Abstracts

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Acute Pulmonary Effects of AFREZZA™ Inhalation Powder Administered Using a Gen2 Inhaler Compared to a MedTone® Inhaler

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Objective:
MannKind Corporation has conducted studies with AFREZZA™ using the MedTone® and Gen2 inhalers. This trial was designed to evaluate bioavailability of insulin delivered using these two inhalers and the acute effects on lung functions immediately after inhalation.

Methods:
Spirometry was performed according to the American Thoracic Society/European Respiratory Society standards at screening and before and after each inhalation of AFREZZA using several different doses of AFREZZA in both inhalers [part I, 20 U Gen2 and 30 U MedTone; part Ib, Gen2 22 U and MedTone 30 U; part II, 10 and 20 U Gen2 and 15 and 30 U MedTone; part III, 20 U Gen2 and 30 U MedTone for two consecutive days]. All tests were submitted electronically for centralized quality review.

Results:
There were no meaningful acute forced expiratory volume in 1 s [FEV_1 (liter)] changes observed from pre- to post-AFREZZA inhalation at 17, 33, 63, or 123 min as follows for Gen2, part I = -0.02, -0.01, -0.04, and 0.02; part Ib = -0.03, -0.02, -0.02, and -0.01; part II = -0.05, -0.04, 0.02, and -0.02; and part III = 0.04, -0.01, 0.03, and 0.05; and for MedTone, part I = -0.10, -0.10, -0.04, and -0.01; part Ib = -0.07, -0.05, -0.06, and -0.07; part II = -0.10, -0.09, -0.12, and -0.15; and part III = -0.08, -0.09, -0.06, and -0.06.

Conclusion:
The acute FEV_1 changes after the administration of AFREZZA with either the Gen2 inhaler or the MedTone inhaler were small and clinically not meaningful. The observed changes in FEV_1 with the Gen2 inhaler were relatively smaller compared with the MedTone inhaler, irrespective of the sequence in which the inhalers were used.

Estimation of Plasma Glucose Values in Type 2 Diabetes Subjects Using BodyMedia Armbands

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Objective:
The objective of the study was to demonstrate the armband's ability to estimate plasma glucose values for restful conditions during the oral glucose tolerance test (OGTT) protocol and for motion-based physical activity.

Methods:
This ongoing study recruited subjects with type 1 and type 2 diabetes. For each subject, the glucose values were obtained by an automated glucose analyzer (plasma oxidase method). All subjects wore the armband on the upper left arm during the trial. The armband measured movement, heat flow from the body, skin temperature, electrocardiogram, and galvanic skin response and estimated energy expenditure, heart rate, and heart rate variability. Data for each subject were collected in two different scenarios: (1) in multiple time points during a restful OGTT protocol and (2) in motion activity (walking at different speeds on a treadmill) under controlled conditions. Separate models were developed for each scenario for predicting plasma glucose values from the data. The models were developed on eight type 2 diabetes subjects and evaluated using by-subject cross validation.

Results:
For the OGTT protocol, the average absolute error between estimated glucose values and plasma glucose values was 31.8 mg/dl (20%) and the correlation between values was 0.72. A Clarke error grid analysis between model predictions and the plasma glucose values yielded 98.8% of points falling in zones A and B. For the treadmill protocol, the average error between predicted glucose and plasma glucose was 13 mg/dl (13.6%) and the correlation between values was 0.9 (95% falling in Clarke error grid zones A and B).

Conclusion:
Preliminary results suggest that the armband is capable of estimating plasma glucose levels for both restful and physically active periods under controlled conditions.

Minimum Frequency of Glucose Measurements from Which Glycemic Variation Can Be Consistently Assessed

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Aims:
There has been considerable debate about the clinical importance of glycemic variation (GV), but little attention has been directed to the requirements for the datasets from which GV is calculated. The present study assessed the minimum frequency of glucose measurements from which GV can be consistently and meaningfully measured.

Methods:
Forty-eight 72 h continuous glucose monitoring traces from 48 children with type 1 diabetes were assessed. Measures of GV included standard deviation (SD), mean amplitude of glycemic excursion (MAGE), and continuous overlapping net glycemic action ($CONGA_{1-4}$). Measures of GV calculated using 5 min sampling were designated as the "100%" or "best estimate" value. Calculations were repeated for each subject using glucose values spaced at progressively longer intervals. For each specified sampling frequency, we then calculated the SD (between subjects) of the estimate based on the reduced subset of data, expressed as a percentage of the "best estimate" obtained using the full dataset with 5 min sampling.

Results:
As the intervals between consecutive observations increases, so does the uncertainty of estimators of GV. Standard deviation exhibited the least variability at all intervals, and MAGE exhibited the greatest variability.

Conclusions:
Mean amplitude of glycemic excursion is more unstable and prone to measurement error than both SD or CONGA. In patients with type 1 diabetes, the GV as measured by SD or $CONGA_4$ becomes unreliable if observations are more than 2–4 h apart; estimates of MAGE become unreliable if glucose measurements are more than 1 h apart. The frequency of glucose measurements can be pivotal in determining the choice of metric for GV.

A Model of Glucagon–Glucose Dynamics for Closed-Loop Glycemic Control

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Objectives:
Comprehensive models for insulin–glucose dynamics have been used to develop algorithms for a closed-loop artificial pancreas. While some control algorithms also manipulate glucagon to minimize the risk of hypoglycemia, current insulin–glucose models have not been extended to include the effect of glucagon. We propose a compartmental pharmacokinetic model to predict the effect of subcutaneous glucagon delivery on plasma glucagon concentration. We further incorporate a glucagon action model to account for the pharmacodynamics of glucagon on net endogenous glucose production. These modeling equations are incorporated into an existing model of insulin–glucose dynamics to form a comprehensive model relating both subcutaneous insulin and glucagon delivery on plasma glucose concentration.

Methods:
A total of 21 closed-loop experiments were carried out in subjects with type 1 diabetes. Subjects were treated with insulin to maintain euglycemia under closed-loop conditions. In some studies, during incipient hypoglycemia, glucagon boluses of 1 mcg/kg were commanded by the algorithm. Plasma insulin and glucagon levels were measured by radioimmunoassay, and insulin on board was calculated every 5 minutes. Using MATLAB software, pharmacokinetic and pharmacodynamic parameters for a three-compartment glucagon model were estimated.

Results:
Plasma insulin levels and calculated insulin on board were highly correlated (R = 0.83). The model effectively predicted glucagon concentration and effect. In addition, the model was able to predict that glucagon has a reduced ability to increase glucose concentration when the insulin on board is high.

Conclusions:
A comprehensive dynamic model relating subcutaneous insulin and glucagon delivery to blood glucose has been developed. This model can be used in simulation studies for closed-loop control; the effectiveness of glucagon delivery will be improved by concurrent prediction of insulin action.

Exterior Artificial Pancreas

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Objective:
The aim was to develop an automatic glucose control system that set the goal to keep glucose between 120 and 150 mg/dl.

Methods:
A pump-sized external artificial pancreas was designed through a computer (not physically) that uses one sensor to collect the current glucose levels from the human body. The sensor collects the current glucose level and sends the data to the artificial pancreas through wireless or cable. The artificial pancreas reads the received glucose value and, through an algorithm table with prerequisites of insulin and glucagon units for each received glucose value, decides how many insulin units are required to decrease the glucose or how many glucagons units are required to increase the glucose to prevent hypoglycemia. The logic is to use glucagons when levels are below 120 mg/dl and use insulin above 150 mg/dl. The artificial pancreas remains on standby when the glucose is between 120 and 150 mg/dl. The artificial pancreas was programmed to make automatic glucose tests every 8 min, while an "emergency test" button was added that allows the artificial pancreas to do an emergency glucose test and choose either glucagons or insulin.

Results:
The artificial pancreas automatically runs tests every 8 min, which means continuous glucose monitoring. It needs insulin that has a duration of 8 min and works instantly, not requiring daily insulin injections or glucose meters.

Conclusion:
The artificial pancreas provides hypoglycemia prevention, runs prerequisite glucose tests, runs emergency tests, and automatically chooses the units required between glucagons or insulin. Diabetes patients have to charge the battery, replace the cartridges of glucagons and insulin, and change the needle and sensor after some days. Ideally, this system is for patients 16 years old and above.

Practical Noninvasive Glucose Monitor Using Raman Spectroscopy

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Background:
In addition to demonstrating adequate measurement accuracy and safety, a practical, wearable, noninvasive glucose monitor requires a small footprint, sufficient battery life, comfortable mounting arrangements that do not impair activity or appearance, and convenient means of data communication. We report on major progress from results reported at DTM 2009 in achieving full compliance with these goals.

Methods:
Signal collection efficiency was optimized, and key platforms were modified to reduce size. Appropriate protocols for wireless communication with mobile handsets were implemented. Devices were fabricated and, mounting arrangements to the abdomen and thigh—which provide long-term comfort—and operational robustness to activity were also implemented. Experiments were undertaken to show that cross calibration between devices was practical. Preliminary data from human studies were collected.

Results:
Optical collection efficiency has been increased approximately three times, resulting in significant improvements in measurement accuracy. The volume of the device was reduced by about two-thirds, and the footprint of the revised design is 64 × 58 mm. Power consumption is consistent with >1 day of battery life. Blue tooth 2.1 communication protocol was implemented and communication with mobile smart phones demonstrated. Feasibility of a unified calibration for the family of devices was experimentally demonstrated. Scaling of accuracy with the size of the calibration set has been estimated. For statistically sufficient sets, this design is projected to have accuracy consistent with an 80–90% "A" zone (consensus grid) target. Preliminary results from testing on human subjects in support of regulatory approval will be discussed.

Conclusion:
A device design suitable for broad deployment to patients, including all necessary features for practical continuous noninvasive glucose monitoring, was demonstrated. Enabling technology that supports telemedicine applications was also implemented.

Continuous Glucose Monitoring: Exercise Training Level and Differences in Glucose Variability

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Objective:
We use continuous glucose monitoring (CGM) in subjects with type 1 diabetes mellitus to observe blood glucose (BG) changes during exercise and to quantify BG variability by fitness level (athlete, moderate exerciser, sedentary).

Methods:
All subjects wore CGM sensors (Dexcom, Inc., San Diego, CA) during a training camp. One athlete was from team type 1, and 12 subjects [7 women (1 athlete, 2 moderate exercisers, and 4 sedentary) and 5 men (2 moderate exercisers and 3 sedentary)] were part of Diabetes Training Camp, LLC.

Days had at least 80% of possible readings for each day and checked for completeness and calibrations. Variables included percentage in target (% target; 80–130 mg/dl); percentage in low (% low; <80 mg/dl); percentage in high (% high; >130 mg/dl); percentage coefficient of variation (% CV); minimum, mean, and maximum BG (mg/dl); and standard deviation (SD). Data were analyzed using one-way analysis of variance (SigmaStat, Systat Software, San Jose, CA).

Results:
Values described are mean ± SD. For the sedentary group (30 days), % target was 33.5 ± 14.4, % low was 8.5 ± 10.1, % high was 58.0 ± 22.3, and % CV was 31.6 ± 8.8. For the moderate exerciser group (42 days), % target was 38.0 ± 13.2, % low was 15.5 ± 11.6, % high was 46.5 ± 15.5, and % CV was 37.5 ± 8.2. For athletes (6 days), % target was 26.2 ± 13.3, % low was 6.0 ± 11.8, % high was 67.8 ± 18.7, and % CV was 36.0 ± 10.3. Groups were significantly different ($p \leq .01$) for % low, % high, and % CV.

Minimum, mean, maximum BG, and SD were 70.6 ± 22.1, 152.0 ± 35.5, 266.8 ± 62.8, and 47.4 ± 15.2 for the sedentary group, 50.6 ± 11.9, 135.2 ± 20.9, 256.5 ± 46.8, and 50.6 ± 13 for moderate exercisers, and 74.5 ± 25.9, 163.2 ± 22.5, 328.0 ± 54.3, and 57.3 ± 15.1 for athletes. Minimum and mean values were significantly different, $p < .01$, and maximum values were significantly different, $p < .05$.

Conclusion:
Exercise and fitness level must be considered when identifying patterns of glucose variability.

Tale of Two Women: Continuous Glucose Monitoring and Exercise

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Objective:
We use continuous glucose monitoring (CGM) to quantify blood glucose (BG) variation during exercise training.

Methods:
One woman (SK, 33 years, 132 lbs, 66") without type 1 diabetes from team type 1 wore a CGM device (Dexcom, Inc., San Diego, CA) during training and races (45 days), kept daily diet and activity records, and wore an activity monitor (Actical, Phillips Respironics/MiniMitter, Bend, OR) for 39 days. Another woman (BK, 28 years, 180 lbs, 70") with type 1 diabetes and a moderate exerciser training for a marathon wore a CGM device (28 days) and kept daily diet and activity records.

Days had at least 80% of total possible readings and were checked for completeness and calibrations. Variables included percentage in target (80–130 mg/dl); percentage in low (<80 mg/dl); percentage in high (>130 mg/dl); percentage coefficient of variation (% CV); minimum, mean, and maximum BG (mg/dl); and standard deviation (SD). Data were analyzed using one-way analysis of variance (SigmaStat, Systat Software, San Jose, CA).

Results:
Days were identified as sedentary/light, moderate, or vigorous exercise. Moderate exercise days were used for analysis. Values are mean ± SD. Percentages in target were 67.1 ± 13.5 and 33.7 ± 12.6 for SK (24 days) and BK (17 days), respectively, and significantly different, $p < .01$. Percentages in low were 20.8 ± 17.3 and 15.1 ± 11.0, percentages in high were 11.4 ± 10.3 and 51.2 ± 16.8, and % CVs were 22.3 ± 6.7 and 37.9 ± 6.2 for SK and BK, respectively. Percentage in high and % CV were significantly different, $p < .01$.

Minimum values were 57.8 ± 13.7 and 50.5 ± 13.0, means were 99.5 ± 12.4 and 140.2 ± 23.5, maximums were 169.8 ± 35.2 and 257.3 ± 44.0, and SDs were 22.3 ± 7.1 and 52.9 ± 10.5 for SK and BK, respectively. The mean, maximum, and SD were significantly different, $p < .01$.

Conclusion:
Continuous glucose monitoring is needed for longer time periods with detailed activity and diet records to determine variations in BG during exercise and the effect of fitness.

Efficacy of Tissue-Stimulation Tests for Patients with Diabetic Neuropathy through Infrared Thermography

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Background:
Temperature measurement using dynamic tests through physical as well as thermal stimulation of tissue provides an important measure of diminished or absent response of the thermoreceptors in diabetes patients.

Methods:
In this study, we recruited seven subjects in three groups [neuropathic (N = 2), non-neuropathic (N = 3), and healthy (N = 2)] to evaluate plantar foot temperatures through infrared thermography at baseline, 6 weeks, and 12 weeks. All subjects underwent a baseline temperature measurement, repetitive stress assessment, and cold recovery test at each visit. Delta T, the temperature difference from baseline, was calculated for both the stimulation tests.

Results:
For the cold recovery tests, the non-neuropathic diabetes group had the highest Delta T among the three groups and was statistically significant at the forefoot region when compared to the neuropathic group (p = .0085 for left foot, p = .01 for right foot) and the healthy group (p = .0059 for left foot, p = .007 for right foot). The differences were not statistically significant between the healthy and the neuropathic groups. The differences at the heel region were not statistically significant. For the repetitive stress tests, the differences were not statistically significant for either group but suggest poor thermoregulation during walking.

Conclusion:
The measured temporal response is linked to a complex interplay between plantar loading, tissue health (perfusion and metabolic status), and ambient conditions. The response is more pronounced at the forefoot region for cold immersion recovery because of punctuate distribution of the sensory receptors. The response at the heel is slower due to presence of adipose tissue, which may change the heat transfer characteristics.

Handleability and Characterization of Inhalation Profiles Using the Gen2 Delivery System in a Pediatric Population

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Objective:
AFREZZA™ [insulin human (rDNA origin)] is delivered to the lung with a proprietary delivery system (Gen2), which is an easy-to-use, breath-powered, high-resistance inhaler with single-use, unit-dose cartridges. The objective of this research was to evaluate the ability of a pediatric population to handle, assemble, and operate the Gen2 delivery system and to characterize the inhalation profiles (pressure versus time) without exposure to investigational drug.

Methods:
In total, 74 subjects were divided into five age groups: 4–5 years (n = 14), 6–8 years (n = 15), 9–10 years (n = 15), 11–13 years (n = 15), and 14–17 years (n = 15). Subjects were given a brief introduction to the system and then shown a sequence of pictures and scripted verbal instruction to demonstrate system assembly and operation. Inhalation profiles were measured using the BLUHALE™ inspiratory system.

Results:
All handling, assembly, and operation steps with the Gen2 inhaler were performed correctly by pediatric subjects 6 to 17 years of age. In the youngest population group, 92.9% of subjects were able to perform all steps correctly, with only 1 subject observed having difficulty with one step. All subjects in all age groups were able to demonstrate inhalations that exceeded the minimum required for acceptable device performance [characterized by area under the curve ($AUC_{0-1\,s}$) ≥ 1.2 kPa/s and piperacillin ($PIP_{0-2\,s}$) ≥ 2.0 kPa]. The mean values across all age groups for $AUC_{0-1\,s}$ and $PIP_{0-2\,s}$ were 3.4 kPa/s and 4.3 kPa, respectively.

Conclusion:
Pediatric subjects as young as 4 years of age can successfully handle, assemble, and operate the Gen2 delivery system.

Impact of Bolus and Food Calculator "Diabetics" on Glucose Variability in Children with Type 1 Diabetes Treated with Insulin Pump: Results of a Randomized Controlled Trial

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Objective:
High glucose variability during the day that results from difficulties and errors made in food counting and prandial insulin adjustments have influence on hemoglobin A1C levels. The aim of the study was to determine whether traditional food counting and the "Diabetics" software as food and bolus calculator have influence on glucose variability in children with type 1 diabetes treated with insulin pumps.

Method:
Patients were educated in food counting where carbohydrate unit and fat-protein unit were taken into account in prandial insulin dosing by normal-wave or dual-wave boluses and subsequently randomly allocated to the experimental group (GA), which used Diabetics, and group B (GB), which used caloric tables. This 3-month, randomized, open-label study included 48 children aged 1–18 years.

Result:
We noticed significant differences between groups in glucose variability parameters described by the mean of all glucose values ($Mean_T$), standard deviation of all glucose values (SD_T), percentage in target range 70–180 mg/dl , percentage above 180 mg/dl, and high blood glucose index (HBGI). Mean value and SD of glucose variability in GA versus GB presents as follows:

- $Mean_T$ (mg/dl): 136 ± 17 versus 154 ± 25; $p = 0.007$
- ST_T: 65 ± 13 versus 79 ± 18; $p = 0.002$
- Percentage in target range 70–180 mg/dl: 65 ± 10 versus 56 ± 10; $p = 0.005$
- Percentage above 180 mg/dl: 22 ± 9 versus 31 ± 12; $p = 0.005$
- HBGI: 5 ± 2 versus 8 ± 3; $p = 0.002$

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We did not observe statistically significant differences in percentage of glycemia values below 70 mg/dl and low blood glucose index.

Conclusion:
Introducing the Diabetics software as a bolus calculator stabilized glycemic profile. Moreover, the algorithm implemented in that software is a safety for patients with diabetes, as we did not observe more hypoglycemia events than in the control group.

Finesse™ Patch for Insulin Delivery Compared to Injected Insulin by Pen or Syringe in Adults with Diabetes Mellitus

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Objective:
This study compared a new insulin delivery patch, Finesse™, to multiple daily injections with pen/syringe to deliver prandial insulin for glycemic control and subject preference. Subjects continued their usual basal insulin.

Method:
A total of 38 adults with diabetes (26 type 1 and 12 type 2) participated in a multicenter, randomized, 6-week crossover study (6 weeks on Finesse™ and 6 weeks on usual injection device [55% pen, 45% syringe]). During the study, subjects followed their previously prescribed insulin regimen. Hemoglobin A1c (HbA1c) and 3-day seven-point self-monitored blood glucose were measured both at baseline and after 6 weeks of each device. Insulin delivery system rating questionnaires and diabetes-specific quality-of-life scales were done at baseline, crossover, and end of study.

Results:
At baseline, mean (standard deviation; range) subjects' age was 47.3 (15.4; 22–75) years and HbA1c 8.1 (0.7; 7.0–9.5)%. At crossover, an interim analysis for safety was performed using the results from 30 subjects (16 Finesse, 14 injection). There were no serious adverse device events. There was no difference in adverse events or insertion site reactions between Finesse versus injection. No subjects had any severe hypoglycemia episodes. The mean (standard error) daily blood glucose level using Finesse was similar to injection [157.1 (8.9) versus 162.6 (9.4) mg/dl] as was the HbA1c level [7.4 (0.2) versus 7.9 (0.1)%]. Of the first 16 subjects who used Finesse, 88% preferred Finesse versus injection, while none preferred injection. Finesse users reported improved quality of life versus pen/syringe users (6/7 versus 0/7 subscales).

Conclusion:
Delivering prandial insulin with Finesse achieved similar glycemic control versus usual injection methods. For intensive insulin therapy, Finesse is preferred over pen/syringe for bolus insulin.

Development of a Diabetes Behavior-Change Measurement Dashboard

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Objective:
In 2008, the American Association of Diabetes Educators convened the Behavior Score Workgroup with experts in the field of measurement, behavioral science, and diabetes education. The group oversaw the development of a behavior-score instrument and an accompanying behavior-score dashboard. The objective of this project is to share information about the design and development of the behavior-score dashboard.

Methods:
We designed the behavior-score dashboard to communicate with patients their diabetes behavior scores and the need for action on each of the AADE7 Self-Care Behaviors. We conducted two focus groups of diabetes educators in 2008 and field testing in 2009.

Results:
The diabetes educators participating in the focus groups recommended the use of graphics for the dashboard that were similar to stop and go lights or gas gauges in an automobile. We designed the dashboard with literacy and numeracy in mind. The behavior-score instrument feeds into the dashboard to calculate and present scores for each of the AADE7 Self-Care Behaviors and a composite score. Responses to questions on the behavior-score instrument translate into a numeric score that is represented on the dashboard as a green light, yellow light, or red light.

Conclusion:
Following field testing, we adjusted the dashboard to make it usable in practice. A next step includes pilot testing the behavior-score dashboard to validate it as an effective component of diabetes self-management education.

In Vitro Evaluation of a Novel Viscometric Affinity Sensor for Continuous Glucose Monitoring

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Objective:
We propose a novel sensing mechanism for continuous glucose monitoring based on the glucose-dependent viscosity of a sensitive solution. Affinity sensing offers several advantages over electrochemical methods, bringing better stability in subcutaneous tissues. Moreover, the sensor incorporates technologies requiring low power and enabling extreme miniaturization achievable through microelectromechanical systems (MEMS) fabrication, therefore leading to a well-suited device for long-term implantation.

Methods:
A prototype of the sensor was realized using two piezoelectric diaphragms, a microchannel exhibiting a resistance to the flow circulating through, and a nanoporous anodic alumina oxide membrane as selective interface. The sensor was extensively tested *in vitro*, in buffer solution during more than 25 days, and in fetal bovine serum during several days. Solutions with two physiologically relevant glucose concentrations (2 and 12 mM) were sequentially pumped in the vicinity of the sensor.

Results:
The sensor showed a very good stability and reproducibility over more than 25 days in buffer solution at 37 °C. In fetal bovine serum, a small loss of sensitivity was noticed, but the stability and reproducibility were still remarkable. Moreover, the response time of the sensor did not increase in fetal bovine serum. Biofouling due to protein adsorption on the nanoporous membrane is therefore not an issue.

Conclusion:
A prototype of a viscometric affinity sensor for continuous glucose monitoring was realized and extensively tested *in vitro*. The sensor was shown to work well both in buffer solution and in fetal bovine serum. The sensing mechanism is therefore very promising and could possibly enable long-term implantable glucose sensing in the future. Miniaturization of the device using MEMS technology and extensive *in vivo* tests will be the next forthcoming steps.

Safety Supervision System: First Clinical Trials

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Objective:
Safety is fundamental to ongoing developments of continuous glucose monitoring (CGM)-enhanced insulin pumps. We demonstrate the feasibility of a safety supervision system (SSS) for insulin treatment of type 1 diabetes mellitus (T1DM) and its capacity to reduce hypoglycemia and hyperglycemia risks in 10 T1DM subjects during an exercise protocol.

Methods:
The SSS uses CGM and insulin pump feedback to perform three functions: (1) detect imminent hypoglycemia, (2) attenuate insulin delivery, and (3) intercept boluses potentially requiring additional carbohydrate. In addition, the system mitigates hyperglycemia by automatically injecting hourly correction boluses calculated using the patient's correction factor.

Ten T1DM patients followed a randomized crossover protocol at Montpellier University Hospital and the University of Virginia using a CGM device (Abbott Navigator® or Dexcom 7®) and an insulin pump (Omnipod). Admissions contained meal challenges and moderate exercise. The SSS was activated during the treatment admission from 2:00 PM to 8:00 AM.

Results:
When the SSS was active, (i) 100% of hypoglycemic events were detected at least 10 min in advance; (ii) overall hypoglycemic events were reduced two-fold 12 versus 6 as follows: hypoglycemia during exercise was unaffected (3 versus 2), hypoglycemia postexercise (3 versus 1), and overnight (5 versus 3) was significantly reduced; and (iii) 100% of meal boluses were intercepted. In addition, average glucose was reduced, 136 versus 155 (p = .033), and percentage in target ranges 70–180 and 80–140 mg/dl increased, 82% versus 66% (p = .007) and 54% versus 38% (p = .018), respectively.

Conclusion:
We demonstrated that the SSS is capable of significantly improving glucose control in adults with T1DM, detecting in advance all hypoglycemic events and reducing hypoglycemia two-fold during an exercise protocol. The results are consistent with previous *in silico* testing data.

Use of a Hybrid Closed Loop to Restore Metabolic Control at the Onset of Diabetes

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Objective:
As part of a randomized controlled trial, we have utilized the Medtronic MiniMed ePID system to rapidly restore metabolic control within 7 days of the diagnosis of diabetes. This system combines an external subcutaneous insulin infusion pump and subcutaneous sensor with a proportional-integral-derivative insulin infusion rate algorithm, which also utilizes insulin feedback. The goal of these is to restore euglycemia as rapidly as possible and to facilitate islet-cell recovery following the diagnosis of diabetes.

Methods:
Subjects are admitted within 1 week following the diagnosis of diabetes for 3 to 4 days of hybrid closed loop therapy. About 75% of the estimated insulin for a meal is given prior to the meal. There are no food restrictions, and subjects often have meals of 1.5–2 g/kg of carbohydrate. Blood glucose levels are obtained every half hour with the reference device.

Results:
The system was utilized an average of 3 days for a total of 711 h in 11 subjects. The average insulin dose was 1.2 U/kg/day. The mean sensor glucose was 134 mg/dl, and 0.2% of readings were <50 mg/dl, 0.5% were 50–59 mg/dl, 1.2% were 60–69 mg/dl, 85% were 70–179 mg/dl, 5.9% were 179–200 mg/dl, 6.2% were 201–250 mg/dl, and 1.1% were >250 mg/dl. There were no severe hypoglycemic or hyperglycemic events.

Conclusion:
Hybrid closed-loop therapy can rapidly and safely restore metabolic control in the week following the diagnosis of diabetes.

Decoupling Continuous Glucose Monitoring Sensor Response Linearity and Lag

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Objective:
Continuous glucose monitoring (CGM) system characterization is important for artificial pancreas use, because these factors can influence glucose control errors. Methods of evaluating linearity can be confounded by lag, noise, and apparent nonlinearities due to data distribution. For example, a perfectly linear system with lag can appear to have an affine relationship when a least-squares-error-fit of a line is performed. An offline method to determine the linearity and lag of CGM systems is presented. Artificial pancreas use of CGM systems is limited by federal (United States) law to investigational use only.

Methods:
Pairs of CGM and reference glucose readings were used to determine effective lag and residual difference across reference glucose levels in order to identify linearity and effective lag across different glucose levels. Static nonlinearity not properly compensated by the CGM system can be identified with this analysis. Data from previously published (registration numbers NTC00920881 and NCT01076218) FreeStyle Navigator® CGM systems were used as an example.

Results:
The FreeStyle Navigator CGM system data exhibited a static linearity with a glucose-range-dependent R^2 value of 0.9998, an offset of 5.4 ± 1.0 mg/dl, a slope of 0.97 ± 0.0, and an effective lag of 10.9 ± 0.3 min across the glucose range. In contrast, paired points regression suggests an offset of 13.4 ± 1.2 mg/dl and a slope of 0.93 ± 0.0. Robustness is demonstrated by evaluating the effective linearity and lag when the CGM signal is perturbed by a polynomial nonlinearity or by a combination of added gain and offset.

Conclusion:
An offline method to assess the linearity of a CGM system was presented. The method was shown to robustly identify linearity over the glucose range without influencing apparent lag.

Bolus Advice Use, Metabolic Control, and Treatment Satisfaction with a New Integrated Insulin Pump System

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Objective:
To evaluate the effects of day-to-day use of a new integrated insulin pump system on metabolic control, treatment satisfaction, and patient safety.

Methods:
Adult patients on continuous subcutaneous insulin infusion therapy for ≥6 months with hemoglobin A1c (HbA1c) ≤10% were included in this prospective study conducted at nine sites (United Kingdom/Netherlands). Subjects were trained on the Accu-Chek Combo system comprising an infusion pump and a smart blood glucose meter integrating various advanced features, including a unique bolus advice algorithm and remote control of the pump. Hemoglobin A1c values were measured at baseline and at months 1, 3, and 6. Device data were downloaded at study visits. The standardized diabetes treatment and satisfaction questionnaire (DTSQ) and additional questionnaires were used.

Results:
A total of 86 patients (73 type 1, 13 type 2) were enrolled, and 80 patients completed the study. Hemoglobin A1c was 7.9% ± 0.9% at baseline with a mean change of -0.34% ± 0.67% after 6 months (n = 74; p < .001, signed-rank test). The frequency of severe hypoglycemia (third-party help) was 0.08 events per patient year. There was no case of ketoacidosis. Treatment satisfaction at baseline was high (DTSQ status score 31.3 ± 3.8; scale score 0–36) and significantly increased to study end (DTSQ change score 10.6 ± 7.2; scale score -18 to +18; p < 0.0001 Wilcoxon signed-rank test). Overall satisfaction with the system was high (5.9 ± 1.6 on a 1–7 scale). The majority of patients used default settings for the new bolus advice parameters and did not adjust them during the study.

Conclusion:
The new integrated infusion pump system and use of the default bolus advice settings for the new parameters unique to the algorithm proved to be safe and effective in everyday use. The system has the potential to improve metabolic control and treatment satisfaction.

Prospective Data Evaluation of the Application of a Multisensor Device for Noninvasive Continuous Glucose Monitoring

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Introduction:
In this study, a multisensor version with fully integrated sensors and battery in a miniaturized housing (54 × 65 × 13 mm) was experimentally tested to compare the outcome to previous findings using earlier versions.

Materials and Methods:
Six type 1 diabetes patients (aged 44 ± 16 years, body mass index 24.1 ± 1.3 kg/m^2, duration of diabetes 27 ± 12 years, hemoglobin A1c 7.3 ± 1.0%) wore the same multisensor on the upper arm. In total, these patients performed 45 in-clinic study days; each patient performed, on average, 7 study days (minimum 5 days and maximum 10 days). A study day lasted approximately 10 h and glucose changes were induced by the administration of an oral or intravenous glucose solution. The first 22 study days' data spanning all subjects were used to train a linear regression model. The global model derived was then prospectively applied to the data of the remaining 23 study days, allowing for external validation. One initial baseline adjustment at the very beginning of each study day was used to adjust the level of the glucose estimate.

Results:
When comparing the estimated glucose to the blood glucose reference values, the model yielded a mean absolute relative difference of 40.8%, a mean absolute difference of 51.9 mg/dl, and an R^2 of 0.70, on average, per study day. The Clarke error grid analyses showed 89.0% of paired glucose values in zones A and B, 4.5% in C, 4.6% in D, and 1.9% in E.

Conclusions:
This work demonstrates that glucose variations under controlled conditions can be monitored noninvasively by a prospectively applied multiple regression statistical model. The findings from this study indicate that further development steps in the multisensor system should not affect the estimation performance.

Simultaneous Noninvasive Continuous Glucose Monitoring on the Left and Right Arms Using Two Multisensor Devices

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Introduction:
We have previously reported the findings of clinical–experimental studies with a novel multisensor system for noninvasive continuous glucose monitoring. In this study, a multisensor version with fully integrated sensors and battery in a miniaturized housing (54 × 65 × 13 mm) was experimentally tested, investigating location-related characteristics.

Materials and Methods:
Four type 1 diabetes patients (aged 43 ± 9 years, body mass index 24.5 ± 3.7 kg/m^2, duration of diabetes 22 ± 11 years, hemoglobin A1c 7.7% ± 0.5%) performed 4 in-clinic study days with a multisensor attached to the left and right upper arms. As a result, 32 data sets from 16 study days were obtained. The multisensors were exchanged between the patients and the left and right arm according to a Graeco-Latin square. Glycemia was varied using four different glucose profiles. Global (identical coefficients) and personal (personal coefficients) models were used for cross validation.

Results:
In each model, an initial baseline (IB) calibration was used at the beginning of each study day as well as a full day baseline (FB) calibration, with average R^2 = coefficient of determination on average over the study days, mean absolute difference (mg/dl), and mean absolute relative difference (%). Global IB: 0.76, 47, 32.3; global FB: 0.75, 29.9, 21.3; personal IB: 0.85, 43.3, 30.7; personal FB: 0.84, 24.1, 17.6. Clarke error grid analysis for IB global model yielded A 44.9%, B 48.0%, C 3.6%, D 3.0%, and E 0.5%.

Conclusion:
The glucose time courses estimated by the multisensors from the two arms are repeatably comparable, even with a global model with one IB calibration only. This indicates that the sensor signal characteristics are robust enough to allow changing from one arm to the other using the same device settings and calibration.

Improving Closed-Loop Control by Considering Uncertainty and Minimizing Clinical Risk

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Objective:
Uncertainty in blood glucose (BG) control exposes the patient to risk of diabetic complications. Closed-loop controllers should act to reduce estimated risk. We present a novel extended model-predictive controller (EMPC) that explicitly minimizes the combined risk of hypoglycemia and hyperglycemia using predictions of the BG value and standard deviation.

Method:
The controller infuses subcutaneous insulin to minimize a novel, controller-friendly risk function, such as the blood glucose risk index (BGRI), over multiple possible BG trajectories spread around the predicted mean trajectory by multiples of the standard deviations. The predictions stem from multiple linear meal-glucose-insulin models that are weighted according to their agreement with the continuous glucose data and meal probabilities. The meal probabilities encode what humans eat when awake and wait between meals.

Result:
Prediction on simulated and clinical data resulted in more accurate and robust uncertainty estimates, a 25% reduction in meal detection time relative to published work, and reduced root mean squared error for 1-, 2-, 3-, and 4-hour predictions by 6%, 15%, 28%, and 40% and 19%, 24%, 35%, and 46% relative to a predictor with and without linear meal detection. We compared control performance with a published proportional-integral-derivative (PID) controller and a linear five-state glucose–insulin-based model-predictive controller (MPC) tuned to minimize the BGRI. Using the University of Virginia/Padova Diabetes Simulator, the controllers (PID/MPC/EMPC) achieved BGRI values of high, 4.18, and 2.86 for adult patients controlled over 36 h with six unannounced meals. These correspond to 74%, 86%, and 90% of time spent euglycemic ($70 < BG < 180$ mg/dl).

Conclusion:
Incorporating meal probabilities improves uncertainty estimation and markedly improves prediction accuracy. Minimizing the combined hypoglycemic/hyperglycemic risk using estimated uncertainties and meal probabilities leads to noticeable improvements in control behavior, 30% lower BGRI, and 29% less time spent outside the euglycemic range.

Investigating the Effect of a Novel Warming Device on the Pharmacodynamics and Pharmacokinetics of Rapid-Acting Insulin in Youth with Type 1 Diabetes

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Background/Objective:
Postprandial blood glucose excursions could be mitigated by accelerating insulin absorption and action in both open- and closed-loop insulin delivery systems.

Methods:
The glucose clamp technique was used to examine the effect of a novel infusion site warming device, InsuPatch, on the pharmacodynamics (PD)–pharmacokinetics of a 0.2 U/kg bolus of aspart insulin in pump-treated subjects. Studies were performed on two separate mornings with and without the activation of the InsuPatch device. On both days, the basal infusion was suspended and glucose levels were maintained between 80 and 100 mg/dl by a variable-rate dextrose infusion for up to 5 h after the bolus. To date, seven subjects (14 ± 1 years old, hemoglobin A1c 7.2% ± 0.5%) have completed both clamps.

Results:
Time to peak insulin action occurred earlier with InsuPatch than without the InsuPatch; whereas the area under the time action profile and peak action did not differ with and without infusion-site warming. Pharmacokinetic parameters were in agreement with PD parameters, namely, a significantly earlier time to peak insulin action with InsuPatch.

Conclusion:
Our preliminary data suggest that warming of the infusion site with InsuPatch is an effective means to accelerate rapid-acting insulin absorption and time to maximal insulin action. Such improvements in time-action responses have the potential to enhance the performance of open- and closed-loop insulin delivery systems with less postprandial hyperglycemia and late hypoglycemia.

Relationship between Insulin Sensitivity and Insulin-Modulated Microvascular Recruitment in Patients with Type 1 Diabetes Mellitus

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Background:
Capillary recruitment in the skeletal muscle is essential for the efficient transfer of insulin from plasma to muscle tissue to stimulate glucose uptake. We investigated the relationship between metabolic insulin sensitivity (IS), the volume of capillaries perfused after an overnight insulin infusion, and the ability of hyperinsulinemia to further enhance capillary recruitment in insulin-sensitive versus more resistant patients with type 1 diabetes mellitus (T1DM).

Methods:
Twenty-six euglycemic hyperinsulinemic clamps were performed on T1DM patients. Their IS was determined from the glucose infusion rate normalized by body weight and plasma insulin concentration at steady state of the clamp. Capillary recruitment was assessed as the microvascular blood volume (MBV) using contrast-enhanced ultrasound imaging; images were analyzed using a previously published methodology. Basal MBV was assessed 10 min before the start of the clamp, and MBV during hyperinsulinemia was captured 30 min after starting the clamp.

Results:
More insulin-sensitive patients had higher basal microvascular recruitment (correlation between basal MBV and log SI of 0.62, $p = 0.008$). Under hyperinsulinemia, less sensitive subjects experienced increased capillary recruitment while more sensitive ones experienced decreased capillary recruitment (correlation between relative change in MBV and log SI of -0.55, $p = 0.022$).

Conclusion:
The results suggest that the ability to recruit capillary at basal levels of plasma insulin is a significant determinant of IS in patients with T1DM. While insulin-induced capillary recruitment is triggered at the basal level of plasma insulin in insulin-sensitive subjects, higher concentrations of insulin are needed to promote capillary recruitment in more resistant subjects.

A Web-Based Simulation Model for Predicting Human Body Weight Change

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Background:
Over the past several years, our research group has developed and validated nonlinear mathematical models of human metabolism that accurately predict the dynamics of body weight change in response to given lifestyle interventions. However, weight management professionals and obese patients need easier access to accurate simulation models to help set realistic body weight goals and maintain weight loss.

Methods:
We created a Java Applet using NetBeans IDE 6.7.1 software for Mac OS X that implements a nonlinear ordinary differential equations model of human metabolism and predicts changes in body weight, body fat, extracellular fluid, and lean tissue compartments. This implementation will allow for wide distribution online.

Results:
Users input basic demographic data to initialize the model, which then simulates the time course of body weight and body fat change in response to up to two sequential lifestyle interventions specified by the user. Alternatively, the model can automatically calculate the intervention required to reach a given goal weight within a specified time period as well as what will be required to maintain that goal weight. Assuming perfect adherence to the interventions, the model also presents the range of expected body weight trajectories resulting from the inherent uncertainty of the initial state of energy imbalance. The applet has been validated and is currently undergoing user testing in preparation for its online release.

Conclusion:
By making accurate models of human body weight change available for general use, we plan to give clinicians and patients the tools and information they need to accurately design lifestyle interventions, track progress, and help them achieve and maintain body weight goals over long time periods.

An Optical System for Diagnosing and Monitoring Dermal Microvascular Health

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Objective:
Decrease in peripheral vascular compliance is thought to be reduced with age and with some diseases. To assess the compliance of peripheral microvasculature, we developed a quantitative technique for measuring microvascular elasticity based on the qualitative nail-blanch test.

Methods:
We assessed microvascular reperfusion dynamics by measuring associated changes in reflectance spectra following the application and release of light pressure on the fingernail bed. Forty-three adult subjects aged 18–83 years were tested on the prototype. Fingernail reflectance spectrum was measured using a fiber optic spectrometer (Ocean Optics). Subjects applied a force of 0.2 lb. to the load cell (Interface) for 10 s to obtain baseline measurements. When a stable signal was obtained, force was quickly released for at least 5 s to obtain a curve presumed to reflect vascular reperfusion. A minimum of 15 trials was performed on each subject over a period of 5 min. The variation in optical thickness of the spectrum of hemoglobin/oxyhemoglobin over time (486 nm < λ < 590 nm) was analyzed using a personal computer equipped with MATLAB 7.7.0 (MathWorks) and LabView 7.1 (National Instruments). Individual runs for each subject were averaged together and analyzed; runs were eliminated when a stable baseline was not established or when there was an insufficient signal-to-noise ratio for measurement. Optical thickness of blood responses were fitted to a simple exponential restoration to baseline, yielding a time constant of response.

Results:
Fingernail reperfusion in healthy adults (n = 43 subjects) was significantly faster than reperfusion in the younger subjects (p = .019; analysis of variance). There were no significant differences based on gender (p = .972).

Conclusion:
Microvascular reperfusion can be measured successfully using a simple noninvasive technique. Studies in normal adults demonstrate decreasing microvascular elasticity with age.

First Clinical Use of Automated Insulin Suspension Using the Medtronic Veo: Results of a User Evaluation

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Background:
Prolonged and profound hypoglycemia is known to lead to morbidity and even mortality through seizures, arrhythmias, or injuries. Despite hypoglycemia alarms available in most continuous glucose monitoring (CGM) devices, reports suggest that patients often sleep through these alarms, and trials have been unable to show a significant reduction in hypoglycemia with the use of CGM. The Medtronic Paradigm Veo suspends insulin delivery for up to 2 h if the patient fails to respond to a hypoglycemia alarm. We report results of the first clinical use of this system.

Methods:
A total of 31 subjects with type 1 diabetes treated with insulin pump therapy in six U.K. secondary care centers used the Medtronic Veo system for a total of 6 weeks. After a 2-week run-in period, the low glucose suspend (LGS) feature was introduced. We evaluated the number of suspends and glucose readings during and after suspend and assessed patient satisfaction of this feature.

Results:
A total of 29/31 subjects completed the study. There were a total of 166 (43 at night) episodes of LGS in 25/29 subjects. Only 9/166 episodes continued for the complete 2 h without any patient response, all between 00:00 and 11:00 h, 13/20 episodes lasting >60 min were nocturnal, and 107/166 episodes were terminated within 10 min. There were no episodes of ketosis, and mean glucose level on termination of LGS was 75 mg/dl. All users expressed a very high degree of satisfaction with the system, and 96% expressed a desire to continue its use.

Conclusion:
The LGS feature incorporated in the Medtronic Veo pump appears to be safe and well tolerated by patients. It is a potentially useful tool in protecting patients against prolonged severe hypoglycemia.

Using Mobile Phone Technology to Improve Adherence to Diabetes Therapy

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Objective:
The objective of this study was to observe the effect of a mobile-phone-based multifaceted, personalized technological intervention on diabetes self-management behaviors.

Methods:
This study analyzed patient utilization of DiabetesManager, mobile-phone-based diabetes management software designed to support effective diabetes self-management behavior, including blood glucose (BG) monitoring and medication adherence. The system provided patients with mechanisms for recording BG coupled with real-time feedback, recording prescribed medication regimen and monitoring adherence, and communicating with health care providers. Additionally, the system provided messaging, which provided diabetes education as well as support for behavior change and managing standards of care. Data are drawn from a randomized controlled trial of the DiabetesManager system. Patients (n = 164) were randomized to one control and three intervention groups and followed for a year.

Results:
Preliminary results showed that the patients' engagement with the system had a direct relationship with their adherence to diabetes medications. The system captured a total of approximately 48,000 BG entries. Of those entries, 44,000 (or 92%) had medication data. Additionally, there were over 3300 messages sent between the patients and providers using the system. The most frequently addressed themes were BG control and medication adherence.

Analyses are currently underway to determine the association between both BG entry frequency and medication entry frequency on improvement in patient-reported hemoglobin A1c values. Variation in data entry frequency over time is also being assessed.

Conclusion:
Results provide evidence that a mobile-phone-based behavior change intervention can provide support for improving adherence to diabetes therapy. Furthermore, patient utilization patterns around medication adherence offer useful information for developing a more robust technology system to influence medication management behaviors.

Comparison of Three Glucose Meters with Laboratory Standard Value

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Objective:
Comparisons were conducted between three glucose meters (Accucheck®, Contour®, and Welltrak®) and a laboratory standard value for blood glucose measurement among 18 adult patients in a metropolitan Washington DC area hospital. Glucose measurements were evaluated using finger-stick and venipuncture blood samples.

Methods:
For each patient, morning preprandial glucose measurements were conducted. Finger-stick measurements were conducted within 5 min of venipuncture in an arm preferred by each patient. Blood draw was performed by a trained phlebotomist, and all finger sticks were performed by the same pharmacist overseeing the project. All finger sticks were obtained using manufacturer-recommended lancets, lancet devices, and caps. Preliminary comparisons were conducted using Spearman's correlation coefficient and are reported here. Analysis utilizing error grid analysis is pending results.

Results:
Spearman's rho analysis reported statistically significant correlations between each meter and the laboratory reference. For the Accucheck meter, compared to the laboratory venipuncture value, the correlation coefficient was 0.929 ($p < .001$). The correlation coefficient between the Contour meter and the laboratory venipuncture value was 0.985 ($p < .001$). For the Welltrak meter and the laboratory venipuncture, the correlation coefficient was 0.924 ($p < .001$)

Conclusion:
Pending results of the error grid analysis, correlation coefficient reports that each of the comparison meters provided glucose measurements that were strongly associated with the laboratory reference value.

Assessment of Circadian Variation of Postprandial Glucose Turnover Using Triple Tracer Technique

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Objective:
Diurnal variations in postprandial insulin action that influence glucose excursion have not been studied with cutting-edge technology and therefore remain a key limitation for development of closed-loop subcutaneous insulin delivery systems in type 1 diabetes. An improved understanding of these factors will facilitate optimization of insulin delivery, limit postprandial hyperglycemia, and improve current artificial endocrine pancreas software. The aim of this study was to address these critical issues by examining healthy subjects while controlling for meal composition and physical activity.

Methods:
Six healthy subjects (aged 35 ± 3 years, body mass index 27.7 ± 1.0 kg/m2, fasting glucose 87 ± 3 mg/dl, hemoglobin A1c 5.4% ± 0.1%) ingested identical triple tracer mixed meals (50 g carbohydrate, 35% carbohydrates, 30% protein, 35% fat) on three occasions (breakfast, lunch, dinner) in randomized Latin square order on three consecutive days in the Clinical Research Unit of Mayo Center for Translational Science Activities. Triple tracer methodology minimizes variability in tracer-to-tracee ratios, thus limiting nonsteady state errors in postprandial glucose turnover calculations. All other meals had similar macronutrient composition as the tracer meals.

Results:
Postprandial glucose excursions did not differ between meals. While insulin concentrations from 0–60 min tended to be higher (p = .05) for breakfast than during lunch or dinner, C-peptide concentrations were similar for all three meals, implying reduced hepatic insulin extraction for breakfast over lunch or dinner. Percent suppression of endogenous glucose production (EGP) at breakfast tended to be greater (p = .06) from 0–30 min but returned quicker to baseline than during lunch or dinner.

Conclusions:
The data suggest presence of circadian variation in postprandial glucose turnover in nondiabetic individuals due to greater initial suppression and faster recovery of EGP and reduced hepatic insulin extraction at breakfast than at lunch or dinner.

Artificial Pancreas and Prediction Models: Autoregressive Moving Average and Neural Networks for the Individualized Estimation of Future Glucose Levels

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Objective:
The prediction of glucose concentration in the near future is of major importance for the design of efficient control algorithms to be used in the external artificial pancreas. To this end, two adaptive, data-driven models for near-future glucose prediction, based on statistical and artificial intelligence methods, are developed and comparatively accessed.

Method:
Two different models have been developed: (1) an autoregressive moving average (ARMA) model and (2) a recurrent neural network (RNN) model. The models are fed with information regarding glucose concentration measured by continuous glucose monitors and past insulin infusions delivered through insulin pumps while they provide glucose concentration predictions for a horizon of 30 and 45 minutes. Both models have the ability to be individualized to each specific type 1 diabetes patient. In order to design and evaluate the models, a database of 30 *in silico* subjects (10 adults, 10 adolescents, and 10 children), using the Food and Drug Administration-approved metabolic simulator of the University of Virginia, has been used. The data were extracted under appropriate meal and insulin infusion scenarios.

Result:
The comparative assessment has shown that the performance of the two methods is quite similar. Specifically, both models had a root mean square error in the order of 11.0 and a correlation coefficient of approximately 0.95, while the majority of the glucose predictions are in the A and B zones of the grid analysis for the different time horizons.

Conclusion:
Both ARMA and RNN behave accurately in the prediction of glycemic profile for the near future and seem to be appropriate for an individualized external artificial pancreas. Further investigation is needed in order to identify which model is the optimal to be used.

The Science of Diabetes Communication: Health Care Provider to Health Care Provider and Health Care Provider to Patient

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Objective:
Effective communication between health care providers and between providers and patients is key to positive outcomes. Communication should not be ignored or left to old habits proven counterproductive. We will review the literature and discuss practical examples.

Method:
Literature review of diabetes communication research, including 2010 evidence-based American Diabetes Association Clinical Practice Recommendations, demonstrates improved glycemic, quality-of-life, and costs outcomes. Negative outcomes of language between health care providers, including the terms "noncompliant" and "sliding scale insulin," will be noted. Medical research and adult learning theory expose misconceptions that influence providers. Specific, time-saving patient examples will be demonstrated, such as, "Will you tell me more about what you've heard about starting insulin?" which provides opportunities for solicited advice, collaboration, and teach back, rather than an often drawn-out confrontation or persuasion model for inconsistent obedience, not optimal outcomes. Additionally, "Let's look at your blood sugar records and decide what is our next move," employs scientific self-determination and motivational methodology.

Result:
The empowerment-based model in diabetes became standard of practice, and more recently, research uses models such as motivational interviewing. Despite all professional bodies' endorsement of these as foundational for care delivery, these techniques may still be viewed by some as primarily for professionals without prescriptive authority rather than as critical tools for all diabetes experts.

Conclusion:
No physician or other provider has time to try to undo effects from acute illness model communication habits, which are often demonstrated for patients and health care provider learners. Since over 98% of care is carried out by patients, one of our most important tools is to role model appropriate problem solving in order that patients are helped with skill enhancement for daily decision making.

Individualization of Artificial Pancreas Controller: A Novel Nonparametric Strategy

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Objective:
A crucial issue that has to be faced in the artificial pancreas is the high intraindividual variability of the insulin–glucose system. Controller individualization, i.e., tailoring the controller to individuals, is expected to significantly improve control quality.

To achieve individualization, we explored the possibility of identifying an individual model of the glucose insulin system, because a reliable model-based predictor is the essential ingredient of any model-predictive control algorithm.

Method:
We focused on the identification of linear models, an approximation of the real dynamics but sufficient for control design proposes. First, the classical parametric black-box linear-model identification techniques were considered. Beside auto-regressive models with auxiliary inputs (ARX) previously used in literature, we also analyzed autoregressive moving-average models with auxiliary inputs (ARMAX) and Box–Jenkins ones. Model order selection for parametric methods can be troublesome, especially if parameter uncertainty is not accounted for. For this reason, we also investigated the application of proposed Kernel-based nonparametric methods that, on the contrary, control complexity through the tuning of few hyperparameters. Both *in silico* and *in vivo* data were used to test the approaches.

Result:
In silico experiments show that ARX and ARMAX models were outperformed by the more general Box–Jenkins one, which provided more reliable predictions. Moreover, when *in silico* data were considered, the nonparametric technique led to a further improvement in the prediction capability of the model and remarkably reduced the computational time. When *in vivo* data were considered, the performance gap between nonparametric and parametric techniques increases.

Conclusion:
We investigated different parametric and nonparametric approaches to glucose–insulin system identification. Both *in vivo* and *in silico* experiments suggest that the nonparametric approach should be preferred.

Cost and Availability of Smart Phone Applications for Patients with Diabetes

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Objective:
An increasing number of patients with diabetes are utilizing the rapidly growing market of smart phones to help manage their diabetes. Our aim was to assess the number and cost of diabetes-specific applications available among the five most popular smart phone operating systems in the United States.

Methods:
A private Internet marketing research company database was accessed to determine smart phone usage statistics and market share. The proprietary stores of each smart phone platform were searched using the phrases "diabetes," "diabetic," "glucose," "insulin," and "A1c." Additionally, five U.S.-based nonproprietary smart phone application stores were searched. Textbook applications were excluded from the study.

Results:
In an average month from December 2009 to February 2010, the top five smart phone platforms in the United States were RIM's Blackberry (19.1 million users), Apple's iPhone (11.5 million), Microsoft's Windows Mobile (6.9 million), Google's Android (4.1 million), and Palm's webOS (2.5 million). Of these, the iPhone has the largest number of diabetes-specific applications (105), followed by Android (27), webOS (25), Windows Mobile (21), and Blackberry (16). Free applications are also more common on the iPhone (27) than on the Android (11), Windows Mobile (8), webOS (5), or Blackberry (1). Among nonfreeware diabetes applications, the lowest mean price found was for Android ($3.16) followed by the iPhone ($4.86), Blackberry ($10.46), webOS ($16.71), and Windows Mobile ($21.62).

Conclusion:
In the United States, Apple's iPhone has the largest selection of diabetes-specific applications, while the least expensive applications, on average, are available on the Android operating system. Availability and pricing of diabetes-specific applications do not correlate with platform market share. Our findings may affect purchasing choices for patients with diabetes and may guide industry toward addressing unmet software needs.

Chemical Stabilization of Glucagon for Use in Dual-Hormone Closed-Loop Systems

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Objective:
Glucagon aggregation in aqueous solution has been purported to generate cytotoxic amyloid fibrils. This limits the use of glucagon to immediate administration after reconstitution from a lyophilized powder. However, these preparations result in low pH solutions that are ideal for amyloid fibril formation. Using size exclusion chromatography, we investigated glucagon monomer stability in solutions of varying pH with various buffers.

Method:
Using a Tosoh size exclusion column in an Agilent 1100 HPLC device, we examined the stability over time of native glucagon in buffers of citrate (pH 3), phosphate-buffered saline (pH 7.4), tris(hydroxymethyl)aminomethane (pH 8.5), and glycine (pH 10). These glucagon solutions were aged for 55 days at 37 °C. Stability was judged by the degree of preservation of the glucagon monomer peaks, which elute at 19.5 min (3500 daltons MW).

Result:
At pH 3, the monomer area under the curve (AUC) dropped rapidly over the first 24 h. At pH 7.4, glucagon was relatively insoluble. At pH 8.5, there was improved stability of the monomer during the initial several weeks, with slow decline thereafter. By far, the best stability was observed in glucagon prepared in glycine buffer at pH 10. Under these conditions, glucagon monomer AUC was largely preserved for up to 55 days. Spectroscopic analysis of thioflavin-T-stained samples provided additional evidence that glycine-stabilized glucagon forms negligible amyloid.

Conclusion:
Native glucagon, dissolved in a low-concentration glycine buffer, clearly prolongs survival of glucagon monomer in aqueous solution. This formulation provides a potential means of stabilizing glucagon for use in a dual-hormone closed-loop system with insulin for treatment of type 1 diabetes. Currently, we are investigating the bioactivity and safety of glucagon dissolved in glycine for future use in human studies.

Retinal Flavoprotein Fluorescence as a Biomarker for Detection and Monitoring of Diabetes

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Background:
In the United States, it is estimated that 25% of persons with diabetes and most individuals with pre-diabetes are undiagnosed. Early detection and treatment are essential to prevent irreversible cell damage that can lead to severe complications, including retinopathy and blindness. Thus a rapid method for medical care providers to identify patients at risk for diabetes and its complications may be useful to target at-risk individuals requiring immediate conventional diabetes testing and management.

Method:
We previously described a noninvasive method for detecting flavoprotein fluorescence (FPF), a biomarker of diabetic retinal mitochondrial oxidative stress. Subsequently, we designed a second-generation prototype with an optimized optical train and electronic system to enhance retinal signal and reduce lenticular contributions. Four images were taken of diabetic eyes with and without retinopathy and age-matched control eyes in three consecutive decades of life (30–39, 40–49, and 50–59). Histograms of the pixels in the monochromatic images captured by the cooled, electron-multiplying charge-coupled device chip in the instrument were analyzed.

Result:
In each decade, FPF intensity was significantly increased in diabetic eyes compared to age-matched control eyes. Diabetes patients with retinopathy in at least one eye had significantly greater FPF intensities compared to diabetes patients without retinopathy. Asymmetry between eyes was significantly increased in diabetes patients compared to age-matched controls. The current prototype has low shot-to-shot variability, a 15-degree field of retinal acquisition, and a FPF image with structure.

Conclusion:
This study corroborated our previous work, indicating that FPF may be useful for detection of diabetes and monitoring for retinopathy. Therefore, this easy-to-use method, which provides quantitative results, may be a rapid, non-invasive clinical tool to assist medical care providers in diabetes screening and disease management.

Multivariate Glucose Prediction Models

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Objective:
The objective of this work is to develop subject-specific models that can capture a subject's daily glucose variations and predict his/her future glucose excursions. A subject's metabolic, physical activity, emotional stimuli, and lifestyle conditions are known to have a significant effect on glucose metabolism and daily glucose excursions. We use such physiological signals measured continuously with a multisensor body monitor and the subject's recent glucose history from a continuous glucose sensor to develop the proposed subject-specific models.

Methods:
The subject-specific glucose prediction model is developed using measurements from a glucose sensor and physiological signals from a multisensor armband. The frequent data from the sensors are analyzed by time-series methods. Adaptive system identification is proposed to estimate model parameters, which enables the adaptation of the model to intersubject/intrasubject variation and glycemic disturbances. It consists of an online parameter identification using the weighted recursive least squares method and a change detection strategy that monitors variation in model parameters. Univariate models developed from the subject's continuous glucose measurements are compared to multivariate models that are enhanced with physiological signals from an armband.

Results:
Errors in predictions are significantly reduced with additional measurements from the armband when compared to predictions done solely on glucose measurements. The proposed algorithm is also used to provide *early* (30 min in advance) hypoglycemia/hyperglycemia alarms, and preliminary results from a closed-loop study are demonstrated.

Conclusion:
Models developed are linear, low order, and easy to identify, which makes them a good candidate for early hypoglycemia/hyperglycemia alarms and closing the loop with an automated insulin pump. The Raman light scattering and the change detection methods proposed enable the dynamic adaptation of the models to intersubject/intrasubject variation and glycemic disturbances.

Comparison of Different Neural Networks Structures for the Real-Time Prediction of Glucose Level

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Objective:
The real-time prediction of the future glucose concentration from continuous glucose monitoring (CGM) data is a task of great importance to prevent hypoglycemic/hyperglycemic events. A preliminary work of Pérez-Gandía and colleagues proved that feed-forward neural networks (FFNNs) can be satisfactorily exploited to predict the future glucose levels. In this work, we further develop the FFNN prediction algorithm of Pérez-Gandía and colleagues, testing the influence of other inputs/structures.

Method:
Ten *in silico* datasets, consisting of 7-day CGM data and meal and insulin information, were created by using a Type-1 Diabetic Simulator (Dalla Man and associates). Several FFNN prediction algorithms have been tested. We considered as candidate inputs the CGM level, the rate of appearance of glucose and insulin in the blood, and all their derivatives. The root mean square error (RMSE) and the temporal gain (TG) introduced from the prediction have been considered as evaluation indices. The FFNN of Pérez-Gandía and colleagues was used as reference.

Result:
A *k*-fold cross-validation strategy has been adopted to set the number of neurons and to select features. Compared to the original FFNN of Pérez-Gandía and colleagues, the FFNN embedding information of meal only presents comparable RMSE but a significant increase in TG, insulin only presents no significant improvement, and both meal and insulin performs significantly better both in terms of RMSE and TG.

Conclusion:
Feed-forward neural network prediction algorithms are reliable solutions for the prevention of hypoglycemic/hyperglycemic events. In addition, combining information of meals and injected insulin further improves the accuracy of prediction. The application to real data is under investigation.

New Index to Optimally Design a Continuous Glucose Monitoring Glucose Prediction Algorithm

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Objective:
Continuous glucose monitoring (CGM) data can be exploited to prevent hypoglycemic/hyperglycemic events in real time by forecasting future glucose. In the past few years, several glucose-prediction algorithms have been proposed, but how to compare them (e.g., polynomial versus autoregressive models) and how to design the optimal parameter setup for a given method (e.g., prediction horizon and forgetting factor) is an open problem, because solid quantitative criteria for their assessment are missing.

Method:
We propose a new index *J* that takes into account two key ingredients: the regularity of the predicted profile and the time gained due to prediction. The effectiveness of the index is proved on 10 real Menarini Glucoday datasets. We also use *J* to assess performance of different prediction algorithms and compare its results against other criteria like root mean square error (RMSE) and continuous glucose-error grid analysis (CGEGA).

Result:
J is able to find the optimal parameter setup better than RMSE and CGEGA, and also, it is able to return information about the optimal prediction horizon that should be used. The predictions assessed by using the parameter set found by *J* are more useful both in terms of stability of the predicted profile and clinical usefulness. In addition, the minimization of *J* can be reliably used as a selection criterion in the comparison among different prediction methods.

Conclusion:
The new index *J* could be a useful tool to design the optimal parameter setup of a prediction method and to compare different prediction strategies finalized to the prevention of hypoglycemic/hyperglycemic events.

Average Daily Risk Range as a Measure of Glycemic Variability and Insulin-Dependent Glucose Metabolism Variability Are Predictive of Mortality in the Intensive Care Unit: A Retrospective Study in a Burn Center

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Objective:
Although tight glycemic control has been associated with improved outcomes in the intensive care unit (ICU), glycemic variability may be the influential factor in mortality. The main goal of the study was to relate blood glucose (BG) variability of burn ICU patients to outcomes using a sensitive measure of glycemic variability, the average daily risk range (ADRR). We also related outcomes to variability in insulin-dependent glucose metabolism (IDGM).

Methods:
Data from patients admitted to a burn ICU were used. Patients were matched by total body surface area (TBSA) and injury severity score (ISS) to test whether increased BG variability measured by ADRR was associated with higher mortality risk and whether we could identify ADRR-based classifications associated with the degree of risk. Additionally, IDGM was assessed in patients on intravenous insulin by quantifying BG change due to insulin administration. Then IDGM variability was related to outcomes.

Results:
Four ADRR classifications were identified: low risk, medium–low, medium–high, and high. Mortality progressively increased from 25% in the low-risk group to over 60% in the high-risk group ($p < .001$). In a *post hoc* analysis, age also contributed to outcome. Younger (age < 43 years) survivors and nonsurvivors matched by TBSA and ISS did not differ in age, mean BG, or standard deviation of BG; however, nonsurvivors had higher ADRR ($p < .01$). Despite similar average IDGM, nonsurvivors had higher IDGM variability ($p < .05$).

Conclusion:
Independent of injury severity, glycemic variability measured by the ADRR was significantly associated with mortality in the ICU. When age was considered, ADRR was still the single most significant predictor of mortality in younger patients with burns. Furthermore, variability in IDGM appears related to mortality as well.

Potential Use of Alpha Cell Inhibitors to Improve Glucagon Counterregulation in Closed-Loop Glucose Control Systems

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Objective:
Glucagon counterregulation (GCR) is compromised in insulinopenic diabetes and is typically accompanied by abnormally high basal glucagon. Our previous work suggests that partial glucagon suppression may repair defective GCR, and here we test *in silico* the impact of alpha-cell inhibitors (ACI) on glucagon secretion to design an ACI infusion strategy that repairs GCR while providing substantial glucagon inhibition during euglycemia and hyperglycemia.

Method:
We use a differential equation-based mathematical model of pancreatic glucagon release to simulate the effect of different ACI on GCR and glucagon secretion with regard to their potential application in closed-loop systems. The strategies include a switch from an almost complete (during euglycemia and hyperglycemia) to partial (during hypoglycemia) glucagon suppression when glucose levels fall below a certain threshold. We also tested how failure to detect on time impending hypoglycemia impacts the glucagon response.

Result:
Our simulations show that, in complete insulin deficiency, the amplitude of the GCR response to hypoglycemia can be restored by partial (35–45%) suppression of alpha-cell activity. To restore basal glucagon to normal levels, additional glucagon suppression is required during euglycemia and hyperglycemia. In particular, a switch from 60% suppression of glucagon to 40% suppression when blood glucose crosses a threshold of 80 mg/dl restores to normal both basal glucagon release and the hypoglycemia-stimulated GCR. A delay in detection of impending hypoglycemia of up to 30 min has no significant impact on the restoration of GCR.

Conclusion:
The results suggest that ACI can be used in closed-loop glucose control systems to normalize both the basal glucagon release (thereby reducing the amount of required insulin) and the glucagon responses to hypoglycemia to levels typical for the healthy pancreas.

Improving Diabetes Self-Management with a Diabetes Education Registry: AADE7™

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Objective:
Diabetes self-management education and training (DSME/T) is a collaborative process through which people with or at risk for diabetes gain the knowledge and skills needed to modify their behavior and successfully self-manage the disease and its related conditions. Diabetes educators provide DSME/T to empower patients so that they can achieve behavior change goals. The overall aim is to achieve optimal health status, attain a better quality of life, and reduce the need for costly health care.

There is a need to build and maintain a comprehensive body of knowledge about diabetes education that can be used to advance DSME/T. This goal is hampered, however, by shortage of comprehensive, nationwide data that can be used to assess the effectiveness of DSME/T.

Method:
The AADE7 System™ is a validated tool that is used by diabetes educators to support the delivery of DSME/T and, coincidentally, is building a nationwide repository of diabetes education information. The AADE7 System provides robust online software available to diabetes educators to accomplish the following:

- Collect and track patients' behavior change goals, clinical indicators, and medications for outcomes assessment and continuous quality improvement.
- Administer online patient self-assessments and follow-ups.
- Track information about
  - demographics,
  - educational services provided,
  - medications taken,
  - clinical and laboratory data,
  - goal setting and achievement, and
  - source of payment.
- Generate reports on individual patient progress and diabetes education program quality.

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Results:
The findings from data gathered in the AADE7 System on hemoglobin A1c and cholesterol (total, high-density lipoprotein, low-density lipoprotein) are consistent with those from other national data sets.

Conclusion:
Diabetes educators, who use the AADE7 System of online data collection, are helping to build a repository of information that is essential to understanding best practices and evaluation of DSME/T outcomes.

Characterization of Pharmacokinetics and Toleration of Three Variant Formulations of Linjeta™

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Objective:
To compare pharmacokinetic characteristics and toleration of Linjeta™ vs two modified formulations of Linjeta (BIOD-102 and BIOD-103). The modifications are variations of ratios of ingredients in Linjeta designed to optimize the toleration profile of this ultrafast-acting insulin.

Method:
A phase 1, single-center, randomized, double-blind, three-period, crossover trial in 13 subjects with type 1 diabetes. Each formulation was administered on separate days with a meal. In addition to pharmacokinetic measurements, toleration was assessed with a 100-mm visual analog scale (VAS).

Result:
BIOD-102 and Linjeta were similar with respect to AUC 0-480 [area under the insulin concentration curve for time period in minutes (mU·min/liter)] [9871.81 vs 9746.93; ratio/difference (confidence interval [CI]) 1.01 (0.97,1.06)], AUC 0-60 [2347.18 vs 2777.90; ratio/difference (CI) 0.84 (0.65, 1.09)], and TINS50% early [time to reach 50% of the maximal insulin concentration (min)] [12.64 vs 10.75; ratio/difference (CI) 1.89 (-3.51, 7.28)]. BIOD-102 and BIOD-103 had significantly lower CINSmax [maximal insulin concentration (mU/liter)] compared to Linjeta [56.03, 56.05, 69.72: BIOD-102 vs Linjeta: ratio/difference (CI) 0.80 (0.67, 0.97)); BIOD-103 vs Linjeta: ratio/difference (CI) 0.80 (0.67, 0.96). BIOD-102 had a significantly lower (p = .028) VAS score compared to Linjeta (mean ± SE were 3.96 ± 1.172 and 20.56 ± 6.682; 9.00 ± 2.55 for BIOD-103).

Conclusion:
BIOD-102 had a similar TINS50% early compared to Linjeta. BIOD-102 and BIOD-103 had similar AUCs 0-480 (BIOD-103, 10061.57) and significantly lower CINSmax compared to Linjeta. BIOD-102 had significantly less discomfort on a VAS assessment.

Pilot Study for the Evaluation of Laser Doppler Scanning in the Assessment of Early Microvascular Dysfunction in Insulin-Resistant and Type 2 Diabetes Patients

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Objective:
The aim of this study was to investigate early morphological and functional pathology in the retinal microcirculation in patients with insulin resistance or type 2 diabetes mellitus.

Method:
Fifty-four subjects were recruited for study participation and were classified into three study groups according to their metabolic staging: C, nondiabetic subjects with a homeostasis model assessment (HOMA) score ≤2 (7 male, 11 female; aged 52.7 ± 11.6 years; mean ± standard deviation); IR, nondiabetic subjects with a HOMA score >2 (7 male, 11 female; aged 54.9 ± 8.7 years); and DM, type 2 diabetes subjects (12 male, 6 female; aged 55.8 ± 9.6 years). All subjects were free from morphological features of diabetic retinopathy as assessed by funduscopy. Retinal microvascular blood flow was assessed using scanning laser Doppler flowmetry (LDF) at 670 nm (Heidelberg Retina Flowmeter, Heidelberg Engineering, Germany). The arterial wall-to-lumen ratio (WLR) was calculated as (arteriole diameter - lumen diameter)/lumen diameter. Retinal endothelial function was assessed as a percentage of increase in LDF after three times of repetitive flicker light stimulation for 30 s (10 Hz; Photo Stimulater 750, Siemens-Elema AB, Germany).

Results:
In insulin-resistant and in type 2 diabetes subjects, the WLR was reduced compared to an age-matched, insulin-sensitive control group (IR, 0.39 ± 0.08; DM, 0.41 ± 0.07; C, 0.45 ± 0.09). A slightly, even nonsignificant, higher endothelial response could be observed in the IR and D group compared to C (IR, 15.2% ± 18.5%; DM, 12.8% ± 13.3%; C, 9.0% ± 15.3%). No correlation was found between the WLR and the endothelial response to flicker stimulation.

Conclusion:
This pilot study generates the hypothesis that early retinal microvascular dysfunction in insulin resistance starts with a paradoxical vascular hyperreactivity.

Postprandial Intact Proinsulin as a Marker for the Beta-Cell Relieving Effect of Different Treatments in Patients with Type 2 Diabetes Mellitus

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Objective:
The rationale of our study was to investigate the impact of different treatment strategies on beta-cell stress and the release of intact proinsulin in type 2 diabetes.

Method:
In this cross-sectional study, the postprandial excursions of intact proinsulin, insulin, and blood glucose were measured in well-controlled type 2 diabetes patients (hemoglobin A1c ≤7.6%) treated with either insulin glargine or sulfonylurea and an age-matched nondiabetic control group. After an 8 h overnight fast, the study subjects received a standardized breakfast (27 g protein, 15 g fat, 48 g carbohydrates). At baseline and for 5 h postprandial, venous blood was taken for the measurement of intact proinsulin, insulin, and blood glucose. The area under the curve (AUC_{0-5}) was calculated using the trapezoidal rule.

Results:
Twenty-seven type 2 diabetes patients and 19 nondiabetic control subjects were included in the study. Sixteen patients were treated with sulfonylurea and metformin (SU+) and 11 patients were treated with insulin glargine and metformin (GLA+). Type 2 diabetes patients were found with higher fasting blood glucose levels compared to nondiabetic controls. No difference in fasting or postprandial blood glucose could be observed between SU+ and GLA+. The postprandial release of insulin ($AUC_{0-5\ Ins}$) and intact proinsulin ($AUC_{0-5\ PI}$) were increased in SU+ compared with the nondiabetic control group (C), while no significant difference was found between GLA+ and C ($AUC_{0-5\ Ins}$ C, 8.8 ± 3.7; GLA+, 13.1 ± 13.7; SU+, 18.4 ± 10.6 MU/liter^{-1}/min^{-1} and $AUC_{0-5\ PI}$ C, 9.7 + 3.9; GLA+, 17.0 + 7.8; SU+, 31.5 + 16.0 pmol/liter^{-1}/min^{-1}).

Conclusion:
The measurement of postprandial intact proinsulin could be used for the judgment of the beta-cell stress-releasing effects of different glucose-lowering treatments.

Local Heat Application by InsuPatch™ Insulin Infusion Set: Faster Insulin Action and Reduced Blood Glucose Excursion

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Objective:
The importance of good glycemic control in therapy of people with type 1 diabetes is well-known. In this study, the effect of the local skin heating device InsuPatch™ (InsuLine Medical, Ltd., Israel) on postprandial insulin and blood glucose (BG) levels after differently composed meals was investigated.

Methods:
Twenty-four type 1 diabetes subjects on continuous subcutaneous insulin infusion (10 male, 14 female, aged 43.5 ± 11.3 years, hemoglobin A1c 7.4% ± 0.8%, daily insulin need 0.58 ± 0.15 U/kg/d [mean ± standard deviation]) were included in this study. InsuPatch was worn on two days, and venous blood samples were drawn every 10 min after breakfast. On one of the two days, InsuPatch was heating the infusion site for 30 min after bolus delivery to 38.5 °C. The impact of local skin heating on insulin absorption was measured using the normalized area under the curve (AUC) 0–60 min above baseline insulin and BG concentrations.

Results:
The AUC 0–60 minutes for the venous insulin concentration after breakfast was significantly larger with heated InsuPatch ($p < .001$, $n = 23$, AUC 0–60 for insulin concentration above baseline not heated 42.8 ± 23.4 mU/liter, heated 53.1 ± 28.8 mU/liter). The venous insulin concentration reached a higher maximum with heated InsuPatch. The venous BG concentration was significantly lowered by the heating ($p = .0123$, $n = 19$, AUC 0–60 for BG concentration above baseline not heated 44.2 ± 24.9 mg/dl, heated 33.2 ± 25.9 mg/dl). The number of hypoglycemic events showed no statistically significant difference.

Conclusion:
This study shows that local heating of the skin around the infusion site was significantly increasing early insulin levels postdelivery as well as reduce postprandial BG increase without causing more hypoglycemia. If the effect remains significant in everyday use, this device could help reduce postprandial BG excursion.

Noninvasive Glucose Monitoring: Increasing Accuracy by Overcoming Environmental/ External Influences by Using Multisensors

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Background:
Previous publications suggest improvement of glucose measurement validity through combination of three noninvasive technologies: ultrasonic, electromagnetic, and thermal. However, the measured signal in each technology is influenced by both tissue and ambient temperatures. Therefore, in order to measure ambient and tissue temperatures correctly and receive more reliable glucose readings, an external temperature sensor was added.

Methods:
A new temperature sensor was added in a more inert location in the device, less accessible by the user and less influenced by the device heat dissipation. Each channel's reading was corrected and compensated by using the ambient temperature from the new sensor. A weighted combination of the outputs of the three technologies produced a final glucose reading.

The new performance of GlucoTrack® was evaluated for eight subjects: two with type 1 diabetes and six with type 2 diabetes, aged 46.5 ± 24.5 years with a body mass index of 31.7 ± 5.0 kg/m^2. Each subject performed the measurement procedure by him/herself in home/work environment. The device readings were compared with the participants' own (invasive) glucose monitoring device, which also served as the reference for calibration.

Results:
Clarke error grid analysis of 414 points shows 96% of the points in the clinically accepted A and B zones, of which, 51% are in zone A. The MARDmean is 26.6%, and the MARDmedian is 19.7%. The study demonstrates that users are able to easily operate and use the device under normal home environment and conditions.

Conclusions:
Initial results under real home-use conditions suggest that GlucoTrack gives good results. The new location of the temperature sensor is a key solution in overcoming temperature influences upon the measurement. Further efforts should be conducted in order to improve the results by reducing impacts of other external causes.

Comparison of Hyaluronidase and Human Regular Insulin versus Insulin Lispro in a Basal–Bolus Regimen in Patients with Type 1 Diabetes

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Objective:
We aimed to compare INSULIN-PH20, regular human insulin (RHI) formulated with recombinant human hyaluronidase (rHuPH20), relative to insulin lispro injection (Humalog®) for the treatment of type 1 diabetes.

Method:
After a 1-month run-in using bid insulin glargine and prandial insulin lispro, 46 patients with type 1 diabetes (42 ± 13 years, body mass index 26 ± 4 kg/m^2, hemoglobin A1c 6.8 ± 0.5, 24 male) were randomized in a open-label crossover trial to INSULIN-PH20 or insulin lispro in a random sequence for two consecutive 12-week periods as the prandial insulin in an intensive treatment regimen.

Result:
The mean glucose excursion for INSULIN-PH20 (17 ± 36 mg/dl) was comparable to that for insulin lispro (14 ± 35 mg/dl), and thus the prespecified primary endpoint noninferiority margin of 21.6 mg/dl was met. Overall, eight-point glucose profiles were also comparable. Good glycemic control (hemoglobin A1c) was maintained for both study drugs—7.0 ± 0.5 for INSULIN-PH20 and 6.9 ± 0.6 for insulin lispro—and both met the commonly applied noninferiority margin of 0.4% (upper 95% confidence interval = 0.23%).

Hypoglycemia was comparable for the two study drugs ($p > .05$). Overall rate of hypoglycemia (≤70 mg/dl) was 24.1 events per patient for INSULIN-PH20 and 22.4 events per patient for insulin lispro. There was no difference in other adverse events or immunogenicity between treatments, and both were well tolerated.

Conclusion:
Unlike commercially available formulations of regular insulin, a formulation of RHI with rHuPH20 was comparable to insulin lispro for control of glucose excursions in a basal–bolus treatment regimen for patients with type 1 diabetes. In this study, glycemic control and overall safety profiles were comparable, and both treatments were well tolerated.

Wound Chemotherapy: Novel Therapeutics for Negative Pressure Wound Therapy and Continuous Infusion

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Objective:
Use of negative pressure wound therapy (NPWT) alone may, in some patients, promote a change in the wound microbiota and result in colonization that can impede healing. The possibility of standardizing and streamlining continuous delivery of targeted therapies in conjunction with NPWT is not only attractive, but necessary as we move toward more controlled therapeutic regimes. We present several representative case examples of our provisional experience with continuous streaming therapy through two foam-based negative pressure devices.

Methods:
Four case reports for patients with diabetic foot wounds are presented. We describe a method of "wound chemotherapy" by combining NPWT and a continuous infusion of Dakins' 0.5% solution either as a standardized technique in one device (ITI Sved) or as a modification of standard technique in another (KCI VAC) NPWT device. The twin goals of both techniques are to effectively reduce bacterial burden and to promote progressive wound healing.

Results:
Negative pressure wound therapy treatment combined with a continuous infusion of Dakins' 0.5% solution was initiated for all four patients. The combined use of Dakins' infusion in addition to NPWT did not appear to adversely impact wound healing through reinfection/recolonization; in fact, they appeared to be accentuated during the period of evaluation.

Conclusion:
Wound chemotherapy was successfully applied to patients with diabetes without adverse reactions, complications, or recolonization observed during the course of treatment. We believe this to be a promising method to derive the benefits of NPWT without the frequent adverse sequela of wound colonization.

Insulin Pump Settings Associated with Degree of Glycemic Improvement in Adults with Type 1 Diabetes Using Sensor-Augmented Pump Therapy

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Objective:
The STAR 3 study showed that sensor-augmented pump (SAP) therapy resulted in a significant reduction in glycated hemoglobin (A1C) in comparison to multiple daily injection (MDI) therapy in a cohort of 166 adults. Additional data were analyzed to determine the association between glucose sensor usage, insulin delivery, sensor glucose (SG) values, and A1C reduction with the purpose of identifying possible factors or behaviors that enhance overall glycemic control of patients.

Method:
At study entry on MDI therapy, A1C values were ≥7.4% and ≤9.5%. The SAP patients (n = 166) were seen at 3, 6, 9, and 12 months; A1C was measured, finger-stick blood glucose testing and sensor and pump data were uploaded into the Clinical Medtronic CareLink® Therapy Management System and reviewed by patients and study clinicians, and therapy was adjusted accordingly. Analyses were performed with fourth quarter data.

Result:
The percentage of time with SG in target (70–180 mg/dl), sensor wear, and number of boluses per day using Bolus Wizard® (integrated onboard insulin dose calculator) were positively associated with greater decreases in A1C at 1 year. The A1C reduction was not associated with the total daily dose of insulin or with bolus-to-basal-insulin ratio. The standard deviation of mean SG was inversely associated with the degree of A1C reduction at 1 year.

Conclusion:
Indicators of improved glycemic control, notably A1C reduction, were greater the more the participants wore the sensors and used the Bolus Wizard feature. Unexpectedly, total daily dose and bolus-to-basal ratios did not appear to correlate with A1C change. These results suggest that patients should be encouraged to use the Bolus Wizard and sensor consistently to improve glycemic control when using SAP therapy.

Zone Model-Predictive Control Based on an Average Subject Model for the Artificial Pancreatic β Cell

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Objective:
Normalizing glucose concentration to the near-normal range can be compared to walking on a high wire. Avoiding both hypoglycemia and hyperglycemia is an extremely burdensome process for people with type 1 diabetes mellitus. An automatic control algorithm for a future artificial pancreatic β cell was designed to control glycemia to a predefined zone. The design features a universal model for each age group and the ability to be used with and without meal information.

Method:
A universal autoregressive with exogenous input model for the controller was identified based on the average model from the University of Virginia/Padova, Food and Drug Administration-accepted metabolic simulator for the adult and adolescent population, respectively. Zone model-predictive control (MPC) was evaluated on twenty *in silico* subjects from the simulator cohort following announced and unannounced meal challenges. A three-meal protocol of 75, 75, and 50 g carbohydrate at 7:00 AM, 1:00 PM, and 8:00 PM, respectively, was used.

Results:
Zone MPC demonstrated excellent glycemic control for both age groups and meal challenges. The adult population with and without meal announcement presented 86% and 63% time in range (70–180 mg/dl), mean glucose value of 126 and 165 mg/dl, and an average standard deviation of 37 and 45 mg/dl, respectively. The adolescent population with and without meal announcement presented 70% and 52% time in range, mean glucose value of 149 and 181 mg/dl, and an average standard deviation of 51 and 61 mg/dl, respectively.

Conclusions:
A single universal model combined with the zone MPC algorithm presented excellent glycemic control for both adults and adolescents. This novel design allows a fully automated artificial pancreas that will normalize glycemic control to a predefined zone with minimal to no user intervention.

Glucose Rate of Appearance and Plasma Insulin Concentration Models for Use in Prediction Algorithms

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Objective:
Algorithms for prediction of future glucose concentration from the past history of continuous glucose monitoring signals may take advantage of additional information on meals and insulin intakes. In particular, a rough estimation of the future plasma rate of appearance of glucose and insulin based on knowledge of meals and injection time/dose may be used as known external input to help track the plasma glucose signal.

Methods:
Two models are considered to generate, respectively, the rate of appearance of glucose into the plasma after the transit through the gastrointestinal tract and that of insulin after a dose injection in the subcutaneous tissue. The models exploit only the information of glucose and insulin inputs and a set of population parameters that were estimated exploiting blood glucose and insulin concentration data collected within the FP7 European Project "DIAdvisor" (www.diadvisor.eu). The models were implemented in two MATLAB functions, later referred to as "generators," which can be iteratively called by a generic prediction algorithm to provide an estimate of the expected glucose meal rate of appearance and insulin concentration profiles after a meal and insulin injection, respectively.

Results:
The generators were tested *in silico* with different input scenarios and yielded reliable profiles that closely reproduce the main dynamics observed in the data. The functions will be also invoked by the prediction algorithms implemented in the DIAdvisor device, which will be tested in clinical trials.

Conclusion:
Two physiological models are proposed to generate profiles of plasma rate of appearance of glucose and insulin concentration, respectively, after a meal and an insulin dose, which may be fruitfully employed for improving the performance of glucose prediction algorithms.

Methods for Reporting the Performance of a Hypoglycemia Predictive Algorithm

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Background:
A major component in the design of the artificial pancreas is the inclusion of a safety system to detect extreme events such as hypoglycemia. There is a lack of consensus on metrics for reporting the performance of predictive algorithms. A set of metrics has been developed that reflects the accuracy of each algorithm and the usefulness of the alarms it produces.

Method:
Performance metrics included a true positive alarm rate that reflects the percentage of events detected and a false positive alarm rate that reflects the rate of alarms in time regions not associated with a hypoglycemia event. The proximity of the first alarm to an event was also documented, as this reflects the warning time in which action can be taken. A voting suite of five algorithms was tested on historical data from a study on 18 people with type 1 diabetes (mean age of 20 years) and compared directly using the set of proposed metrics.

Result:
Comparing aggressive versus conservative tuning of the voting algorithm with a 15 min prediction horizon, the true positive rate fell from 100% to 64%, while the false positive rate was decreased by 98% from 35 min of false alarms per day. The warning time varied from 45% of first alarms occurring more than 15 min before an event for aggressive tuning to 14% with conservative tuning. The warning time is useful for choosing an algorithm or tuning for the purpose of prevention (early warning) versus alerting (late warning).

Conclusion:
Metrics by which hypoglycemia predictive algorithms are measured have been developed that can be applied to any novel algorithm for direct comparison to other algorithms and parameter tunings.

Development of a Point-of-Care Rapid Test for Intact Proinsulin

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Background:
Type 2 diabetes is characterized by insulin resistance, obesity and β-cell dysfunction. Recent publications demonstrated that elevated proinsulin is a highly specific marker for beta-cell dysfunction and insulin resistance. Detection of fasting intact proinsulin may function as an important diagnostic tool to identify patients eligible for insulin sensitizer therapy, or to monitor treatment success. Highly specific assays were used to establish a close correlation between enhanced cardiovascular risk and intact proinsulin concentrations in plasma. Hence, it has a prognostic value in cardiovascular risk assessment. This investigation explored the use of a lateral-flow-based rapid test to detect intact proinsulin in serum samples with not more than 10µl sample volume.

Method:
Different antibodies were tested on their specificity to selectively detect human intact proinsulin in a two-site enzyme immunofluorescent assay. Monoclonal antibodies (MAb) were chosen that were successful in direct coating of prohormone in serum samples. Detection was performed by fluorescence reading. Thereafter, a rapid test for the detection of human uncleaved "intact" proinsulin was built-on a membrane solid phase, immunometric assay. The test utilizes a combination of colloidal gold conjugate and anti-intact proinsulin antibodies. The test is based on the filtration of sample through a porous membrane on which a capture agent for biotinylated anti-human proinsulin antibodies is fixed. If present, intact proinsulin binds to both biotinylated anti-human proinsulin antibodies and FITC-coupled anti-human proinsulin antibodies as a sandwich. The positive reaction leads to coupling of colloidal gold conjugate resulting in a staining of the reaction band. A cut-off valiue of 11 pmol/liter is specific for insulin resistance in a Caucasian population. Therefore, the minimum detection level (MDL) of this test was aimed at 11 pmol/liter.

Result:
The MAb-pairs chosen were used either biotinylated (capture) or coupled to FITC (detection). Out of six combinations tested by enzyme immunofluorescent assay only one MAb pair specifically detected human intact proinsulin and met a low detection limit of 6 pmol/liter. In a second step, transferring the selected MAb pair on the rapid test platform allowed detection of intact proinsulin

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down to a concentration of 11 pmol/liter by applying a volume of 10µl human serum. The evaluation of the MDL of the rapid test is currently under way as well as the use of venous whole blood derived from a finger stick.

Conclusion:
The intact proinsulin point-of-care rapid test may be a valuable addition to other routine diagnostic procedures as a specific marker for insulin resistance and to monitor treatment approaches.

A Novel Bio-Inspired Glucose Controller

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Objective:
To date, control algorithms used in the context of an artificial pancreas (AP) have been mainly based on classical control engineering techniques such as proportional-integral-derivative control and model-predictive control. Developments of mathematical models of β-cell physiology, which are able to describe the glucose-induced insulin release at a molecular level, have opened the door to a new class of promising bio-inspired glucose control algorithms. In this work, a novel bio-inspired glucose controller is presented.

Method:
A recently developed subcellular model of glucose-stimulated pancreatic insulin secretion is used as the core of the proposed controller. As the subcutaneous route is employed for both glucose sensing and insulin delivery, the new controller incorporates an insulin feedback term in order to deal with time delays and avoid insulin overdosing. A type 1 diabetic subject simulator (University of Virginia) was used to validate the controller *in silico*.

Result:
For the 10 adult subjects of the simulator, using a standard meal protocol with meal announcement, the following results were obtained: mean blood glucose = 120.9 mg/dl, percentage below target = 0, percentage above target = 6.5, and percentage within target = 92, where glucose target was [70, 180] mg/dl. For the 10 adolescent subjects, mean blood glucose = 135.2 mg/dl, percentage below target = 0, percentage above target = 17.3, and percentage within target = 82.7.

Conclusion:
A novel bio-inspired glucose controller is presented and validated *in silico*. The proposed technique is currently being implemented in hardware and integrated in an AP platform. The controller is expected to be clinically tested in the following year.

A Simple Method for Estimating the Rate of Glucose Appearance from Mixed Meals

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Objective:
Estimating the rate of glucose appearance (Ra) in the peripheral circulation after a mixed meal is valuable in diabetes management. For the artificial pancreas, it is important to estimate the contribution of Ra to the overall glucose kinetics, as an accurate prediction of plasma glucose is crucial for most glucose controllers. Existing techniques for estimating Ra are either experimentally complex (multitracer protocols) or numerically complex (Bayesian estimation). A novel, simple method is proposed.

Method:
Unlike existing methodologies based on the glucose–insulin minimal model, the presented method does not require a gastrointestinal absorption model. This leads to a simple solution because it avoids the identifiability problems that arise with such a model. To estimate Ra, an estimate of the insulin sensitivity is computed from glucose and insulin profiles without any hypothesis on the shape of Ra. To validate the proposed technique, a type 1 diabetes simulator (University of Virginia) was used. The new technique was also tested using two sets of clinical data from the literature.

Result:
For 10 virtual subjects, the average coefficient of determination between the estimated individual Ra and the "real" one from the simulator was $R^2 = 0.94$. For the two clinical data sets, the correlation was $R^2 = 0.92$ and $R^2 = 0.65$, respectively. For the second data set, the lower correlation can be explained by the need to assume some parameters not provided in the paper.

Conclusion:
A novel and simple method for estimating Ra is presented and validated. The proposed technique is currently being applied to build a library of mixed-meal models using data from the literature. This library can be used in simulations in order to provide more realistic, and varied, mixed-meal conditions.

The Role of Postural Compensatory Strategy in Balance Control of Healthy and Diabetes-Related Neuropathy Patients

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Background:
Currently, diagnosis of patients with postural instability relies on a rudimentary clinical examination. This study suggests an innovative, portable, and cost-effective prototype to evaluate balance control objectively.

Method:
The proposed system uses low-cost microelectromechanical systems body-worn sensors to measure the motion of ankle and hip joints in three dimensions. We have also integrated the resulting data into a two-link biomechanical model of the human body for estimating the two-dimensional sway of the center of mass (COM) in anterior–posterior (AP) and medial–lateral (ML) directions. A new reciprocal compensatory index (RCI) was defined to quantify postural compensatory strategy (PCS) performance. Postural control and PCS of 21 healthy subjects and 17 diabetic peripheral neuropathy (DPN) patients were examined using the suggested technology.

Results:
Results demonstrated that DPN patients exhibit significantly greater COM sway than healthy subjects for both eyes-open (EO) and eyes-closed (EC) conditions ($p < .005$). The difference becomes highly pronounced while eyes are closed (197 ± 44 versus 68 ± 56 cm^2). Furthermore, the results showed that PCS assessed using RCI is significantly better in healthy subjects compared to DPN subjects for both EO and EC conditions as well as in both ML and AP directions ($p < .05$). Alteration in somatosensory feedback in healthy subjects resulted in diminished RCI values that were similar to those seen in the DPN subjects ($p > .05$).

Conclusion:
Results suggest that sensory deterioration due to DPN will significantly impact PCS. This compensatory strategy in healthy subjects allows them to reduce the variation of COM during both voluntary and involuntary movements. Deterioration in PCS in DPN subjects may make them vulnerable in maintaining balance while closing the eyes or in face of high amplitude of sway for either the proximal or distal segments.

Safety Supervision System: *In Silico* Design and Testing

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Objective:
Safety is a fundamental element of the design of complex engineering systems, ensuring reliable deployment and operation. We now introduce a safety supervision system (SSS) for insulin treatment of diabetes, applicable to routine pump therapy, advisory, or open- or closed-loop control.

Method:
The SSS is intended for implementation within an insulin pump, residing between insulin request and insulin delivery, and operating independently from the person or device generating insulin recommendations. The SSS uses continuous glucose monitoring and insulin pump data to perform three functions: (1) attenuate smoothly or discontinue insulin delivery when risk for hypoglycemia is detected, (2) issue warning for imminent hypoglycemia if pump shutoff is insufficient, and (3) intercept boluses that are large enough to cause hypoglycemia if carbohydrates are not consumed. To test this system, we used *in silico* experiments with two scenarios associated with risk for hypoglycemia: (1) increased insulin sensitivity (e.g., resulting from exercise) and (2) an overinsulinized meal.

Results:
In silico experiments with test scenario 1 showed that the SSS (i) attenuated insulin delivery and prevented 43% of hypoglycemic episodes (blood glucose below 60 mg/dl) and (ii) issued warnings for 74% of imminent hypoglycemic episodes not prevented with average warning time of 35.3 min. When treatment with 16 g carbohydrate was simulated at the time of warning, 98% of hypoglycemic episodes were prevented. In test scenario 2, 100% of all premeal boluses were intercepted prior to delivery and appropriate warnings were issued.

Conclusion:
An independent SSS that intervenes between insulin request and insulin delivery can dramatically reduce the incidence of hypoglycemia. Therefore, use of SSS is critical for insulin pump therapy, including closed-loop control and advisory systems.

Role of Auditory Brainstem-Evoked Responses to Assess Auditory Neuropathy in Type 2 Diabetes Mellitus

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Objective:
We aimed to study the role of auditory-evoked response in patients with longstanding history of type 2 diabetes mellitus (T2DM) who have hearing loss.

Methods:
A retrospective study was conducted in the clinical neurophysiology department of King Abdul Aziz University Hospital, KSU, Saudi Arabia. The tests were done from January 2007 to November 2009. A total of 46 cases (92 ears) with a longstanding history of T2DM having some degree of hearing impairment were selected. In all cases, auditory-evoked response was recorded according to the standard criteria.

Results:
The patient results were divided into four groups:

- Group I: 85 ears had increased hearing threshold around 40 to 60 dB.
- Group II: 54 ears showed significant increase in I–V interpeak latency at 80 dB.
- Group III: 31 ears had evidence of peripheral auditory pathway involvement.
- Group IV: 6 cases had unilateral involvement with sudden hearing loss and ABR showed no reproducible response even at 95 dB. Suggesting profound degree of hearing loss.

However, there is a fair number of overlap in the previously mentioned auditory brainstem-evoked response (ABR) abnormalities.

Conclusion:
Unilateral or bilateral hearing impairment is not an uncommon complication of longstanding T2DM. The consistent abnormalities in ABR showed increased hearing threshold and increased I–V interpeak latency, which is suggestive of auditory neuropathy. Thus ABR can be a useful means to identify auditory neuropathy in longstanding T2DM, and it may help in the management of diabetes patients with hearing loss.

Integration of Five Commercial Devices Makes the Artificial Pancreas System the Most Versatile Platform Available for the Clinical Evaluation of Artificial Pancreas Control Algorithms

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Objective:
The objective in developing the artificial pancreas system (APS) was to design a flexible platform that facilitated four-way communication between the mathematical control algorithm, insulin pump, glucose sensor, and the end user in order to support clinical evaluation of an artificial pancreas.

Method:
The APS's modular architecture is completely flexible with respect to the algorithm/controller such that it can be designed as a proportional-integral-derivative (PID), model-predictive control, or other control algorithm. The controller can be implemented in different computer languages such as Matlab, C, FORTRAN, C #, or Java. Human–machine interfaces were standardized with similar functionalities and design to allow simple toggling between the different supported pumps, Insulet Omnipod® system, Roche's Accu-Chek® Spirit Combo, and Animas's OneTouch® Ping® as well as two continuous glucose monitors, DexCom Seven®/Seven Plus® and Abbott FreeStyle Navigator®.

Result:
By simplifying user interaction and streamlining communication, the APS allows clinical researchers to focus on the evaluation of control algorithms. Simple PID controllers written in C and Matlab were shown to function identically in simulations with all APS-compatible devices without the need to customize the algorithm to a specific device. In addition, the newly integrated Animas and Roche pumps are capable of remote communication at an impressive distance (~5 m), allowing the possibility of closed-loop testing while patients participate in exercise away from the machine running the APS.

Conclusion:
The APS is the most versatile tool available for the clinical evaluation of artificial pancreas control algorithms across devices and computer languages. The APS allows standardization in data management, user–machine interfaces, device communication, and application program interface.

Highly Sensitive Carbon Nanotube Field Emission Transistor Sensor for Salivary Glucose Detection

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Objective:
Invasive blood collection methods for self-measurement of blood glucose levels often cause anxiety and stress to the patients. To obviate this stress and encourage better compliance in routine monitoring, various noninvasive glucose measuring methods continue to garner great attention. Blood-alternative body fluid (e.g., saliva, tear, urine, interstitial fluid) measurement strategies continue to be considered and may yet yield a practical alternative to finger-stick measurements. To further explore the possible use of saliva for glucose measurements, a highly sensitive salivary glucose detection method has been developed.

Method:
To detect a tiny level of glucose in saliva (almost 1/100 of blood glucose), we used directly assembled fine carbon nanotube field emission transistor devices with a conventional microfabrication method. For glucose oxidase immobilization, surface activation/silanization/glutaraldehyde deposition and enzyme immobilization processes were sequentially followed.

Results:
Test results show that the sensor signal responded well to salivary glucose at the level of interest concentration range (sub mg/dl range: 0.1–1 mg/dl). Correlation between blood glucose level and salivary glucose level were also observed through combined oral glucose tolerance test.

Conclusion:
Sensor signal responded well to salivary glucose at the concentration range of interest, and blood and salivary glucose levels were well correlated through oral glucose tolerance tests.

Highly Sensitive Glucose Measurement for Ultra-Low Glucose Levels

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Objective:
An enabling advancement to using nonblood bodily fluids for glucose monitoring is the measurement of ultra-low glucose concentrations.

Method:
Methods exist or are being developed for minimally invasive glucose monitoring, which use body fluids other than blood (e.g., sweat, tears, and saliva). Whereas sweat, saliva, and tear fluids are relatively simple to collect, the concentration of glucose in these samples is only a fraction of the level found in blood. One promising method for making ultra-low glucose measurements is the use of a electrode/dye-color method.

Result:
In this study, we tested an electrode and several dye combinations on low-level (0–10 mg/dl) glucose concentrations. Specifically, we configured our test system with a widely used carbon electrode and chromogen [N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3, 5-dimethoxyaniline] DAOS and leuco dye DA-67[10-(carboxymethylaminocarbonyl)-3, 7-bis (dimethylamino) phenothiazine sodium for a chomogen optic glucose device.

Conclusion:
Our results indicate a tight correlation of glucose response to laboratory standards for ultra-low concentrations of glucose.

Effect of Rate of Change and Calibration Frequency on Performance of the DexCom SEVEN™ PLUS® Continuous Glucose Monitor

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Objective:
Use of DexCom SEVEN™ PLUS® continuous glucose monitor requires that system calibration be updated at minimum every 12 h, at minimum. The system is designed to allow calibration regardless of glucose rate of change (ROC). This study evaluated system performance when calibrated at intervals more frequent than 12 h and when calibrated at fast (or slow) ROC.

Method:
Continuous glucose monitor and meter data were collected from 53 adult subjects with insulin-dependent diabetes over 7 days (18 subjects wore 2 systems). Data were postprocessed with the SEVEN PLUS algorithm using the following calibration schemes: with the meter values taken (1) approximately every 12 h, regardless of ROC; (2) every 8 h; (3) every 6 h; (4) at the slowest ROC within ±6 h of the 12 h interval; and (5) at the fastest ROC within ±6 h of the 12 h interval. Per system, accuracy was evaluated with absolute relative difference (ARD) and percentage of values within 20 mg/dl (meter <80 mg/dl) or 20% of meter (%20/20). The one-way analysis of variance test was used to detect differences in accuracy between groups.

Result:
Calibration every 12, 8, or 6 h resulted in a mean (standard deviation) ARD of 16.6 (5.5), 16.7 (5.5), and 15.9 (4.1), $p = .59$. Corresponding %20/20 was 72.8 (12.3), 72.2 (12.9), and 73.0 (11.5), $p = .93$.

With 12 h calibration regardless of ROC, at slow or at a fast ROC, mean ARD was 16.6 (5.5), 17.5 (6.0), and 16.8 (5.8), $p = .59$ and %20/20 was 72.8 (12.3), 71.3 (11.9), and 73.8 (12.7), $p = .48$. The ROC at calibration in the slow and fast groups was 0.4 (0.4) and 1.2 (1.1) mg/dl/min. Within the fast group, 19.6% of calibrations were at a ROC ≥2 mg/dl/min.

Conclusion:
SEVEN PLUS performance remained consistent when calibrated more frequently than every 12 h or when calibrated at a fast ROC.

"Smart" Basal Insulin Formulation That Releases Insulin in Response to Changing Blood Glucose Concentrations

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Objective:
SB is a "smart" basal insulin formulation that self-regulates insulin release in response to changing glucose concentration in the subcutaneous environment.

Method:
In vitro insulin release from SB in the presence of 300 mg/dl glucose and absence of glucose was tested in a two-chamber cell culture plate. For the test set, the donor cell contained 1 ml of SB formulation with 200 µl of phosphate buffer saline (PBS) with glucose. The receiver well contained 1.5 ml of 300 mg/dl glucose PBS as the release medium. The control set was set up as the test set, except no glucose was added to it. We analyzed 500 µl aliquot for amount of insulin. For *in vivo* evaluation, six diabetic swine were administered a 0.25 U/Kg dose of basal insulin and SB subcutaneously. The pigs were fed 500 g of swine food 360 min post dosing. Plasma glucose levels (PGLs) were determined every 15 min.

Result:
In vitro insulin released from SB was dependent on glucose concentration. Higher glucose concentrations resulted in monotonically increasing insulin concentrations. Following subcutaneous administration, SB decreased the PGL of the SB group faster than basal insulin group. After the meal challenge, a more rapid insulin release and absorption from SB relative to basal was seen, which persisted in the SB group. SB reduced the postmeal hyperglycemia seen in the basal group.

Conclusion:
In vitro and *in vivo* studies in diabetic swine showed insulin released from the SB was in response to changing glucose concentrations, demonstrating a self-regulating formulation. SB was able to manage the PGL more rapidly than basal insulin alone. SB may be a significant improvement over basal insulin and has the potential to benefit patients with diabetes.

Continuous Analyte Monitoring during Extreme Physical Exercise

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Objective:
Our aim was to continuously monitor glucose and lactate under extreme conditions of physical exercise and during recovery. Investigation of changes in metabolic levels during physical exercise will provide insight on how the body responds to extreme conditions.

Methods:
A male rat model was used to monitor metabolism with the aid of a microdialysis setup. Briefly, two 20 kD molecular weight cutoff microdialysis probes (CMA Microdialysis) were implanted in the left external jugular vein and the subcutaneous tissue (back of the rat), respectively. The animals were forced to run on a treadmill (IITC Life Sciences) until exhaustion, and they were then allowed to recover. During the exercise, Ringer's solution was pumped through the probes at a steady rate of 5 μl per minute, and samples were collected periodically and analyzed for glucose and lactate concentrations.

Results:
Glucose levels started dropping steadily as soon as the exercise activity commenced. Short resting periods during the experiment (1 to 2 s each) resulted in the trend temporarily reaching a plateau. The lactate concentration rapidly increased during exercise, as opposed to glucose, which fell. Following short resting periods, the lactate concentration rapidly decreased, and depending on the length of the rest period, the lactate levels reduced toward normal levels. Moreover, as soon as the running speed was decelerated, the lactate levels dropped, following the same rate as the recovery period. This was not observed in the case of glucose.

Conclusions:
The metabolic trends obtained provide an insight into how the body responds to extreme physical conditions. We have determined that lactate is much more responsive to the amount of strain imposed during exercise when compared to glucose.

Changes in Glycemia in Children and Youth on Sensor-Augmented Pump Therapy from the STAR 3 Study: Use of the CareLink® Data

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Objective:
The STAR 3 study showed that sensor-augmented pump (SAP) therapy resulted in significant glycated hemoglobin (A1C) reduction in comparison to multiple daily injection therapy in a cohort of 156 children and teens. Additional data were analyzed to identify the characteristics of insulin delivery in the SAP therapy group.

Method:
At study entry, A1C values were ≥7.4% and ≤9.5%; subjects were seen at 3, 6, 9, and 12 months. First, A1C was measured, then finger-stick blood glucose testing, sensor, and pump data were uploaded into the Clinical Medtronic CareLink® Therapy Management System, and reviewed by patients and study clinicians, and therapy was adjusted accordingly. Analyses were performed on 4th-quarter data.

Result:
In 78 pediatric subjects (7–18 years of age) using SAP therapy, percentage of time wearing sensors (p = .0006), mean number of basal rates (p = .049), number of boluses per day using Bolus Wizard® (integrated onboard insulin dose calculator; p = .012), and time in target (70–180 mg/dl; p = .0008) were associated with change of A1C (general linear model for difference between A1C decrease of <0.5, 5–1.0, >1.0% A1C at 12 months). Final A1C quartile (≤7.3, >7.3–7.7, >7.7–8.2, >8.2%) at 12 months was related to bolus number and type of bolus but not total daily dose of insulin per kilogram or bolus to basal ratio.

Conclusion:
Improvement in A1C or achieving final A1C quartile was related to sensor wear time, basal rate number, and bolus behaviors over the study time period. These data suggest that matching insulin delivery with food intake and correcting abnormal blood glucose levels as suggested by the programming of the Bolus Wizard and implementing multiple basal rates should be considered in subjects being placed on SAP therapy in an attempt to improve glycemia.

Extended Exposure to an Oral Insulin Formulation Yields Decreased Insulin Secretion in Type 2 Diabetes Subjects

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Objective:
We aimed to assess the safety and tolerability of an oral insulin formulation (ORMD-0801) administered daily for a period of 6 weeks. In addition, the effect of ORMD-0801 on a range of diabetes-related markers was evaluated.

Method:
This work was a multisite, placebo-controlled, randomized, double-blind study evaluating the response of 29 type 2 diabetes patients to ORMD-0801. Volunteers received once-daily, fixed dose capsules (8 mg/capsule, 2 capsules/day) for a period of 6 weeks. Three subjects were otherwise on diet, while 27 were on diet + Metformin (≥2.5 g/day) management programs before the start of the study. Blood samples of fasting subjects drawn at the start of the study (week 0) and at the end of the study (week 6) were compared.

Result:
The 6-week ORMD-0801 treatment regimen proved safe and tolerable, with no reports of serious adverse events throughout the study period. No negative cumulative effects of extended exposure to ORMD-0801 were observed, and only two mild hypoglycemic events were reported. In parallel, mean decreases in insulin and C-reactive protein levels were found to be statistically significant in the insulin-treated cohort, when compared to the placebo group. Furthermore, the percentage of subjects demonstrating clinically relevant reductions in insulin, C-peptide, fasting blood glucose, and hemoglobin A1c levels was consistently higher in the ORMD-0801 cohort, when compared to placebo.

Conclusion:
These results substantiate the safety and tolerability of ORMD-0801 and demonstrate a clinically relevant impact at the tested dose. More specifically, when administered daily for 6 consecutive weeks, ORMD-0801 can induce gradual rectification of insulin profiles.

Advisory Proposals for the Adaptation of Insulin Therapy According to Computed Predictions

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Objective:
Innovative information and communication technologies are expected to provide better decision support for diabetes patients, both in terms of glucose prediction models as well as in terms of bolus calculators, with the aim to reduce the number of erroneous insulin doses to be delivered. Ideally, an advisory system would compute the optimal insulin delivery profile required or even enforce it directly, as in the artificial pancreas. While no real system will be perfect, an advisory system can be helpful if it suggests more appropriate insulin doses while avoiding all critical errors. By computing the predicted insulin effects on glucose levels, we investigated how an advisory system could improve adaptation of insulin delivery versus common practice based on self-experience.

Method:
Measurement data from a group of type 1 diabetes patients were collected, including carbohydrate content of the meals, slow and fast insulin doses, and continuous glucose monitoring traces. These data were used both to derive individual predictors as well as for control design. During data collection, the patients followed their usual mode of treatment modulation. For each advisory system, the suggested insulin dose was computed, and these values were used for short-term prediction of the blood glucose changes that would have occurred if the patient had followed the advice of the advisory system, i.e., to simulate the behavior of the advisory system.

Result:
The advisory systems invetsigated allowed a fast estimation of different therapeutic proposals under the very same conditions.

Conclusion:
The proposed method allows a systematic comparison of the effectiveness of different advisory systems. While it is "simulation based," as most *in silico* methods are, it allows easy incorporation of actual measurement data.

Physiological Data Format for Diabetes

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Objective:
There is currently no widely accepted open-source format specification for presenting continuous glucose monitoring (CGM) and insulin infusion data obtained in clinical experiments and/or simulations. The goal of this work is to suggest such a data format and its handling toolset so that collaboration between different academic and industry groups can be facilitated.

Method:
The format is derived from a proven model known as PhysioNet, the research resource for complex physiological signals, funded by the National Institutes of Health, the National Institute of Biomedical Imaging and Bioengineering, and the National Institute of General Medical Sciences. The PhysioNet databank and toolset have been successfully used since the 1990s for electrocardiography and electroencephalography signal analyses.

Result:
Although the major ideas for the data representation have been inherited from PhysioNet, we suggest several modifications, taking into account specific needs of the Diabetes research community. In particular, time management has been modified to account for time gaps in the sensor signals. A reference toolset implemented in Matlab and pseudo code together with format specification is made available under general public license. The PDFD (physiological data format for diabetes) has been successfully used by Medtronic for clinical data representation, validation, and verification activities.

Conclusion:
Lack of a commonly accepted and publicly available CGM data representation makes it difficult to publish and exchange data in a transparent and reusable fashion. We hope that the suggested format will attract comments from research groups, leading to its further development, maturation, and acceptance. Data standardization is consistently found to be an important driving force behind efficient research collaboration, and we believe it must eventually lead to the advancement of diabetes technologies.

Membrane Dynamics of an Implantable Osmotic Glucose Sensor

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Objective:
Nanoporous membranes with selectivity at the molecular level are a prerogative for a functioning osmotic glucose sensor. As well as offering immunological protection and retention of the concanavalin A (ConA)–dextran affinity assay components, a rapid confluence of glucose is required in order to realize a successful sensor. In this study, the transmembrane dynamics of different membrane candidates have been assessed in order to identify the most successful sensor configuration.

Method:
A laboratory model based on albumin (65 kDa) of comparable size to ConA–dextran and glucose (180 Da) were used to investigate the dynamics of several nanoporous membranes with pores offering a molecular weight cutoff (MWCO) ranging from 500 Da to 500 kDa during a 12 h experimental timeframe.

Results:
In the test with the membranes offering a MWCO of 500 Da and 500 kDa the osmotic pressure (from 78–37 mBar) was used to indicate the confluence of albumin. The higher pressure suggested a better retention rate, which slowly decreased with increasing pore size. The fouling effects from albumin were negligible, and the corresponding response time of the glucose ranged from 2.5 h down to 2 min.

Conclusion:
It was found that membranes based on anodic aluminum oxide with a pore size of 4–6 nm (approximately 50 kDa) and 1 μm film thickness represented the best compromise between low assay component leakage and glucose confluence offering a response time of 15 min.

Photokinetic Transdermal Drug Delivery: A Novel Platform Technology for Insulin Delivery

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Objective:
Photokinetic drug delivery is a novel platform technology to deliver drugs into tissue. Pulsed, incoherent light of narrow wavelength is used as an energy source for reversible conformational change of the molecule, thus enhancing the permeation flux into skin, without causing harm or damage to the tissue. The tissue acts as a depot, and the drug loaded within the skin is slowly released into the deeper layers over time. The purpose of this study is to assess the feasibility of photokinetic transdermal drug delivery of insulin in a noninvasive manner.

Methods:
A typical Franz cell system was used for *in vitro* studies. Insulin levels in the samples were analyzed using commercially available ELISA (enzyme-linked immunosorbent assays). Statistical analysis was performed using one-way analysis of variance with Bonferroni's correction versus control (passive) permeation.

Results:
We first optimized permeation parameters and found that 405 nm at 100 cycles/s achieved the highest permeated amounts (up to 40 times over passive diffusion) and tissue deposition (up to 100 times over passive diffusion). Next, we performed experiments to estimate the kinetics of active transport and showed that we were able to deliver up to 120 IU of insulin/cm^2/24 h. Finally, we investigated whether the type of insulin used (fast acting or lente) affected permeation and deposition and found that permeation through skin was higher for fast-acting insulin, while tissue deposition was higher for long-acting insulin.

Conclusion:
Photokinetic transdermal drug delivery is a novel method for noninvasive, painless insulin delivery through intact skin. We were able to achieve clinically relevant insulin levels without harm to tissue or the insulin molecule.

Overnight Closed-Loop Insulin Delivery in Adults with Type 1 Diabetes Mellitus

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Objective:
The aim was to evaluate an overnight closed-loop (CL) system in adults with type 1 diabetes mellitus (T1DM).

Method:
Two randomized, crossover studies compared CL with conventional continuous subcutaneous insulin infusion (CSII). In a feasibility study, a medium-sized evening meal containing 60 g carbohydrate (CHO) was consumed. In a follow-up study, subjects consumed a large evening meal (100 g CHO) accompanied by 0.75 g/kg ethanol as 13% white wine (mean intake 564 ± 133 ml). Prandial insulin boluses were administered with all meals, using subjects' own bolus calculator. Twenty-four subjects (male/female 10/14, aged 37.5 ± 9.1years, T1DM duration 20.6 ± 9.7 years, hemoglobin A1c 7.8% ± 0.6%; mean ± standard deviation) were studied over 48 nights at a clinical research facility. During CL nights (n = 24), every 15 min, subcutaneous continuous glucose monitoring values from the Freestyle Navigator CGM System were fed into a model-predictive control algorithm, which calculated the infusion rate of aspart to be adjusted manually for delivery via the Deltec Cozmo pump. During control nights (n = 24), subjects' usual insulin pump settings were applied. Plasma glucose was measured every 15 min to assess CL performance.

Result:
Following a 60 g CHO meal, overnight CL increased time in target plasma glucose 70–145 mg/dl (80% versus 51%; CL versus CSII, p = .002), with similar outcomes following a 100 g CHO meal and alcohol (70% versus 47%, p = .01). Secondary analysis of pooled data documented increased time in target (76% versus 50%, p < .001), reduced time below 70 mg/dl (2.8% versus 6.7%, p = .04) and above 145 mg/dl (18% versus 30%, p = .006), and reduced standard deviation glucose measuring glycemic variability (1.4 versus 2.0 mmol/liter, p = .001). There was no difference in the average overnight insulin infusion rate (0.8 versus 0.8 U/h, p = .83).

Conclusion:
Overnight CL may significantly improve glucose control and reduce the risk of nocturnal hypoglycemia in adults with T1DM.

Design Improvements of a Disposable, Noninvasive Tear-Glucose Sensor

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Background:
A prototype noninvasive tear-glucose (TG) sensor system was previously demonstrated. Here we present the iterative design refinements necessary for preparation of future animal and clinical studies, improving ergonomic design, testing for potential interferents, and reducing background noise.

Methods:
An ergonomic redesign and replacement material for the fluidics system was made. Poly-styrene-ethylene-butylene silicone (SEBS) was made with differing percentage of weights of resin to mineral oil and compared with poly-dimethyl siloxane (PDMS) for tensile strength, bond strength, and resistance to transpiration. We investigated electrochemical reduction of interference due to physiological levels of ascorbic and uric acid as well as acetaminophen and various saccharides.

Results:
The SEBS material had an improved manufacturability, with the fabrication process being four times faster than for identical parts made from PDMS. Evaporation through SEBS was two orders of magnitude lower than through PDMS, and a variable tensile strength was developed, trading off some strength for better flexibility (and hence pumping action). Electrochemical testing showed that +0.35 V was optimal for reduction of noise from common physiological interferents in both tears and blood. A more ergonomic design was also achieved by placing the capture port on the distal end of the device.

Conclusion:
With the redesign of the sensor, a more ergonomic design was achieved. The change in material should allow for quicker manufacture, lower cost, and improved material properties for the fluidics system. The effects of possible interferents enough at physiological levels were established, quantified, and deemed not significant in interfering with TG measurements. The next step for this device is irritation and TG-to-blood-glucose correlation in the animal studies.

Improving Postprandial Model Identification Using Ambulatory Data from Type 1 Diabetes Patients

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Objective:
The aim was to evaluate new techniques for identification of postprandial models based on ambulatory continuous glucose monitoring (CGM) in patients with type 1 diabetes.

Method:
A model composed of the Wilinska insulin pharmacokinetic model, the Dalla Man glucose absorption model, and a modified version of the Panunzi glucose–insulin model was considered. Insulin bolus and meals were separated using two meal configurations as a result of an optimal experimental design. The first involves a big meal (100 g carbohydrate) with a bolus administered 30 min in advance. The second involves 40 g carbohydrate meals with an insulin bolus delay of 90–150 min after beginning the meal. A clinical protocol for the implementation of experiments using outpatient CGM data was developed. After 3 days for model identification, where the protocol was followed, 3 more days following a standard bolus treatment were used for validation. Model-based glucose predictions were computed in a 5 h horizon by means of modal interval analysis to cope with uncertainty in the meal size and insulin sensitivity. A glycemia prediction band was then obtained. Finally, minimum and maximum estimated glycemic exposures were calculated as area under the curve $(AUC)_{0-5\,h\_min}$ and $AUC_{0-5\,h\_max}$, respectively.

Result:
By separating dynamics, improvements of up to 60% in model parameters identifiability can be obtained. To date, 5 patients underwent 13 weeks of monitoring, showing that 5 h glucose range prediction cover confirmed data for at least one out of three validation days. In the remaining postprandial periods, the prediction band near-completely includes the CGM data, although for less than 5 h. Also, more than 70% of measured glycemic exposure ($AUC_{0-5\,h\_validation}$) fell into calculated ranges.

Conclusion:
Using planned model identifications, good predictions have been achieved in individual diabetes patients using ambulatory CGM registries.

A Web-Based Clinical Software Tool to Assist in Meeting Diabetes Guidelines and Documenting Patient Encounters

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Background:
The care of the diabetes patient is complex and requires the clinician to assess a multitude of parameters and then create an appropriate plan. Diabetes guidelines are useful in helping to achieve a goal of reducing morbidity and mortality due to microvascular and macrovascular disease. Creating a comprehensive well-documented assessment under time constraints is extremely challenging. A software tool has been created to assist the clinician in rapidly assessing the diabetes patient using current guidelines and then instantly generating a "dictation" of the assessment and plan, which can be placed into an electronic medical record (EMR) or paper-based medical record.

Methods:
The Web-based tool contains a unique, sliding form to enable rapid information entry. Simple point-and-click input methods are in place to collect data and make selections. During the assessment, various patient-specific guidelines may be selected. The tool can be easily updated as new guidelines and circumstances require. Clinicians can quickly select various options to create a plan. "Free text" may be entered to document special considerations. As a full assessment of glycemic control, blood pressure, lipids and eye and foot exam are performed, a complete "dictation" is created in real time.

Results:
The result is a readable dictation that concisely conveys the patient's current status, assessment, and plan. The resulting text can then be copied into virtually any EMR or printed for paper-based records.

Conclusion:
This software tool is effective in rapidly creating a thorough diabetes assessment and plan based on current guidelines and producing a readable dictation immediately during an encounter. The tool has the potential for improving diabetes care, improving health record documentation, and improving clinician efficiency.

Pilot Trials of the STAR Tight Glycemic Control Protocol in a Cardiac Surgery Intensive Care Unit

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Background:
Tight glycemic control (TGC) has shown benefits in cardiac surgery intensive care unit (ICU) patients. Stochastic TARgeted (STAR) protocol is a model-based TGC protocol accounting for patient variability with a stochastically derived maximum 5% risk of blood glucose (BG) below 72mg/dl. We describe the first clinical pilot trials of the STAR protocol.

Method:
The glycemic target was 125 mg/dl. Each trial was 24 h, with BG measured every 1–2 h. Two-hourly measurement was used when BG was between 110 and 135 mg/dl for 3 h. Each intervention leads to a predicted BG level and outcome range (5–95th percentile). Carbohydrate intake (all sources) was monitored but not changed from clinical settings except to prevent BG <100 mg/dl. Insulin infusion rates were limited (6 U/h maximum), with limited increases based on current infusion rate (0.5–2.0 U/h). Approval was granted by the Ethics Committee of the Medical Faculty of the University of Liege (Liege, Belgium).

Results:
Two patients were recruited immediately postoperative, and two were in the ICU 3–5 days prior. Median per-patient results were BG 116–146 mg/dl, carbohydrate administered 2–11 g/h, and insulin 0.2–2.0 U/h. Median prediction errors ranged from 9.8–17.7% (12–24 mg/dl), with larger errors due to small meals and other clinical events. The minimum BG was 63 mg/dl.

Conclusion:
The STAR protocol effectively controlled all patients to target. Observed patient variability in response to insulin and thus prediction errors were higher than expected, likely due to the recent insult of cardiac surgery and their immediate recovery. The STAR protocol effectively managed this variability with no hypoglycemia, and the high density BG data allows comparison of variability between surgical and medical ICU patients.

Accuracy Assessment of Real-Time Continuous Glucose Monitoring Systems in an Intensive Care Unit: A Pilot Study in Medical and Surgical Patients

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Objective:
The objective was to assess the accuracy of continuous glucose monitoring systems in an intensive care unit (ICU) and, furthermore, to determine if the accuracy varies depending on the type of patient or poor tissue perfusion.

Method:
Thirty-six patients with insulin therapy at the ICU of the Dr. Josep Trueta Hospital (Girona, Spain) were included (APACHE II 18.5 ± 5.2, SOFAs 8.4 ± 3.3, 13 medical/23 surgical). Patients were monitored for 72 h using the Guardian® REAL-Time (RT-CGMS) system (Medtronic, Northridge, CA). Arterial blood glucose (ABG) samples were obtained following the standard glycemic control protocol established at the hospital ICU and determined using HemoCue® 201DM (HemoCue AB, Ängelholm, Sweden). Additionally, ABG measurements (3–4 per day) were used for calibration. Results were evaluated using paired values (ABG/RT-CGMS), excluding those used for calibration. Accuracy was assessed using mean and median relative absolute difference (RAD) and International Organization for Standardization (ISO) criteria.

Result:
Eight hundred ABG/RT-CGMS data points were analyzed (323 medical/477 surgical). Overall mean and median RAD were 16.2% and 12.6%, respectively. Measurements meeting ISO criteria were 70.8%. The median RADs in medical and surgical patients were 13.1% and 12.1%, respectively, and the nonparametric contrast was not significant ($p > .05$). By ISO criteria, 71.5% of medical data and 70.2% of surgical data were accurate. Median RADs of 13.4/12.2% and ISO criteria of 67.7/74.2% were reported for patients without and with poor tissue perfusion, respectively.

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Conclusion:
RT-CGMS accuracy in the ICU was similar to the results reported in studies in type 1 diabetes patients. Accuracy in medical and surgical patients was not significantly different. Accuracy was not significantly changed in terms of poor tissue perfusion. Preliminary results suggest that RT-CGMS can be applied in the ICU for monitoring critically ill patients with appropriate medical supervision.

Glucometer Using Ubiquitous Health Care Service with Mobile Phone

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Objective:
The interest in ubiquitous health care (u-health care) continues to increase with the proliferation of information technology. Wireless communication systems have been proposed as a means of supporting patients with chronic medical conditions. Specifically, mobile-communication-enabled glucometers represent a natural u-health care solution to assist consistent monitoring of diabetes mellitus. In this research, we discuss the development of a glucometer/mobile communication prototype system.

Method:
The glucometer component of the system is a "dongle" style meter based on standard test strip technology (electrochemical, 5 s test time). Additionally, glucose measurements are corrected for errors due to hematocrit (electrical conductivity) and altitude (global positioning system) variations. The device allows for simple annotation of measurement conditions (e.g., postmeal, premeal, fasting) and, in turn, transmits the data set to a mobile phone via a Bluetooth connection.

Results:
A software application (based on the Android operating system) is hosted on a companion mobile phone and is configured to receive and manage individual user glucose measurements and histories. A system to convey and manage measurement and historical data to health care providers is concurrently under development to close the ubiquitous telemedicine loop.

Conclusion:
Phase II of our system development study is the incorporation of multiparameter strips into the dongle device to include such measurements as hemoglobin A1c, blood urea nitrogen, and hematocrit.

Evaluation Study of Plasma-Calibrated Bayer's CONTOUR® Glucose Meter

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Objective:
The aim was to evaluate the performance of the evaluation for plasma-calibrated CONTOUR® blood glucose monitor.

Method:
Precision: low, normal, and high control solutions were used to test precision. Twenty measurements were performed with three meters calibrated to plasma using control solutions by trained personnel. RiliBÄK accuracy: average values of the precision measurements in the series (n = 20) of low, medium, and high control solutions were compared with the target value of control solutions and with the ±11% target range. Comparitive accuracy to lab: measurements were performed under routine conditions between CONTOUR and hexokinase laboratory method with 100 type 1 and type 2 diabetes patients.

Results:
Precision: average coefficient of variation (CV) for low, normal, and high control were 1.9%, 1.5%, and 1.5%. Average overall CV was 1.6%. RiliBÄK accuracy: with low, normal, and high control solutions, deviations from the target value were between -2.3% and 2.9%, well within permissible relative deviation of the individual value of the control sample measurement (±11%). Comparitive accuracy: resultant regression analysis was r = 0.99. All measurements were in zone A of the Clarke error grid analysis.

Conclusion:
The CONTOUR blood glucose meter has very good precision and accuracy. Specifications of the new RiliBÄK guidelines were clearly met, and correlation with hexokinase laboratory method was very good (r^2 = 0.99), with all measurements in zone A of the Clarke error grid. The performance data of the plasma-calibrated device comply with the specifications of International Organization for Standardization standard 15197. The CONTOUR is an accurate and easy-to-operate blood glucose meter.

Evaluation Study of Plasma-Calibrated Bayer's CONTOUR® USB Glucose Meter

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Objective:
The objective was to perform a performance evaluation of the plasma-calibrated CONTOUR® USB blood glucose monitor.

Method:
Precision: low, normal, and high control solutions were used to test precision. Twenty measurements were performed with three meters calibrated to plasma using control solutions by trained personnel. RiliBÄK Accuracy: average values of the precision measurements in the series (n = 20) of low, medium, and high control solutions were compared with the target value of control solutions and with the ±11% target range. Comparative accuracy: measurements were performed under routine conditions between CONTOUR USB and hexokinase laboratory method with 100 type 1 and type 2 diabetes patients.

Results:
Precision: average coefficient of variation (CV) for low, normal, high control were 2.6%, 1.8%, and 1.8%. Average overall CV was 2.1%. RiliBÄK accuracy: with low, normal, and high control solutions, deviations from the target value were between 1.2% and 4.5%, well within permissible relative deviation of the individual value of the control sample measurement (±11%). Comparative accuracy: resultant regression analysis was r = 0.99. All measurements were in zone A of the Clarke error grid analysis.

Conclusion:
The CONTOUR USB blood glucose meter has very good precision and accuracy. Specifications of the new RiliBÄK guidelines were clearly met, and correlation with hexokinase laboratory method was very good (r^2 = 0.99), with all measurements in zone A of the Clarke error grid. The performance data of the plasma-calibrated device comply with the specifications of International Organization for Standardization standard 15197. The CONTOUR USB is an accurate and easy-to-operate blood glucose meter.

A Novel Portable Minimally Invasive Human Glucose Detection Instrument Based on Surface Plasmon Resonance Technology

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Objective:
A portable minimally invasive human glucose detection instrument was studied, which is based on a miniature integrated surface plasmon resonance (SPR) sensor.

Method:
The D-galactose/D-glucose Binding Protein (GGBP), which has strong affinity with the glucose molecule, is used to modify the gold surface of SPR sensor for higher sensitivity and stability. The instrument includes an interstitial fluid extractive unit, a liquid flow unit, a SPR sensor unit, and a circuit control unit. Interstitial fluid is extracted from the body by the interstitial fluid extractive unit and then transported to the SPR sensor by the liquid flow unit. The SPR sensor detects the glucose concentration of interstitial fluid. The acquisition and process of data are controlled by the circuit control unit, which controls the operation of the whole system as well.

Result:
The glucose detection resolution could reach 0.625 mg/liter, and the experiment result has good linearity relationship when the glucose concentration is from 0.625 to 5mg/dl.

Conclusion:
Quick and precise glucose detection results without the extraction of human blood are obtained. Twenty-four-hour continuous glucose detection is achieved, which can satisfy the clinical requirement on dynamic, continuous, and accurate detection of human glucose concentration.

How Accurately Can We Predict Glucose Levels in Real Time?

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Objective:
The purpose of this study was to determine the maximum time horizon for which we can consistently and accurately predict glucose signals in real time using data-driven models based on continuous glucose monitoring (CGM) data.

Method:
We proposed a method to denoise and predict CGM signals in real time using data-driven, autoregressive (AR) models and Kalman filtering techniques. To this end, we first smoothed the raw CGM signals of a patient offline using the method of regularized least squares. Next, we fitted an AR model on the smoothed signal through the ordinary least squares method, where the order of the model was determined by Akaike's information criterion (AIC). Then we used the AR model to denoise the raw CGM signals and make predictions in real time via a Kalman filter, where the state-transition matrix of the Kalman filter was constructed from the AR model and its tuning parameters were obtained *ad hoc* from the CGM signals. Finally, we tested the universality of this approach, where we used the AR model and the tuning parameters of the Kalman filter estimated from one patient's CGM signal to denoise and predict the signals of another patient. We evaluated the predictive performance using root mean square error (RMSE) and prediction delay.

Results:
We report results from three different studies consisting of recorded CGM signals from 34 distinct patients, including both type 1 and type 2 diabetes, heterogeneous population, and three different types of CGM devices. Based on glycated hemoglobin, we found that the optimal AR order was 6 and that, using an AR(6) model together with the Kalman filter, we were able to effectively predict up to 10 min ahead with an average RMSE of ~9 mg/dl [standard deviation (SD) = 3] and without prediction delays. We also found that the coefficients of the AR(6) model were similar for the 34 patients and that the predictions were insensitive to interindividual differences in the Kalman filter tuning parameters.

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Conclusions:
We were able to consistently predict CGM signals in real time with effective time horizons of up to 10 min ahead with an average RMSE of ~9 mg/dl (SD = 3) and without prediction delays. The results demonstrated that the AR models and Kalman filters were invariant across different diabetes types, CGM devices, and study populations, confirming the "universality" of the proposed modeling techniques for real-time glucose predictions.

Performance of Continuous Subcutaneous Glucose Monitoring Using Microdialysis in Different Groups of Critically Ill Patients

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Objective:
Studies indicate that glycemic control is beneficial for critically ill patients at surgical and medical intensive care units. Continuous glucose monitoring can help minimize the workload of nursing staff. Continuous subcutaneous glucose monitoring (CSGM) has been vastly tested in diabetes patients, but data from critically ill patients are scarce. The aim of the present study was to test CSGM in two different critically ill patient populations and to investigate whether the introduction of a run-in period improves signal quality.

Method:
In 30 critically ill patients (20 surgical after major cardiac surgery [surgical intensive care unit (SICU): aged 68.6 ± 7 years, body mass index (BMI) 28.2 ± 4.9 kg/m^2, Acute Physiology and Chronic Health Evaluation (APACHE) II score 10.1 ± 3.2] and 10 medical with severe sepsis [medical intensive care unit (MICU): aged 56.8 ± 11.4 years, BMI 34.9 ± 15.4 kg/m^2, APACHE II score 31.1 ± 4.3]), CSGM was performed using microdialysis technique. A microdialysis catheter was inserted in subcutaneous adipose tissue (SAT) of the abdominal wall and continuously perfused with an isotonic solution (flow rate 1 µl/min). Interstitial fluid of SAT and arterial blood were sampled in hourly intervals and analyzed for glucose concentrations. The SAT glucose was then calibrated to reference either at hour 1 or hour 6.

Result:
Median absolute relative difference (MARD; interquartile range) 1 h after catheter insertion was 9.9(4.2;17.9)% in the SICU group, whereas a calibration at hour 6 indicated a MARD of 6.2(2.6;12.4)% ($p < .05$). For MICU, calibration at hour 1 indicated a MARD of 11.8(5.0;22.3)% and did not result in a significant improvement when calibrated at hour 6 [MARD 11.1(4.8;22.9)%; $p = .11$].

Conclusion:
Continuous subcutaneous glucose monitoring indicated similar performance in critically ill patients after major cardiothoracic surgery versus medical patients with severe sepsis. Introduction of a 6 h run-in period indicated a better signal quality in terms of MARD only in the SICU group, whereas there was no apparent improvement in the MICU group, which might be attributed to altered tissue perfusion in sepsis.

Short-Term Unblinded Continuous Glucose Monitoring for Long-Term Glucose Control

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Objective:
We aimed to evaluate the effect of one week unblinded continuous glucose monitoring (CGM) on hemoglobin A1c (HbA1c) and pump settings in type 1 diabetes mellitus (T1DM) on continuous subcutaneous insulin infusion (CSII).

Method:
Retrospective analysis of the effect of one week unblinded CGM (Medtronic REAL-Time or DexCom Seven) on HbA1c 3–6 months later. Inclusion criteria were T1DM diagnosed at least 1 year prior, age ≥8 years, CSII for minimum 3 months, and 1 week CGM. Exclusion criteria were patients on multiple dose insulin, on steroids, major surgery, serious infection, hospitalization, and pregnancy 3 months before or after CGM. Factors evaluated include age, sex, changes in total daily dose, percentage basal (B), carbohydrate ratio (CR), and sensitivity factor (SF), and HbA1c.

Result:
Data were collected on 29 patients (16 females, 13 males), average age 46.75 (18 to 75) years, baseline HbA1c 7.91% (6.3 to 11.3), baseline percentage B 47.08% (32.25 to 62.71), CR baseline 13.95 (6 to 70 g/U insulin), baseline SF 45.51 (18 to 100 mg/dl decreased by 1 U insulin). Hemoglobin A1c improved by ≥0.3% (average 0.5%) in 14/29 (48.25%) patients and worsened by ≥0.3% (average 0.9%) in 7/29 (24.15%) patients, and in 8/29 (24.15%) patients, there was a change of ≤0.2%. There was no statistically significant difference in age, percentage B, CR, SF, and HbA1c before and after CGM among these groups.

Conclusion:
Forty-eight percent of patients on CSII who underwent unblinded CGM for only 1 week showed improved HbA1c at 3 to 6 months. We were unable to identify any change in insulin dose or pump settings that led to improvement in this small study.

eHealth2go Personal Health Record for Microsoft HealthVault

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Objective:
We set forward to demonstrate that minority and vulnerable patients with diabetes can successfully adopt a patient-centric, Web-based personal health record (PHR) as an information technology tool to enable engagement in self-care behaviors, improvement in health outcomes, and sharing of personal health information with providers.

Method:
The eHealth2go PHR leverages the Microsoft HealthVault platform. In this project, health navigators assist patients, including those with low levels of computer literacy, to set up and maintain an eHealth2go PHR, including medical history and medication lists. Hemoglobin A1c (HbA1c), blood glucose (BG), blood pressure (BP), and low-density lipoprotein cholesterol (LDL-C) are performed at baseline and at 3 months. Patients are encouraged to update the PHR at home and download BG data from meters (J&J One Touch) into eHealth2go via the HealthVault Connection Center. Patients are actively followed for 3 months then continue to have unlimited access to their PHR.

Results:
Of the 31 patients enrolled to date, 21 have completed the 3-month intervention. Interim data analysis reveals HbA1c average pre = 9.0% and post = 7.46%, BG average pre = 160 mg/dl and post = 148 mg/dl, BP average pre= 132/75 mmHg and post = 127/73 mmHg, and LDL-C average pre = 86 mg/dl and post 84.5 mg/dl. Eighty five percent of completers reported that they will continue using the PHR postintervention.

Conclusion:
Preliminary data suggest that a PHR can be leveraged as a tool to enable improvement in clinical outcomes in patients with diabetes. The high percentage of participants indicating that they will continue to use the PHR suggests high satisfaction with the application.

Range Correction Module with Model-Predictive Control for Type 1 Diabetes

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Objective:
In order to develop an artificial pancreas, the layers considered in the modular architecture must be optimized. The range correction module (RCM) is the core of the entire system, as it computes and sends to the safety supervisor module (SSM) the amount of insulin to be injected. It receives CGM and pump insulin values from the hardware interface platform and information for controller individualization from the "offline" layer.

Method:
The key concept of this RCM is the notion of *nominal open-loop profile,* determined offline for each individual from patient records or observations. The RCM is a model-predictive control and acts by introducing corrections to the nominal treatment strategy. It is based on a linear model, no integral action is included, and no constraints are explicitly considered, so that online optimization or region search algorithms are avoided. The aggressiveness of control action is individualized as a function of the body weight, carbohydrate ratio, and basal subcutaneous insulin delivery.

Result:
The proposed algorithm was tested on 100 virtual patients included in the Food and Drug Administration-approved simulator. Robustness tests in the face of perturbed meals and perturbed insulin sensitivity were performed. Some clinical experiments are also presented.

Conclusion:
The use of open-loop informed closed-loop control appears a practical and promising strategy in taking into account all the available information regarding each patient without requiring *ad hoc* experiments for model individualization.

Modeling Glucose Time Course in Critically Ill Patients

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Objective:
The control of glucose levels in critically ill patients [e.g., those in intensive care unit (ICU) therapy] is one important target. To optimize insulin administration protocols and compare different administration rules suggested by the scientific community and in use in hospitals, it is very useful to have a model of the patient behavior and evaluate its capability of describing the real world. This work aims to evaluate an already published model in several critically ill patients admitted to the Niguarda hospital.

Method:
We considered and adapted to hospitalized critically ill patients the model developed by Dalla Man and colleagues for nonhospitalized normal and diabetes subjects. In particular, meals or oral glucose administrations are not present in such patients, and only glucose infusions are generally performed. Moreover, the insulin is also provided directly in the blood central compartment. Least squares identification techniques and Monte Carlo simulation algorithms were used to evaluate the adequacy of the model to describe these complex situations.

Result:
Data collected in the daily hospital monitoring activity coming from approximately 50 different patients (both hospitalized in ICU and diabetes unit) were considered. The monitoring periods range from a few to 10–15 days. The model was able to describe, at least from a qualitative point of view, all the considered situations. Model parameters change over time, showing a remarkable difference between the first hours after the hospitalization and the following ones. Common patterns are recognizable in subgroups of subjects.

Conclusion:
The proposed model seems to be a promising base to evaluate different protocols to control glucose levels and to optimize therapies in these types of critical patients.

Effect of Calibration Finger-Stick Error on Performance of the DexCom™ SEVEN® PLUS Continuous Glucose Monitor

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Objective:
Continuous glucose monitoring (CGM) systems are calibrated with finger-stick blood glucose (FSBG) measurements. The FSBG measurements are accurate when tested per International Organization for Standardization guidelines but may have considerable error in actual use. The DexCom™ SEVEN® PLUS CGM is designed to mitigate the influence of FSBG error. This study evaluates the effect of various magnitudes of FSBG error on SEVEN PLUS performance.

Method:
Continuous glucose monitoring data were collected from 16 adult subjects with insulin-dependent diabetes for one 7-day wear period (6 subjects wore two systems). An 8 h in-clinic tracking study was conducted on day 4, with YSI and FSBG measurements taken every 15 min. For each system, data were postprocessed using the SEVEN PLUS algorithm. Calibration FSBG error was simulated by adjusting the first FSBG measurement of the day 4 tracking study by up to ±20% in 5% increments. Performance was evaluated in terms of absolute relative difference (ARD), and relative difference (RD) versus YSI. Then 95% confidence intervals (CIs) were constructed around the difference from control (performance using FSBG with no added error) for each test group.

Result:
Mean (standard deviation) of ARD and RD when calibrated using control FSBG were 14.2(11.1)% and 0.8(18.0)%. When calibrated using FSBG with +20% error, ARD and RD were 16.4(12.7)% and +8.9(18.8)%. Calibration using FSBG with -20% error yielded ARD and RD of 16.6(10.7)% and -11.7(15.9)%. For all test groups, mean change in CGM output error (compared to control) was less than the magnitude of FSBG input error. Corresponding 95% CIs were also less than the input FSBG error.

Conclusion:
The SEVEN PLUS is able to reduce the magnitude of error introduced by FSBG inaccuracies.

Effect of Disinfectants on Glucose Monitors

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Objective:
Monitoring of blood glucose levels is an integral part of routine diabetes management. To minimize the risk of transmission of blood-borne pathogens during monitoring, the Centers for Disease Control and Prevention (CDC) recommends that glucose meters be disinfected when used to test multiple patients. The objective of this study is to assess the compatibility of disinfectants on certain blood glucose meter systems.

Method:
We tested six disinfectants for adverse effect on meter performance or harm to the exterior meter surfaces. The disinfectants tested were sodium hypochlorite 0.525% (Gluco-Chlor wipes, Medtrol, Niles, IL); 20% 2-propanol, 10% ethanol (Incidin® Foam, Ecolab GmbH & Co. OHG, Dusseldorf, Germany); 17.2% isopropanol (Caviwipes™, Metrex Research Corp, Orange, CA); 55% isopropanol (Sani-Cloth®, PDI, Orangeburg, NY); 70% isopropanol (RelyOn™, DuPont, Wilmington, DE); and hydrogen peroxide (OxivirTB™, JohnsonDiversey, Oakville, Ontario Canada). To assess meter performance, we tested two meters each of OneTouch® Ultra®, Ultra®2, and UltraMini® blood glucose monitoring systems that use OneTouch Ultra test strips (LifeScan, Inc., Milpitas, CA) with control solution before and after application of either water or disinfectant. To assess the effect on exterior meter surfaces, we used a proprietary protocol that simulates long-term exposure to disinfectant testing to test three meters of each meter type.

Result:
Paired *t*-test results showed that the control solution data associated with disinfectant and with water application were not significantly different for each meter type. However, most of the meter types were adversely affected by hydrogen peroxide and/or by higher concentrations of alcohol-based disinfectants.

Conclusion:
In conclusion, while none of the six disinfectants affected meter performance, hydrogen peroxide and isopropanol >20% adversely affected the exterior surfaces of the tested meters. When complying with CDC instructions for meter disinfection, users should use caution and choose disinfectants that have been validated by the manufacturer.

Exercise Measured with a Physical Activity Monitoring System Correlates with Continuous Glucose Monitoring Glucose

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Objective:
Physical activity (PA) results in dynamic changes in insulin action, hence contributing to glycemic variability (GV). Precise quantification of PA is a prerequisite to defining the relationship between PA and GV. The physical activity monitoring system (PAMS) can accurately quantify PA, while GV can be measured by continuous glucose monitoring (CGM). The aims of this study were to (i) evaluate the temporal relationship between PA and GV and (ii) predict PA-induced glucose oscillations as measured with CGM.

Methods:
Six healthy subjects (4 males, aged 35±3 years, body mass index 27.7 ± 1.0 kg/m^2, fasting glucose 87 ± 3 mg/dl, hemoglobin A1c 5.4 ± 0.1%) were studied in the Clinical Research Unit at Mayo Clinic, Rochester, MN, for an 88 h period during which a planned program of PA was captured with PAMS (a system that has accelerometers and inclinometers in duplicate for highly accurate recording of all body postures and movement up to 3 mph) and GV was captured with a Dexcom Seven® Plus CGM. Every subject participated in a controlled activity schedule to minimize interday variability in energy expenditure. All ingested meals (breakfast, lunch, and dinner) during the 3 days had similar macronutrient composition that did not differ between meals or between days.

Results:
Among the six subjects, two showed clear correlation between accelerometer output and CGM rate of change and two subjects showed some correlation, while there were no correlations in the remaining two subjects.

Conclusions:
Our preliminary results show that (i) PAMS technology is able to accurately capture PA in a noninvasive way and (ii) accelerometer measurements are potentially usable to predict glucose fluctuations due to PA.

Bioequivalence and Dose Proportionality of AFREZZA™ Inhalation Powder Administered Using a Gen2 Inhaler Compared to the MedTone® Inhaler

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Objective:
MannKind Corporation has conducted phase III studies with AFREZZA™ using the MedTone® inhaler. The Gen2 Inhaler is designed to be smaller and easier to use, and to require less inspiratory effort and fewer inhalations. This trial was designed to show bioequivalence between 20 U Gen2 and 30 U MedTone and to show that 2 × 10 U and 1 × 20 U of Technosphere insulin (TI) deliver bioequivalent doses.

Method:
Healthy volunteers (24 to 29 years old) received all doses of AFREZZA in a crossover manner on 3 consecutive days. Inhalation maneuver training and evaluation took place at the screening visit and throughout the study with an empty cartridge. Blood samples for glucose, insulin, and C peptide measurements were taken over a 4 h period. C-peptide-corrected insulin was used for the primary boundary element (BE) analysis; baseline-corrected and uncorrected insulin was also evaluated.

Results:
A total of 64 subjects were randomized, 68 were exposed to TI, and 46 subjects were included in the pharmacokinetic population; 66 subjects completed the study.

- MedTone (30 U) and Gen2 (20 U) inhalers were bioequivalent
- Area under the curve $(AUC)_{0-120}$ (min/μU/ml): MedTone 4060, Gen2 4294, ratio 1.060, 90% confidence interval (CI) 0.981, 1.145
- Maximum concentration (Cmax; μU/ml): MedTone 97.4, Gen2 105, ratio 1.082, 90% CI (0.992, 1.180)
- Equivalence between 2 × 10 and 1 × 20 U cartridges of AFREZZA was also met since the AUC and Cmax fell within a BE limit of 0.80 and 1.25.

Conclusion:
Bioequivalence was established between two different inhalation devices and two different dosage strengths as the Gen2 inhaler is a more "efficient" device than the MedTone inhaler. The Gen2 device also provides for dose linearity as 2 × 10 U were bioequivalent to 1 × 20 U.

Development of the Gen2 Inhaler: Use of Engineering and Clinical Trials in a Feedback Development Cycle

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Objective:
MannKind Corporation completed phase III studies with AFREZZA™ using the MedTone® inhaler. The Gen2 Inhaler is designed to be smaller and easier to use, and to require less inspiratory effort and fewer inhalations. Several studies were done to provide both information on the "human factors engineering" as well as the clinical performance and delivery of insulin. These culminated in a novel design (Gen2) with a lower powder load and insulin dose that performed identically to the MedTone device.

Method:
Three clinical trials were done in a sequential manner to evaluate insulin doses and inspiratory flow and its relationship to exposure [insulin and fumaryl diketopiperazine (FDKP]) as well as evaluate the effects of differing inspiratory flow parameters (kPa and duration of inhalation) on the pharmacokinetics of insulin and FDKP. Device design was updated based on the feedback obtained from the clinical results.

Result:
The first study (140) demonstrated that a lower dose (FDKP) with the Gen2 device would be comparable to the MedTone device and that bioavailability was relatively insensitive to inspiratory effort and duration. Device changes were then implemented and used in the subsequent study (141), which evaluated insulin and FDKP pharmacokinetics. The results from this preliminary study were then used to do clinical trial simulation to determine optimal doses and design for the full bioequivalence trial (142). The 142 trial demonstrated that the 20 U Gen2 device produced an insulin profile that was bioequivalent to the insulin profile from 30 U MedTone.

Conclusion:
A combination of engineering assessment and design based on clinical data and clinical trial simulation was able to produce a new inhalation device that delivered bioequivalent exposure to the previous device despite a 33% reduction in insulin dose.

Relationship between Two Insulin Assays Used to Determine Bioequivalence and Dose Proportionality of AFREZZA™ Administered Using a Gen2 Inhaler Compared to a MedTone® Inhaler: Simulation of Clinical Trials and Actual Data

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Background:
MannKind Corporation has conducted phase III studies with AFREZZA™ using the MedTone® inhaler. The Gen2 Inhaler is designed to be smaller and easier to use, and to require less inspiratory effort and fewer inhalations. A bioequivalence trial was conducted using the Roche enhanced chemiluminescence immunoassay (ECLIA), which was found to not be fully consistent with the Food and Drug Administration guidelines for assays used in bioequivalence trials. Subsequently, a radioimmunoassay (RIA) method that was fully consistent with the guidelines was used on the same plasma samples.

Method:
Bioequivalence samples that were measured by the Roche ECLIA method were analyzed for bioequivalence. Using published data on the linear relationship and error [coefficient of variance (CV)] between the Roche ECLIA and a RIA method, 1000 bioequivalence trials were simulated. The RIA analysis was then done, and the results were analyzed for bioequivalence.

Result:
The results for the bioequivalence analysis using the Roche ECLIA assay demonstrated boundary element (BE) for all groups (20 U Gen2 versus 30 U MedTone and 2 × 10 U Gen2 and 15 U MedTone). The simulations showed all BE trials using the published error (4.5% CV) passed, and 22 out of 1000 simulated trials failed using a higher than published error (10% CV). The samples that were then subsequently determined by a RIA method also demonstrated bioequivalence but with larger confidence intervals.

Conclusion:
The conclusions of the bioequivalence trial were not substantially changed in the simulations. The simulations demonstrated that, by reanalyzing the samples with an assay of higher variability, the conclusion of the trial did not change, but it was shown that the assays with a higher CV% were more likely to result in a type 1 error. This was confirmed by the actual reanalysis using the RIA assay.

New Metrics for Glucose Variability Using Continuous Glucose Monitoring Data

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Objective:
Glycemic variability contributes to oxidative stress, which has been linked to long-term complications of diabetes. Hemoglobin A1c (HbA1c), routinely used to measure sustained hyperglycemia, correlates with complication risk but does not adequately reflect fluctuations in blood glucose levels. Mean amplitude of glycemic variability (MAGE) correlates with serum 1,5-anhydroglucitol (AG) level, which reflects postprandial glucose excursions, but these measures are not routinely used in practice. This study aims to provide new metrics that can be routinely applied to continuous glucose monitoring (CGM) data to determine quality of glycemic control.

Method:
Nine of 28 patients with type 1 diabetes on insulin pump therapy have completed a 90-day protocol in an ongoing study. Patients provide CGM data, which is scored each day for MAGE and three new metrics: total daily fluctuation, or "distance traveled;" number of fluctuations >75 mg/dl that leave the normal range; and excessive variability, as determined by a naive Bayes classifier trained on physician ratings of daily CGM plots. Measurements are aggregated for the first and last two weeks of each patient's participation in the study and compared to initial and final serum AG levels.

Result:
Preliminary results suggest that the change in excessive variability as measured by the naïve Bayes classifier varies with the change in serum AG level and agrees with clinician appraisal better than the change in MAGE.

Conclusion:
New metrics providing an assessment of overall glycemic control quality could potentially be incorporated with CGM software to augment HbA1c for routine patient screening and to aid in evaluating the effects of treatment. Additional work to validate and refine these metrics is underway.

InnovaStar: Precalibrated Point-of-Care Testing Diabetes Analyzer with Unit-Dose Reagents

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Objective:
The objective of the development was the construction of a small clinical chemistry analyzer for point-of-care testing (POCT). The photometric system enables the measurement of colorimetric and turbidimetric assays with liquid unit dose reagents. Two dedicated diabetes parameters, hemoglobin A1c (HbA1c) and glucose, are available. Both reagents are provided in ready-to-use bar-coded cartridges. The reagents are precalibrated. The system is designed to use capillary whole blood as sample material.

Method:
The system assembles a collection of dedicated microcomponents in its photometric and fluidic path. Liquid-stable high-quality reagents were adapted to this particular POCT system.

Result:
A method comparison with International Federation of Clinical Chemistry and Laboratory Medicine samples to a routine laboratory system delivered for HbA1c the correlation $y = 1.01 \times -0.22$, $r = 0.995$, $n = 12$. A method comparison with patient samples to a commercially available method delivered for glucose $y = 0.969 \times -0.957$, $r = 0.995$, $n = 56$. Data according to Clinical and Laboratory Standards Institute guideline EP 5-A1 show, at 6.1 % HbA1c, Diabetes Control and Complications Trial (DCCT) precision within run coefficient of variation (CV) = 3.08%, between day CV = 1.92%, and total precision CV = 4.03%. At 9.5 % HbA1c, DCCT precision data are within run CV = 1.5%, between day CV = 1.8%, and total precision CV = 3.3%. Precision data for glucose at 88.8 mg/dl are within run CV = 2.5%, between day CV = 0.4%, and total precision CV = 3.8%. For glucose at 285 mg/dl, precision data are within run CV = 1.8%, between day CV = 1.5%, and total precision CV = 2.6%.

Conclusion:
The performance of the InnovaStar® flow-through photometric system is comparable to laboratory-based automated clinical photometric analyzers. Liquid unit dose reagents are precalibrated and provided in bar-coded cartridges. Both parameters can be performed from one hemolysate without previous sample preparation.

Using a Strip-Free System for Self-Monitoring of Blood Glucose Resulted in Increased Test Frequencies in Nonadherent Testers on Flexible Insulin Therapy: A User Survey

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Objective:
Nonadherence (NON-AD) to guideline-recommended test frequencies is common. NON-AD behavior correlates with poor glycemic control. Current self-monitoring of blood glucose (SMBG) systems are either single-strip systems (SSS) or integrated systems (IS; 10–17 strips in a disk/drum). The strip-free Accu-Chek® Mobile system (SFS) significantly reduces the number of steps to perform a test. This user survey was intended to provide feedback on testing habits, including adherence to recommended testing.

Methods:
New SFS users in Denmark were asked to complete an Internet survey. A total of 1112 new SFS users performing flexible insulin therapy voluntarily documented their self-reported weekly test frequencies (WTFs) online prior to and after having used the new system. Patients not meeting American Diabetes Association guideline-recommended testing frequencies (≥21 tests per week) at the start were classified "NON-AD."

Result:
A total of 1072 subjects had complete and eligible data (defined as WTF <100). Their average age was 46 years, the share of diabetes type 1/2/missing was 72/10/18%, and 20% of subjects were NON-AD. The SSS/IS users had an initial NON-AD rate of 31/16%. NON-AD patients started with a WTF of 8.2, increasing to 18.4 ($p < .0001$). Adherent patients started with 37.1, slightly decreasing over time. In the subgroup of 607 previous IS users (57%), NON-AD patients started with a WTF of 7.5, increasing to 18.4 ($p < .0001$), and WTF of adherent patients (36.5) remained unchanged.

Conclusion:
Initial NON-AD in IS users was half the rate of SSS users, indicating that integration could improve testing adherence. The doubling of WTF in NON-AD patients indicates that a SFS may specifically help to overcome some hurdles to testing, independent of the prior system type. Results should be replicated in a controlled study with objective WTF data.

Comparison of I-Stat and Accu-Chek Whole Blood Glucose Measurements in Rats and Humans

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Objective:
Point-of-care (POC) blood glucose (BG) analyzers are useful instruments in animal studies when multiple timely measurements are necessary *in vivo*. They are especially useful when using small animals, where total blood volume may be under 10 ml. In this laboratory, Accu-Chek and I-Stat are commonly used for BG measurements; however, I-Stat requires greater blood volume, and BG cartridge costs are significantly higher than for Accu-Chek. We therefore investigated the accuracy of these two POC instruments for the measurement of BG in rats and humans.

Methods:
Human and rodent whole blood samples were collected to compare BG in the Accu-Chek Inform System and I-Stat analyzer. A YSI 2300 was used as the reference instrument. Samples were spiked with sterile dextrose solution, and sterile saline was used as a diluent to decrease hematocrit. Human and rat BG concentrations from each instrument were analyzed using Bland and Altman analysis and analysis of variance.

Results:
Using YSI as the reference measure, BG bias was similar between Accu-Chek and I-Stat at the hypoglycemic BG range in human blood; mean absolute relative difference (MARD) were 9% and 8%, respectively. At the higher BG concentration, Accu-Chek and I-Stat MARD were 9% and 10%, respectively. At low hematocrit, with normoglycemia, bias was significantly higher for Accu-Chek compared to I-stat (MARD 16% versus 2%). In the rat, bias was elevated at the high BG concentration for Accu-Chek and I-Stat with MARD of 37% and 31%, respectively. At low hematocrit and low BG concentrations, MARD were 29% and 3% for Accu-Chek and I-Stat, respectively.

Conclusion:
The POC instruments used in this study had similar accuracy for human whole blood with normal and low normal hematocrit concentrations. I-Stat was more accurate than Accu-Chek when human hematocrit concentrations were reduced by more than 50% in human blood. In the rat, at high BG and normal hematocrit concentrations, both POC instruments had higher than acceptable BG measurement errors. At lower hematocrit concentrations, I-Stat had <10% error compared to 20–30% error for Accu-Chek. I-Stat BG measurement accuracy is retained under low hematocrit concentrations with no advantage over Accu-Chek when measuring rodent blood at high BG concentrations and normal hematocrit.

p53 Expression in Diabetic Foot Ulcers

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Objective:
Apoptosis is a necessary component in proper wound healing, eliminating cells once their function is no longer needed. Delayed healing is often observed in the diabetic foot ulcer. There is limited human data on the specific role of p53 expression in wound healing. Therefore, we evaluated p53 expression in nondiabetic control tissue and diabetic wound tissue to examine the differences in apoptosis.

Methods:
Samples were collected using 4 mm punch biopsies of diabetic foot ulcers from four subjects. Controls consist of normal skin and keloid tissue. Gene expression data were collected via qRT-PCR using a BioRad CFX96 thermocycler. Relative mRNA expression was then quantified using the $2^{-\Delta\Delta Ct}$ method with samples normalized to glyceraldehyde 3-phosphate dehydrogenase and β-actin. Statistical analysis of the data was performed using a one-way analysis of variance.

Results:
Our results indicate that the nondiabetic skin tissue has 2.57-fold ($p = 7.42 \times 10^{-11}$) higher p53 expression than that of the diabetics ulcer samples. In addition, the keloid sample had 8.31 ($p = .037$) times the p53 expression of the diabetic ulcer samples and 4.032 ($p = 3.35 \times 10^{-3}$) times the expression of the normal skin sample.

Conclusion:
Decreased p53 expression in the diabetic foot ulcer could be responsible for the delayed wound healing observed in these patients. Cells from the inflammatory and proliferative phases of wound healing need to be eliminated in order for epithelialization to occur. Future experiments are required to optimize the wound biopsy collection and provide a temporal profile of p53 expression as well as its modulation in chronic wounds.

Nocturnal Hypoglycemia Alarm System Algorithm Development on Multiple Clinical Data Sets

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Objective:
The HypoMon® (AiMedics Pty., Ltd., Sydney, Australia) is a noninvasive alarm system for detecting nocturnal hypoglycemia in young people with type 1 diabetes mellitus (T1DM). The device has been validated in four in-hospital clinical trials (studies I–IV) on 298 participants with T1DM. We describe methods for establishing the equivalence of real-time algorithm performance (study III) and retrospective algorithm performance on independent data (study IV). These methods enable further retrospective testing to establish the clinical efficacy of new algorithms on large data sets and across multiple clinical trials.

Method:
An algorithm developed on clinical data from 46 T1DM patients (study II) was tested in real time during study III. This real-time result is compared to retrospective analysis of performance on further independent data collected in study IV to establish equivalence. New algorithms developed using study III data were then tested on independent study IV to establish the clinical efficacy of the HypoMon on a large data set.

Result:
Statistical testing (binomial exact test) indicates real-time algorithm outputs on study III data, and retrospective analysis on independent (study IV) data provide clinically equivalent sensitivity and specificity. The same statistical approach enables newly developed algorithms to be applied retrospectively to study IV, without requiring a real-time trial to show the clinical efficacy of the HypoMon to be sensitivity 78% (18/23), specificity 83% (44/53), positive predictive value 67%, and negative predictive value 90%.

Conclusion:
The efficacy of the HypoMon system algorithms for detecting nocturnal hypoglycemia has been clinically tested both in real time and in retrospective analyses on a broad spectrum of clinical trial data. We conclude that, with appropriate statistical methods, retrospective analysis enables robust algorithm development.

Excessive Use of Mobile Phone: Is It a Risk Factor to Develop Diabetes Mellitus?

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Objective:
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—the mobile phone—and diabetes mellitus. The aim was to determine the effects of excessive use of mobile phones on fasting blood glucose and serum insulin in Wistar albino rats.

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

Results:
Wister Albino rats exposed to a mobile phone longer than 15 min/day for a total period of 3 months had a significantly higher fasting blood glucose ($p < .015$) and serum insulin ($p < .01$) relative to their control. HOMA-IR was significantly increased ($p < .003$) in the groups that were exposed for 15–30 and 46–60 min/day compared to their control.

Conclusion:
Long-term exposure to mobile phone causes hyperglycemia associated with insulin resistance in Wistar albino rats.

A Model of Glucagon-Like Peptide-1 Action on Insulin Secretion during an Oral Test

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Objective:
Glucagon-like peptide-1 (GLP-1) is an incretin hormone that acts as a powerful insulin secretagogue. Moreover, GLP-1-based therapy is part of the treatment of type 2 diabetes. The ability to quantify GLP-1 action on insulin secretion could provide insights into the pathogenesis and treatment of diabetes. Dalla Man and colleagues proposed a model of GLP-1 action on insulin secretion using data from a hyperglycemic clamp with GLP-1 infusion. However, such methodology is cumbersome and therefore not widely applicable. The aim of this study was to determine if the GLP-1 model can be adapted to measure GLP-1-induced potentiation of insulin secretion during an oral test.

Method:
The model is based on the C-peptide minimal model, which assumes that secretion is made up of a static and a dynamic component, proportional to glucose concentration, through parameter Φ_s, and its rate of change, through parameter Φ_d, respectively. Moreover, the above-basal insulin secretion depends linearly on total GLP-1 concentration, through a parameter π, which represents GLP-1-induced potentiation. Total instead of active GLP-1 is used because it represents net hormone secretion. The model was tested on 22 impaired fasting glucose subjects (18 females, 4 males, age = 54.7 ± 1.8 years, body mass index = 32.9 ± 1.2 kg/m^2) studied on two occasions with a standardized meal containing 73 ± 0.5 g of carbohydrates.

Result:
The GLP-1 model provided a good fit of C-peptide data and a precise estimate of Φ_s [32.9 ± 2.1 10^{-9} min^{-1}, coefficient of variation (CV) = 6 ± 1%], Φ_d (488.6 ± 49.9 10^{-9}, CV = 14 ± 2%), and π (7.9 ± 1.3% per pmol/liter, CV = 33 ± 4%). Parameter values well agree with those previously reported in the literature.

Conclusion:
A new oral GLP1-1 model has been proposed that allows quantification of GLP-1 action on insulin secretion during a meal study.

A Model of Glucagon Secretion and Action in Healthy Subjects

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Objective:
A model of the glucose–insulin system in the postprandial state has been proposed by Dalla Man and colleagues. However, such a model does not take into account counterregulatory hormones, such as glucagon, and is thus unable to properly describe hypoglycemic events. We therefore undertook this study with the aim of modeling the secretion, kinetics, and action of glucagon in normal subjects.

Method:
The model makes several assumptions, namely, that glucagon kinetics can be described with a single compartment model, that secretion by α cells depends on plasma glucose concentration under a certain threshold and is modulated by plasma insulin. In addition, glucagon stimulates endogenous glucose production and inhibits insulin secretion. The validity of the model is assessed by comparing glucose-, insulin-, and glucagon-simulated profiles with those measured *in vivo* in various experimental conditions (e.g., a stepped hypoglycemic clamp).

Result:
The glucose, insulin, and glucagon concentrations simulated by the model of the glucose–insulin system incorporating the new glucagon model generally reproduces the profiles reported in the literature.

Conclusion:
The proposed glucagon model was successfully integrated into the healthy state simulator of the glucose–insulin system. Future work will include the extension of the model to describe glucose–insulin–glucagon interactions in type 1 diabetes.

Development of an Electronic Data Tool to Capture Behaviors and Outcomes at the Baylor Diabetes Health and Wellness Institute for the Improvement in the Health of High-Risk Patients

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Objective:
This project demonstrates the development of an electronic data tool so that certified diabetes educators (CDEs) can interactively, at the point of patient care, capture important behavior and outcome information so that patients and CDEs can track the progress of patients on a longitudinal basis in improving their behaviors and resulting outcomes when participating in programs, including education, nutritional instruction, and counseling.

Method:
An electronic data tool was developed so that CDEs can interactively, at the point of patient care, capture and score health risk assessment information, including seven health behaviors; medical and behavioral (family) history; quality of life (based on the EuroQol 5-D), including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and value analog scale; and biometrics, including glucose levels, weight, body mass index, and blood pressure.

Result:
A community-wide assessment found that this population engages in unhealthy behaviors with 40% who have a high-fat diet on a daily basis, 44% who smoke, and only 18% who engage in strenuous exercise. Approximately 41% of the population report health to be a major concern, with 57% having a family member with diabetes, 44% with high blood pressure, and 28% with high cholesterol.

Conclusion:
The electronic data tool facilitates improvement in the behaviors and outcomes, as it provides important information for the patients and the CDEs related to programs that focus on education, nutritional instruction, and counseling for the purpose of (1) preventing the incidence of diabetes in high-risk patients or (2) managing the condition and related morbidities when the onset of diabetes as occurred.

Evaluation of Tubeless Continuous Subcutaneous Insulin Infusion Therapy in Children Newly Diagnosed with Type 1 Diabetes Mellitus

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Objective:
The incidence of type 1 diabetes (T1DM) is increasing, especially among younger children. Use of continuous subcutaneous insulin infusion (CSII) early after diagnosis can be effective in lowering hemoglobin A1c and preserving beta-cell function. This was a pilot feasibility study evaluating tubeless CSII therapy in young children in the immediate period following diagnosis.

Method:
Fourteen patients at the Children's Hospital of Alabama were recruited within two weeks of diagnosis; 11 patients completed the study. Patients and families received introductory diabetes education and were started on a basal–bolus insulin regimen. There were two instruction sessions: general CSII therapy principles and specific device training with the OmniPod™ insulin pump. Data were collected via phone, email, and regular clinic visits. Insulin adjustments were made at clinic visits, via phone, via email, and independently by parents.

Results:
Patients' age at diagnosis ranged from 1.4 to 10.2 years (mean 6.7 ± 2.9). hemoglobin A1c at diagnosis ranged from 6.4% to 12.2% (mean 9.4% ± 1.9%). The time period from diagnosis to CSII initiation was 0.9 to 5.6 months (mean 2.2 ± 1.2). The CSII therapy duration ranged from 4.2 to 10.9 months (mean 6.9 ± 2.3). Hemoglobin A1c at study conclusion ranged from 6.1% to 9.0% (mean 7.5% ± 0.9%). There were no severe adverse events (emergency room visits, hospitalizations, hypoglycemia requiring glucagon) during the period between CSII initiation and study conclusion.

Conclusion:
This was a small pilot study to test feasibility of instituting tubeless pump therapy in the immediate postdiagnosis period. Patients were able to be easily transitioned to CSII, and no adverse events were reported. Our study showed that early initiation of tubeless CSII therapy in young children with T1DM is safe and effective.

A Wireless Vital Sign Monitoring System for Enhanced Insulin Delivery

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Objective:
A multisensory system that provides real-time information on the physiological state of the body will have tremendous impact on the ability of a future artificial pancreas (AP) to improve glycemic control. This information will enable exercise, illness, and stress detection and will facilitate control regulation and subject monitoring that will improve both safety and efficacy of glucose regulation via AP.

Method:
To effectively monitor subject activity, we have designed and tested a wireless device that can be worn by the user in an armband. The device senses the subject's heartbeat, acceleration, and galvanic skin resistance.

Result:
We have shown the successful wireless transmission of vital sign parameters using our device controlled by an onboard Arduino microcontroller. The skin resistance measurement is made using a custom-built circuit and then processed using a moving average filter. The skin resistance in the resting state is measured to be 2 MΩ and after mild exercise drops to ~1 MΩ, which are well within the acceptable range. The accelerometer has a full scale range of ±3 g. The heartbeat sensor is derived from an electrocardiogram measurement. The polling is done for approximately 30 s on each parameter, and the delay when switching between each parameter is 2–3 s. These parameters can also be changed, if desired, via software control using the microcontroller onboard. The device consumes about 30 mA of static current and can be operated continuously for 3 days without recharging.

Conclusion:
This multisensory system provides the needed information for a fully automated AP that can address day-to-day challenges. Such a system would improve both safety and quality of life of people with type 1 diabetes mellitus.

Intraoperative Point-of-Care Glucose Meter Accuracy

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Objective:
Usefulness of point-of-care (POC) glucose meters in hospitals has been raised. Accuracy has been questioned, especially in critically ill patients. Although commonly used in intensive care units (ICUs) and operating rooms (ORs), POC meters are not Food and Drug Administration labeled for in-hospital patients. Point-of-care glucometer performance during surgery is lacking. We evaluated POC meters in the intraoperative setting.

Method:
Anesthesia information management system was queried for the time and value of intraoperative blood glucose (BG) values (Accu-Chek® and central laboratory) in diabetes patients undergoing surgery from November 2005 through January 2010. Laboratory specimens receiving 20 min of the Accu-Chek time were considered as simultaneous. Differences, computed as the laboratory BG–Accu-Chek BG, were analyzed by the method of Bland and Altman and the Clark error grid analysis. Curve fitting was by maximum likelihood.

Result:
A total of 10,996 cases in diabetes patients (13.6%) were identified in 80,379 records, 6727 of which had 1 intraoperative Accu-Chek or laboratory BG determination. There were 307 simultaneous measurements, with a BG difference bias -4.0 mg/dl and precision of 24.1. Differences were fit by a Laplace/Double Exponential (p = .18), with location -5.0, scale 23.7. Of the Accu-Check BG, 5% would be 59 mg/dl higher and 5% 49 mg/dl lower than the laboratory BG; 80% of Accu-Chek values would be within -33 and +43 mg/dl and 75.4% within 20% of the laboratory BG. Error grid analysis showed 4 patients in the inappropriate treatment section (area C) and 3 patients with missed, potentially dangerous hypoglycemia/hyperglycemia misinterpretations (area D).

Conclusion:
We found intraoperative POC glucometer inaccuracy to be similar to reported ICU studies. Because 5% of laboratory BG would be 49 mg/dl lower than a simultaneous Accu-Chek BG, targeting a normal BG (80–110 mg/dl) would result in 5% incidence of unrecognized hypoglycemia if the Accu-Chek were relied on. This could increase patients' morbidity because signs of hypoglycemia are masked during general anesthesia. Central laboratory measurements are needed if intensive insulin therapy is implemented in the OR to minimize the risk of hypoglycemia.

Quantitative Assessment of Potential Surrogate Markers for Postprandial Values and Excursions

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Objective:
Research suggests that postprandial hyperglycemia and glycemic variability are independent risk factors for long-term diabetes complications, including cardiovascular disease and death. Current clinical research also recommends limiting postprandial excursions to less than 50 mg/dl. Still, the requirement for postprandial monitoring remains controversial. This study was designed to quantitatively evaluate subsequent preprandial (SPP) blood glucose (BG) values as potential surrogate markers for postprandial testing in poorly controlled patients with type 2 diabetes mellitus (T2DM).

Method:
Structured BG monitoring forms were randomly selected from 100 subject visits (intervention group only) from the Structured Testing Protocol (STeP) study, a large, cluster-randomized, multicenter study of 522 poorly controlled (hemoglobin A1c ≥7.5%) T2DM subjects. Regression analysis was utilized to evaluate SPP values as a surrogate marker for postprandial values and excursions (n = 755). This analysis was then used to calculate the standard error of the estimates (SEE) and assess the accuracy of the prediction in identifying postprandial excursions >50 mg/dl.

Result:
Postprandial BG values and excursions are weakly correlated with SPP values (R^2 = 0.278 and 0.0385, respectively). Retrospective estimation of postprandial values and excursions utilizing SPP values resulted in high standard error values (SEE = 51.42 and 53.82 mg/dl, respectively). Additionally, predictions based on this regression failed to identify 94.05% of excursions >50 mg/dl.

Conclusion:
Estimations of postprandial BG values based solely on SPP values do not have adequate clinical accuracy to serve as surrogates for measured postprandial BG values or postprandial excursions. Most estimations will also fail to identify postprandial hyperglycemia and excursions over 50 mg/dl, which are both important risk factors for long-term complications in patients with T2DM.

Integration of an Optical Glucose Sensor into an Insulin Infusion Catheter

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Objective:
A feasibility study to integrate an optical glucose monitor into an insulin infusion catheter, which could be the heart of an artificial pancreas, is presented. Integration of a phosphorescent sensor into the insulin catheter solves two fundamental technical problems. First, the sensor is located in the body only for a short time, leading to less bioincompatibility. Second, insertion and removal of the sensor imposes no additional burden on the patient. Present work is also aimed at designing and characterizing different combinations of phosphorescent oxygen indicators based on specially tailored palladium and platinum complexes of benzoporphyrins and naphtoporphyrins.

Method:
The outer surface of an insulin catheter is covered with an enzymatic phosphorescence-based glucose sensor as well as a reference oxygen sensor. Contactless read-out of signals is performed via near-infrared radiation. Usability of the concept is demonstrated in preliminary studies with layers of varying heights of beef meat and fat, simulating absorption and scattering, respectively. In a proof-of-principle in vivo experiment, catheters coated with glucose sensor were implanted subcutaneously into a pig's abdomen and side, measuring the signal loss in correlation with depth of implantation.

Result:
Generated in vivo data are similar to the simulated data in meat. Even though an evident signal loss can be observed, time-resolved measurements with two-frequency correction lead to confidential results for implantation depths of up to 5 mm.

Conclusion:
We have demonstrated that the concept of subcutaneous glucose measurement is feasible. Measurement of phosphorescence signals through skin, fat, and flesh is possible with the setup and implantable sensing materials used.

Fading Memory Algorithm for Computerized Glucose Control in Surgical Intensive Care Unit Patients

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Objective:
Hyperglycemia is commonly encountered in critically ill patients and is associated with increased mortality and morbidity. We evaluated the feasibility of a new fading memory (FM) glucose control algorithm to safely and effectively control blood glucose in surgical intensive care unit (ICU) patients within a desired range of 140 ± 20 mg/dl. The fully scalable FM algorithm mimics the biphasic insulin response of a normal pancreas and can be integrated with a continuous glucose sensor.

Method:
The FM algorithm was built into a computer program to work at a patient's bed side. After institutional review board approval, the algorithm was applied on 15 consented patients who were scheduled to have elective surgery. Upon postsurgical ICU admission of a patient, insulin infusion was either continued from the operating room or initiated when the glucose level exceeded 140 mg/dl. Hourly glucose measurements were performed and entered into the computer program that then prescribed the insulin dose. The new algorithm was applied for the first 8 h of ICU stay, after which the existing paper-based algorithm was used.

Result:
Patients' demographic data are age 67 ± 10 years, type 2 diabetes in 8 cases, and cardiac surgery in 10 cases. Glucose control data are: preoperative glucose level 154 ± 43 mg/dl, starting glucose level 199 ± 59 mg/dl, starting insulin dose 4.8 ± 2.3 U/h, time to reach target glucose 2.4 ± 1.9 h, and mean glucose level after reaching target 144 ± 12 mg/dl. The feasibility study had no incidences of hypoglycemia (glucose <60 mg/dl) or excessive hyperglycemia (>300mg/dl). Once the target was reached, only 30% of subsequent glucose measurements were outside the desired range.

Conclusion:
The initial evaluation of the FM algorithm shows promise in controlling glucose levels effectively and safely in surgery patients.

Importance of Time Spent Standing for Those at Risk of Diabetic Foot Ulceration

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Background:
Despite the high cumulative plantar stress associated with standing, previous physical activity (PA) reports of diabetes patients at risk of foot ulceration have not taken this activity into account. This study aimed to monitor spontaneous daily PA in diabetic peripheral neuropathy (DPN) patients and to examine both walking and standing activities as important foot-loading conditions.

Method:
To gain a more comprehensive understanding of PA, 13 DPN patients (aged 59 ± 8 years, body mass index 34.6 ± 4.2) were asked to wear a comfortable shirt, including an unobtrusive body-worn sensor for 48 h. PAMSys enables extracting body postures (sitting, standing, lying) and locomotion (walking, number of steps, speed). An algorithm was designed to identify those periods in which the shirt was not worn by the subject.

Results:
Results demonstrate that the period of standing is almost twice the period of walking ($p < 10^{-6}$). On average, DPN patients' activity consisted of 13 ± 5% standing, 6 ± 3% walking, 38 ± 9% sitting, and 43 ± 9% in lying posture. The total number of steps per day was averaged 7754 ± 4087, and the number of episodes of continuous steps was 357 ± 167, with maximum duration of 3.6 ± 4.2 min. The most active patient walked an average 19,363 steps per day (13% of total activity), while the least active patient walked 4259 steps (3.8% of total activity). The duration of standing for the most and the least active patients was 21% and 5.8%, respectively.

Conclusion:
This study demonstrates that standing accounts for a large portion of total PA in patients at risk of diabetic foot ulcers. With a duration nearly twice as long as the time spent ambulating, standing merits consideration when treating and preventing diabetic foot ulcers.

In Early Walking Phase, Plantar Temperature Is Sharply Increased in Charcot Patients but Is Reduced in Healthy Subjects

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Objective:
It has been well established that asymmetrical plantar temperature (PT) is one of the trauma of Charcot foot and may be used for early diagnosis of this symptom. However, little attention has been paid to how walking influences the dynamic of PT fluctuation. In this study, we designed a novel thermometry camera toolbox that may be used for better screening PT behavior in Charcot patients.

Methods:
We assessed spatial distribution of foot temperature (SDFT) prewalking and postwalking in two high-risk Charcot neuroarthropathy (CN) subjects and five healthy subjects. The number of steps was measured using an ambulatory device based on body-worn motion sensors. Using the designed toolbox, the 5th, 50th, and 95th percentiles of the SDFT for each foot were identified as low, medium, and high temperature spots, respectively.

Results:
In CN patients at baseline, a difference of approximately 3 °C was observed between two feet in the hot spot area, while almost no difference was observed in healthy subjects. After 100 steps, the PT in the CN patients' hot spot increased on average by 2.7 °C, while the temperature difference between contralateral feet was reduced to less than 1.6 °C. After 200 steps, the PT was increased on average by 6.6 °C compared to the baseline for the CN foot. However, no difference was observed between contralateral feet. Interestingly, healthy subjects' PT was slightly reduced during the first 200 steps, but linearly increased between 400 and 1600 steps on average by 2 °C.

Conclusion:
The apparently different thermal response to the initiation of walking between CN and healthy subjects warrants future investigation to provide further insight into the correlation between thermal response and ulcer development.

Effect of Meter Performance on Insulin Dosing and Outcomes

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Objective:
Numerous factors contribute to insulin dosing errors, including glucose meter inaccuracy and carbohydrate (CHO) estimation error. The effect of meter error alone has been assessed by a number of simulation studies, but the effect of CHO estimation error is less well understood. This Monte Carlo simulation studies the impact of meter performance on insulin dosing and outcomes in the presence of CHO estimation errors.

Method:
We simulated 5000 *in silico* patients about to eat a meal, who use their measured blood glucose and CHO estimate to calculate insulin doses. The patients' true blood glucose and meal CHO content were randomly distributed. The study measured the frequency of insulin dosing errors (of at least 1 U) and postprandial outcomes, including "glucose at goal" (70–130 mg/dl) for various levels of meter performance and CHO estimation accuracy.

Result:
This *in silico* study demonstrates that systematic biases in meter error and CHO estimation have an additive effect. A positive overall bias increases the postprandial likelihood of hypoglycemia, while a negative bias increases the likelihood of hyperglycemia.

Conclusion:
The study further shows that, while CHO estimation accuracy is a significant factor, meter performance can still impact insulin dosing errors and postprandial outcomes. The impact of meter performance is most pronounced when CHO estimation errors are minimized.

Transdermal Delivery Using Polymer Microneedles

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Objective:
Microneedles are small-scale needle-shaped devices that are being considered for transdermal delivery of insulin, incretin mimetics, and other protein-based agents. In this study, microneedles with several geometries were created using a two-photon polymerization microfabrication poly(dimethylsiloxane) micromolding process out of a photoreactive acrylate-based polymer. In a previous study, viability of human epidermal keratinocytes on the acrylate-based polymer was similar to that on polystyrene. The structural, mechanical, and biological properties of acrylate-based polymer microneedles created using a two-photon polymerization microfabrication-micromolding process were examined by scanning electron microscopy, compression testing, and dye delivery studies.

Method:
Two-photon polymerization was used to make master structures of microneedles. The master structures were then used to make negative molds out of poly(dimethylsiloxane). The negative molds were subsequently used to cast microneedles out of an acrylate-based polymer (Envisiontec, Ferndale, MI). Depth of penetration was determined using Lucifer Yellow dye, which is a hydrazine-derivative dye that covalently combines with proteins.

Result:
Scanning electron microscopy was used to image microneedles with various geometries. The microneedles penetrated porcine skin without difficulty. Fluorescent imaging demonstrated transdermal delivery of Lucifer Yellow dye along microneedle-fabricated pores into cadaveric porcine skin.

Conclusion:
Our results suggest that a two-photon polymerization microfabrication poly(dimethylsiloxane) micromolding process may be used to fabricate microneedle structures with appropriate structural, mechanical, and biological properties for transdermal drug delivery. These devices may be employed for delivery of insulin and other protein-based agents, which are used for treatment of diabetes mellitus.

Pediatric Diabetes Education Portal: Asynchronous Telemedicine with Ongoing Education Improves Pediatric Diabetes Care

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Objective:
Type 1 diabetes requires lifelong medical management. Education is given to patients and their families at the time of diagnosis, but these materials can be overwhelming and are often not fully understood. We proposed to use telemedicine to provide ongoing, patient-specific feedback on diabetes management to improve care for children with type 1 diabetes.

Method:
All children with type 1 diabetes seen in our clinic were consecutively enrolled over 1 year in the Pediatric Diabetes Education Portal (PDeP). Patients were given access to a certified diabetes educator who coordinated (1) quarterly finger-stick hemoglobin A1c (HbA1c) testing, (2) periodic use of iPro CGMS, and (3) a Website for patients to immediately access their HbA1c, CGMS, and other testing results from home. The Website allowed families to view educational materials related to their testing results, post questions, and read comments from the diabetes educator. Users of the Website were defined as families who logged in two or more times. The cohort for analysis were patients whose baseline HbA1c was above American Diabetes Association (ADA) age-recommended guidelines. Hemoglobin A1c was measured quarterly.

Result:
A total of 52 patients were enrolled. Patients excluded from analysis were new onset (10), moved out of the area and lost to follow-up (10), or baseline HbA1c within ADA age-recommended guidelines (16). In the user group, HbA1c decreased by a mean of 1.36% from baseline after six months of use of PDeP versus a mean increase of 0.98% for nonusers of the Website ($p = .04$). CGMS use alone did not correlate with change in HbA1c.

Conclusion:
Children with type 1 diabetes who actively used our telemedicine approach to diabetes management showed considerable improvement in HbA1c.

Association between Sitagliptin Adherence and Self-Monitoring of Blood Glucose

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Objective:
Adherence with diabetes medications, including newer ones with fewer side effects, is poor. However, not surprisingly, studies have associated medication compliance with glycemic control. Similarly, some studies have suggested self-monitoring of blood glucose (SMBG) is associated with improved outcomes for patients with type 2 as well as type 1 diabetes. One potential reason may be improved drug adherence as a result of increased disease awareness or feedback regarding therapeutic adjustments.

Method:
In this study, we investigated if SMBG is associated with improved sitagliptin adherence using a large insurance administrative claims database in the United States. Utilizing logistic regression, we analyzed the relationship between patient demographics, diagnosis codes, procedure codes, and SMBG availability with sitagliptin compliance, defined as achieving a medication possession ratio of at least 75%. Data for each patient 12 months pre and post sitagliptin initiation was obtained.

Result:
This analysis included 7306 patients (57.6% male; average age 54.2 years). The average pre and post sitagliptin hemoglobin A1c values were 7.9% and 7.4%, respectively. A total of 58% of patients were compliant with sitagliptin. Age, male gender, and receiving diabetes treatment before starting sitagliptin were found to significantly impact the chance of being compliant. Having SMBG test strips available was also associated with improved compliance [odds ratio (OR) 1.198 for patients continuing to use SMBG and 1.338 for patients who did not use SMBG pre sitagliptin] compared to those who never used SMBG. Greater SMBG availability was associated with better compliance (OR 1.449 for higher versus 1.246 for lower availability) for patients who began SMBG after starting sitagliptin.

Conclusion:
This study demonstrated that SMBG availability is associated with improved sitagliptin compliance. This relationship is strengthened with greater SMBG availability.

The Spectral Fingerprint of Glucose *In Vivo* Using Raman Spectroscopy

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Objective:
Today's diabetes patients benefit from highly accurate and compact blood glucose meters for personal use. However, the pain associated with finger pricking remains one of the largest barriers to routine monitoring compliance. In this study, we investigate a potential device for a noninvasive glucose monitoring using Raman spectroscopy technology.

Method:
Optical technologies such as near-infrared and Raman spectroscopy employ direct interaction between the glucose molecules and photonic energy as a sensor captures light that is scattered or transmitted directly from the glucose molecule. This optical technology approach yields a spectral fingerprint of the target analyte, glucose, which is presented in the form of a calibration vector (a product of the partial least squares method). In this study, we constructed a high-throughput dispersive Raman system comprising an 830 nm multimode laser, a multiple optical fiber bundle, and a back-illuminated charge-coupled device. *In vitro* tests as well as *in vivo* pilot tests were performed, and calibration vectors were collected. The quality of the calibration vectors and the quantitative error values were then compared.

Results:
Correlation coefficients between a pure glucose spectrum and calibration vectors were consistently calculated greater than 0.8. We present spectral fingerprints of glucose that is noninvasively obtained and highly discriminated from interfering spectra using Raman spectroscopy.

Conclusion:
Clark error grid analysis alone cannot validate whether such glucose predictions are based on the target glucose molecules or some other interferer or uncontrolled experimental artifact. Results from the present study show that the specificity of Raman technology allows the successful capture of the glucose spectrum noninvasively.

Impact of Health Insurance Coverage on Pediatric Diabetes Management

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Objective:
The aim was to assess the relationship between health insurance coverage, the use of intensive management plans with insulin pens and pumps, and glycemic control in a cohort of type 1 diabetes patients.

Method:
A retrospective cohort design was drawn from the medical records of the Pediatric Endocrinology Clinic at the University of Louisville, Kentucky, in June 2010.

Results:
Out of 521 patients, 170 (33%) had public insurance and 351 (67%) had private commercial insurance with a significant difference in mean hemoglobin A1c (HbA1c) found (9.4% public versus 8.5% private, $p < .0001$) between the two insurance types. A total of 71% of all publically insured patients used a multiple daily injection (MDI) plan or insulin pump versus 84% of privately insured patients. Of those on an MDI plan, 94% used insulin pen devices. Although insulin pumps made up 21.9% of all plans, only 9.4% of those publically insured used an insulin pump versus 27.4% who were privately insured. Mean HbA1c for all pump users was 8.4% (8.8% public versus 8.3% private, $p = .14$). Privately insured MDI and pump patients had the best HbA1c levels.

Conclusion:
The majority of patients utilized an intensive management plan with either MDI or insulin pump. Privately insured patients had a significantly lower HbA1c than the publically insured group. Although the percentage of MDI use between insurance types was not statistically different, pump use was three times greater in those with private insurance. Further evaluation to assess prescribing practices and patient management choices is needed to increase access and use of pump technology in this population.

A Novel Way to Calculate Insulin Doses

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Objective:
This work demonstrates a novel method for calculating dose size for both rapid- and long-acting insulin for intensive multiple daily injection (MDI) therapy. The method is compared to a titration procedure using two *in silico* models of type 1 diabetes.

Method:
By making various simplifying assumptions about the kinetics of both rapid- and long-acting insulin analogs, as well as the form of disturbances (e.g., meals and unexpected deviations from euglycemia), the Bergman Minimal Model is used to derive a simple closed-form insulin therapy calculator. The performance of this calculator is then evaluated using on two cohorts of *in silico* patients, one based on the Bergman Model itself and the other based on the AIDA model. The incidence and severity of hypoglycemia, hemoglobin A1c (A1C) level, and mean amplitude of glycemic excursions are all tracked over a simulated three-month trial. As a control, the same three-month trial is also simulated given insulin doses from a titration procedure using an insulin sensitivity factor and an insulin-to-carbohydrate ratio.

Result:
Patients from both cohorts treated with the novel insulin therapy calculator have less frequent and less severe hypoglycemia as well as lower A1C levels when compared to the titration group. The differences are more pronounced for patients in the Bergman cohort.

Conclusion:
A novel insulin therapy calculator has been demonstrated to provide better glucose control for MDI therapy than a typical titration-based protocol. This calculator is attractive as an intermediate for patients awaiting closed-loop pump-based glucose control. In addition, the calculator is a great boon to the roughly three-fourths of type 1 diabetes patients who are on MDI therapy.

Impact of Fat-Protein Meal on Postprandial Hyperglycemia in Type 1 Diabetes Patients Treated with an Insulin Pump: The Results of a Randomized Study

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Background:
In intensive insulin therapy programs, prandial insulin dose is calculated based on carbohydrate (CHO) intake multiplied by insulin-to-CHO ratio (IR). There is no evidence that fat-protein food influences postprandial glycemia. The aim of this study was to assess the impact of mixed meal (pizza) on the postprandial glycemia excursions during 6 h after the meal, where fat-protein contents are taken into account in boluses dose.

Materials and Methods:
From 23 type 1 diabetes patients treated with insulin pumps, 12 were randomly allocated to the experimental group (EG) and 11 to the control group (CG; hemoglobin A1c 7.5 ± 1.3%, aged 14.9 ± 2.0 years, diabetes duration 6.5 ± 2.8 years, insulin requirement 0.9 ± 0.2 IU/kg/day). Patients in the EG received dual-wave boluses for dinner (pizza: 45 g CHO + 400 kcal from fat-protein products [4 filter paper units (FPU)]), and the dose of insulin was calculated by the algorithm *n*CU × IR + *n*FPU × IR / 6 h (normal + extended boluses). In the CG, the dose of meal boluses was *n*CU × IR. Glucose *n*, C-peptide, and glucagon concentration were assessed before meal and 30, 60, 120, 240, and 360 min after.

Results:
The average blood glucose rose significantly from 60 to 360 [for 60, 98.7 standard deviation (SD) 40 mg/dl versus 151.5 SD 70.5 mg/dl, $p = .04$; for 120, 88.5 SD 40 mg/dl versus 165.3 SD 76.5 mg/dl, $p = .02$; for 240, 93.8 SD 45.5 mg/dl versus 196.4 SD 90.2 mg/dl, $p = .004$; and for 360, 77.0 SD 40.3 mg/dl versus 188.4 SD 95.6 mg/dl, $p = .003$] in the CG. The delta of blood glucose was significantly higher at 120, 240, and 360 min in the CG. There were not differences between glucagon and C-peptide concentration.

Conclusions:
Fat-protein meal increases postprandial glycemia until 6 h. The dual-wave boluses in which insulin is calculated for CHO and fat protein is effective in controlling postprandial glycemia.

In Vivo Performance of a Nonenzymatic Intravascular Glucose Sensor for Continuous Monitoring during Critical Illness and Surgery

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Objective:
Blood glucose level is thought to be closely related with infection and the wound-healing process. Based on this hypothesis, studies on active blood glucose control for critically ill patients are being conducted intensively. Blood glucose level monitoring during surgery is also an important issue, because there are reports that present that the outcome of patients in surgery is enhanced by tight glucose control. The final goal of our research is to develop an automated system that monitors a patient's blood glucose level by accessing blood through an intravascular (IV) catheter in surgical and intensive care unit (ICU) patients.

Method:
An electrochemical glucose sensor was fabricated by our proprietary method. Nanostructured platinum was adopted as a working electrode. The sensor was inserted into a medical tube connected to an IV catheter in a rabbit animal model. By a computer-controlled syringe pump connected to the other end of the tube, the sensor was periodically exposed to blood sample and then rinsed with saline. After the noise-reduction process, the acquired amperometric signal was calibrated to estimate glucose concentration.

Result:
The developed sensor output shows a fairly good response to the glucose concentration of the blood sample after the appropriate calibration process. Clarke's error grid analysis results also show the applicability of the system with a clinically useful degree of accuracy.

Conclusion:
An automated continuous blood glucose monitoring system using a proprietary nonenzymatic sensor was developed and characterized *in vivo*. A nonenzymatic sensor has intrinsic advantages of compatibility with the sterilization procedure and immunity to the operating environmental changes. The system is expected to be connected to the IV catheter to provide continuous blood glucose levels for surgical and ICU patients.

A Population-Based Study of Hypoglycemia Requiring Ambulance Services

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Objective:
The aim was to study the epidemiology of hypoglycemia requiring ambulance services.

Methods:
We retrieved all ambulance calls activated for hypoglycemia in Olmsted County between January 1, 2003, and December 31, 2009. These represent >95% of such events in Olmsted County.

Results:
A total of 1475 calls were made by 915 people [with diabetes 82% (210 type 1 diabetes [T1DM], 506 type 2 diabetes [T2DM], 30 undetermined type), without diabetes 16%, unknown diabetes status 2%]. Mean age was 60 ± 16 years, with 49% female. Mean (standard deviation) blood glucose concentration during hypoglycemic episode was 50 ± 17 mg/dl. Proportional to the sample composition, a higher percentage of calls were made by persons with diabetes (87%) with proportionally fewer calls coming from persons without diabetes (11%) (GOF test, $p < .001$). Emergency room transportation was needed by 546 (60%); 276 (30%) were hospitalized. Emergency room transportation and hospitalization was significantly higher in people without diabetes compared to people with diabetes ($p < .001$) and T2DM compared to T1DM ($p < .001$), and 20% of the patients needed ambulance assistance more than once.

Death occurred in 240 (T1DM 33, T2DM 172, non-DM 35) at age 73 ± 11 years (T1DM 66 ± 14, T2DM 77 ± 9, and non-DM 64 ± 14) 1.5 ± 1.2 years after first event. Respiratory illnesses caused the highest mortality (19%), while metabolic complications (hypoglycemia, diabetic ketoacidosis) caused 5%. Mortality was significantly associated with age ($p < .001$), end stage renal disease ($p = .02$), and chronic liver disease ($p = .01$). After adjusting for age and co-morbidities, mortality was significantly higher in people without diabetes compared to people with diabetes ($p < .001$) but not different between the two types of diabetes.

Conclusion:
While diabetes patients account for a higher percentage of ambulance service for hypoglycemia, hypoglycemia in the nondiabetic population is still prevalent.

Engineering Standards for Closed-Loop Control of Diabetes: Defining the Artificial Pancreas Operating System

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Objective:
As the medical community embraces new technology for treating diabetes and manufacturers venture into developing increasingly complex devices, modular design and standardization will play a key role in defining next-generation systems. Our objective here is to define a standard set of core functions and user/technical interfaces that allow plug-and-play composition of sensors (continuous glucose monitoring and others), actuators (continuous subcutaneous insulin infusion and others), and algorithms to enable closed-loop control of diabetes in clinical and field operating environments.

Methods:
Standardization is based on two fundamental concepts: (1) modular architecture for system design and (2) universal hardware interface.

Results:
The modular architecture features decomposition of control functions into safety, real-time corrections, (closed-loop feedback or open-loop control), and control of meals and exercise based on observation and optimal response to patient physiological and behavioral characteristics. A set of standardized module interactions defines application interfaces, common data structures, and timing allowing for synchronous or asynchronous execution of module functionality.

The universal hardware interface as demonstrated via the artificial pancreas system features a modular set of communication protocols that are streamlined to a common data structure, methods to extract and manipulate data by the control and safety algorithms at different time intervals, checklists and internal interlocks that prevent misuse or erroneous use by the user or algorithm, as well as hocks and methods to facilitate end user interface and device display.

These concepts were implemented in the design of the Juvenile Diabetes Research Foundation-sponsored control-to-range system, scheduled for multicenter trials in late 2010.

Patek cont. ⟶

Patek cont. ⟶

Conclusion:
Agreement on engineering and communication standards, and the development of a diabetes-specific operating environment (system), will accelerate the research progress and the commercialization of closed-loop control systems.

Mitigating Solutions in Insulin Pump System Security

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Objective:
Insulin pump systems are now the preferred method of treatment for type 1 diabetes patients. New features of insulin pump systems continue to add convenience and better treatment, including remote programming and continuous blood glucose management. Unfortunately, these new insulin pump features present new vulnerabilities that can result in an unsafe insulin pump system. Our objective is to help create a secure insulin pump system platform that withstands targeted malicious attacks against an insulin pump system.

Method:
The main threats of an insulin pump system can be broken into two parts: monitoring and control. By changing monitored information (e.g., blood glucose values), a patient might use incorrect information to program the insulin pump system. In control, an attacker can transmit commands using an unauthorized device. By analyzing these different components, we can better understand the potential vulnerabilities and build secure insulin pump system architectures.

Result:
In February 2010, we implemented a remote attack on a commercially deployed insulin pump system where we remotely programmed an insulin pump system using an unauthorized device, and we were able to do this attack from 100 ft. away. Since that time, we have continued to identify ways that a malicious attacker could potentially affect a patient's health. We plan to present mitigations against these and similar attacks at the workshop.

Conclusion:
Insulin pump system threats and vulnerabilities exist. Attackers can and will take advantage of insulin pump insecurity. An attacker who is able to influence the insulin pump system presents a very real risk to a patient. Based on our findings, we recommend implementing both new security protocols and securing insulin pump system architectures to protect against these attacks.

Accelerated Development of Glucose Sensors via *in Silico* Electrochemical Modeling

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Objective:
We discuss the development of an *in silico* electrochemical glucose sensor model that allows the sensor development team to rapidly reduce the time and cost of continuous glucose monitoring sensor development.

Method:
The model allows a single scientist to investigate key parameters and make development decisions without leaving the office and venturing into the laboratory. It allows for rapid empirical development iterations of the sensor to be performed, which currently would take multidisciplinary scientific team months to formulate, manufacture, and test.

Result:
The *in silico* model allows for the rapid assessment of a number of parameters:

1. Enzyme loading
2. Enzyme kinetics
3. Enzyme immobilization
4. Mediator loading
5. Mediator kinetics
6. Mediator immobilization
7. Glucose mass transport
8. Reference electrode drift
9. Counter electrode reactions
10. Electrode area
11. Electrode geometry
12. Assessment of two- and three-electrode geometry
13. Temperature effects

The model was developed using finite element modeling of classical electrochemical equations.

Conclusion:
As manufacturers seek smaller, less invasive geometries or product cost reductions through reduction of enzyme loading, the model will quickly predict the impact of design changes.

Accuracy of the Medtronic NexSensor™ for 6 Days in an Inpatient Setting Using Abdomen and Buttock Insertion Sites

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Objective:
Continuous glucose monitoring sensors should provide users with accurate readings regardless of insertion site. The objective of this study was to evaluate whether the Medtronic NexSensor™ was accurate for 6 days of sensor wear and in multiple insertion sites, the abdomen and buttock.

Method:
The NexSensor features improvements over the Medtronic Sof-sensor® to improve operating life and consistency. Sixty-three adults (aged 18–75 years) with type 1 diabetes wore two NexSensors simultaneously for 6 days, one each inserted in the abdomen and buttock. Subjects underwent a single frequent blood sampling study for 12 h, during which time reference plasma blood glucose values were collected and analyzed using the YSI STAT 2300 Plus™ every 15 min and compared to sensor values.

Result:
Over 85% of sensors were operational into the sixth day of use. The mean agreement rate between sensor and reference values for 6 days of wear was 75.5% [95% confidence interval (CI), 69.5, 81.4] at the abdomen site and 73.8% (95% CI, 68.8, 78.8) at the buttock site. Over 90% of paired sensor-reference values on Clarke and consensus error grids were within the A and B zones (Clarke, 93% at abdomen site, 94% at buttock site; consensus, 97% at abdomen site, 98% at buttock site). The mean and median absolute relative differences were 17.1 ± 16.9% and 12.3 at the abdomen site and 16.5 ± 16.1% and 11.5 at the buttock site. One adverse event unrelated to the device occurred during the study.

Conclusion:
The NexSensor was accurate for 6 days when inserted into the abdomen and buttock. The results of this study also provide evidence that both the abdomen and buttock areas are suitable as sensor insertion sites.

Unsafe Diabetes Care Practices: 10-Year Review of Hepatitis B Outbreaks and Patient Notification Events

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Objective:
Opportunities for blood borne pathogen (BBP) transmission exist when equipment used for diabetes care procedures (DCPs) is not dedicated for individual use (i.e., finger-stick devices, insulin pens) or cleaned and disinfected between each use (i.e., blood glucose meters). The Centers for Disease Control and Prevention has published safe practice guidelines for assisted monitoring of blood glucose (AMBG), yet outbreaks of hepatitis B virus (HBV) infection and patient notifications due to equipment misuse continue.

Method:
We reviewed public health investigations of confirmed outbreaks associated with AMBG in the United States between 2000 and 2009. For this same period, we also reviewed reports of patient notification events that resulted in groups of patients receiving notifications recommending BBP testing following a potential exposure to another patient's blood during DCP.

Result:
During the 10-year period, 15 HBV infection outbreaks and 3 patient notifications were identified; 9 outbreaks (60%) and all of the patient notifications occurred in the last 3 years. All outbreaks occurred in long-term care facilities where AMBG was performed; almost 900 persons underwent BBP testing and 116 (13%) residents acquired HBV infection due to equipment misuse during AMGB. Patient notifications occurred in two hospitals and a community health center; 3305 persons were contacted. The predominant unsafe practices identified were use of reusable (penlet-style) finger-stick devices or insulin pens on multiple persons, and sharing of glucose meters without cleaning and disinfection between each use.

Conclusion:
Hepatitis B virus infection outbreaks and patient notifications due to equipment misuse during DCP have been identified with increasing frequency. These findings suggest the need for better labeling, validated instructions for blood glucose meter cleaning and disinfection, and engineering controls and innovation in equipment design specific for applications involving AMBG or insulin delivery.

Hardware Implementation of Blood Glucose Prediction

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Objective:
Commercially available continuous glucose monitors report interstitial fluid glucose concentrations that lag behind changes in blood by several minutes. The objective of this work was to identify a model for prediction of glucose concentrations in hardware and implement it on a microcontroller for use in portable medical devices. Predictions up to 30 min (i.e., prediction horizon = 6) are required to compensate for the lag of interstitial fluid monitors and for early detection of hyperglycemic and hypoglycemic events.

Method:
A simple linear model with constant coefficients can be used to obtain short-term predictions. The significant advantages of these algorithms are the computability and the simple, interpretable model forms. Recursive identification of the coefficients improves the prediction results by enabling the model to react to unexpected fluctuations such as those caused by stress, exercise, or meal consumption. Autoregressive exogenous models with time-varying parameters were simulated in MATLAB and programmed into a PIC microcontroller. To test the algorithm in hardware, the predicted output was compared with the simulation. Performance of the algorithm was analyzed with the consensus error grid using data sets collected from 10 type 1 diabetes patients.

Result:
For 10 min predictions, 98.5% and 1.5% of all glucose measurements are considered as accurate (zone A) and benign errors (zone B). In the hypoglycemic range (<70mg/dl), 88.5%, 9.3%, and 2.2% of the 30 min prediction result in accurate readings, benign errors, and erroneous readings.

Conclusion:
Simple linear models of low order can be used for hardware implementation of predictive models to estimate future glucose concentrations. The proposed model provides satisfactory results for predictions up to 30 min.

Three-Dimensional Consensus Error Grid for Analyzing Performance of Glucose Prediction

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Objective:
Real-time continuous glucose monitoring systems require accurate hypoglycemic/hyperglycemic alarms. An effective warning system is an important safety mechanism to ensure appropriate action at times of glucose excursion. Subcutaneous glucose measurements require predictive algorithms to compensate for the lag between interstitial and blood glucose concentrations. Conventional analysis uses the Clarke or the consensus error grid to evaluate the model for one specified prediction step. A novel method is proposed, augmenting the consensus error grid to analyze the prediction performance over time.

Method:
The consensus error grid has been used to assess the clinical significance of differences between the predicted glucose concentration and the glucose reference measurement. However, for each prediction step, a separate error grid has to be constructed to evaluate the accuracy of the predictor. By introducing a third dimension with the prediction time set as the z axis, the accuracy of the predictive model can now be analyzed over various time steps. The three-dimensional (3D) consensus error grid displays predicted glucose concentration on the y axis, actual glucose concentration on the x axis, and prediction horizon (in minutes) on the z axis. The 3D consensus error has been implemented using MATLAB.

Result:
Visualization and comparison of the accuracy and consensus error of multiple time prediction windows is possible from one 3D consensus error grid.

Conclusion:
The proposed model evaluates the performance of predictive models for blood glucose estimation and, for each prediction step, displays prediction accuracy, prediction horizon, and consensus error.

Development of a DNA-Panel Macroarray Chip to Determine the Risk of Atherosclerosis and Related Disorders

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Objective:
Atherosclerosis is a complex disease which is characterized by lipid aggregation in the endothelium induced by chronic systemic inflammation. Risk factors include age, sex, smoking habits, low HDL-cholesterol levels, and diabetes mellitus. Next to family history and risk assessment, genetic analysis may be a helpful tool for risk prediction and diagnosis. The aim of this project is the development of a fast genotyping method for all relevant DNA polymorphisms described to be associated with increased risk for atherosclerosis and related disorders by using a new array-technology platform.

Method:
Genetic markers were identified by extensive literature review and selection was based predominantly on results from randomized clinical studies. A macro-array DNA-chip platform was identified allowing for detection of multiple genetic variations at the same time. The macroarray layout has 15 × 15 spots with a distance of 160 µm from each other and is implemented into a common 1.5 ml reaction tube. This macro-array chip technology can be handled with equipment found in common laboratories. The DNA is extracted from blood or other sources, and amplified and biotinylated in one PCR reaction. PCR-products are hybridized with allele-specific primers bound on the chip representing the wild-type or the mutated probe, respectively. Visualization of targets bound to the probes is performed by means of a specific precipitation reaction using a specially designed reading device.

Result:
Allele discrimination was successfully established for several genes including eNOS (Endothelial nitric oxide synthase 3), PTGS1, (Prostagladin-endoperoxide H synthase 1) MTHFR (Methylentetrahydro-folatreductase), ALOX AP (Arachidonate 5-lipoxygenase activating protein), CETP (Cholesterol ester transfer protein), ApoE (Apolipoprotein E), LTA (lLmphotoxin alpha) and LPL [Lipoprotein(a)]. Each of these genes carries mutations known to be associated with a several-fold increased risk for atherosclerosis. The detection accuracy of this method was confirmed to be 100% with real-time PCR by using hybridization probes and sequencing techniques.

Pfützner-Riehn cont. ⟶

Pfützner-Riehn cont. ⟶

Conclusion:
The described method offers an easy, fast and cost-effective genotyping of relevant atherosclerosis alleles. This chip may lead to an earlier detection of subjects at high risk and to an early, personalized therapy. Further studies will have to demonstrate whether this chip is suitable for prediction of atherosclerosis development and progression.

A New Formulation of Insulin Glargine with an Extended Release Profile

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Objective:
Insulin glargine (IG; Lantus®) has a sustained release absorption profile due to the formation of a microprecipitate post injection. In many patients, IG does not last a full 24 h. Therefore, the objective of this new formulation is to extend the duration of IG.

Method:
Excipients were combined with IG and tested *in vitro* using a solubility assay. Solubilized insulin was collected following centrifugation to remove the precipitate. The insulin in the supernatant was quantified by high-performance liquid chromatography. The experimental formulation with the least amount of soluble insulin following the dilution experiment (BIOD 809) was then tested in diabetic miniature swine to define its pharmacokinetic and pharmacodynamic profile. Duration of action in the diabetic miniature swine was established by the time the insulin and blood glucose values returned to baseline levels after evaluation for 24 h.

Results:
The solubility test showed the new formulation BIOD 809 was 40% less soluble than IG. Plasma data from IG swine runs showed an average duration of 18.5 h. In comparison, the BIOD 809 formulation's duration on average was in excess of 24 h. In addition, the pharmacokinetic profile of BIOD 809 was flatter than IG.

Conclusion:
A novel formulation of BIOD 809 can have a longer duration of action if excipients are added that reduce the solubility of the precipitate post injection. This increased duration is useful for patients who currently use Lantus and find the duration of action short of 24 h.

Automated Decision Support Tool Identifies Patterns of Hypoglycemia in a Population of Poorly Controlled Type 2 Diabetes Patients Undergoing Treatment Intensification

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Objective:
Hypoglycemia may be the most important adverse effect of treatment intensification (TI) in patients with type 2 diabetes mellitus (T2DM). Use of structured self-monitoring of blood glucose (SMBG) data and a proprietary decision support tool (DST) that identifies glycemic patterns from this data may allow for increased recognition of patterns of hypoglycemia in T2DM patients undergoing TI.

Method:
Structured SMBG data was collected quarterly (n = 991 forms) from 256 poorly controlled T2DM patients (hemoglobin A1c ≥7.5%) in the intervention arm of a large, cluster-randomized, multicenter study (STeP). Self-monitoring of blood glucose data were analyzed with the DST using a pattern-identification algorithm. The DST defines a pattern as two or more abnormal blood glucose values at the same time on subsequent days. Patterns of hypoglycemia were then further analyzed by visit, time of occurrence, and medication use.

Result:
Hypoglycemia was identified as the primary glycemic abnormality (PGA) in 10.9% of all analyzed visits. At the first clinical visit in the study, hypoglycemia was identified as the PGA for 6.6% (15/229) of subjects. At month 12, the last clinical visit of the study, hypoglycemia was identified as the PGA for 14.3% (25/175) of subjects. The average hypoglycemic measurement was 70.4 ± 8.9 mg/dl (n = 340). Hypoglycemia was most frequently identified before lunch (25%) and before breakfast (18%) (n = 340). Patients experiencing patterns of hypoglycemia were most commonly utilizing sulfonoylureas (31.3%), biguanides (28.2%), and/or thiazolidinediones (17.9%).

Conclusion:
These findings suggest that patterns of hypoglycemia can be identified by use of structured testing and a DST in T2DM patients undergoing TI. Health care providers may be able to use this information to reduce hypoglycemia and adverse events during TI.

Noninvasive Polarimetric-Based *In Vivo* Glucose Monitoring

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Objective:
The objective of this study was to demonstrate a noninvasive technique to measure *in vivo* physiological glucose levels in the aqueous humor of the eye that are correlated to those of blood.

Method:
Measurements were acquired using a custom-designed laser-based optical polarimetry system in six New Zealand white rabbits. The rabbits were anesthetized using an isofluane-only anesthesia protocol. Aqueous-humor-based polarimetric measurements were obtained by coupling light through the anterior chamber of the eye. Blood glucose levels were first stabilized and then altered with intravenous dextrose and insulin administration and measured every 3–5 min with a standard handheld glucometer and intermittently with a YSI analyzer. Acquired polarimetric glucose signals were calibrated to measured blood glucose concentration, which were subsequently used for prediction.

Result:
Based on a total of 37 data points, Clarke error grid analysis indicated 92% in zone A, 8% in zone B, and zero in zones C and D. Reference blood glucose concentrations ranged from 93 to 521 mg/dl from the glucometer and 107 to 408 mg/dl from the corresponding YSI analysis. Polarimetric signals predicted ranges from 117 to 480 mg/dl. Errors in prediction are shown to be related to gross movement of the rabbit during the procedures, incurring time-varying corneal birefringence effects that directly affect the measured polarimetric signal. These effects can be compensated for with appropriate design modifications.

Conclusion:
An optical polarimetry technique was used for *in vivo* physiological glucose monitoring. The technique demonstrated is noninvasive and provides a basis for the eventual development of a commercial home-based polarimetric glucose monitor.

Monte Carlo Analysis of a Glycemic Control Protocol in Less Acute Wards

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Objective:
Tight glycemic control (TGC) can benefit medical and surgical intensive care patients by reducing complications associated with hyperglycemia. However, once patients are transferred to less acute wards, continuing the same level of TGC is difficult. Less acute wards have much fewer nursing resources, creating a pressing need to develop insulin delivery protocols that can be implemented with minimal clinical effort. This abstract uses an *in silico* Monte Carlo analysis to quantify the performance and robustness to errors (physiological variability and sensor errors) of protocols using a combination of Specialized Relative Insulin Nutrition Tables (SPRINT) and insulin glargine (SPRINT + glargine) to ease the transition of SPRINT patients to less acute wards.

Methods:
The pharmacokinetic/pharmacodynamic system model integrates a validated insulin glargine compartmental model and a clinically well-validated glucose–insulin dynamics model for intensive care unit patients (ICING). Patient data (N = 25) were selected from the SPRINT cohort based on periods of long-term stability and low insulin requirements, indicating patients who would benefit from a transition to subcutaneous insulin administration. The SPRINT + glargine protocol seeks use of insulin glargine to gradually replace intravenous insulin. A total of 100 simulations per patient were performed with added sensor noise of 7% in blood glucose measurement error and variability in subcutaneous absorption. Safety and performance are evaluated by avoidance of hypoglycemia (<2.2 mmol/liter), median and interquartile range (IQR) of blood glucose measurements, percentage in desired band (4.0–6.1 and 4.0–7.0 mmol/liter), amount of insulin prescribed (intravenous boluses + glargine), amount of nutrition given, and nursing effort intensity based on number of interventions.

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Results:
There is zero hypoglycemia in any analysis. Virtual trials (per patient) median blood glucose is 5.29 (IQR: 4.90, 5.59) mmol/liter with 65.8% (IQR: 56.2, 72.9), 88.5% (IQR: 83.9, 91.2) time in the 4.0–6.1 and 4.0–7.0 mmol/liter bands. Median insulin per patient was 70.1 U/day (IQR: 64.3, 77.4), with carbohydrate administration of 140 mmol/day (IQR: 129, 143). Nursing effort was 36.2 interventions/day (IQR: 34.4, 38.2). Monte Carlo simulations show 5.44 (IQR: 4.93, 5.88) mmol/liter, 62.5% (IQR: 59.3, 73.4), 87.5% (IQR: 85.1, 92.2) for performance. Monte Carlo insulin and nutrition were 68.4 U/day (IQR: 58.2, 76.5), 109 mmol/day (IQR: 84, 146), requiring 36.9 intervention/day (IQR: 33.6, 37.3). This last analysis validates the robustness of the SPRINT + glargine protocol in a noisy clinical environment.

Conclusion:
An effective, robust, and safe subcutaneous transition protocol is presented. *In silico* analysis allowed accurate quantification of nursing effort and the impact of the time for insulin glargine to reach full effectiveness, which may thus define the time required for a safe subcutaneous insulin transition across a diverse range of patients. The results justify a clinical pilot study to fully validate these *in silico* results.

Automated Bolus Calculators Differ in Management of Postprandial Hyperglycemia

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Objective:
Postprandial hyperglycemia (PPH) is a known independent risk factor for cardiovascular diseases. Automated bolus calculators (ABCs) can aide users in preventing and managing PPH. The objective of this study was to compare how six ABCs differ in their prevention and management of PPH.

Method:
This study compared six ABCs: the Accu-Chek® Combo, Accu-Chek® Expert, OmniPod®Insulin Management System, Minimed Paradigm Veo® System, Minimed Paradigm® System, and OneTouch® Ping™. Identical insulin therapy parameters were entered in each ABC. Two additional parameters (meal rise, offset time) were entered into the Combo and the Expert. A preprandial blood glucose (BG) of 168 mg/dl and a meal size of 80 g carbohydrate (CHO) were entered into each ABC. After 2 h, a postprandial (PP) BG of 284 mg/dl was entered. The ABC dosing advice and insulin on board (IOB) were recorded.

Result:
All ABCs recommended similar preprandial BG corrections and CHO doses. At 2 h PP, the Combo, Expert, and OmniPod reported less IOB than the Paradigm, Veo, and Ping (0.7, 0.7, 0.6 versus 2.7, 2.7, 2.67 U of insulin, respectively). The Combo, Expert, and OmniPod recommended larger correction doses at 2 h than the Paradigm, Veo, and Ping (2.1, 2.0, 2.85 versus 0.1, 0.1, 0.8 U of insulin, respectively).

Conclusion:
The difference in PP bolus recommendations calculated by the ABCs is related to how each ABC's algorithm calculates IOB. The Combo, Expert, and OmniPod count only insulin given to correct preprandial hyperglycemia as IOB. The Combo and Expert also consider meal rise and offset time, which influence correction of PPH. Due to these differences, the Combo and Expert may manage PPH more aggressively than the other bolus calculators in this study.

Proteomic Identification of Human Urinary Biomarkers in Type 2 Diabetes Mellitus and Effect of High-Dose Thiamine on Their Levels

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Background:
During the proteomic era, one of the most rapidly growing areas in biomedical research is biomarker discovery, particularly using proteomic technologies. The urinary proteome is known to be a valuable field of study and has become one of the most attractive subdisciplines in clinical proteomics, as urine is an ideal source for the discovery of noninvasive biomarkers for human diseases. We have described the levels of protein biomarkers specific to type 2 diabetes mellitus in the local population of Pakistan using proteomic technology.

Methods:
More then 100 type 2 diabetes patients with age- and sex-matched normal healthy controls were recruited from Sheikh Zayed Hospital, Lahore, Pakistan. Plasma proteins were analyzed by one- and two-dimensional liquid chromatographic systems by reverse-phase high-performance liquid chromatography micrOTOF analysis. All the samples belonging to the control and diabetes groups were then analyzed by enzyme-linked immunosorbent assay and estimated four proteins that were found to vary.

Results:
Levels of transthyretin, zinc α2 glycoprotein, alpha-1-microglobulin/bikunin precursor, and haptoglobin precursor were found to decrease by -30.8%, -29.23%, -55.2%, and 81.45% while albumin, retinol-binding protein-4, and E-cadherin were increased by +486.5%, +100%, and +693%, respectively, in the diabetes patients as compared to the controls. The level of albumin decreased by 35% after thiamine therapy as compared to the controls and the placebo, while other protein markers did not show a significant change after the therapy.

Conclusion:
Since albumin-level variation has been reported in other pathological states, the role of thiamine may have a significant bearing on the prognosis of such diseases. The discovery of these marker proteins might thus provide an adjunctive method for early detection of risk for this disease.

Effect of Peanuts on Glycemic Response, Appetite, and Food Intake in Obese Women

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Objective:
We evaluated the effect of peanut butter and whole peanuts on glycemic response, appetite, and food intake in obese women.

Method:
This was a crossover study in which eight obese women participated in random order in three study sessions in which a breakfast meal consisting of Cream of Wheat containing whole peanuts (CWP) or peanut butter (CPB) or without peanuts (CWAP) was consumed. Biochemical parameters (glucose, insulin, free fatty acids) and subjective appetitive sensations were assessed 10 min before eating breakfast and at 15, 45, 60, 90, 120, 180, 240, 265, 295, 319, 340, 370, 430, and 490 min after the consumption of that meal. Lunch consisting of a strawberry jam sandwich and water was served 240 min after breakfast.

Result:
The area above the free fatty acids levels curve and the area under the glucose levels curve were lower after CPB ingestion than after CWP (p = .05) ingestion. The area under the insulin levels curve was higher after breakfast (p = .015) and lunch (p = .003) in response to the consumption of CPB compared to the other two test meals. Daily energy intake in the day that CPB was consumed was approximately 200 kcal lower (p = .86) compared to the habitual intake or the energy intake in the days that CWP and CWAP were consumed. The habitual fat consumption was higher (p = .07) than the one observed on the days in which the three test meals were consumed.

Conclusion:
These results indicate that, although the consumption of peanut butter and whole peanuts do not affect appetite and food intake, the consumption of peanut butter may lead to a beneficial effect on glycemic control.

High Accuracy of Continuous Glucose Monitors in Children Susceptible to Critical Illness Hyperglycemia

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Objective:
We evaluated a minimally invasive device to continuously monitor blood glucose (BG) levels during pediatric critical illness, which may aid in the detection and treatment of disorders of glucose regulation.

Methods:
A prospective, observational study was conducted in our center's pediatric medical/surgical and cardiac intensive care units (ICUs). The sensor of a continuous glucose monitor (CGM; Medtronic Guardian) was inserted into the interstitial space of the thigh or abdomen in mechanically ventilated children. Continuous glucose monitor interstitial glucose levels (measured every 5 min) were compared to routine BG levels. In our center, BG >140 mg/dl is treated with insulin infusions with a target of 80–140 mg/dl.

Results:
A total of 50 patients were enrolled, and 47 had analyzable data. The mean age was 4.3 years (6 weeks to 16 years). All were on mechanical ventilation, 30 were on vasoactive drips, 6 on continuous renal replacement therapy, and 3 progressed to venovenous ECMO (extracorporeal membrane oxygenation). There were no complications related to CGM. There were 20 patients with BG levels persistently greater than 140 mg/dl treated with insulin. There were 1555 total comparisons of BG and CGM interstitial glucose levels; 97.9% of these were in Clarke zone A or B. The mean absolute difference of values was 19.2 mg/dl. In subpopulation analysis, patients <1 year, on vasopressors, or receiving insulin infusions all had Clarke zone A + B correlations of >95%.

Conclusions:
In one of the largest studies of CGMs in any critical care setting, existing apparatuses appear very accurate and safe in children, who are some of the most vulnerable and susceptible ICU patients. This refutes theoretical concern about their functionality in critically ill patients. We are initiating a National Institutes of Health-sponsored pediatric glycemic control trial that will employ such CGM devices.

Improved Sensitivity for Detection of Differences between Alternative Therapeutic Modalities Using Simultaneous Analysis of Risk of Hypoglycemia and Measures of Glycemia

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Objective:
We sought to develop more sensitive methods for comparison of different therapeutic approaches by use of simultaneous analysis of responses in terms of glycemia [hemoglobin A1c (A1C) or mean glucose] and risk of hypoglycemia.

Method:
For each patient, the values or change in values of A1C or mean glucose are displayed on the abscissa; risk of hypoglycemia is displayed on the ordinate. Each treatment modality displays a smooth continuous relationship. We fit curves for each treatment group and tested whether the curves characterizing each type of treatment were statistically significantly different, adapting and extending previously described principles.

Results:
The method has been applied successfully for analysis of several studies. It can detect statistically significant differences between therapeutic approaches when use of a single dimension (either mean glucose or hypoglycemia) fails to detect a difference. Glycemia can be characterized by changes in mean glucose or mean A1C within subjects and risk of hypoglycemia by the percentage of glucose values below prespecified thresholds or using indices that provide more weight to lower values (e.g., hypoglycemia index, low blood glucose index, or the hypoglycemia component of GRADE scores).

Conclusion:
This "two-dimensional" approach increases the sensitivity of comparison of competing therapeutic approaches.

Insulin Infusion Set Failure Detection

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Objective:
The goal was to develop algorithms to detect continuous insulin infusion set failures (ISFs) in real time using continuous glucose monitoring (CGM) and insulin infusion data.

Methods:
The proposed algorithms include model-based fault detection (MBFD) and data-based fault detection (DBFD). The MBFD approach detects ISFs differently for daytime versus nighttime. During the day, meal and insulin models are used to calculate future glucose levels. Infusion set failures are detected by an elevated glucose beyond the probability of the usual models of ingested food. At night, meals are not present, therefore ISFs are detected by elevated glucose levels that do not correspond to the modeled effect of infused insulin. In DBFD, the ISF is characterized by a function, *P*, that includes glucose rate of change and calculated insulin levels and varies by time (day or night). *P* weights the probability that, at any sampled point in time, the glucose is elevated in relationship to the effective insulin on board. In both cases, ISF events are assumed if the calculated probability is greater than a defined threshold.

Results:
Algorithms were tested using six clinical data sets where the infusion set was removed at the end of the study period due to ISF. The average length of infusion set wear was 1.96 days. Both algorithms were capable of detecting all the ISF events with 0.25 and 0.42 false positives per day for MBFD and DBFD, respectively. A major determinant of success of the algorithms was how well the patient's blood glucose was controlled. Those in better glucose control had fewer false detections of set failure.

Conclusions:
Both MBFD and DBFD methods are able to predict insulin infusion site failure with relatively few false positives.

Continuous-Time Glucose Monitoring Using the SenseWear® Pro3 Armband

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Objective:
The objective of this work was to accurately predict glucose concentration using information from the SenseWear® Pro3 armband for noninsulin-dependent people.

Method:
This research collected 3 days of subject data on 25 non-diabetic patients and 25 diabetes patients and 4 weeks of subject data on 25 diabetes patients. A model was developed on the most reliable 4-week subject data using a food index scheme for a small, medium, and large meal; variables from the SenseWear Pro3 armband; and time of day. The meal information is collected by using the time stamp button on the armband. Using four glucose measurements per day and this model, a corrective/adaptive modeling scheme was developed and evaluated. The corrective scheme uses glucose measurements to correct prediction to the most recent glucose measurement. The adaptive scheme uses recent glucose measurements to change the normalizing level and the gain for meals. Specifically, the data were used to adjust the model coefficients for the intercept and carbohydrates. In addition, model coefficients were reestimated for activity variables to further improve accuracy.

Result:
The preliminary results for the model and subsequent correction/adaption scheme, for many of the subjects (both with and without diabetes), resulted in excellent correlations (as high as 0.7) and average absolute error (as low as 7 mg/dl) of predicted and measured values.

Conclusion:
The proposed noninvasive continuous-time monitoring method using one model that adapts to the subject and corrects for modeling discrepancies with lancet glucose meters, the armband for activity, and the time stamp button for food appears to have promise as a monitoring scheme for noninsulin-dependent people.

Accurate Monitoring of Blood Glucose Monitoring Device TaiDoc 4277 Compare to Standard Analyser YSI 2300 STATPLUS and Compare to the Reference Meter One Touch® Ultra Easy®

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Objective:
The requirements for blood glucose measurement systems for self-monitoring in diabetes mellitus are defined in the German norm EN (DIN) ISO 15197. Here, 95% of all blood glucose measurements may not exceed ±15 mg/dl for blood glucose concentrations <75 mg/dl and must be within ±20% in glucose concentrations of ≥75 mg/dl compared to reference. This requirement was tested for TaiDoc 4277 Technology Corporation.

Methods:
Two TaiDoc 4277 devices were compared to YSI 2300 STAT PLUS as standard analyzer and compared to OneTouch® UltraEasy® by LifeScan, Inc., by using it as a reference meter. Capillary blood samples within the defined glucose concentration ranges were drawn from 100 subjects.

Results:
The combined system accuracy of both TaiDoc 4277 devices was 98%. Blood glucose concentrations below 75 mg/dl were ±5 mg/dl within limits in 71% and 38%, ±10 mg/dl in 86% and 75%, and ±15 mg/dl in 86% for both devices of all measurements. Blood glucose concentrations above 75 mg/dl were ±10% within limits in 74% and 91%, ±15% in 91% and 92%, and ±20% in 99% for both devices of all measurements. The combined system accuracy for OneTouch UltraEasy as a reference meter was 99%.

Conclusion:
The TaiDoc 4277 blood glucose measuring device as well as the reference meter One Touch Ultra Easy fulfill the requirements for system accuracy according to EN (DIN) ISO 15197. The use of the TaiDoc 4277 for type 1 and type 2 diabetes patients as well as for gestational diabetes is safe.

Design, Development, and Analysis of the Medtronic Next Generation Subcutaneous Glucose Sensor

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Objective:
The Juvenile Diabetes Research Foundation and the Sensor-Augmented Pump Therapy for A1c Reduction studies demonstrate that continuous glucose monitoring (CGM) technology can reduce hemoglobin A1c levels without increasing hypoglycemia risk in type 1 diabetes mellitus patients. Furthermore, increasing frequency of sensor wear is associated with improved outcomes. To advance CGM therapy adherence, Medtronic has developed the next generation Enlite™ sensor with the goal of expanding utilization by improving glucose sensor accuracy, reliability, and comfort.

Method:
Rapid prototyping techniques combined with early stage clinical studies provided a development methodology that enabled timely optimization of critical sensor design features.

Enlite sensors from the final design were worn by 26 type 1 and type 2 diabetes subjects, where each subject wore one sensor implanted in their abdomen and one in their buttock for 7 days. Performance was evaluated against capillary blood glucose values obtained from a One-Touch Ultra Link meter.

Results:
User and performance feedback received during early trials resulted in a sensor inserted at a 90-degree angle using a self-contained 26-gauge retractable needle. Enlite implanted volume was reduced by 75% when compared to existing Medtronic sensor offerings.

The mean absolute relative difference (MARD) was 14.77%, and 95.97% of sensor reference values were within the Clarke A and B zones when used with current market Medtronic CGM devices. A next generation algorithm yielded slightly lower MARD, and 97.78% of sensor reference values were within the Clarke A and B zones. Median lifetime of the 52 sensors was over 6.6 days.

Conclusion:
Rapid prototyping, testing, clinical feedback, and design iteration resulted in development of the next generation Medtronic Enlite. Based on feasibility trial results, this design produced major enhancements, including improving accuracy, reliability, and comfort over a longer sensor lifetime aimed at increasing patient CGM utilization.

Q-Score: A New Method to Assess the Quality of Continuously Measured Glucose Profiles

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Objective:
Continuous glucose monitoring (CGM) allows us to monitor blood glucose profiles over several days and to identify quickly and safely weak points in metabolic control. However, an easy, objective, practicable evaluation method is missing. The aim of our study was therefore to develop a quality score (Q-score) that considers all aspects of CGM profiles for a complex and objective analysis.

Method:
A total of 1495 registered CGM profiles provided the database for this study. First, a factor analysis addressing all quality-affecting parameters was performed to identify factors with major impact on CGM. For each factor, one parameter was selected (mean, mean amplitude of glycemic excursions, time above or below target range, mean of daily differences [MODD]) and used for the development of the Q-score.

Results:
This study resulted in a Q-score for quality assessment of CGM profiles. To verify the Q-score, two diabetes specialists (DS) diagnosed independent 729 and 194 CGM profiles, respectively. There was a high correlation between the Q-score and the results of both DS (Kendall's $\tau = 0.766$ and 0.719; $p < .001$). To establish a practicable outcome tool, the Q-score was tested for categorization of CGM profiles. A total of 729 profiles were categorized by one of the DS in very good (Q-score, 3.4 ± 0.8), good (4.9 ± 1.2), satisfactory (7.1 ± 1.6), borderline (10.0 ± 1.9), and not satisfactory (13.8 ± 2.6). The Q-score was also correlated with hemoglobin A1c ($r = 0.50$), mean sensor glucose (0.68), range (0.88), MODD (0.63), and time above (0.86) and below (0.24) target range.

Conclusion:
The Q-score combines all quality criteria for CGM profiles in one total value. The Q-score is independent of subjective errors and can be used for automatic evaluation of CGM curves. The Q-score has the potential to become a practical diagnosis tool for routine diabetes care.

Use of Structured Blood Glucose Monitoring Results in More Timely and Successful Management of Poorly Controlled, Noninsulin-Treated Type 2 Diabetes: Results from the Structured Testing Protocol (STeP) Study

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Objective:
Many physicians do not initiate or intensify therapy appropriately, which contributes to long-term hyperglycemia. In the Structured Testing Protocol (STeP) study, we assessed whether collaborative use of structured self-monitoring of blood glucose (SMBG) results contributes to more timely and effective treatment change recommendations.

Method:
In STeP, a prospective, cluster-randomized, multicenter, clinical trial with 522 poorly controlled [hemoglobin A1c (HbA1c) ≥7.5%], insulin-naïve type 2 diabetes mellitus (T2DM) subjects, we showed that subjects participating in a structured SMBG protocol [structured testing group (STG)] displayed significantly larger HbA1c reductions over 12 months than control subjects [active control group (ACG)]. Each quarter, STG subjects completed the Accu-Chek® 360° View Blood Glucose Analysis Tool (a paper tool that facilitates collection and interpretation of seven-point glucose profiles over 3 consecutive days) and brought it to medical visits. The STG physicians and patients were instructed in SMBG pattern recognition and interpretation, and STG physicians received an algorithm for medication changes in response to observed SMBG patterns.

Result:
At 12 months, more STG physicians than ACG physicians ($p < .0001$) recommended at least one medication change (81% versus 50%) or lifestyle adjustment (66% versus 33%). Even at the first treatment visit (1 month postbaseline), more STG than ACG physicians ($p < .0001$) recommended

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a medication change (60% versus 23%) or lifestyle change (41% versus 9%). Subjects with a recommended treatment change, medication, and/or lifestyle achieved a larger HbA1c reduction at 12 months than those with no recommendation (-1.3 versus -0.8, $\Delta = 0.5$, $p < .002$).

Conclusion:
Collaborative use of structured SMBG data promotes timely treatment changes in poorly controlled T2DM. Treatment changes are linked to significant glycemic improvement over 12 months and may explain why STG subjects evidenced greater HbA1c reductions than ACG subjects.

Effect of Diabetes Mellitus on Outcomes of Hyperglycemia in a Mixed Medical Surgical Intensive Care Unit

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Objective:
Glucose control in the intensive care unit (ICU) has been widely debated as to how tightly it should be regulated and in which patient it is most beneficial. We hypothesized intensive insulin therapy in ICU patients with diabetes mellitus (DM) would result in decreased morbidity and mortality.

Methods:
We performed a retrospective chart review of 232 diabetes patients in the ICU who received an intravenous insulin protocol targeted to a blood glucose (BG) of 80–140 mg/dl between 2005 and 2008. Patient BG was recorded hourly. Outcomes were compared between patients with DM who were controlled (80–140 mg/dl) and uncontrolled (>140 mg/dl) and survivors and nonsurvivors.

Results:
Well-controlled patients with DM had a significantly lower mean BG (131 versus 166 mg/dl; $p < .01$) compared to the uncontrolled group. There was no significant difference in hypoglycemic episodes (<60 mg/dl) between controlled and uncontrolled diabetes patients. Uncontrolled patients had a higher preadmission hemoglobin A1c (8.2% versus 7.3%; $p = .02$). There was no difference in admission Acute Physiology and Chronic Health Evaluation scores, total parenteral nutrition use, vasopressors, or steroids. There was no difference in hospital or ICU length of stay, ventilator days, ICU readmissions, or mortality between groups. Nonsurvivors had a significantly higher rate of hypoglycemic episodes (6% versus 0.5%; $p < .05$)

Conclusions:
Despite the achievement of tight glucose control, diabetes patients did not have improved morbidity and mortality. A significantly high number of hypoglycemic episodes were seen in nonsurvivors, suggesting diabetes patients may benefit from a less aggressive intravenous insulin protocol.

Noninterventional Study to Investigate Suitability for Daily Use of Blood Glucose Meter CONTOUR® USB in Routine Application in Insulin-Treated Diabetes Patients

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Objective:
We investigated the CONTOUR® USB blood glucose meter with integrated data software management GLUCOFACTS®-DELUXE.

Method:
Using questionaires, features were evaluated by 1127 insulin-treated patients and 129 physicians/diabetes advisors in Germany. Overall evaluation was also performed. Study duration per patient was 4–6 weeks.

Results:
Data of 1095 available for statistical analysis (mean age, 40.5 years; mean duration of diabetes, 13.5 years), and 17% had prior data management software use. Patients rated CONTOUR USB features positively (excellent, very good, good) ranging 93.3% and 99.5% for blood glucose meter in general, 89.8% and 98.5% for setup functions, 76.4% and 96.2% for sensors, 91.8% and 93.4% for user guide instructions, and 87.9% and 96.6% for data management. Overall usability was excellent, very good, or good in 98.2% of patients. The data management software was judged as excellent, very good, or good in 97.3% of patients. Suggestions for improvement mainly focused on software/data management (15.9% of patients), additional functions, and equipment (each 13.2%). Physicians'/advisors' judgments were more positive than patients' evaluations. Diabetes experts noted improved compliance, improved interactions, and easier identification of metabolic crises that may improve compliance and may lead to better glucose control. Subanalysis was performed on 237 patients [initial mean blood glucose was 133.8 mg/dl (fasting) and 181.2 mg/dl (postprandial)]. At the final examination, mean blood glucose levels were lower: 122.6 mg/dl (fasting) and 162.0 mg/dl (postprandial). Mean hemoglobin A1c was 7.8% at the start of the study and 7.4 % at the end.

Conclusion:
The combination of blood glucose meter and integrated data management offers advantages for patients and physicians. The CONTOR USB supports diabetes self-management and also strengthens the interaction between doctor and patient.

Use of Self-Monitoring of Blood Glucose and a Diary Report from Accu-Chek® Smart Pix in a Primary Care Setting Improves Hemoglobin A1c in Poorly Controlled, Noninsulin-Treated Type 2 Diabetes: A Case Study

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Background:
Few primary care practices use information management systems (IMS) to download self-monitoring of blood glucose (SBMG) data. Most rely on verbal reports or patient log books.

Method:
In Structured Testing Protocol (STeP), a study on SMBG use in poorly controlled patients with type 2 diabetes mellitus (T2DM), Accu-Chek® Smart Pix (SP) was used to upload SMBG data to a server for later analysis. Generation of reports from site's SP was blocked, but one study site (S22) in the control group (CG) inadvertently discovered a method to generate the diary report (DR) from the SP. Instead of maintaining its usual care of patients with T2DM, S22 used the information on the DR to manage its patients (n = 22). Outcomes from S22 are compared in an exploratory manner to another CG site that had similar practice and subject demographics (S14, n = 30) and did not access SP reports.

Results:
Baseline hemoglobin A1c (HbA1c) levels were similar (S22: 8.9 ± 1.0; S14: 8.6 ± 1.1%). Analysis revealed that S22 subjects had greater mean improvement in HbA1c than S14 subjects over 12 months (-1.3 ± 1.5% versus -0.7 ± 1.3%). The SMBG test frequency was identical, averaging 1 test/day. The S22 physician changed subjects' therapy plans at more visits than the S14 physician (1.3 + 1.1 versus 0.7 ± 0.8 visits, respectively, p = .02). The S22 physician made therapy changes for 45.5% of subjects at visit 1 compared to 3.3% for the S14 physician (p < .001).

Conclusion:
These findings suggest that use of SMBG and visualization of data with IMS might have accelerated S22 physician action and contributed to improved HbA1c. Differences in the physicians' approach to diabetes management may have also contributed to differences in outcome.

Doxycycline as a Wound Chemotherapeutic Agent with Negative Pressure Wound Therapy: Effects on Wound Healing

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Background:
Negative pressure wound therapy (NPWT) is frequently employed in the treatment of complex wounds. We present a description of real-time streaming therapy using doxycycline as a wound chemotherapeutic agent in conjunction with NPWT. Doxycycline is an anti-inflammatory agent and acts as a competitive inhibitor of matrix metalloproteinases and tumor necrosis factor alpha.

Method:
In this single-patient case study, we enrolled a 57-year-old female with past medical history of mixed connective tissue disease, scleroderma/CREST syndrome, rheumatoid arthritis, and pulmonary hypertension presented with a long history of bilateral lower extremity wounds secondary to vasculitis. After several weeks of inadequate therapy, the patient was started on continuous streaming NPWT with 100 mg doxycycline/100 ml normal saline at a rate of 20–30 cc/h administered twice daily and 0.025% Dakins at 30 ml/h at all other times. Oral doxycycline (100 mg) was also given bid in concert with the local wound therapy.

Results:
After two dressing changes over 5 days, the wound sizes had decreased substantially and granulation tissue increased bilaterally to nearly encompass 100% of the wound. The patient subsequently underwent successful split thickness skin grafting at two-weeks follow-up.

Conclusion:
Negative pressure wound therapy alone may not fully address the myriad of microbiological and biochemical factors that contribute to the complexity of chronic wounds. The augmentation of NPWT dressings to permit instillation of various therapeutics for "wound chemotherapy" may be promising. To our knowledge, this is the first report in the literature describing this method of delivery of doxycycline.

Antidiabetic and Hypolipidemic Effects of *Ficus bengalensis* in Streptozotocin-Induced Diabetic Models

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Objective:
Ficus bengalensis Linn. (Moraceae) root is used in Indian traditional medicine for the treatment of diabetes. We performed further scientific exploration of the antidiabetic potential of *F. bengalensis* aerial roots in severely diabetic animals in addition to its effect on diabetes-induced disturbed lipid profile.

Method:
The antidiabetic activity of aqueous extract of *F. bengalensis* aerial root was evaluated by using normal and streptozotocin (STZ)-induced diabetic rats. The acute effect of aqueous extract was evaluated by administering 300 mg/kg to normal and STZ-induced severely diabetic animals (fasting blood glucose [FBG] > 250 mg/dl) were treated once a day for 30 days. Blood glucose levels, body weights, and different biochemical parameters were also carried out.

Result:
Severely diabetic (FBG >250 mg/dl) animals were treated once a day for 30 days with the most effective dose of 300 mg/kg, identified in the previous study in case of sub- and mild-diabetic rats, and found to have reduced FBG by 44.4%, and also, the same dose brought about a fall in total cholesterol, triglyceride, low-density lipoprotein, and very low-density lipoprotein levels of 31.8%, 22.7%, 42.7%, and 23%, respectively, and an increase of 28.5% in high-density lipoprotein levels. Levels of serum enzymes were also observed in treated rats as compared to diabetic control.

Conclusion:
These results suggest that aqueous extract of aerial roots of *F. bengalensis* possess significant antidiabetic and hypolipidemic effects.

Transdermal Basal Insulin Delivery in Patients with Type 1 Diabetes: Pharmacokinetic Comparison to Continuous Subcutaneous Insulin Infusion

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Objective:
A daily transdermal patch is being developed to provide basal insulin levels in type 1 or type 2 diabetes patients. A single-dose open-label randomized crossover pharmacokinetic/pharmacodynamic study in type 1 diabetes patients was conducted to evaluate the PassPort® Transdermal Insulin Delivery System versus continuous subcutaneous insulin infusion (CSII) using an insulin pump.

Method:
Subjects were randomly assigned to one of two treatment arms: an insulin patch applied for 12 h followed by CSII treatment at 1.0 U/h for 12 h or a crossover with CSII treatment at 1.0 U/h for 12 h followed by an insulin patch applied for 12 h. After receiving both treatments, subjects received CSII at 2.5 U/h for 12 h.

Result:
The patch tested reached a C_{max} of approximately 42 μU/ml at 5 h. The 1.0 U/h CSII treatment reached a steady state level of 27 μU/ml at 7 h that was maintained until the pump was discontinued at 12 h. The 2.5 U/h CSII treatment demonstrated serum insulin levels that increased continuously to approximately 50 μU/ml at 12 h when the pump was discontinued, indicating that steady state was not achieved. The relative bioavailability of the patch compared to the 2.5 U/h treatment was approximately 5%, although the PassPort System was not optimized for bioavailability. The patch was well tolerated, with skin response limited to mild transient erythema at the application site. Skin response and barrier function were consistent with that found in patch studies involving healthy human subjects.

Conclusion:
This study demonstrated that insulin can be delivered through the skin at therapeutic basal infusion rates comparable to subcutaneous infusion in patients with type 1 diabetes.

Immune System Responses from Candidate Materials of an Implantable Osmotic Glucose Sensor

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Objective:
A fundamental understanding of immune system reactions is of particular importance concerning biomedical implants that sample and measure glucose in the tissue fluids. Activation of the complement system and neutrophils are crucial mechanisms mediating inflammatory responses that may encapsulate the sensor and lead to a dysfunctional device. Thus a protocol measuring activation of complement and neutrophils by materials to be used in an implantable osmotic glucose sensor was developed.

Method:
Fourteen candidate materials—encapsulation (3), membrane (6), carrier (2), and sealing (3)—were incubated in serum for 30 min. Surface deposition of the terminal complement complex (TCC) and the serum concentrations of C4d, Bb, C3b, and TCC were analyzed. The materials were also incubated in lepirudin-anticoagulated whole blood for 20 min to investigate neutrophil activation, analyzed by expression of CD11b.

Result:
The TCC deposition on the material surfaces after incubation was significantly larger than the negative control (polystyrene) for 7 of the 12 materials ($p < .05$). The concentration of TCC in serum from the membrane materials cellulose, polyamide, and aluminum oxide was significantly higher than the negative control ($p < .05$). The concentrations of Bb, C4d, and C3b were increased only after incubation with cellulose ($p < .01$), whereas the expression of CD11b was only increased after incubation with cellulose and polyamide.

Conclusion:
Both solid-phase and fluid-phase complement activation are required to investigate the biocompatibility of biomedical devices due to different properties of the protocol. Polydimethylsiloxane and silicone 3145 were the best candidates for capsule and sealing with a TCC deposition and CD11b expression lower than the negative control. Polycarbonate was the best membrane candidate, but further modification is needed to prevent TCC deposition.

A Stabilized Liquid Glucagon Formulation For Bihormonal Pump Use

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Objective:
We aimed to develop a formulation of glucagon, stable as a clear solution at a pH of 7 and essentially free of particulate matter, gel, and degredants for a period of at least 7 days at 37 °C.

Method:
Experimental glucagon formulations were studied for stability at 25 and 37 °C. Chemical degradation was quantified by reverse phase high-performance liquid chromatography (HPLC; Waters 2695, YMC hydrosphere C-18 column). Physical changes were studied using light obscuration, laser light scattering (Malvern Nanosizer), and visual observations. Biological activity was assessed by measuring changes in blood glucose levels post injection in diabetic miniature swine.

Result:
Glucagon content of BIOD 900 and two control formulations of Lilly glucagon at pH 2 and pH 4, as measured by HPLC, was 100% at 7 days compared to 87% and <7%, respectively. Light obscuration measurements showed the Lilly pH 4 formulation had a reduction in transmitted light the first day of measurement, indicating opaque gel formation, while the BIOD 900 formulation remained essentially unchanged beyond 50 days at 37 °C. As measured by laser light scattering, Biodel glucagon size range remained steady, while the Lilly glucagon at pH 4 rapidly increased in size. Visual observations confirmed these results. Biological activity, measured by changes in blood glucose level, of BIOD 900 prepared fresh compared to BIOD 900 incubated for 3 days at 37 °C in diabetic miniature swine was unchanged.

Conclusion:
BIOD 900 is a stabilized formulation at physiological pH and remains chemically and physically stable beyond 7 days at 37 °C and physiologically active after exposure to at least 3 days at 37 °C, suggesting its utility for use in a bihormonal pump.

Analysis of 24-Hour Glycemic Excursions in Patients with Type 1 Diabetes by Using Continuous Glucose Monitoring

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Background:
There is little information available regarding postprandial glycemic excursions and hypoglycemia in Japanese patients with type 1 diabetes mellitus (T1DM).

Methods:
Four male and eight female patients who were on intensive therapy with rapid-acting insulin plus basal insulin underwent retrospective continuous glucose monitoring (CGM). Clinical characteristics of the patients were given as median: aged 40.5 years, body mass index 22.2 kg/m^2, urinary C-peptide 0.75 g/day, hemoglobin A1c (HbA1c) after 2 months of CGM 6.5%, and total insulin doses 40.0 U.

Result:
The largest glycemic excursions were observed after breakfast. The time intervals from the start of each meal to the highest postprandial glucose levels peaked at 65 to 100 min. Hypoglycemia (blood glucose <70 mg/dl) was observed for more than 100 min per 24 h. Hemoglobin A1c and 24 h mean glucose levels were significantly correlated (r = 0.727, p = .007).

Twelve participants were divided into two groups by HbA1c level after 2 months: 6 whose HbA1c exceeded the median (HbA1c >6.5%) and 6 whose HbA1c fell below the median (HbA1c <6.5%). The premeal glucose levels/the highest postprandial glucose levels after breakfast were insignificantly higher in the HbA1c >6.5% group (183/247 mg/dl, respectively) than the HbA1c <6.5% group (117/221 mg/dl, respectively). The duration of hypoglycemia lasts longer in the HbA1c <6.5% group, with these episodes often occurring during nighttime.

Conclusions:
These findings suggest that preventing nighttime hypoglycemia and correcting glucose spikes after breakfast are required in patients with T1DM receiving intensive therapy to stabilize and improve glycemic control.

Noninvasive Assessment of Photoreceptors, Capillaries, and Leukocytes for Early Stages of Diabetic Retinopathy

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Objective:
We demonstrate a noninvasive method to investigate diabetic retinopathy in human eyes on a cellular scale.

Method:
High-resolution retinal videos were acquired noninvasively using an adaptive optics scanning laser ophthalmoscope (AOSLO). Overlapping videos were acquired in the parafoveal region for a 26-year-old male with type 1 diabetes and nonproliferative diabetic retinopathy. Videos were processed to generate montages of photoreceptors and perfused capillaries. Photoreceptors, capillaries, and leukocytes were analyzed using offline video and image analysis algorithms. AOSLO data were compared to (1) AOSLO databases of normal subjects and (2) conventional clinical methods, including fluorescein angiography (FA) and spectral domain optical coherence tomography.

Result:
Retinal features were resolved with greater detail using AOSLO compared to conventional clinical methods. Individual cone photoreceptors were resolved; cone density appeared to be normal except at the foveal center of this particular patient. The AOSLO capillary montage showed fusiform and saccular microaneurysms, local regions of capillary dropout, capillary loops, and other nonspecific irregularities in the organization of the capillary network. The area, diameter, and shape of the foveal avascular zone were different from normal, but both the average capillary density and the leukocyte speeds appeared to be within normal ranges. These imaging biomarkers can potentially be used to monitor the progression of diabetic retinopathy.

Conclusion:
Adaptive optics scanning laser ophthalmoscope imaging may give new insights into how diabetic retinopathy affects the photoreceptors, capillaries, and leukocytes. The main advantages are (1) the method is noninvasive and can be applied at earlier time points than FA; (2) multiple classes of biomarkers can be derived from one dataset, based on photoreceptors, capillaries, and leukocytes; and (3) higher resolution and contrast can be achieved compared to conventional clinical methods.

Novel I_1-Imidazoline S43126 Enhance Insulin Signaling Pathways in PC12 Cells

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Objective:
The I_1-imidazoline receptor is a novel target for drug development for hypertension and insulin resistance, which are major disorders associated with metabolic syndrome X and type 2 diabetes. In previous experiments, using the SHR model, we showed that moxonidine, and novel I_1-imidazoline compound S43126, reduced blood pressure when injected into the medulla region of rat brain. In order to investigate whether S43126 affects components of the insulin signaling pathways, we examined the effects of S43126 on phosphorylation of protein kinase B (Akt) and ERK42/44 in PC12 cells, which are known to possess both insulin and imidazoline receptors.

Method:
PC12 cells were treated with varying doses of S43126 (10^{-10} to 10^{-6} M) in the presence of insulin (10^{-6} M) for 10 min.

Results:
Western blot analysis of treated samples showed that the combination of insulin with S43126 (10^{-6}–10^{-10} M) enhanced phosphorylation of Akt and ERK42/44 above the level of insulin (10^{-6} M) alone. Furthermore, S43126 enhanced Akt and Erk42/44 phosphorylation in insulin-treated cells in a dose- and time-dependent manner. Using siRNA against Nischarin (mouse homologue of I_1-imidazoline receptor), we showed that the increased Akt and Erk42/44 phosphorylation was mediated by the I_1-imidazoline receptor since siRNA against Nischarin reduced the phosphorylation of both proteins following combination treatments.

Conclusion:
These preliminary results indicate that I_1-imidazoline agonists (S43126) have the potential to amplify insulin action and should be further studied as possible candidate drugs for the treatment of metabolic syndrome X and type 2 diabetes.

DiaPort: Experience from 11 DiaPort Users from Germany

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Objective:
The daily DiaPort care from 11 type 1 diabetes patients, using the DiaPort system, was investigated to evaluate the comparison between the DiaPort care trained in the clinic versus the daily care months afterward.

Research Design and Methods:
The indications for the treatment were subcutaneous insulin resistance (*n* = 4, 36%), large blood glucose fluctuations (*n* = 3, 27%), and each one with dermatological problems, lipohypertrophy, lipoatrophy, and metabolic reasons (hemoglobin A1c >8.5% despite optimal continuous subcutaneous insulin infusion). The mean age was 46–49 years [standard deviation (SD) 13.4], the diabetes duration was 29.3 years (SD 12.9), and the mean duration of using the DiaPort was 28.6 months (from 15 days up to 6 years). With a questionnaire and in three discussion groups, we collected the data from the daily DiaPort care.

Results:
The DiaPort care decreases from mean once per 1.3 days (SD 0.5) in the first weeks after implantation to mean once per 2.8 days (SD 2.1) after three months.

For cleaning the DiaPort, the users spent a mean time of 7.2 min (SD 2.6) per day; most patients used alcohol solutions (*n* = 5) and sterile physiological solution (*n* = 4).

The patients were trained to change the infusion set and fixation disc at every change of the cartridge. 58% changed the fixation disc, 42% changed the infusion set, and 33% of the users exchange the infusion set every 1 to 3 days, 17% after 4 to 5 days.

The patients were trained to use the fixation disc the first three months after implantation, but all without wearing the fixation disc all the time.

Conclusions:
The real-life DiaPort users spent much less time for the DiaPort care compared to the training. One explanation could be that the DiaPort use changes unconsciously from a "special therapy" after implantation to a "normal therapy" after several weeks.

Glucowizzard™: A Splinter-Sized Continuous Glucose Monitoring Device

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Objective:
Various invasive, noninvasive, and minimally invasive devices for continuous glucose monitoring (CGM) are currently under development, with a few invasive devices approved by the regulatory authorities for short-term (3–7 days) use. Unlike noninvasive and minimally invasive devices, invasive devices require less rigorous calibration and exhibit smaller subject-to-subject variability. However, they currently suffer exhibits such as negative tissue responses, lack of miniaturization, and short lifetime. To this end, Biorasis, Inc., together with University of Connecticut has been developing a totally implantable CGM device with particular emphasis on device miniaturization, enhancing lifetime, and eliminating negative tissue responses.

Methods:
Keeping in mind that device lifetime and magnitude of negative tissue response is affected by device size, Glucowizzard™ is developed at the smallest possible footprint (0.5 × 0.5 × 0.5 mm). This miniaturization is made possible by utilizing light both for powering and wireless communication. In addition, Glucowizzard utilizes "smart" hydrogel coatings intended for localized release of various tissue-response modifiers for effective control of negative tissue responses. The device utilizes enzymatic sensing of glucose and operates in a classic electrochemical mode.

Results:
The use of light-based powering and communication together with advanced microelectronic design rules has allowed the fabrication of a CGM device with dimensions of 0.5 × 0.5 × 0.5 mm. The "smart" drug-delivery coating has enabled substantial reduction of negative tissue responses for up to 3 months (rat model). Continuous glucose monitoring in small laboratory animals and development of advanced calibration logic are currently underway.

Conclusions:
The Glucowizzard possesses some key advantages over currently available CGM device technologies. With further development, we expect that this device will be ideal for a truly "user-independent" continuous glucose monitoring.

GlucoMen® Day: A Novel Continuous Glucose Monitor for Interstitial Fluid and Venous Blood Applications

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Objective:
The GlucoMen® Day (GMD) is a new microdialytic continuous glucose monitoring (CGM) system from A. Menarini Diagnostics. The GMD disposable kit is configured with two distinct microdialysis probes, one suitable for collecting glucose from the interstitial fluid (ISF) and CGM in diabetes patients, the other compatible with standard intravenous (IV) catheters and for possible use in intensive care or surgical units to continuously monitor glycemic levels directly in blood. Objectives of this research were both a further assessment of the clinical accuracy of GMD in its ISF configuration and a preliminary evaluation of the performance of the IV kit.

Methods:
The ISF kit was tested through two independent clinical trials; the corresponding accuracy was then estimated as recommended by the POCT05-A guideline. The IV configuration was first tested *in vitro* using a simulation device that allowed us to mimic the fluidodynamics of the vein. Preliminary *in vivo* tests on human volunteers were additionally performed.

Results:
The continuous glucose error grid analysis relative to the ISF configuration showed >95% accurate results in all glycemic ranges (98% in hypoglycemia). Mean absolute and relative deviation values as favorable as 10% and 12 mg/dl, respectively, were also calculated. Both *in vitro* and *in vivo* tests of the IV kit confirmed the absence of relevant matrix effects and clinical performance in line with those of the ISF configuration.

Conclusions:
The advantageous features of the GMD system in its ISF configuration (ability to follow rapid glycemic excursions, accurate detection of severe hypoglycemic events, and stability of CGM signals for up to 100 h) were confirmed. Furthermore, the results for the IV kit were highly encouraging; its potential will be further explored in real critical settings.

Remote Testing of Fasting Blood Glucose in a Self-Collected Capillary Blood Sample

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Objective:
We demonstrate the accuracy and effectiveness of a test kit for collecting, transporting, and testing of self-collected capillary blood samples for measurement of glucose in a remote clinical laboratory.

Method:
Meta-analysis was performed on combined clinical trials in a community setting, which included a total of 441 volunteers using the kit. The kit includes a capillary blood collection cassette with filter paper insert, printed instructions for use, sample packaging materials, and a prepaid, preaddressed mailer to send the sample to a qualified clinical chemistry laboratory. The paper insert consists of a precoated, glass-fiber strip, which separates blood into cell and serum/plasma components, creating two separate specimens. The cell specimen is used for testing hemoglobin A1c, and the serum/plasma specimen is used for testing glucose and a complete lipid profile. Venous blood was drawn from each volunteer for comparison. All samples arrived at the clinical laboratory within the prescribed sample stability period of 21 days. The serum portion of each blood sample was punched, eluted, and tested for glucose. The final glucose concentration was calculated according to the algorithm, which compensates for differences in sample volume.

Result:
A total of 93% of participants were able to collect an adequate sample (≥60 µl). Correlation of the results from testing capillary and venipuncture samples yielded this equation: Calculated Capillary Glucose = 2.17 + 0.979 × Venous Blood Glucose (R^2 = 0.981, p < .001). Mean glucose measurement was 113 mg/dl, and the range of concentrations was 59–457 mg/dl. A bias at medical decision points of 100 and 125 was 0.11% [0.95 confidence interval (CI): -1.97% ± 2.1%] and -0.33% (0.95 CI: -1.7% ± 1.39%), respectively. The average absolute bias for the whole tested range was 4.6 mg/dl, or 4.1%.

Conclusions:
When using the kit, laypeople are capable of self-collecting an adequate capillary blood sample that can be mailed to a qualified clinical chemistry laboratory for testing, resulting, and reporting. The kit can be used to remotely verify glucose meter readings for individuals with diabetes and, as a screening tool, to test hard-to-reach individuals and subpopulations.

Transport and Testing of Self-Collected Capillary Blood for Measurement of Hemoglobin A1c

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Objective:
We demonstrate the accuracy and effectiveness of a test kit for collecting, transporting, and testing of self-collected capillary blood samples for measurement of hemoglobin A1c (HbA1c) in a remote clinical laboratory.

Method:
Volunteers in the clinical trial were asked to use the kit to self-collect, package, and mail a capillary sample to the clinical laboratory. The kit includes a capillary blood collection cassette with filter paper insert, printed instructions for use, sample packaging materials, and a prepaid, preaddressed mailer to send the sample to a qualified clinical chemistry laboratory. The paper insert consists of a precoated, glass-fiber strip, which separates blood into cell and serum/plasma components, creating two separate specimens. The cell specimen is used for testing HbA1c, and the serum/plasma specimen is used for testing glucose and a complete lipid profile. EDTA venous blood was drawn from each volunteer for comparison. Upon arrival at the laboratory, the cell portion of each capillary blood sample was punched, eluted, and tested for HbA1c by National Glycohemoglobin Standardization Program (NGSP)-certified method.

Result:
Out of 169 of participants who provided a sample of capillary blood, 162, or 96%, collected an adequate sample. All samples arrived at the clinical laboratory within the prescribed sample stability period of 21 days. The capillary HbA1c values were plotted against venous blood values in a scatter-plot, and linear regression was drawn. The R^2 was 0.967, the slope was determined to be 1.042 ± 0.015, and the intercept was determined to be -0.26 ± 0.09. Mean HbA1c value in the tested population was 5.77, with the range of 4.62–11.47. Biases at medical decision points of 5.7, 6.5, and 8 were -0.02 (or -0.31%), 0.02 (or 0.26%), and 0.08 (or 1.0%), respectively. The average absolute bias through the whole range was 0.16, or 2.6%.

Conclusions:
When using the kit, laypeople can self-collect adequate capillary blood samples that can be accurately tested in a NGSP-certified laboratory with NGSP-certified method. The kit can be used to remotely manage individuals with diabetes and, as a screening tool, to test hard-to-reach individuals and subpopulations. Remote counseling can be also be provided.

Evaluating Algorithms for Glycemic Control in Intensive Care Units: Computer Simulations Can Be Useful

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Objective:
Computer simulations can be used to compare algorithms for glycemic control in intensive care units (ICUs).

Methods:
A virtual population of 56 critically ill subjects was created from routine data collected at four European surgical and medical ICUs. Two published clinical studies were used to assess the validity of predictions made when utilizing this virtual population. The first study compared the performance of enhanced model-predictive control-based algorithm (eMPC) at two ICUs in the United Kingdom and Belgium. The second study compared three glucose control algorithms: the eMPC, the absolute glucose protocol (Matias), and the relative glucose change protocol (Bath) in a single ICU in Czech Republic.

Results:
In agreement with the first published clinical study, computer simulations reproduced the main findings and discriminated between the two ICUs in terms of the glucose sampling interval (1.3 versus 1.8 h; United Kingdom versus Belgium; $p < .01$). Other glucose metrics were similar between the simulations and clinical results. The principal outcome of the second study was also reproduced. The eMPC demonstrated better performance compared to the Matias and Bath algorithms as assessed by the time when plasma glucose was in the target range between 70 and 110 mg/dl (64% versus 42% versus 41%; $p < .001$; eMPC versus Matias versus Bath) without increasing the risk of severe hypoglycemia.

Conclusions:
Computer simulations may provide alternative resource-efficient means to test algorithms for glycemic control in the critically ill.

Universal Design: Innovation for Today, Tomorrow, and Beyond

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Objective:
The aim is to define universal design (UD) and discuss the history, principles, and rationale for using UD principles for diabetes technology intended for patient use.

Method:
Universal design is defined as the design of products, services, and environments to be usable by all people to the greatest extent possible, without the need for adaptation or specialized design for people of varying abilities. In contrast, average person design (APD) is design for the middle "80–90% of the population. Following a brief history of the philosophies of APD as contrasted with UD, the 7 Principles of UD as they were developed for architecture will be presented and illustrated with examples drawn from improvements in design of diabetes technology designed for patients. Rationale for considering the full range of abilities in typical populations of persons with diabetes, which include disproportionately large percentages of persons with sensory, motor, and cognitive disabilities, will be presented.

Result:
A few simple rules for UD of diabetes technology will be proposed.

Conclusion:
Well-executed UD results in designs that are easy to use and can benefit average persons as well as persons with disabilities.

Improving Pharmacokinetic and Pharmacodynamic Profiles of Injected Rapid-Acting Insulin Analogs Using the InsuPad 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 (IDDS). InsuLine has developed a technology to accelerate insulin PK and PD profiles by applying controlled heat to the insulin delivery site. The InsuPatch device was developed for insulin infusion, and the InsuPad device was developed for insulin injections. In previous clinical studies with the InsuPatch device and insulin pumps, we found that the main benefits of using the device were an increase of 45% in the available insulin in the blood during the first hour post injection. A reduction of 33% in the average glucose level during the first 2 hours post meal.

Most IDDS use syringes or insulin pens to inject insulin. It is therefore important to test InsuLine's technology with insulin injections. In this feasibility study, the effect of the InsuPad device on insulin PKs and postprandial glucose levels was investigated for the first time.

Methods:
The effect of the InsuPad device on insulin PKs and postprandial glucose levels was tested by comparing insulin and glucose concentration in the blood with and without the device in a meal tolerance test protocol.

Results:
Using the InsuPad device was found to increase insulin concentration during the first hour after injection and reduce postprandial glucose levels similar to the results obtained with the InsuPatch.

Conclusions:
These results suggest that the InsuPad may be used to improve glycemic control in IDDS with injections.

Preclinical Studies with Cobalamin™ Nanoparticles for Oral Drug Delivery of Insulin

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Objective:
Proprietary Cobalamin™ technologies of Access Pharmaceuticals are based on the body's natural handling of vitamin B12 (VB12). Access has formulations based on polymers and nanoparticles that utilize these pathways for drug delivery. We have investigated this technology for oral drug delivery of insulin.

Methods:
Nanoparticles with surface VB12 and loaded with insulin were made and dosed orally to rats in which diabetes had been induced by streptozotocin. Blood glucose levels in these animals were monitored over time.

Results:
Vitamin B12 was covalently linked to modified dextran, and this polymer, when mixed with other polymers in an aqueous environment, formed nanoparticles. In the presence of insulin, nanoparticle formation resulted in insulin incorporation. Measurement of glucose levels in rats dosed orally with the VB12 insulin nanoparticles showed significant glucose reduction, peaking at approximately 4 h post dosing. Area under the curve comparison of these data with area under the curve obtained from mice given subcutaneous insulin (and correcting for relative dose) gave a pharmacologic availability of oral Cobalamin insulin of approximately 80%.

Conclusions:
Significant reduction in blood glucose levels was obtained in a rat model following oral dosing of Cobalamin insulin. Reduction in blood glucose levels was also seen following oral dosing of these nanoparticles in larger animals. Data are now being generated to allow a Cobalamin insulin formulation to advance into clinical trials.

Accuracy of a Novel Continuous Glucose Monitoring System Using Intravenous Microdialysis

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Objective:
A continuous glucose monitoring system (CGMS) promises to be an important tool to achieve tight glycemic control without hypoglycemia in patients at intensive care units or general wards. Current CGMS techniques, however, often need frequent calibrations and/or have substantial (physiological or technical) lag times in displaying glucose results. We investigated the performance of a novel CGMS combining intravenous microdialysis (MicroEye, Probe Scientific) and online glucose analysis (TRACE C2, Trace Analytics).

Method:
Using a high-perfusion flow rate of approximately 125 µl/min, glucose results were available every minute without significant time delays. Thirty-eight healthy subjects (8 females, mean age 34 (19–45) years, body mass index 24.7 (19.6–28.9) kg/m^2) participated in 10 h experiments under varying glucose conditions (fasting, oral glucose tolerance test, and/or variable glucose infusion). Reference samples were taken manually and analyzed using a laboratory device (Super GL) at half-hour intervals when blood glucose was stable and at 10 min intervals during periods of rapid changes in blood glucose concentration. Clinical accuracy of the CGMS was evaluated using Clarke error grid analysis for 2146 paired values covering a glucose range of 40–240 mg/dl.

Result:
Accurate or acceptable glucose results were found for 99.3% of the data points: 93.9% within zone A and 5.4% within zone B. The remaining data points were located within zone C (0.1%) and zone D (0.6%). Mean absolute deviation was 8.8 ± 9.5 mg/dl and mean relative deviation was 8.7 ± 8.5%. In N = 14 subjects, mean measurement precision of the CGMS, determined as the coefficient of variation under glucose steady state conditions, was 3.8 (1.1–9.7)%. No safety issues were reported during the study.

Conclusion:
In conclusion, this novel CGMS using intravenous microdialysis to sample glucose from the blood shows good agreement with reference blood glucose measurements without the need for frequent calibration.