic Effect of *Psidium guajava* Raw Fruit Peel in Diabetic Rats

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Objective:
This study evaluated the hypolipidemic potential of unripe *Psidium guajava* fruit peel aqueous extract in streptozotocin (STZ)-induced severely diabetic rats by assessing their triglyceride (TG), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL) levels.

Method:
Severely diabetic albino Wister rats of the same age group were treated orally once a day up to 3 weeks with a dose of 400 mg/kg body weight of lyophilized extract. TG, TC, and HDL levels were estimated using standard kits of Bayer Diagnostics, India. LDL and VLDL cholesterol levels were calculated from the aforementioned measurements using Friedwald's formula.

Results:
A significant decrease in TG ($P < 0.01$), TC ($P < 0.01$), HDL ($P < 0.01$), VLDL ($P < 0.001$), and LDL ($P < 0.01$) levels was observed after 21 days of treatment.

Conclusion:
The extract showed significant hypolipidemic activity in addition to its hypoglycemic and antidiabetic activity reported earlier by our research group. In view of its hypolipidemic, hypoglycemic, and antidiabetic activity, *P. guajava* raw fruit peel may be developed as an antidiabetic agent.

Three Percent Slab Gel Electrophoresis Method for Low-Density Lipoprotein Subfractionation

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Objective:
Metabolic syndrome characterized by truncal obesity, insulin resistance, noninsulin-dependent diabetes, glucose intolerance, hypertension, and atherogenic dyslipidemia is considered to be widely prevalent in Indians. One of the important components of atherogenic dyslipidemia is small dense low-density lipoprotein (LDL). Several methods are available for subfractionation of LDL. Methods include density gradient ultracentrifugation, nondenaturing gradient gel electrophoresis (NDGGE), and nuclear magnetic resonance (NMR) spectroscopy. These methods are labor-intensive, time-consuming, expensive, not suitable for high-throughput screening, and therefore not suitable in clinical practice. A simple method for screening the LDL subfraction is required. We developed a simple native polyacrylamide 3% slab gel electrophoresis method for LDL subfractionation.

Method:
Thirty samples were analyzed by the GGE method and 3% slab gel method. Correlations between mean particle diameters obtained by the two methods were computed. Using the 3% slab gel method the mean particle diameter was determined in 50 subjects with metabolic syndrome and 200 controls.

Result:
A good correlation of 0.950 was observed when the particle diameter obtained by our method was compared with the GGE method. Using the new method, small dense LDL was analyzed in 50 subjects with metabolic syndrome and 200 normal subjects. The mean LDL particle diameter was 26.2 ± 0.68 in subjects with metabolic syndrome, which was significantly lower than the mean particle diameter in normal subjects (26.8 ± 0.59 nm).

Conclusion:
In conclusion, the 3% slab gel electrophoresis method described compares well with the other GGE method, which is the gold standard; because 24 samples can be analyzed by the dual slab gel it is suitable for screening a large number of samples.

Effect of Peanut Processing Method on Glycemic Response and Food Intake

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Objective:
The goal of this study was to investigate the effect of a peanut processing method on glycemic response and food intake.

Method:
This is a clinical trial (n = 13) in which one of four types of test meals was consumed after 10–12 hours of overnight fasting: raw peanuts with skin (RPWS), roasted peanuts without skin, ground roasted peanuts without skin (GRPWS), or a cheese sandwich (control meal). Test meals were consumed with 200 ml of water. These meals had the same nutritional composition. The glycemic response was evaluated for 2 hours after test meal consumption. The energy intake at baseline and during 24 hours after consumption of each type of meal was assessed by food records. Kruskal–Wallis and Mann–Whitney tests were applied to compare the results using SigmaStat software (version 2.03). The criterion for statistical significance was $p < 0.05$.

Result:
The area under the glycemic response curve after the consumption of RPWS was greater ($p < 0.05$) than the one obtained for GRPWS. Food intake was not affected by test meal type.

Conclusion:
These results suggest that among meals tested in this study, the consumption of ground roasted peanuts without skin may be more beneficial to control and prevent diabetes and cardiovascular diseases due to its lower postprandial glycemic response.

Calculation of the Best Basal–Bolus Combination for Postprandial Glucose Control in Insulin Pump Therapy: An *in Silico* Validation

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Objective:
The aim of this work was to validate *in silico* an innovative methodology for calculating the most appropriate combination of basal and bolus insulin for a good postprandial glucose control.

Method:
Ten adult patients in the educational version of the University of Virginia diabetes simulator were used as the test population. In order to emulate discrepancies between the patient model and the real patient behavior, the Hovorka model, structurally different from the virtual patient model, was used and identified from 4-day data, following an optimal experiment design procedure. Then, the Set Inversion Via Interval Analysis algorithm was applied to obtain the set of feasible bolus dose, basal deviation from baseline at mealtime, and time of restoration of basal to baseline so as to fulfill International Diabetes Federation guidelines of postprandial control (no hypoglycemia and 2-hour postprandial glucose below 140 mg/dl). This allows determining the best bolus administration mode: standard, square wave, dual wave, or "superbolus" (temporal basal decrement and bolus increment) for a given meal.

Result:
Feasible sets were computed for the test population, for basal baseline leading to a basal glucose near 100 mg/dl and meals in the range of 20–140 grams of carbohydrates. Standard therapy has been compared with three different selections from the computed feasible set (central, best "superbolus," best dual wave). Significant improvement was obtained for most of the patients for meals starting from 60 grams. Generally, for intermediate-size meals, either a dual-wave bolus or a "superbolus" is suitable. However, for higher meals, only a "superbolus" can yield good postprandial control.

Conclusion:
This methodology can improve postprandial control significantly, especially for big-sized meals, showing robustness with respect to the patient model.

Improved Optical Sampling Method for Noninvasive Glucose Measurements

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Objective:
The ability to make accurate noninvasive optical measurements is predicated on the ability to procure stable and repeatable tissue spectra. Contact-based forearm sampling systems have been subject to tissue compression during the measurement and site-to-site variation because of an inability to sample the same area of tissue. These variances create undesirable spectral noise. Our objective was to develop an improved optical sampling method that addressed these known sources of spectral noise.

Methods:
A noncontact optical sampling system based on diffuse reflectance measurements from the back of the finger was developed. The near-infrared system uses cross-polarization to eliminate photons associated with epidermal reflection. The system preferentially collects photons that have undergone multiple scattering events, resulting in a randomized polarization state. The use of an optical smoothing agent on the finger further improves the signal-to-noise ratio of the resulting spectra. Elimination of site-to-site variation is achieved using the many intrinsic markings on the finger, such as the nail bed. These marks are used to ensure proper alignment prior to sampling.

Results:
The resulting optical system produces noninvasive tissue spectra that are highly repeatable and remarkably stable over the measurement period. The noninvasive measurement capabilities of the system were evaluated in a study involving 35 subjects with diabetes, resulting in 982 measurements. Spectra produced noninvasive glucose measurements with greater than 85% of results in region A on a Clarke error grid, a mean absolute relative difference of 11%, and a standard error of prediction of 18 mg/dl.

Conclusion:
The noncontact finger sampling system addresses a number of known tissue sampling problems and enables accurate noninvasive measurement of glucose.

Use of Activity and Stress Inputs for Improving Blood Glucose Control in Type 1 Diabetes Subjects

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Objective:
The objective of this work was to illustrate the potential impact of activity and stress monitoring in improving blood glucose control for subjects with type 1 diabetes (T1DM).

Method:
Although blood glucose levels are affected by several factors, such as food, activity, and stress, current modeling relies mainly on food and insulin for predicting glucose levels. So to study the advantages of including physical activity and stress in glucose modeling, a pilot study was conducted where glucose, activity-related data, insulin infusion, and food consumption were recorded by a T1DM subject for 3 days under free-living conditions. Glucose was measured continuously using a Medtronic CGMS Gold™ monitor. Activity information was recorded using BodyMedia's SenseWear® Pro3 armband, which measures movement, heat flow, skin temperature, and galvanic skin response and estimates energy expenditure. A block-oriented Wiener model with all inputs (from food, armband, and insulin) showed excellent performance, whereas a partial model (with inputs only from food and insulin) showed much poorer performance. Being causal, the Wiener model provides information on how disturbances such as meals, stress, or exercise impact glucose and thus can be used to adjust insulin proactively via a multivariable feed-forward controller.

Result:
For training data (first 2 days), the full model had an R^2 value of 81.5% and an average absolute error (AAE) between predicted and CGMS value of 22 mg/dl. For testing data (third day), the full model had an AAE of 38 mg/dl and a correlation coefficient (between predicted and CGMS value) of 0.87. In contrast, the partial model had an R^2 of 68.4% and an AAE of 29 mg/dl in training and an AAE of 80 mg/dl and a correlation coefficient of 0.40 in testing.

Conclusion:
By using activity and stress data from an armband in glucose modeling, tremendous improvement can be made in predictive modeling and feed-forward control for T1DM.

Insulin Resistance Contributed to Cardiovascular Risk Factors Independent of Obesity in Saudi Women with Polycystic Ovary Syndrome

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Objective:
The goal of this study was to study the role of insulin resistance independent of body mass index (BMI) in contributing to cardiovascular risk (CVR) factors among women with polycystic ovarian syndrome (PCOS).

Methods:
All women presenting with infertility to King Abdulaziz University Hospital, Jeddah, Saudi Arabia, were interviewed, had a physical examination, and had a standard infertility workup to study the role of insulin resistance and CVR factors in our population. Women diagnosed to have PCOS from clinical, biochemical, and ultrasonographic criteria were requested to have a 75-gram oral glucose challenge test. Insulin, glucose, total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol levels were measured in the fasting state. This preliminary report compared 65 women with PCOS (age: 26.8 ± 6.6 years) to 130 healthy women (age: 26.4 ± 5.2 years) matched for age and ethnicity. The CVR factors score was calculated for each woman, including waist circumference, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure measurements, and the presence of diabetes mellitus.

Results:
Women with PCOS who were hyperinsulinemic (n = 28; insulin levels were 157 ± 39 pmol/liter) exhibited higher CVR factors (composite score for CVR factors = 2.90 ± 1.32) than their normoinsulinemic (n =37; insulin levels were 49.3 ± 18.8 pmol/liter) counterparts, who in turn exhibited more CVR factors (composite score for CVR factors = 1.22 ± 1.09) than corresponding healthy controls (insulin levels were 48.9 ± 16.1 pmol/liter with composite score for CVR factors = 0.62 ± 0.72), respectively ($P < 0.005$). Women with PCOS exhibited a significantly abnormal lipid profile: increases in the levels of total cholesterol, LDL cholesterol, and triglycerides and decreases in HDL cholesterol, respectively, as compared to the corresponding control group. In addition, women with PCOS exhibiting variable BMI showed greater insulin resistance, suggesting that PCOS per se, together with BMI, contributed to the observed insulin resistance.

Conclusion:
Insulin resistance contributed to the extent of CVR factors independent of obesity in Saudi women with PCOS.

The Diabetes and Technology for Increased Activity Study: Remote Self-Monitoring Tools and Lifestyle Intervention for Improved Health Outcomes

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Objectives:
Key risk factors for the development of cardiovascular complications (CVCs) of type 2 diabetes (T2DM) include elevated blood pressure (BP), cholesterol (CHOL), and glucose (BG) levels. Increased exercise, use of self-monitoring technologies, and education to manage these important health indicators may help reduce the aggregation of risk factors of disease and improve metabolic control, especially among rural or underserved populations.

Methods:
An 8-week feasibility study was conducted with 24 people from rural Ontario who had at least two risk factors: overweight, high BP, BG, and/or CHOL levels. Clinical measures included fasting glucose, hemoglobin A1c, lipid profile, triglycerides, and C-reactive protein (CRP). Assessments included waist circumference, weight, vascular health measures with Doppler ultrasound, step test, and physical activity staging. Participants monitored their BP (weekly) and BP (daily) wirelessly using a BlackBerry and Bluetooth-enabled devices. Daily pedometer steps and weekly weight were sent via a BlackBerry. These measurements were linked to a database and were monitored by research staff.

Results:
Eighteen women and six men with a mean age of 56.6 (±8.9) completed the 8-week intervention. Six people had T2DM. The technology burden was minimal and compliance was 95% (±2.2) for all Blackberry measures. From baseline, improvements were found in diastolic BP ($p = 0.046$), body mass index ($p = 0.03$), waist circumference ($p = 0.002$), CHOL ($p = 0.009$), VO_{2max}, ($p = 0.00$), and training heart rate ($p = 0.00$). Daily pedometer steps increased ($r^2 = 0.3099$). BG, CRP, and LDL levels decreased from baseline, but changes were not statistically significant.

Conclusions:
Self-managed monitoring technology is feasible, usable, and may assist in the prevention of developing CVCs of T2DM, especially where access to health care is inconsistent. Willingness to change, patient satisfaction, and interest in improving health indicators were positive outcomes.

A Tool for Analysis of Continuous Blood Glucose Monitoring Time Series

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Objective:
This work presents a software tool for the analysis of continuous glucose monitoring (CGM) time series in diabetes patients.

Method:
We developed a tool for the analysis of blood glucose (BG) time series collected through CGM. In addition to basic data visualization and analysis, the possibility of defining and retrieving customized complex patterns in BG time series is introduced. The tool is able to analyze one patient at a time or a group of patients. In the single-patient interface, the user can visualize overall BG behavior and daily time series, detect the required BG patterns (hypo- or hyperglycemic episodes, BG trends, etc.), and calculate the most common BG variability indexes (mean amplitude of glycemic excursion, BG risk index, liability index). In the multipatient interface, it is possible to retrieve and analyze specified patterns on a set of patients.

Result:
We analyzed a set of 108 type 1 diabetes mellitus patients who underwent Medtronic CGMS® monitoring at the diabetes unit of the Niguarda Hospital (Milan, Italy). Patients had a median length of stay of 4 days, with a median number of 811 measurements each. The following patterns were defined and retrieved in data: overnight hypoglycemia (more than two consecutive BG values ≤ 65 mg/dl), overnight hyperglycemia (more than 1 hour of consecutive BG values > 200 mg/dl), and dawn phenomenon (high BG values in early morning with no hyper- or hypoglycemic episodes overnight). A total of 144 hyperglycemic episodes on 61 patients, 146 hypoglycemic episodes on 54 patients, and 19 dawn episodes on 15 patients were detected.

Conclusion:
The presented tool can be used conveniently to support decisions and therapy revisions in diabetes care.

Outcome and Acceptance of Patient-Focused Decision Support after 2 Years of Application in Routine Diabetes Care

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Objective:
The goal of this project was to evaluate the medical outcome and the acceptance of patient-focused decision support in conventional diabetes care after 2 years of running a patient-focused diabetes care decision support system.

Method:
In April 2007, the German health insurance company BBK Taunus launched the Diabetiva® program. Diabetiva offers continuous glucose monitoring (CGM) and decision support generated by the Karlsburg diabetes management system KADIS® to their insured diabetes patients. Diabetiva is open for diabetes patients with cardiovascular risk and a focus on improvement of routine outpatient diabetes care according to internationally accepted diabetes care guidelines. The Diabetiva time line includes annual CGM followed by decision support for therapy optimization and quarterly check-up and hemoglobin A1c (HbA1c) detection by physicians. Patients with two CGM readings were analyzed retrospectively for acceptance of KADIS-based decision support using a questionnaire and the outcome of the Diabetiva program, with HbA1c as the primary outcome parameter and daily glucose pattern as the secondary outcome parameter.

Results:
After running Diabetiva for 24 months, 580 insured diabetes patients (95.4% type 2 diabetes) were enrolled and had received 950 CGMs. Patients were cared for by 469 general practitioners (GP) and 44 diabetes specialists (DSP). Approximately 70% of physicians accepted KADIS as patient-focused support to optimize diabetes therapies. Thirty percent did not accept KADI S-based decision support. Logistic regression revealed that KADIS acceptance depended on HbA1c at baseline ($p < 0.01$). GP or DSP and type of diabetes or diabetes therapy had no significant influence on acceptance or outcome parameters. Multiple regression analysis revealed that HbA1c and secondary outcome parameters 24 months after enrolment in Diabetiva depend only on acceptance of decision support and from HbA1c at baseline ($p < 0.01$). Type of therapy, age, onset of diabetes, body mass index, and gender had no significant influence on outcome parameters. If KADIS-based decision support was accepted, HbA1c could be decreased (HbA1c at baseline <6.5: –0.1%; 6.5–7.5: –0.3%; >7.5%: –1.0 %), whereas if KADIS was declined, the impact of Diabetiva was diminished (HbA1c at baseline <6.5: +0.5%; 6.5–7.5: +0.1%; >7.5%: –0.3 %) ($p < 0.05$).

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Conclusion:
Patient-focused decision support is well accepted by diabetes specialities and general practitioners, especially for diabetes subjects with elevated HbA1c. KADIS, in combination with continuous glucose monitoring, improves the outcome of routine diabetes care significantly.

A Multisite Analytical Assessment of a New Hospital Point-of-Care Glucose Meter for Accuracy, Precision, Correlation, and Interferences Encountered in Hospitalized Patients

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Objective:
Accuracy is a key requirement for glucose meters used in critical care settings. Inaccurate results can lead to potentially fatal errors with insulin dosing. StatStrip™ is a new hospital glucose meter designed to correct and eliminate common interfering substances that affect meter accuracy. The aim of this study was to challenge the accuracy of StatStrip in four German clinical centers comparing the performance to six commonly used hospital glucose meters.

Method:
Method correlation was performed using whole blood patient specimens for the glucose meters and the corresponding plasma samples for the central laboratory analyzer. Accuracy interference studies were performed using acetaminophen, ascorbate, and maltose monohydrate at different glucose levels. Hematocrit interference was tested using three glucose concentrations over a 25–65% hematocrit range.

Results:
The accuracy of StatStrip was not affected by any of the interfering substance tested. The accuracy of the other six meters was affected by low and high hematocrit levels, with percentage bias results deviating by as much as –25% (high hematocrit levels) to 30% (low hematocrit levels) compared to normal hematocrit levels across the range of glucose levels tested. The accuracy of all six meters was also affected by the presence of ascorbate. Maltose interfered significantly with the accuracy of three commonly used meters. Only one meter was affected by acetaminophen.

Conclusion:
In this analytical assessment, interfering substances commonly present in hospitalized patients compromised the accuracy and specificity of six glucose meters commonly used in Germany. The improved accuracy of StatStrip was substantiated in all four clinical sites, indicating that this new meter will provide a new improved level of clinical accuracy and reliability for managing glucose levels in hospitalized patients.

A Design Validation Study of the New ClikSTAR® Reusable Injection Pen Device

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Objective:
ClikSTAR® (sanofi-aventis) is a novel reusable insulin pen device being developed for use with insulin glargine or insulin glulisine.

Method:
This was an open label, single-center study to validate the ClikSTAR pen design. Diabetes patients were evaluated on their ability to deliver their correct insulin dose (75–115% of intended dose) on three repetitions during 1 day following training by a health care professional (n = 256; group A) or self-training (n = 47; group B). Adverse events (AEs) and product technical complaints (PTCs) were recorded.

Result:
Group A was 68% female, 93% Hispanic, and 97% type 2 diabetes patients. Mean (standard deviation) age was 52 (11) years and diabetes duration 11 (7) years; group B was similar. Approximately half of group A had previous insulin pen experience versus 70% of group B. All except one patient (99.6%) in group A delivered three doses successfully; the remaining patient delivered the first two doses successfully, but not the third, a statistically positive result validating the ability of the ClikSTAR pen to deliver the correct dose: lower one-tailed 95% confidence bound of 98.2% was higher than the target of 90%. In group B, 93.6% completed three repetitions successfully, a notable result given the number of patients without previous insulin pen experience. No AEs were reported. One patient (group A) reported a PTC during training, later attributed to a blocked needle.

Conclusion:
This study successfully validated the ClikSTAR pen for use in patients with types 1 and 2 diabetes. The small percentage of patients with type 1 diabetes (<10%) means that additional studies in this patient population are warranted, as are investigations into the ease of use of the ClikSTAR pen versus other available devices.

The GlycoMark (1,5-Anhydroglucitol) Assay Provides Important Clinical Information Missed by Hemoglobin A1c in Moderately or Well-Controlled Patients with Diabetes

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Objective:
The goal of this study was to elucidate the precise role of GlycoMark® in a clinical setting as a marker of postprandial glucose control (PPG)/glycemic variability (GV) by describing three patient cases.

Method:
Three patients treated with interventions that target postprandial glucose were evaluated with serial hemoglobin A1c (HbA1c) and 1,5-anhydroglucitol levels.

Result:
Patient 1: a 47-year-old man with type 2 diabetes was on a stable dose of metformin monotherapy. Hemoglobin A1c was 6.8% with a GlycoMark level of 8.6 μg/ml. Exenatide 5 μg twice daily for 1 month was initiated, followed by exenatide 10 μg twice daily. After 3 months of therapy, HbA1c was 6.5% and the GlycoMark level was 12.5 μg/ml. Patient 2: a 67-year-old woman with type 2 diabetes was on stable doses of metformin, pioglitazone, and glipizide. Hemoglobin A1c was 7.8% with a GlycoMark level of 8.1 μg/ml. Sitagliptin 100 mg daily was initiated. After 3 months of therapy, HbA1c was 7.9% with a GlycoMark level of 17.1 μg/ml. Patient 3: a 59-year-old man with type 1 diabetes was on basal/ bolus insulin (glargine and aspart) with HbA1c of 6.5% and a GlycoMark level of 4.7 μg/ml. The patient was transitioned to an insulin pump. After 9 months of therapy, HbA1c was 6.6% with a GlycoMark level of 10.8 μg/ml.

Conclusion:
These case reports suggest that significant PPG/GV may be present despite HbA1c levels that are considered well controlled. Serial GlycoMark measurements may be useful in assessing PPG/GV, particularly valuable in patients with moderate or good control. In addition, the efficacy of therapeutic interventions that target postprandial glucose can be represented more robustly with GlycoMark levels than HbA1c.

Diabetes Screening in an Ambulatory Population, 2005–2007

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Objective:
Undiagnosed diabetes mellitus is an epidemic affecting 5.1% of the United States population, yet little is known about how effective national diabetes screening guidelines are in clinical practice. This study evaluated diabetes guideline compliance and case finding in an adult clinic practice.

Method:
A retrospective database review of 46,991 nondiabetic patients aged ≥20 at a University of Wisconsin affiliated community practice from 2005 to 2007 was conducted. Patients meeting Wisconsin Collaborative for Healthcare Quality criteria were included. Pregnant patients, persons with diabetes, and patients deceased during the study years were excluded. The prevalence of patients meeting American Diabetes Association (ADA) and/or U.S. Preventive Services Task Force (USPSTF) criteria for diabetes screening, percentage of these patients screened, and yield of new diabetes mellitus diagnoses per guideline were evaluated. Screening rates were assessed by the number of high-risk factors, primary care specialty, and insurance status.

Result:
Of 46,991 patients, 33,823 (72%) met either ADA or USPSTF screening criteria, and 85% of eligible patients were tested. More patients met ADA criteria than 2008 USPSTF criteria (66% versus 26%), and use of 2008 USPSTF guidelines resulted in 34.6% fewer diagnoses of diabetes. By single high-risk factor, prediabetes (16%) and polycystic ovarian syndrome (13%) yielded the highest rates of diagnosis. The number of ADA high-risk factors predicted diabetes, with 23% of patients with six risk factors diagnosed. Uninsured patients were tested significantly less often than insured (55% vs 85%).

Conclusion:
Compared to ADA recommendations, the new USPSTF guidelines result in a lower number of patients eligible for screening and decrease case findings significantly. The number and type of risk factors predict diabetes, and lack of health insurance decreases screening frequency.

Frequency of Exercise-Related Hypoglycemia Using a Closed-Loop Artificial Pancreas: Preliminary Results

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Objective:
The goal of this study was to assess the frequency of exercise-related hypoglycemia in adolescents and young adults with type 1 diabetes (T1DM) in the immediate postexercise and subsequent overnight periods using a closed-loop (CL) versus open-loop (OL) insulin delivery system.

Method:
Subjects were admitted to an inpatient hospital research unit for two separate 72-hour admissions, in random order: usual home OL insulin pump therapy and a CL system in which minute-to-minute sensor glucose levels modulate minute-to-minute insulin delivery using a proportional-integral-derivative–insulin feedback algorithm. A standardized exercise session of four 15-minute periods of brisk treadmill walking to 65–70% maximum heart rate was performed on one afternoon during both admissions. During CL control target glucose was set at 120 mg/dl; hypoglycemia was defined as a blood glucose level <60 mg/dl. To date, four subjects have been studied on CL and four on OL (age 13–26 years, mean hemoglobin A1c 7.5%, T1DM duration 2–12 years).

Result:
Over a mean 60 hours of CL control, two episodes of actual hypoglycemia and three episodes of impending hypoglycemia were treated with 15–30 grams oral carbohydrate, all of which occurred in one subject on the night following exercise. In comparison, during OL control four subjects had a total of 8 episodes of impending and 12 episodes of actual hypoglycemia, of which 10 occurred overnight.

Conclusion:
These preliminary findings suggest that closed-loop insulin delivery has the potential to reduce the risk of exercise-induced hypoglycemia, both in immediate postexercise and later overnight periods. Further studies are currently underway to compare the safety and efficacy of CL vs OL regimens during exercise.

Development of an Automated Blood Glucose Monitor for the Critical Care Environment

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Objective:
DexCom and Edwards Lifesciences have collaborated to develop an intravenous blood glucose monitoring system for use in a hospital critical care environment. This system is designed to address the needs of clinicians to safely and proactively manage blood glucose to within target glycemic ranges. Availability of an accurate, reliable, and automated blood glucose monitor may enable clinicians to optimize glycemic management and safely achieve targeted glycemic ranges while reducing the risk of hypoglycemia in critical care patients. The DexCom/Edwards Lifesciences system consists of a blood glucose sensor that dwells within an intravenous catheter, a fluidics control unit for automated sampling and calibration, and a display unit. The system provides automatic, real-time monitoring and trending of blood glucose values for managing blood glucose in hospitalized patients. An analysis of prospective system accuracy from a pilot study is reported.

Method:
Sensor and laboratory reference blood glucose data were collected from 10 adult subjects with insulin-dependent diabetes in an in-clinic environment. Sensors were inserted intravenously in each subject and monitored continuously for 72 hours. Blood glucose levels varied from 42 to 390 mg/dl. Sensors were exposed to upper therapeutic doses of acetaminophen.

Result:
The system performance met accuracy criteria of International Organization for Standardization 15197 with 97.0% of sensor values within ±15 mg/dl or 20% of corresponding reference values (n = 576). The mean and median absolute relative differences were 5.6 and 3.9%, respectively. R^2 was 0.98. Accuracy was not impaired during acetaminophen exposure.

Conclusion:
Results of this study demonstrated that the system provided accurate, automated glucose measurements in an in-clinic environment. Additional studies in both in-clinic and critical care environments are ongoing.

Antidiabetic Effect of *Ficus bengalensis* Aerial Roots in Experimental Animals

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Objective:
This study deals with scientific exploration of the antidiabetic potential of *Ficus bengalensis* aerial roots in order to develop an effective and safe drug for diabetes management.

Method:
Effects of variable doses of an aqueous extract of *F. bengalensis* aerial roots on the blood glucose level (BGL) of normal, sub-, and mild-diabetic models during fasting blood glucose (FBG) and glucose tolerance test (GTT) studies have been evaluated, and results were compared with the reference drug glipizide. Laser-induced breakdown spectroscopy (LIBS)-based detection of high concentrations of Mg and Ca elements define their role as glycemic elements.

Result:
The dose of 300 mg/kg^{-1} showed the maximum fall of 43.8 and 40.7% in BGL during FBG and GTT studies of normal rats, respectively. The same dose showed a marked reduction in BGL of 54.3% in subdiabetic and 51.7% in mild diabetic rats during GTT. The concentration of Mg (1.02%) and Ca (0.85%) identified through LIBS in the most effective dose could be responsible for this high percentage fall in BGL as they take part in glucose metabolism.

Conclusion:
The hypoglycemic effect in normoglycemic and the antidiabetic effect in sub- and mild diabetic models of the aqueous extract of aerial roots of *F. bengalensis* are due to the presence of these glycemic elements in high concentration with respect to other elements.

Developing Interactive Educational and Training Tools for Diabetes Self-Management Devices

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Objective:
Despite the availability of a large number of innovative devices aimed to improve diabetes care, lack of appropriate education and sufficient skills remains a significant barrier to learning how to best utilize these new technologies for maximum benefit. Medical devices present patients and health care providers with burdens that are often associated with intensive training requirements, which contribute to the costs of therapy on all fronts. A new kind of educational tool is required to facilitate access to the best possible therapies by reducing these training costs and educational hurdles.

Method:
Drawing on the principles derived from information design, educational curriculum development, and advanced learning theories, we describe a conceptual framework focused on interactive education, training, and device simulation to assist patients and their health care providers in adopting an innovative diabetes management device.

Result:
A computer-based interactive training environment was designed to guide patients through key areas of diabetes management and use of the OmniPod insulin management system. The educational tool incorporated numerous training tasks in one standardized educational resource and provided appropriate learning tracks for new and advanced users. Patients were able to simulate insulin management tasks, interact with the device in a safe virtual environment, and develop a better understanding of diabetes management.

Conclusion:
A computer-based, interactive training program offers an engaging learning environment for patients, their family members, and health care providers. It reduces training time and associated costs, eliminates educational barriers, and facilitates the rapid and efficient introduction of new technologies in diabetes self-care.

Clinical Evaluation of a Noninvasive Alarm System for Nocturnal Hypoglycemia

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Objective:
The goal of this study was to evaluate the performance of a prototype noninvasive alarm (HypoMon®) for the detection of nocturnal hypoglycemia.

Design:
A prospective cohort study evaluated an alarm system, including a sensor belt, a radio frequency transmitter for chest belt signals, and a receiver. The receiver incorporated integrated "real-time" algorithms, which are designed to recognize hypoglycemia "signatures" in the physiological parameters monitored by the sensor belt.

Methods:
Fifty-two children and young adults with type 1 insulin-dependent diabetes mellitus (T1DM) participated in this blinded, prospective, in-clinic, overnight study. Participants had a mean age of 16 years (standard deviation 2.1, range 12–20 years) and were asked to follow their normal meal and insulin routines for the day of the study. Participants had physiological parameters, including electrocardiography and galvanic skin response, monitored overnight by a single HypoMon system. Their blood glucose levels were also monitored overnight at regular intervals via an intravenous cannula and read on two independent Yellow Springs Instrument analyzers. Hypoglycemia was not induced by any manipulations of diabetes management, rather the subjects were monitored overnight for natural occurrences of hypoglycemia. Performance analyses included comparing HypoMon system alarm times with allowed time windows associated with each hypoglycemia event.

Results:
Recognition algorithms in the prototype alarm system performed over a range of acceptable sensitivity/specificity settings. The best balance was achieved by algorithm 1, which correctly recognized 8 out of the 11 naturally occurring overnight hypoglycemic events and falsely alarmed on 13 out of the remaining 41 normal nights.

Conclusion:
The prototype HypoMon shows promise as a noninvasive alarm system for monitoring overnight hypoglycemia events in young people with T1DM.

In Vitro Performance Improvement Realized in a Next Generation Dry Powder Delivery System

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Objective:
Technosphere® formulations have been delivered successfully to patients with the MannKind MedTone® delivery system (MTDS). This system includes dry powder formulations, premetered into single-use cartridges and inserted into a high-resistance, breath-powered, reusable MedTone inhaler. The Next Generation delivery system (NGDSb), founded on these attributes, has been developed as an alternative to MTDS. *In vitro* powder performance for these systems was compared.

Method:
Particle sizing by laser diffraction and quantification of emitted mass are common tools for characterizing inhaler system performance. Here, a laser diffraction instrument (Sympatec HELOS) was adapted with a novel pressurized inhaler chamber to facilitate analysis of powder plumes. MTDS cartridges were discharged twice per determination versus once with NGDSb. Peak pressures of 4 kPa were used to assess powder-emptying percentage and volumetric median geometric diameter (VMGD) with Technosphere particles and Technosphere insulin (TI).

Result:
For NGDSb, powder-emptying percentages were 97.8% (TI, fill weight 3.5 mg; n = 20), 96.8% (TI, fill weight 6.7 mg; n = 20), and 92.6% (Technosphere particles, fill weight 10.0 mg; n = 15); VMGDs (μg) were 4.37, 3.69, and 6.84, respectively. For MTDS, powder-emptying percentages were 89.9% (TI, fill weight 5.0 mg; n = 30), 91.7% (TI, fill weight 10.0 mg; n = 30), and 89.4% (Technosphere particles, fill weight 10.0 mg; n = 30); VMGDs (μg) were 10.56, 11.23, and 21.21, respectively.

Conclusion:
These data support clinical use of NGDSb as a viable and improved alternative for delivering Technosphere formulations. Percent emptying was improved with NGDSb, offering users the significant advantage of a single discharge per cartridge compared with two discharges with MTDS. Reductions in median geometric particle size suggest increased powder deagglomeration within NGDSb. The clinical impact of this improved deagglomeration must now be assessed.

Infinite Horizon Prediction of Postprandial Breakfast Plasma Glucose Excursion

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Objective:
The objective of the study was to investigate infinite horizon prediction of postprandial blood glucose dynamics after breakfast ingestion using subspace-based identification.

Method:
Four, 3-day-long, patient records (type 1, two continuous subcutaneous insulin infusion and two multiple daily injection) collected at the Montpellier hospital within the European DIAdvisor project were used. Data records contained frequent finger prick measurements (38 samples/day), continuous glucose monitoring system (CGMS), and data on insulin and carbohydrate ingestion. The plasma glucose curve was reconstructed from finger prick measurements by interpolation. Using the reconstructed curve as output and reconstructed glucose fluxes from the gut, and insulin fluxes from subcutaneous depots, derived by the meal and insulin data together with models from the literature, as inputs, a state space model was estimated on data from the first night and the second day breakfast. The model was cross validated against the first and third breakfasts.

Result:
Infinite horizon prediction was evaluated for both validation breakfasts for all patients and compared with performance of the CGMS signal in terms of prediction error/measurement error in relation to the reconstructed plasma glucose curve. The infinite horizon predictor outperformed the CGMS in terms of both root mean squared error (mean 16 vs 27 mg/dl) and Clarke grid analysis (average 90.7% vs 72.9% in zone A; nothing in zone C or D, except one patient: 2% vs 13% in zone D).

Conclusion:
Even though the study was small, results indicate that subspace-based models can be used for prediction of postprandial plasma glucose excursion following breakfasts with the same or better accuracy as a CGMS. Further studies will be undertaken on larger data sets to test the methodology.

Continuous Glucose Monitoring Reduces the Incidence of Hypoglycemia Observed during Tight Glycemic Control in the Pediatric Intensive Care Unit

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Objective:
The ability of continuous glucose monitoring (CGM) to reduce the incidence of hypoglycemia during tight glycemic control (TGC) in the pediatric intensive care unit was evaluated.

Method:
Children age 3 and under enrolled in a randomized prospective trial of euglycemia following cardiac surgery were studied under standard of care (STD; $N = 84$) or TGC ($N = 80$). CGM (Medtronic CGM-RT) was used to aid in the titration of intravenous (IV) insulin and to recommend IV glucose if blood glucose (BG) was anticipated to fall below 60 mg/dl (mild hypoglycemia). Blood glucose was checked at a minimum every 2 hours when insulin was being delivered (target BG 80–110 mg/dl). Additional therapy recommendations based on CGM were made only after confirmation by BG measurement (SureStep® Flexx®, LifeScan). CGM hypoglycemic detection rate (%) and mean absolute relative difference (MARD) were assessed retrospectively at regular intervals, and adjustments in the hypoglycemic threshold were made to compensate for bias in sensor readings. An incidence of BG <40 mg/dl (severe hypoglycemia) was calculated as total episodes divided by total number of subjects.

Result:
The MARD was 16.8%. CGM overestimated BG below values of 106 mg/dl (regression slope 0.68 ± 2, intercept 34 ± 2 mg/dl; different from 1 and 0, $p < 0.05$). With the CGM hypoglycemic alarm threshold set at 60 mg/dl, none of the first 9 occurrences of BG <60 mg/dl were detected. Increasing the threshold to 70 mg/dl and adding a 15-minute forward prediction resulted in 10 of 19 subsequent occurrences being detected and 6 occurrences averted entirely. The overall incidence of severe hypoglycemia during TGC was 3.1%.

Conclusion:
Continuous glucose monitoring reduces the incidence of mild hypoglycemia during TGC control and results in low overall rates of severe hypoglycemia.

A Randomized Six-Way Crossover Study of Nasulin,™ Saline, and Lispro Subcutaneously in Subjects with Type 2 Diabetes to Determine Optimum Dose Timing

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Objective:
Previous studies with CPEX Pharmaceuticals' intranasal prandial insulin formulation, Nasulin™, indicate that it has an ultrarapid-acting time-action profile. This study compared the pharmacodynamic (PD) effects of varying the time of administration of Nasulin in relation to a meal.

Methods:
After stabilization of glucose values at 90–140 mg/dl with an overnight insulin drip, 13 subjects with type 2 diabetes received 25 IU Nasulin at the start of the meal (SOM), at the end of the meal (EOM), 60 minutes after the start of the meal (SOM 60), 50 IU (25 IU SOM and 25 IU SOM 60), 5 IU lispro subcutaneous SOM, or saline SOM. Pharmacodynamic activity was evaluated for 4 hours.

Results:
Nasulin 25 IU given at SOM or EOM, as well as the split 50 IU dose, had similar results. The C_{max} values for glucose were 109.2 (44.1), 118.2 (35.2), and 121.8 (41.40) mg/dl, respectively. The area under curve $(AUC)_{0\text{-}2}$ showed similar results with values of 139.1 (60.9), 152.7 (58.3), and 148.2 (56.9) mg*hr/dl, respectively. $AUC_{0\text{-}4}$ showed similar results for all three regimens. Saline and Nasulin 25 SOM 60 had the least favorable impact. Lispro had the most favorable impact on glucose with a C_{max} of 102.6 (41.6) mg/dl and an $AUC_{0\text{-}2}$ of 129.5 (56.1) mg*hr/dl.

Conclusions:
(1) Nasulin 25 IU can be administered at the start or end of a meal with a similar PD outcome and would be valuable in replacing the missing initial insulin spike in these patients. (2) Nasulin given 1 hour after a meal has little effect in subjects with type 2 diabetes. (3) Postprandial glucose excursions were high, indicating that higher doses will be required to manage most patients.

Dose Exposure for Single and Dual Nostril Administration of Nasal Insulin (Nasulin™)

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Objective:
The objective of this study was to characterize the dose response of a nasal spray of recombinant regular human insulin (250 IU/ml) in combination with cyclopentadecalactone, a compound that enhances the absorption of molecules across mucous membranes (Nasulin,™ CPEX Pharmaceuticals) when dosed in one or two nostrils. The post hoc objective was to compare the exposure when the same dose was delivered in one or both nostrils.

Method:
In a nine-period crossover study of eight healthy, nonsmoking male subjects (ages 18–50, body mass index <33 kg/m^2, weight >70 kg), subjects were in a fasted state for 5 hours before and for 45 minutes after administration, for pharmacokinetics assessment, and were then given a meal. Each spray contained 100 µl. For single nostril administration, subjects received 25 (one spray/nostril), 50 (two sprays/nostril), or 75 IU (three sprays/nostril). For two nostril administration, subjects received 50 (one spray/nostril), 75 (two sprays one nostril + one in the other), or 100 IU (two sprays each nostril).

Result:
Prospective analyses demonstrated a dose response for both single nostril (C_{max} for 50 and 75 U, were 3.3- and 5.0-fold greater than for 25 IU, p = 0.003 and 0.0004, respectively) and dual nostril dosing (p = 0.04). In post hoc analyses, C_{max} was 1.7 ± 0.39 times higher (p = 0.03) when the second spray was given in the same nostril rather than the other nostril and 1.6 ± 0.36 (not significant, probably due to limited sample size) when one rather than two nostrils was used for the three-spray dose.

Conclusion:
Using either a single or both nostrils for Nasulin dosing showed dose response of systemic exposure. When dosing, two sprays of Nasulin delivering the second administration in the same nostril result in higher systemic exposure than delivery in the other nostril.

Dose Exposure for Two Dose Strengths of Nasal Insulin (Nasulin™)

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Objective:
The objective was to characterize the dose response of two concentrations of a nasal spray of recombinant regular human insulin (low "L"175 IU/ml and high "H" 250 IU/ml) in combination with cyclopentadecalactone, a compound that enhances the absorption of molecules across mucous membranes (Nasulin,™ CPEX Pharmaceuticals).

Method:
In a five-period crossover study of two cohorts, each with 12 healthy, nonsmoking subjects (ages 18–50, body mass index <33 kg/m^2, weight >70 kg), subjects were in a fasted state for 5 hours before and for 45 minutes after administration, for pharmacokinetics assessment, and were then given a meal. Each spray contained 100 µl. Doses tested were 25 IU (one H spray in one nostril), 35 IU (two sprays L in one nostril), 50 IU (two sprays H in one nostril), 70 IU (two sprays L in each nostril), and 100 IU (two sprays H in each nostril). The C_{max} and area under the curve (AUC) were estimated for each dose group.

Result:
The dose response (slope of the natural log response versus dose) was demonstrated by baseline-adjusted C_{max} values of 22, 27, 56, 62, and 84 µU/ml for the 25, 35, 50, 70, and 100 IU dose, respectively ($p < 0.0001$), and baseline-adjusted $AUC_{0\text{-}45\ min}$ of 491, 592, 1231, 1310, and 1894 [(µU/ml)*min] ($p < 0.0001$). Results were similar in both cohorts.

Conclusion:
A dose response was demonstrated for the two formulations, making multiple doses available for clinical development.

Two Randomized Crossover Glucose Clamp Studies of Nasulin™ and Lispro Subcutaneously

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Objective:
Two glucose clamp studies compared the pharmacokinetic and pharmacodynamic results of CPEX Pharmaceuticals' intranasal insulin formulation, Nasulin,™ to lispro subcutaneously, one in healthy volunteers and one in subjects with type 1 diabetes mellitus (T1DM).

Methods:
After stabilization of glucose values (90–100 mg/dl in healthy volunteers and 90–110 mg/dl subjects with T1DM), 17 normal volunteers received 25 IU Nasulin, 25 IU at 0 and 60 minutes, or 5 IU lispro and six type 1 diabetes subjects received 50 IU Nasulin or 10 IU lispro followed by a 4-hour glucose clamp procedure.

Results:
In normal volunteers, Nasulin regimens resulted in higher peak values and earlier peaks in mean baseline-adjusted plasma insulin compared to lispro [C_{max} 62.1 (68) vs 36.9 (10.2) μIU/ml][T_{max} 18 (6) vs 54 (18) minutes]. The geometric mean ratio (GMR) peaked earlier and declined more rapidly with both Nasulin treatments compared to lispro. Mean area under curve–GMRs in the first hour were higher for the Nasulin arms [136.9 (78.7) and 134.8 (70.8 mg/kg)] vs lispro [111.7 (64.1) mg/kg] but were higher for lispro vs the 25 IU Nasulin arm over 240 minutes. In subjects with T1DM, the same results and trends were noted with the exception that C_{max} values were similar for Nasulin and lispro [42.3 (29.9) and 43.7 (17.3)], respectively. The maximum metabolism rate was highest in the lispro arm in both studies. The C_{max} of Nasulin showed more variability.

Conclusion:
These data support the ultrarapid-acting time-action profile of Nasulin and the consequent rapid onset of maximum glucose utilization. These features suggest that Nasulin would be valuable as prandial insulin with the advantage of a more rapid and effective postprandial glucose reduction than lispro in the first hour after dosing.

What Makes Glycemic Control Protocols "T" (Tight)? An Analysis of Data from Two Studies

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Objective:
Tight glycemic control (TGC) remains controversial and successful protocols are elusive. This research analyzed data from two TGC trials to determine root causes of differences achieved in control and thus outcome.

Method:
A retrospective analysis used records from 211 patients in the Glucontrol trial in Belgium and 393 patients from the Specialized Relative Insulin Nutrition Table (SPRINT) in New Zealand. Glucontrol-A and -B cohorts (N = 142, 69) targeted 4.4–6.1 and 7.8–10.0 mmol/liter, respectively. All cohorts were matched by the Acute Physiology and Chronic Health Evaluation II score ($p > 0.40$). Overall cohort and per-patient comparisons [median (interquartile range)] are shown for (a) glycemic levels achieved, (b) nutrition from carbohydrate, and (c) insulin dosing.

Results:
Cohort blood glucose was SPRINT: 5.7 (5.0–6.6), glucontrol-A: 6.3 (5.3–7.6), and glucontrol-B: 8.2 (6.9–9.4) mmol/liter. Insulin dosing was 50.0 (16.7–50.0), 25.0 (8.3–50.0), and 11.7 (0.0–28.3) mU/min, respectively. Nutrition from carbohydrate was 0.42 (0.25–0.52), 0.30 (0.00–0.90), and 0.60 (0.10–1.00) mmol/min. Median per-patient results for blood glucose were 5.8 (5.3–6.4), 6.4 (5.9–6.9), and 8.3 (7.6–8.8) mmol/liter. For insulin dose: 50.0 (33.3–50.0), 25.0 (13.3–33.3), and 8.3 (0.0–16.7) mU/min. For nutrition: 0.37 (0.20–0.48), 0.1 (0.0–0.8), and 0.2 (0.0–0.7) mmol/min. Overall, SPRINT gave approximately two times more insulin with a three to four times narrower range of nutritional input to achieve equally tight TGC with less hypoglycemia.

Conclusion:
Protocols that dose insulin blind to associated carbohydrate nutrition input will suffer more variability in glycemic outcome even if average or median targets are met. Successful TGC protocols must therefore dose insulin in conjunction with knowledge and some specification of nutritional inputs to yield well-managed rates of insulin and nutrition input.

Hypoglycemia Detection Capabilities of a Multisensor Device for Noninvasive Continuous Glucose Monitoring under Home-Use Conditions

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Objective:
We report on findings of the application of a novel multisensor device under development for continuous noninvasive glucose monitoring under home-use conditions (HUC). The multisensor yields signals from the skin-surface sensors for dielectric, optical, temperature, blood perfusion, and hydration measurements. Despite the sparseness of reference blood glucose measurements, data from this multisensor device were used to investigate the possibility of detecting hypoglycemic blood glucose levels and subsequently trigger an alarm based on the online-compatible glucose level estimation model available at this stage of development.

Method:
Sixteen patients with type 1 diabetes mellitus wore the multisensor under HUC. Each patient performed a maximum total of 24 study days (15 patients 24 study days, 1 patient 20 study days) over a period of 4 months with a total of 380 study days collected. Patients collected on average 11 capillary self-monitoring of blood glucose measurements during each study day. The study was split into two blocks; measurements of the first 160 days were used for training a linear regression model followed by a threshold-based hypoglycemia alert system. The trained hypoglycemia alert setting was then validated prospectively on data obtained in the second block of 220 days.

Results:
When the multisensor hypoglycemia alert threshold was set to 70 mg/dl, the prospective application of the hypoglycemia alert system on the second data block resulted in a true alert rate of 74% within a window of ±15 minutes around a reference glucose measurement and a false alert rate of 69%. With a hypoglycemia alert threshold of 90 mg/dl, a true alert rate of 74% and a false alert rate of 48% were achieved.

Conclusion:
With appropriate training, patients could attach the multisensor easily, allowing stable measurements to collect continuous sensor data. Analyses of prospective models have given first indications of how hypoglycemia alarms can be given for such a multisensor device under HUC. Based on these findings, the next development steps have been taken toward a more miniaturized multisensor concept.

Reduced Body Cell Mass in Type 2 Diabetes Mellitus: A Body Impedenziometric Analysis

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Objective:
Subjects with type 2 diabetes are in a continuous catabolic state due to increased neoglycogensis during fasting and frequently during the postprandial period. This study evaluated the extent of this damage and the possibility of reversing it with a specific nutritional formula.

Method:
We examined in fasting conditions with the Akern BIA 101 the body impedenziometric analysis of (1) 244 diabetes subjects 40–65 years of age of both sexes and a matched nondiabetic population of 216 subjects referred for weight loss, (2) a population of 715 diabetes subjects, and (3) 57 diabetes subjects with glucose instability before and after 6 months of treatment with a nutritional formula. All subjects were free of other diseases and of advanced diabetic complications.

Results:
(1) The body cell mass index (BCMI) was significantly lower in diabetes subjects (11.4 ± 2.3 vs 10.3 ± 2.26, $p = 0.000$). (2) There was a significant inverse correlation among the prevailing hemoglobin A1c ($p = 0.000$) and the duration of diabetes ($p = 0.000$) versus the BCMI. (3) After 6 months, the hemoglobin A1c decreased from 7.89 ± 1.33 to 7.19 ± 0.5% ($p = 0.001$), the BMI decreased from 30 ± 6.6 to 28 ± 5.5 ($p = 0.001$), and the BCMI increased from 9.01 ± 1.38 to 10.13 ± 1.1 kg/m^2 ($p = 0.001$).

Conclusion:
As demonstrated in a large population of diabetes subjects, the BCMI is significantly lower than in nondiabetic subjects, this reduction is inversely proportional to the duration of the disease and to the prevailing hemoglobin A1c level, and this defect is partially reversible with use of a specific nutritional formula for 6 months.

Inconsistent Use of Insulin Therapy Parameters: A Roadblock to Achieving Glycemic Control?

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Introduction:
Successful therapy with multiple daily injections (MDI) or continuous subcutaneous insulin infusion depends on consistent use of personalized insulin-to-carbohydrate ratios (I:CHO) and insulin sensitivity factors (ISF). Health care providers (HCP) and patients work together to determine what these parameters should be but new research indicates that patients may use their stated parameters inconsistently, which could lead to inaccurate assumptions when adjustments are needed.

Methods:
Twenty-one type 1 diabetes subjects (34 ± 13.7 years, hemoglobin A1c 7.1 ± 0.9%) completed a 10-week period of intensive monitoring and logging. I:CHO, ISF, CHO intake, and insulin doses were recorded. Data were analyzed to determine if subjects used their stated I:CHO ratios and ISF to calculate mealtime insulin doses. Adherence was defined as number of meals where stated factors were used/total number of meals times 100. A rounding allowance of ±0.5 was allowed to accommodate MDI.

Results:
2715 meals were evaluated for 21 subjects. Adherence to use of therapy rules (I:CHO and ISF) overall for calculation of meal doses was 20.7 ± 12.7 % (range 3.3–42.9%). Adherence to use of I:CHO was higher than use of ISF (44.3% versus 34.3%, respectively). The degree of adherence did not correlate with achieving stated targets.

Conclusions:
Subject use of stated therapy parameters was inconsistent, which raises multiple questions about the accuracy of the parameters, subject ability to perform the calculations, and subject ability to CHO count. Of greatest concern, results suggest that HCPs may be making adjustments to stated I:CHO ratios and ISFs when patients are not actually using the parameters the HCP thinks they are. This behavior may be a significant roadblock to achieving glycemic control.

Layer-by-Layer Assemblies/Poly(Vinyl Alcohol) Hydrogel-Based Stacked Outer Membranes for Implantable Glucose Sensors

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Objective:
Lack of linearity and sensitivity, oxygen dependence, biofouling, and tissue inflammation hinder the development of implantable biosensors for continuous monitoring of glucose. Herein, we report the development of stacked outer membranes based on layer-by-layer (LBL)/poly(vinyl alcohol)(PVA) hydrogels that improve sensor sensitivity, linearity, and oxygen independence and counter biofouling and inflammation. While the inner LBL membrane affords tunable diffusivity, the outer PVA is capable of releasing anti-inflammatory drugs/tissue-response modifying agents to counter acute and chronic inflammation and to induce neoangiogenesis at the implant site.

Method:
Sensors were fabricated by immobilizing the glucose oxidase enzyme on top of 50-μm platinum wires, followed by deposition of stacked LBL/PVA hydrogel membranes. The response of the sensors at 0.7 volt to various glucose concentrations was studied. Michelis–Menten analysis was performed to quantify sensor performance in terms of linearity ($K^{app}_{m,glu}$) and oxygen dependence (K^{app}_{m,O_2}). The interplay between sensor performance and inward glucose diffusivity was elucidated using (i) various LBL membranes and (ii) various freeze–thaw cycles of PVA.

Result:
Incorporation of LBL/PVA stacked membranes resulted in an eightfold increase in sensor linearity and a ninefold decrease in oxygen dependence compared to controls.

Conclusion:
Enhancement in the sensor performance is attributed to (i) the oxygen-storing capability of PVA hydrogel due to the formation of hydrophobic domains during its freezing/ thawing employed for its physical cross-linking and (ii) regulation of glucose flux by the inner LBL membrane. Such membranes offer significant advantages over presently available outer membranes in lieu of (i) their ability to control inflammation, (ii) their modulus that closely matches that of subcutaneous human tissue, (iii) nonnecessity of reactive chemical cross-linking agents, (iv) tunable sensitivity, and (v) supplemental storage of oxygen.

GlucoMen®Day Continuous Glucose Monitor: Enhancing Clinical Performance Levels through an Improved Real-Time Signal Compensation Algorithm

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Objective:
A new real-time signal compensation algorithm has been developed in order to improve the clinical accuracy of GlucoMen®Day (A. Menarini Diagnostics S.r.l., Florence, Italy), a new continuous glucose monitoring system (CGMS).

Method:
The GlucoMenDay is a microdialysis-based wearable device, intended for 100 hours of continuous glucose monitoring in diabetes patients. Glucose is measured once a minute by a disposable glucose oxidase-based biosensor downstream of a microdialysis probe. Preliminary clinical results have been presented recently at the Advanced Technologies and Treatments for Diabetes 2009 conference. Further to the analysis of the existing clinical data set collected during the previous study, a new multiparameter signal compensation algorithm has been designed, refining both the model and the equations used to correct signal in "real time" against temperature variations, enzyme inactivation, linearity, and general instabilities. The key feature is its compatibility with the instrument alarms generation system at hypo- and hyperglycemic events.

Result:
The algorithm was applied to raw data from six type 1 diabetes patients implanted with GlucoMenDay. Glucose levels were monitored continuously in both clinical and home settings for a period of 100 hours and compared with the corresponding reference venous or capillary blood glucose. A total of 148 data pairs were collected. Calibration of the CGMS was performed just once per day. When compared with the uncorrected signal, a relevant improvement in both linearity (R^2 increased from 0.79 to 0.91) and accuracy [percentage of values meeting International Organization for Standardization 15197 criteria (bias plot) increased from 88 to 93%] of the system was observed.

Conclusion:
The new signal compensation algorithm significantly improves the clinical performances of GlucoMenDay. This needs to be assessed further through a multicentric study on a larger number of patients.

Lova Glucose Control for Intensive Care-Insulin Algorithm for Blood Glucose Control in the Intensive Care Unit: A Pilot Test

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Objective:
Hyperglycemia, hypoglycemia, and blood glucose fluctuations are associated with increased mortality and morbidity of critically ill patients. This type of patients is typically admitted to an intensive care unit (ICU). Nurses measure the blood glucose every hour (in the initial phase or in case of complications) to every 4 hours and adapt the insulin infusion flow accordingly. This insulin administration process is labor-intensive and is, at least in our Leuven ICU, only based on a set of guidelines (i.e., no strictly defined protocol).

Method:
We developed a computerized algorithm and a corresponding graphical user interface that can potentially be used for normalizing the blood glucose levels in the critically ill: LOva Glucose control for Intensive Care (LOGIC-Insulin). The algorithm advises the nurse hourly how the insulin rate should be adapted in order to reach the normoglycemic target range (80–110 mg/dl) and to avoid hypoglycemia or glycemic fluctuations. In this pilot test phase, the LOGIC-Insulin algorithm was applied to two critically ill patients during a period of 10 hours that immediately started after admission to the ICU.

Result:
Both patients entered the ICU showing serious hyperglycemia (>215 mg/dl). The insulin flow gradually increased and the normoglycemic target range was reached after 6–7 hours. More importantly, blood glucose levels could be kept in the target range (no hypoglycemia) and the anticipation power of the LOGIC-Insulin algorithm could be shown.

Conclusion:
The LOGIC-Insulin algorithm was tested successfully in two critically ill patients. At present, more pilot tests (with different conditions) are under study as preparation for a larger clinical trial in which the performance of the LOGIC-Insulin algorithm will be compared to that of the Leuven nurses.

Improved Dose Proportionality of Insulin Lispro Injected with Hyaluronidase

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Objective:
The goal of this study was to characterize pharmacokinetic (PK) and glucodynamic (GD) responses to insulin lispro coinjected with hyaluronidase (PH20) compared to lispro alone as a function of both lispro dose and concentration.

Method:
A euglycemic clamp experiment (8 hours at 90% of fasting plasma glucose, without basal insulin infusion) was conducted in three cohorts of four healthy subjects using lispro at a concentration of 25, 50, or 95 units. Each subject underwent six clamp procedures using three doses (2, 6, and 20 units) of lispro+PH20 and lispro alone.

Result:
As shown previously, coadministration of PH20 accelerated the PK and GD profiles of lispro without significantly affecting total insulin exposure or effect. Increasing doses of lispro alone (2, 6, and 20 units) resulted in progressively slower PK profiles [e.g., %area under curve ($AUC_{0\text{-}2\ hr}$) decreased from 77 ± 15 to 64 ± 12% to 57 ± 17%, $p < 0.0001$, and late t50% increased from 103 ± 23 to 137 ± 37 minutes to 174 ± 67 minutes, $p < 0.0001$] with correspondingly slower GD profiles (e.g., $\%G_{0\text{-}3\ hr}$ decreased from 72 ± 30 to 67 ± 19% to 53 ± 13%, $p = 0.03$, and $time_{50\%G}$ increased from 127 ± 98 to 150 ± 55 minutes to 175 ± 39 minutes, $p = 0.05$). This dose nonlinearity was more pronounced for the higher concentrations of insulin lispro (data not shown). Coadministration with PH20 led to PK/GD profiles that were more dose proportional (e.g., $\%AUC_{0\text{-}2\ hr}$ values were 89 ± 11, 84 ± 10, and 77 ± 13%, $p = 0.01$; values for late t50% were 71 ± 10, 87 ± 24, and 103 ± 41 minutes, $p = 0.03$, $\%G_{0\text{-}3\ hr}$ values were 82 ± 27, 79 ± 15, and 67 ± 13%, $p = 0.09$, and $time_{50\%G}$ values were 103 ± 80, 106 ± 29, and 138 ± 25 minutes, $p = 0.17$, for lispro+PH20 doses of 2, 6, and 20 units, respectively).

Conclusion:
Coadministration of insulin lispro with PH20 accelerated lispro PK and GD profiles and improved both dose concentration and dose effect proportionality versus time relative to lispro alone.

Closed-Loop Insulin Delivery Utilizing Insulin Feedback: Overnight Control

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Objective:
This report presents results of clinical testing of Medtronic's closed-loop (CL) algorithm in an overnight period.

Method:
Eight subjects with type 1 diabetes completed the study. Prior to algorithm testing, subjects wore a continuous glucose monitoring system for 72 hours [outpatient open-loop (OL) period]. Inpatient control lasted 30 hours. For analysis, the overnight period was considered as midnight to 6 am. The CL target for overnight was set at 110 mg/dl.

Result:
The target glucose range considered was 70–140 mg/dl. During the OL period, subjects were in target 55.3% of the time, 2.1% below target, and 42.6% above target. In contrast, during CL, subjects were 95.8% of the time in target, 0% below target, and 4.2% above target. Mean blood glucose values during CL were 111.9 ± 7.7 mg/dl vs 141.1 ± 62.1 mg/dl during OL ($p < 0.0001$). The area under the curve (AUC) above 140 mg/dl for OL was 204 ± 232.3 min·mg/dl and was 3.078 ± 4.58 min·mg/dl for CL ($p < 0.04$). AUC below 70 mg/dl for OL and CL was 26.64 ± 52.08 and 0 min·mg/dl, respectively. There was a striking difference in the stability of the glucose profiles between OL and CL (standard deviations of 62.1 vs 7.7, respectively). These were accompanied by the opposite trend in the insulin delivery rate (0.972 ± 0.05 U/hr vs 1.236 ± 0.4 U/hr for OL and CL, respectively). While insulin use during CL was increased compared to OL (8.62 ± 2.56 units during CL vs 5.93 ± 2.33 units in OL; $p < 0.0001$), the absolute value of the increase (Δ2.68 ± 2.53 units) was negligible.

Conclusion:
Data demonstrate that closed-loop control results in a significantly improved nighttime glucose profile without a substantial increase in insulin use. The significant reduction in hyperglycemia was achieved safely with no hypoglycemia.

Development of a Personalized Noninvasive Glucose Monitoring System for Free-Living Environments

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Objective:
Monitoring blood glucose levels continuously and accurately for long durations is one of the key components for the successful treatment of diabetes. We demonstrated the ability of BodyMedia's SenseWear® Pro3 heart rate-enabled armband to predict blood glucose values in a noninvasive manner and in free-living conditions.

Method:
This study was performed on 15 individuals who were either diagnosed with type 2 diabetes or were prediabetic. For each subject, data were obtained by a Medtronic MiniMed continuous glucose monitor (CGM) for a period of 4 weeks. Finger stick readings for glucose levels were also obtained four to six times per day and all subjects wore the armband on the upper left arm during the trial. The armband measures movement, heat flow from the body, skin temperature, electrocardiogram, and galvanic skin response and estimates energy expenditure, heart rate, and heart rate variability. A food log was also maintained by the subject. The variables for modeling were personalized using a subset of each subject's data. Models for predicting blood glucose values were developed from data and evaluated on rest of data for each subject.

Result:
The average error between predicted glucose values and CGM values was 17.2 mg/dl (14.35%), and the correlation between values was 0.83. The correlation between model predictions and finger stick glucose values was 0.81, and the average error was 21.30 mg/dl (15.7%). A Clarke error grid analysis between model predictions and Medtronic CGM values yielded 98.77 % points falling in zones A and B (81% in zone A).

Conclusion:
This study showed the capability of the armband to monitor glucose levels noninvasively and continuously for extended time periods and under free-living conditions.

Automated Analysis of Structured Self-Monitoring of Blood Glucose Data with a Novel Decision Support Tool

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Objective:
In a pilot study, 61 primary care physicians (PCP) interpreted structured self-monitoring of blood glucose (SMBG) data collected with the Accu-Chek® 360° View blood glucose analysis system from patients with type 2 diabetes mellitus 76% of the time. To improve interpretation, a decision support tool (DST) was created to analyze and interpret structured SMBG data and to suggest potential therapeutic actions.

Method:
A DST was developed specifically to analyze structured SMBG data from the Accu-Chek 360° View system (3 days × seven point profiles). Data were analyzed by the DST using the following pattern identification priorities: (1) hypoglycemia, (2) fasting or preprandial hyperglycemia, and (3) postprandial hyperglycemia. Interpretation and therapeutic suggestions were based on results of pattern analysis and reflect accepted medical practice as described in multiple guidelines, including the American Diabetes Association, European Association for the Study of Diabetes, and International Diabetes Federation. To test the medical validity of the DST, 60 case studies were analyzed with the DST, and the output of the analysis, including interpretation and therapeutic actions, was evaluated by two practicing diabetes care experts.

Result:
Evaluation of 60 cases (hypoglycemia 19 cases; fasting or preprandial hyperglycemia 24 cases; postprandial hyperglycemia 17 cases) demonstrated 91.6% approval of the output of the DST, including possible therapeutic actions. In 5 cases, experts recommended modification of the therapeutic recommendations, including drawing more attention to severe hypoglycemic BG values (BG ≤50 mg/dl) and less attention to borderline hyperglycemia.

Conclusion:
A medically validated DST has been created that analyzes and interprets structured SMBG data accurately and provides guidance on possible therapeutic action. This tool may be suitable for use in primary care practice to improve interpretation of SMBG data and guide selection of appropriate therapeutic options.

A Method to Improve Accuracy of Carbohydrate Factor Selection

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Objective:
The goal of this study was to determine improvement in the accuracy of carbohydrate factor (CarbF; grams of carbohydrate covered by 1 unit of bolus insulin) calculations.

Method:
We have previously found CarbF entries error-prone and associated with adverse glucose outcomes. The accuracy of CarbFs is important, as a change from 1 unit/11 grams to 1 unit/10 grams can introduce a 50- to 100-mg/dl shift in the glucose excursion for average size meals. We have previously proposed formulas based on total daily insulin dose (TDD) and others have proposed formulas based on TDD and weight to calculate approximate CarbFs. Here we review a more accurate method to determine CarbFs in insulin-deficient individuals through use of insulin sensitivity times a median CarbF. Although weight is needed to determine insulin sensitivity, CarbFs will be identical for individuals with the same sensitivity to insulin, regardless of weight. An accompanying abstract reviewed CarbF (grams of carbohydrate covered by 1 unit of bolus insulin) entries in pumps and found that many CarbFs are erroneous and have an adverse impact on glucose outcomes. Even a 1-gram change in a CarbF, such as a change from 1 unit/11 grams to 1 unit/10 grams, can introduce a 50- to 100-mg/dl shift in the glucose for average size meals.

Result:
Data from more than 130 pumps worn by well-controlled users with an average glucose of 144.0 mg/dl (median glucose = 129.1 mg/dl) were analyzed to find a median CarbF determined by dividing each individual's average daily carbohydrate intake by their average daily carbohydrate bolus total. We found that the median CarbF in this group of well-controlled pump users equals 1 unit/10.4 grams of carbohydrate.

Conclusion:
Using previously determined calculations for insulin sensitivity in individuals without insulin resistance,

$$\text{CarbF} = 10.4 \times \frac{\text{wt}}{\text{TDD} \times 4}$$

This calculation provides a method for selecting an accurate carbohydrate factor based on sensitivity to insulin, provided that the TDD has been optimized.

Current Carbohydrate Factors in Current Insulin Pumps Are Nonphysiologic and May Impact Glucose Control Adversely

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Objective:
The goal of this study was to assess the accuracy and impact of carbohydrate factors (CarbFs) in insulin pumps.

Method:
Data were extracted from 1000 complaint-free anonymous insulin pumps submitted for routine software upgrades in 2007. A subset of 406 pumps was selected that had more than 85% of glucose readings entered directly from an attached meter. Settings were analyzed.

Result:
A nonphysiologic distribution was found with a preference for the "magic" numbers 5, 10, 15, and 20. An R^2 goodness of fit of CarbF entries found little correlation for any glucose tertile (R^2 = 0.41, 0.41, and 0.43 for low, middle, and high BG tertiles sorted by their mean glucose). These CarbF entries were then compared to actual use, determined by an average of grams carbohydrate consumed daily divided by average daily carbohydrate bolus total (actual CarbF). In contrast to the poor fit for selected carbohydrate factor entries, the R^2 for actual CarbFs used revealed an R^2 = 0.83, 0.83, and 0.61 for lower, middle, and higher tertiles, respectively. Although the lower and middle control tertiles showed similar adaptability to compensate for CarbF errors, the average CarbF number in the lower tertile was significantly lower at 1 unit/10.95 grams compared to the middle tertile at 1 unit/11.98 grams and 1 unit/11.2 grams in the higher tertile.

Conclusion:
These results indicate that CarbF selection is poor and nonphysiologic for many pump wearers. Those with better control tend to select lower CarbF settings that provide larger carbohydrate boluses than those in the middle and higher glucose tertiles and demonstrate a better ability to compensate for nonphysiologic settings by overriding the recommended bolus of the pump compared to the highest tertile. A selection of more physiologic CarbFs may significantly improve glucose control for pump wearers.

Clinical and *in Silico* Evaluation of Adaptive Basal Therapy

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Objective:
We proposed an adaptation scheme for basal insulin infusion to exploit information from a continuous glucose monitor. This study evaluated adaptive basal therapy in clinic and *in silico*.

Method:
Blood glucose (BG) was measured every 15 minutes, and the BG rate of change (ROC) was estimated every 30 minutes using the weighted average of the last three BG samples. Based on the BG and its ROC, an appropriate gain for the basal was obtained from the basal gain mosaic, and the new basal rate was the product of nominal basal and gain. Five minutes later the pump was set to the new basal rate manually.

Result:
Preliminary results from ongoing clinical trials are promising, where hypo- and hyperglycemia were induced by bolus insulin and meal. For the first subject, the algorithm correctly decreased the basal rate by 50% when BG and ROC were 122 mg/dl and –0.78 mg/dl/min, respectively, and an hour later suggested pump suspension in order to prevent a more severe hypoglycemia (BG nadir was 53 mg/dl). For the second subject, the infusion rate was increased by 150% to prevent hyperglycemia following a 15-gram carbohydrate meal; the glucose level was maintained between 111 and 117 mg/dl. Simulation studies conducted on 10 adults from the University of Virginia diabetes simulator following a 24-hour protocol with a breakfast of 70 grams of carbohydrate at 8 am and a bolus of 2 units of rapid-acting insulin at 4 pm successfully maintained, on average, 95.4% of BG values between 60 and 180 mg/dl.

Conclusion:
Because of its simplicity, adaptive basal therapy could work as a bridge from open-loop therapy to closed-loop therapy. Further clinical trials are currently underway.

Use of Personalization of Fuzzy Logic Controller for Physician Decision Making Based on Extremes in Meal Size Using *in Silico* Testing

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Objective:
This study evaluated the effectiveness of using a range of fuzzy logic controller (FLC) personalization factors (PF) as a physician's means of tuning a FLC for individual patients using an extreme range of meal sizes.

Methods:
Testing was done using University of Virginia diabetes simulation on 10 adults, 10 adolescents, and 10 children for meal sizes ranging from 40 to 200 grams of carbohydrate and each of five PF values 1–5 with lower factors being more aggressive treatment. End points included average blood glucose (BG_{avg} mg/dl), low blood glucose risk index (LBGI), high blood glucose risk index, and seven others. The test scenarios ran for 24 hours.

Results:
Using PF1–5 in adults, BG_{avg} values for the 40-gram meal were 100, 110, 118, 126, and 133; an 80-gram meal, 101, 112, 121, 129, and 137; a 120-gram meal, 94, 110, 125, 135, and 143; a 160-gram meal, 97, 111, 127, 143, and 152; and a 200-gram meal, 105, 120, 137, 153, and 165, respectively. LBGI values for the 40-gram meal were 3.1, 1.2, 0.4, 0.1, and 0.0; the 80-gram meal, 7.9, 3.7, 1.7, 0.8, and 0.3; the 120-gram meal, 35.7, 19.0, 4.7, 2.0, and 0.9; the 160-gram meal, 44.2, 33.0, 17.0, 3.8, and 1.7; and the 200-gram meal, 45.3, 34.0, 18.5, 6.0, and 2.1, respectively. Similar findings were obtained in adolescents and children.

Conclusion:
Personalization factors provide physicians an insightful way of tuning the FLC for individual patients to provide the appropriate balance of blood sugar control against the risk of hypoglycemia and hyperglycemia. The FLC personalization method may also allow patients to tailor their own insulin dosing from day to day.

Improved Noninvasive Continuous Glucose Monitoring Device for Glycemic Management

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Background and Objectives:
OrSense has developed a noninvasive blood monitor (NBM) device, which is a general platform for the noninvasive analysis of blood constituents. It has recently been introduced into the market for the fully noninvasive continuous monitoring of hemoglobin and oxygen saturation. The device is based on red/near-infrared occlusion spectroscopy technology, which has been shown previously to measure blood glucose (BG) accurately. The NBM uses a multiwavelength, ring-shaped sensor that is placed on the finger. The pressure applied by the pneumatic cuffs of this sensor temporarily occludes the blood flow in the finger, thereby creating a unique, dynamic optical signal that facilitates accurate glucose measurement. This study evaluated the performance of a new sensor, which includes improved mechanical and optical design, as well as a new calibration scheme. The device was operated in a *profiler* mode, which reports the daily BG profile at the end of each daily session.

Materials and Methods:
The trial was carried out in a home-like setting. The probe of the NBM was placed on each patient's thumb, where it performed noninvasive continuous measurements for up to 10 hours, with readings every 10 minutes. Four calibration points were used in each session in proximity to breakfast and lunch times (one calibration point just before each meal and another, 1 hour after each meal starts). Accuracy was assessed by comparing NBM data with paired self-monitoring blood glucose meter readings (FreeStyle, Abbott Inc.) taken at 30-minute intervals.

Results:
A total of 150 sessions were carried out on nine patients (seven females, 2 males; 26–70 years old; four type 1, five type 2; six subjects participating in 20–26 sessions each, and three others in 2–4 sessions). Twenty sessions were excluded from analysis due to calibration failures as identified by our algorithm. Reference BG values were in the range 47 of 378 mg/dl. In all cases there was good patient compliance and no adverse effects were identified. The median relative absolute deviation was 11.2%. Clarke error grid analysis based on 1926 paired data points showed that 98.3% of the results were in the A+B zone, with 68.8% in the clinically useful A zone, 29.5% in the clinically benign B zone, and none in the potentially dangerous E zone. The Deming regression slope was 1.0 (assuming $\lambda = 1$).

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Conclusions:
This study substantiates the potential use of the NBM device from OrSense as a noninvasive sensor for continuous BG monitoring. The device was comfortable for subjects, safe, and well tolerated. Continuing trials further examine use of this truly noninvasive continuous glucose monitoring device in settings such as hospital critical care and home-like scenarios.

Safety of Overnight Closed-Loop with FreeStyle Navigator® Continuous Glucose Monitoring System and Model Predictive Control Algorithm: *In Silico* Assessment

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Objective:
Hypo- and hyperglycemia during closed-loop (CL) insulin delivery based on subcutaneous glucose sensing may arise due to (i) over- and underdosing of insulin by control algorithm and (ii) differences between plasma glucose (PG) and sensor glucose, which may be transient (kinetics origin and sensor artifacts) or persistent (calibration error). The objective of this study was to assess the safety of overnight CL using simulations and make comparison with open-loop (OL) studies in young people with type 1 diabetes (T1DM) treated by continuous subcutaneous insulin infusion.

Methods:
A simulation environment comprising 18 virtual subjects with T1DM and combining experimentally derived characteristics of FreeStyle Navigator® (FSN) sensing error was used to simulate the overnight CL study with the model predictive control (MPC) algorithm. A 15-hour-long experiment started at 17:00 and ended at 08:00 the next day. CL commenced at 21:00 and continued for 11 hours. At 18:00, the protocol included a meal (50 grams CHO) accompanied by prandial insulin. The MPC algorithm advised on insulin infusion every 15 minutes.

Results:
Episodes of severe (PG <36 mg/dl) and significant (PG <45 mg/dl) hypoglycemia and hyperglycemia (PG >300 mg/dl) were extracted from 18,000 simulated CL nights. Severe hypoglycemia was not observed when the calibration error was less than 45%. Hypo- and hyperglycemia frequency during OL was assessed from 21 overnight studies in 17 young subjects with T1DM (eight males; age 13.5 ± 3.6 years; body mass index 21.0 ± 4.0 kg/m^2; duration diabetes 6.4 ± 4.1 years; hemoglobin A1c 8.5 ± 1.8%; mean ± standard deviation). Severe and significant hypoglycemia occurred once every 133.3 and 5.8 years during CL compared to once every 21 and 10.5 days during OL, respectively. Hyperglycemia occurred once every 69.6 weeks during CL and once every 2.3 days during OL.

Conclusion:
Simulations with experimentally derived FSN error indicate that overnight CL with FSN and MPC control reduces the risk of hypo- and hyperglycemia substantially.

Material–Tissue Interactions: Making Sense of Changes in the Interstitial Analyte Balance at a Sensor–Tissue Interface

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Objective:
The very presence of an implanted sensor (a foreign body) causes changes in the adjacent tissue that may alter the analytes being sensed. The objective of this study was to investigate changes in glucose availability and local tissue metabolism at the sensor–tissue interface in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).

Method:
Microdialysis was used to model implanted sensors. Capillary glucose and subcutaneous (SQ) microdialysate analytes were monitored in five T1DM and five T2DM patients. Analytes included glucose, glycolysis metabolites (lactate, pyruvate), a lypolysis metabolite (glycerol), and a protein degradation by-product not produced in SQ (urea). On 8 consecutive days, four measurements were taken during a period of steady-state blood glucose.

Result:
Microdialysate glucose and microdialysate:blood glucose ratio increased over the first several days in all patients. Although glucose eventually stabilized, lactate levels continued to rise, likely explained by histological signs of local inflammation. Pyruvate in the T2DM microdialysate was significantly higher than T1DM, possibly explained by mitochondrial dysfunction in T2DM. Glycerol in the T2DM microdialysate (but not T1DM) was higher than in healthy volunteers, likely explained by SQ insulin resistance (insulin is a potent antilipolytic hormone). Urea was also higher in the microdialysate of patients with DM compared to healthy volunteers. Urea is a by-product of protein degradation, which is known to be inhibited by insulin. Therefore, insulin deficiency or resistance may explain the higher urea levels.

Conclusion:
Monitoring metabolic changes at a material–tissue interface combined with biopsy histology helped formulate an understanding of physiological changes adjacent to implanted glucose sensors. Microdialysate glucose trends were similar over 1 week in T1DM and T2DM; however, differences in other analytes indicated that wound healing and metabolic activities in the two patient groups differ. We propose explanations for the specific observed differences based on differential insulin insufficiency/resistance and mitochondrial dysfunction in T1DM vs T2DM.

Closed-Loop Insulin Delivery Device: Fabrication and Evaluation of Self-Regulated Insulin Release *in Vitro* and *in Vivo*

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Objective:
The goal of this study was to design, fabricate, and evaluate an innovative implantable device for self-regulated insulin release *in vitro* and *in vivo*.

Method:
A self-regulating, glucose-responsive insulin delivery device was prepared to continuously monitor the glucose concentration and regulate insulin release. An insulin stock solution was encased in the device made from surface-modified silicone material and a hybrid bioinorganic nanocomposite glucose-responsive plug, which served both as a glucose sensor and as an insulin-controlled delivery unit. *In vitro* insulin release was determined at 37°C in buffer solutions at various glucose levels relevant to diabetes patients (e.g., 100, 200, or 400 mg/dl in several alternated cycles). To evaluate the *in vivo* performance, the device was implanted subcutaneously in streptozotocin-induced diabetic rats, and glucose levels and the body weight of the rats were monitored for 7 days.

Result:
In vitro experiments showed that insulin release can be modulated in response to glucose concentration. A 3.7-fold increase in the rate of insulin release was observed when the glucose concentration was increased from normal to hyperglycemic levels. When the glucose concentration was reduced to a normal level, the insulin release rate returned to the baseline level. The insulin release profile exhibited a pulsatile pattern when the glucose concentration was abruptly alternated between normal and hyperglycemic levels in several cycles. The device released insulin up to 5 days and lowered the blood glucose in diabetic rats in comparison to the control group.

Conclusion:
A self-regulated, glucose-responsive insulin delivery device was designed and fabricated successfully. The closed-loop behavior of the device allows for regulated insulin release in response to normal or hyperglycemic glucose concentration in an analogous fashion to a healthy pancreas.

Stability of ITCA 650 for Continuous Subcutaneous Delivery of Exenatide at Body Temperature for up to 12 Months

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Objective:
The goal of this study was to stabilize exenatide for zero-order delivery from DUROS® devices for 3, 6, and 12 months at body temperature.

Method:
The DUROS drug delivery device provides continuous administration of therapeutic molecules at steady rates. The DUROS device is an osmotically driven pump consisting of a small sterile titanium cylinder (4 × 45 mm) that is inserted subcutaneously. Exenatide was formulated into proprietary suspensions containing selected stabilizers and excipients to achieve stability in the DUROS devices for long durations at body temperature (37°C). The stability of exenatide was characterized using reversed-phase high-performance liquid chromatography (RP-HPLC), size-exclusion high-performance liquid chromatography (SEC-HPLC), strong cation-exchange high-performance liquid chromatography, and three bioassay methods. *In vitro* delivery of the formulations was performed at 37°C, and the released formulation was characterized by the RP-HPLC method as a function of time.

Result:
Exenatide was formulated successfully for continuous delivery of 5, 10, 20, 40, or 60 μg/day from DUROS devices for durations up to 12 months. These formulations maintained the stability of exenatide in the DUROS devices at 25 and 40°C for at least 12 months in formal stability studies. Results from analysis of the formulations at 12 months for purity were 99.7 and 99.6% by RP-HPLC and 99.8 and 99.7% by SEC-HPLC at 25 and 40°C, respectively. The bioactivity of the exenatide in the formulations was comparable with its reference standard at all time points and conditions. ITCA 650 exhibited zero-order *in vitro* drug release profiles over the designed delivery durations.

Conclusion:
Exenatide was formulated successfully in various strengths and showed desired stability in DUROS devices. ITCA 650 delivered exenatide at continuous and consistent rates for up to 12 months.

Reengineering Salivary Glands to Secrete Insulin by Reconstructed Adenoassociated Virus Expressing Glucagon-like Peptide 1 *in Vivo*

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Objective:
The goal of this study was to explore the feasibility of using salivary glands (SGs) as a bioreactor expressing insulin to treat diabetes and to observe the possible pathologic and/or transdifferentiate effects of continuous/long-term expression of glucagon-like peptide 1 (GLP-1).

Method:
We constructed the adenoassociated virus (AAV) secreting expression of both GLP-1 and green fluorescent protein (GFP). The submandibular SGs of adult male SD rats were transduced successfully through oral retrograde infusion technology. At 2, 4, and 8 weeks post-transduction, the histological slides of submandibular SGs were stained with hematoxylin/eosin; immunohistochemistry and immunofluorescence performances were used to confirm the expression of GLP-1, insulin, and pyruvate dehydrogenase complex, component X (PDHX).

Results:
Glucagon-like peptide 1 and GFP were expressed continuously within the duct cells of submandibular SGs in long term (8 weeks post-transduction). Duct cells expressing GLP-1 were proliferated and transdifferentiated into insulin production cells. Duct cells expressing GLP-1 not only display cytoplasm GLP-1 positive brown particle, but also show strong positive shading in nuclei. Furthermore, these GLP-1 positive duct cells also showed expression of PDHX, a key transcription factor for insulin production. A full pancreatectomy was performed in these rats transduced with reconstructed AAV (rAAV) after 8 weeks. Without a pancreas, plasma insulin levels were also increased in venous glucose stimulation experiments.

Conclusion:
Our study showed that duct cells transduced with GLP-1, in submandibular SGs, are able to secrete insulin and control the balance of blood glucose after the blood level rises, just like pancreas islet β cells. Our results provide an example of pancreatic reengineering using rAAV expressing GLP-1 in an adult salivary organ and illuminate a particular view in the cellular reprogramming paradigm in addition to the pluripotent stem cell state.

Evaluation of Diabetic Foot Ulcer Development with Hyperspectral Imaging of Oxyhemoglobin and Deoxyhemoglobin

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Objective:
Foot ulceration remains a major and costly health problem for diabetes patients and has a major impact on the cost of diabetes treatment and associated comorbidities. Early detection and preemptive action can reduce the risk of further complications greatly. We have tested a new hyperspectral imaging technology that evaluates microcirculation by quantifying cutaneous tissue hemoglobin oxygenation as a tool for preemptive detection of diabetic foot ulcer development.

Method:
A prospective single-arm blinded study enrolled 210 patients with type 1 and 2 diabetes mellitus and followed them over a 24-week period with 11 total visits. Clinical, medical, and diabetes histories were collected. Superficial tissue oxyhemoglobin and deoxyhemoglobin were measured with hyperspectral imaging. In 24 cases, patients developed diabetic foot ulcers during the course of the study. Oxyhemoglobin and deoxyhemoglobin values were analyzed retrospectively at these known preulcer sites.

Result:
An algorithm was developed based on the retrospective analysis that differentiates preulcerous tissue from surrounding healthy tissue with 92% sensitivity and 80% specificity. Receiver operating characteristic analysis was also performed to give a range of sensitivity/specificity resulting in a Q value of 86%.

Conclusion:
Hyperspectral imaging of tissue oxyhemoglobin and deoxyhemoglobin may be a highly sensitive and specific method to predict the location of developing foot ulcers in diabetes patients based on information obtained from a single visit.

Noninvasive Monitoring of Cutaneous Hemodynamic Functions with a Multisensor System for Metabolic Monitoring

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Objective:
Monitoring of tissue metabolic status is important for the assessment of the conditions of patients with diabetes mellitus. It has also been reported that knowledge of the biophysical skin status in combination with measurements of the various metabolic parameters can improve the quality of glucose estimation by noninvasive glucose monitoring systems. The metabolic status of cutaneous tissue is, to a large extent, determined by the status of blood dynamics. A compact wearable multisensor system incorporating diffuse reflectance optical sensors has been developed for simultaneous and real-time assessment of skin hemodynamic parameters, such as pulse, blood perfusion, plethysmographic amplitude, and tissue oxygenation, combined with activity monitoring using acceleration and skin temperature sensors.

Method:
Preliminary evaluation of the system was performed in the laboratory and a home-use setting in healthy subjects and in clinical settings in patients with type 1 diabetes mellitus (T1DM) undergoing hyperglycemic excursions. Reference measurements of arterial blood oxygenation and pulse were obtained with a clinical pulse oximeter. In laboratory experiments, cutaneous blood perfusion has been affected by standard protocols, such as local warming and venous and arterial occlusions.

Results:
The multisensor system demonstrates high sensitivity to changes in cutaneous blood perfusion and flow, as well as tissue oxygenation induced in laboratory settings. High stability of the measurements can be observed even in a home-use setting, when movements are not restricted. Pulse estimates of the multisensor system are in good agreement with reference oximetry with an accuracy of ±3.5 beats per minute for a 5-second averaging interval. In home-use settings with unrestricted activities, pulse and plethysmographic signals can be estimated from more than 61% of the recorded intervals. In the clinical setting the signal-to-noise ratio of the skin perfusion measurements is above 28 ± 3 dB (mean ± standard deviation). Observed body and skin hemodynamics reveal complex dependencies from the blood glucose level that will stimulate further investigation. Compared to hyperemia (maximum perfusion induced by local heating, set as 100%), skin perfusion during hypoglycemic challenges reached 35.2 ± 11.6% and during hyperglycemic challenges reached 21.2 ± 6.4%, respectively.

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Conclusion:
The multisensor system can provide robust and reliable characterization of the skin hemodynamical function. Additional studies are planned for further evaluation of system performance in the home-use setting on patients with T1DM.