Abstracts

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A Liquid-Stable Enzymatic Assay for Glycated Serum Protein in Human Serum

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Objective:
We aim to develop a liquid-stable enzymatic assay for determination of glycated serum protein (GSP; glycated albumin) in human serum. The assay is used as a short- to medium-term (2–3 week) index for monitoring glycemic control.

Methods:
A unique formulation was used to stabilize a key enzyme, fructosamine, which reacts specifically with ketoamine formed nonenzymatically between glucose and serum albumin molecules. With this unique formulation, a liquid-stable reagent was developed to assay GSP (glycated albumin). The assay (GlycoGap) performance characteristics were evaluated on the Hitachi 917 instrument for precision, method comparison, linearity, and stability using Clinical and Laboratory Standards Institute protocols. The results were expressed in μmol/liter and also expressed in percentage of glycated albumin.

Results:
Diazyme's GSP assay (GlycoGap) was formulated as a two-part, liquid-stable reagent system with an estimated shelf life of 15 months. The assay was highly reproducible with the within-run and total imprecision of ≤1.3% coefficient of variation for both normal and abnormal level controls and patient samples. Method comparison studies showed good correlations with another GSP assay (R^2 = 0.9966) and with Lucica GA-L assay (R^2 = 0.9915). The assay was linear within the range of 21–1354 μmol/liter and was not affected by ascorbic acid, bilirubin, hemoglobin, glucose, triglycerides, or uric acid at concentrations at least five times higher than the normal range in serum samples.

Conclusion:
It is reported that the glycated albumin test may bridge the gap between glucose and hemoglobin A1c tests in diabetes monitoring. Diazyme's GSP assay (glycated albumin) is user-friendly and highly accurate, with no interferences from endogenous-reducing substances that interfere strongly with the traditional nitroblue-tetrazolium-based fructosamine assay.

Effects of Ramadan Fasting on Metabolic Outcomes in Patients with Type 2 Diabetes

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Objective:
Several investigations have been conducted on the effects of Islamic Ramadan fasting on blood glucose levels and lipid profile of patients with type 2 diabetes mellitus (T2DM), but the conclusions are still a matter of controversy. This study is designed to investigate whether this kind of fasting and its combination with structured self-monitoring of blood glucose (SMBG) can be beneficial in controlling blood glucose level and lipid profile of T2DM patients.

Method:
Forty T2DM patients who were receiving oral agent therapy were selected for this study. These patients were randomly divided into two equal groups and matched based on their age and sex. Group A monitored their blood glucose level using a structured SMBG method (seven times per day, three days per week) and group B monitored their blood glucose level in a traditional way (four times per week, two times before Iftar and two times after Iftar). Fructosamine level, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG) were measured in all patients before and after Ramadan. The results were analyzed statistically using *t*-test and chi square.

Result:
Fructosamine level rose from 363 (±53.55) to 400.29 (±73.25; $p < .003$) in group A and from 388.52 (±61.89) to 411.10 (±68.37; $p < .04$) in group B. Total cholesterol, LDL, and TG levels were increased, and HDL levels were decreased in both groups; however, these changes were not statistically significant.

Conclusion:
A significant elevation in fructosamine level was observed among T2DM patients who had fasted during Ramadan.

Analysis of Glycemic Variability in Type 1 Diabetes Mellitus Children versus Type 1 Diabetes Mellitus Adults Using Medtronic Enlite Sensor

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Objective:
The analysis presents a comparison of the glycemic variability of type 1 diabetes mellitus (T1DM) children and adult subjects using continuous glucose monitoring (CGM) data from the Medtronic Enlite sensor. Trending and other information uniquely available from CGM data was used to evaluate differences in glycemic control and challenges related to management of T1DM pediatric subjects.

Method:
Continuous glucose monitoring data from 86 T1DM children and 82 T1DM adult patients in clinical trials of the Medtronic Enlite CGM system were used for the analysis. Sensor glucose (SG) information was evaluated to analyze estimated hemoglobin A1c, distribution of glucose rate-of-change (ROC) ranges, and other measures of glycemic variability.

Results:
Adult subjects had an estimated hemoglobin A1c of 7.0%, with an average SG of 154.7 mg/dl and a standard deviation of 71 mg/dl compared with 8.3% and 191.9 and 89.1 mg/dl in children, respectively. Adults spent an average of 75.8% of the time in stable glucose ROC ranges between -1 and 1 mg/dl/min and 7.0% of time at rapid ROC ranges of either less than -2 mg/dl/min or more than 2 mg/dl/min compared with 67.7% and 10.9% of time for children.

Conclusion:
Higher glycemic variability, including an increased occurrence of high glucose ROCs, are observed in children compared with adults during clinical studies of the Medtronic Enlite CGM system. Trend information, threshold and predictive alerts, and other new features available with CGM technology can be useful tools in assessing glycemic variability and further using it to attain tighter glycemic control and effectively managing T1DM, especially in children who experience high glucose variability.

Efficiency of Cell Phone Management of Patients with Newly Diagnosed Type 2 Diabetes Mellitus

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Objective:
Patients (pts) with newly diagnosed (ND) type 2 diabetes mellitus (T2DM) are a most difficult group for diabetes management because of psychological shock and a general lack of understanding of diabetes. The aim is to assess the efficacy of cell phone management (CPM) and its potential to improve ND T2DM management.

Method:
Forty-two noninsulin ND T2DM pts (18 women, 24 men) were included in the CPM group. Median age was 57 (43–64) years, therefore many methods effective for younger ages (e.g., diabetes computer games) were unacceptable. Everyday CPM contact and feedback with pts were performed. We also used SMS (short message service) for sending brief reminders and information about glucose and blood pressure (BP) levels. Emails were used for lengthier correspondence or education information (our papers from the International Diabetes Program journal *DiabetesLifestyle*). Hemoglobin A1c (HbA1c), fasting glucose (FG), and postprandial glucose (PPG) levels were monitored in both CPM and non-CPM (45 pts) groups.

Results:
A greater reduction of HbA1c (-2.3% and -1.6%), FG (-1.5 and 1.1 mmol/liter), and PPG (2.4 and 1.7 mmol/liter) were observed in the CPM group in a comparison with the control ($p < .05$). Blood pressure and glycemia monitoring were more systematic; the CPM pts actively analyzed their data. Progressively reducing negative problems was associated with drugs and BP measurement omissions and nonattendance of an endocrinologist (the economic motivation is reduced at free medical care).

Conclusion:
Newly diagnosed T2DM management is more effective when CPM (combined with email education) is included in the treatment scheme, because this allows improvement of glycemic and BP controls as well as motivation to have a good life with diabetes.

Accuracy and Acceptability of the Enlite 6-Day Glucose Sensor in Adults

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Objective:
Accuracy and acceptability of the next-generation 6-day subcutaneous glucose sensor (Enlite) was evaluated in an adult cohort (aged ≥ 18 years).

Method:
Ninety-eight of 100 subjects [69 male; 18 type 2; mean age 42.2 ± 15.0 years; hemoglobin A1c 7.6 ± 1.5% (5.5–14%)] completed a prospective study with Enlite sensors (Medtronic MiniMed Inc., Northridge, CA) in abdominal and buttock regions for two 7-day periods. Subjects had 10 h of plasma glucose Yellow Springs Instrument (YSI) sampling every 15 min for sensor/YSI comparison on one randomly assigned day during the 7-day period. Finger-stick glucose measurements [self-monitoring of blood glucose (SMBG)] were obtained at home and compared with sensor values. A questionnaire with Likert-type scale (1–7) and qualitative questions assessed satisfaction.

Result:
The YSI sensor glucose paired points (n = 6505) showed mean absolute relative difference (ARD) of 13.8% and median ARD of 10.1%, with 96.4% of points within the A+B zones of the Clarke error grid. The SMBG sensor glucose paired points (n = 8243) showed mean ARD of 16.0% and median ARD of 11.7%, with 95.4% of points within the A+B zones of the Clarke error grid. The YSI sensor glucose paired points in the 40–80 mg/dl range (n = 748) showed mean absolute difference (AD) of 13.7 mg/dl and median AD of 11.7 mg/dl. Surveys showed that ≥90% of subjects did not fear sensor insertion and found the sensor easy to insert and ≥86% liked the reusable inserter device and found the introducer needle easy to remove and the glucose trending information useful. All subjects surveyed would recommend the continuous glucose monitoring (CGM) system used in the trial.

Conclusion:
The 6-day Enlite sensor demonstrated accuracy overall and in the hypoglycemic range. With high patient satisfaction, this suggests Enlite should improve CGM adoption..

Results from an Ethnographic User Study: Patient Self-Examination at Home for Diabetic Autonomic Neuropathy

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Objective:
The objective of the study was to establish if patients are able to perform examination for cardiovascular autonomic neuropathy (CAN) independently in the home using a portable diagnostic device, Vagus, moving this highly specialized test from a hospital setting to a private home.

Method:
Ten diabetes patients (6 males and 4 females) were introduced to the device at the clinic of their own general practitioner and assigned to self-examine at home in the morning and evening for 3 days. Qualitative methods consisting of observation at the clinic and interviews in the home were used to study introduction and usage. Coding of transcribed interviews and field notes was subsequently applied to identify use patterns and influential parameters on use experience.

Result:
All patients were successful in performing the self-examination. The qualitative analysis identified three parameters central to the execution and experience with patient self-examination: (1) Patient confidence in performing self-examination was closely related to their understanding of what was being measured, how, and why. (2) Patient ability to overcome conflicts between routines related to self-examination and routines related to other activities in daily life also influences use experience. (3) Interaction with the diagnostic device and the user interface affects the perception of self-examination.

Conclusion:
Patients can successfully perform examination for CAN in their own homes. Central to this is thorough instructions, not only to aid interactions with the device, but also to understand relevant clinical perspectives and to assist in translating use from a clinical to a domestic setting. Experts previously performed this examination at the hospital; thus this study provides promising results for elaborate patient engagement in diagnostic work in a domestic setting.

Role of Patient Empowerment and Diabetes-Related Distress on Metabolic Outcomes in Type 2 Diabetes Mellitus

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Objective:
The prevalence of type 2 diabetes is predicted to rise continuously over the next decade. Diabetes is a chronic illness that necessitates a patient-centered approach in order to improve outcomes. Empowerment as a philosophy of care emphasizes a collaborative approach that facilitates self-directed behavior change of patients. The aim of our study was to assess the state of patient empowerment in type 2 diabetes and its role on metabolic outcomes.

Method:
One hundred forty-eight patients with type 2 diabetes were enrolled in the study. Empowerment, diabetes-related quality of life, and diabetes-related distress were assessed in all subjects. An empowerment questionnaire was designed and validated by the Endocrine Research Center and was used for evaluation of patient empowerment. Persian translation of an audit of diabetes-related quality-of-life (ADRQOL) questionnaire and diabetes distress scale were used for evaluation of quality of life and diabetes-related stress, respectively. Diabetes duration, level of education, body mass index (BMI), and glycated hemoglobin were recorded for each patient.

Result:
The empowerment scale showed a moderate level of patient empowerment in this group of subjects. There was a meaningful and inverse relation between empowerment and diabetes distress and glycated hemoglobin level. There was no meaningful relation between empowerment and ADRQOL, age, sex, level of education, BMI, and diabetes duration.

Conclusion:
Diabetes-related distress has a negative impact on patient empowerment and the state of metabolic control. Psychosocial support might be considered as an important intervention to reach the goals of diabetes management.

Improving Pharmacokinetic and Pharmacodynamic Profiles of Injected Rapid-Acting Insulin Analogs Using the InsuPad Device

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Objective:
Pharmacodynamic (PD) and pharmacokinetic (PK) profiles of current insulin analogs are still slow compared with normal physiology. Among other effects, this results in large postprandial blood glucose excursions in insulin-dependent diabetes subjects. InsuLine has developed a technology to accelerate insulin PK and PD profiles by applying controlled heat to the insulin delivery site. This heat increases local blood flow, which can induce faster insulin clearance from the injection site. The InsuPatch device is intended for insulin infusion, and the InsuPad device is intended for insulin injections. Previous studies with the InsuPad device have shown an increase of 18% in available insulin in the blood during the first hour post-injection and a reduction of 21% in the time to maximum insulin concentration when the InsuPad device was used.

Laser Doppler measurements have shown that local blood flow strongly depends on temperature and the temperature temporal profile. In this study, we have tested the effect of the heating temperature and the heating temperature temporal profile on insulin PK and postprandial glucose levels.

Methods:
The effect of the InsuPad device heating temperature and heating temporal profile on insulin PK and postprandial glucose levels was tested in a meal tolerance test protocol by comparing insulin and blood glucose concentrations under different heating temperatures and heating profiles.

Results:
Increasing the heating temperature was accompanied by increased rate of insulin delivery. Changing the heating profile was also found to influence insulin delivery rate. No adverse events were observed.

Conclusions:
These results suggest that the InsuPad device performance may be improved and fine-tuned by changing the heating temperature and the heating profile..

Random Examination of Blood Glucose in Adults by Trained Volunteers in a Hospital Setting

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Background:
We examined the incidence of dysglycemia and diabetes among screened nonhospitalized subjects in a hospital setting.

Methods:
A diabetes and hypertension screening station staffed by trained volunteers was placed in a central location at E. Wolfson Medical Center, Holon, Israel. Volunteers measured height, weight, blood glucose (by glucometer), and blood pressure (by sphygmomanometer). Screened subjects were asked whether they had diabetes. Normoglycemia was defined as glucose level < 100 mg/dl, dysglycemia as 140–190 mg d/l and diabetes as ≥200 mg/dl. Screening was performed free of charge.

Results:
A total of 1401 individuals (50.3% females, 53 ± 15.1 years of age) underwent screening. Of these, 228 reported known diabetes and 136 reported known hypertension. In the 1173 subjects without known diabetes, dysglycemia was detected in 247 (21.1%) adults and diabetes was found in 51 (4.3%) subjects. Compared with normoglycemic subjects, subjects with dysglycemia were significantly older (58.0 ± 14 versus 52.7 ± 15.1 years; $p < .001$) and had significantly higher blood glucose (179.7 ± 46.9 versus 109.3 ± 16.1 mg/dl; $p < .001$), body mass index (28.5 ± 6.1 versus 27.3 ± 5 kg/m^2; $p < .001$), and systolic blood pressure (132 ± 27 versus 126 ± 25mm Hg; $p < .004$). Patients with newly identified diabetes had significantly higher blood glucose (251.3 ± 57.2 versus 118.6 ± 25.5 mg/dl; $p < .001$), but did not significantly differ in terms of age, body mass index, or blood pressure.

Conclusions:
Screening for dysglycemia, diabetes, and hypertension can be conducted by trained volunteers in a public location and may identify incident cases of these conditions that require further medical evaluation.

Local-Model-Based Calibration Algorithms Improve Continuous Glucose Monitoring Accuracy

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Objective:
Accuracy of current continuous glucose monitoring (CGM) devices is yet unsatisfactory and may depend on implemented calibration algorithms (CAs), which do not compensate adequately for the differences of glucose dynamics between compartments. Here we propose and validate an innovative CA for the improvement of CGM performance.

Method:
We obtained CGM data from GlucoDay and paired reference plasma glucose (PG) are available from eight nondiabetic subjects during a euglycemic, hypoglycemic, and hyperglycemic hyperinsulinemic clamp.

We used CA based on a dynamic global model (GM) of the relationship between PG and interstitial glucose as given by the CGM electrical signal. The GM is composed by independent local models (LMs) weighted and added. Local models are defined by a combination of inputs and by a validity function so that each LM represents, to a variable extent, a different metabolic condition and/or sensor–subject interaction. The best-suited LM structure for glucose estimation was of first order, depending on the sensor current I and past glucose estimations $\hat{G}$ at time instants $[I_k, I_{k-1}, \hat{G}_{k-1}]$ (*IIG*). In addition to *IIG*, other exogenous signals were used to obtain the GM, achieving different configurations of the CA.

Result:
Yet in its simplest configuration, considering only *IIG*, the new CA improved the accuracy of the estimations as compared with the manufacturer's CA: mean absolute relative difference (MARD) 10.8 ± 1.5% versus 14.7 ± 5.4% ($p < .05$, analysis of variance). When exogenous signals were considered, the MARD improved further (7.8 ± 2.6%, $p < .05$).

Conclusion:
The LM technique allows intercompartmental glucose dynamics to be identified. Including these dynamics into the CA improves the accuracy of PG estimations.

Hypoglycemia Alarm Systems Based on 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, predict his/her future glucose excursions, and develop a hypoglycemia alarm system. A subject's metabolism, physical activity, emotional stimuli, and lifestyle 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 subject-specific models, monitoring, and alarm systems.

Method:
The subject-specific glucose prediction model is developed using data from a continuous glucose monitor (CGM) and physiological signals from a multisensor armband. The frequent data from the sensors are analyzed by time series methods. Adaptive system identification consisting of online parameter identification using the weighted recursive least squares (RLS) method and a change detection strategy that monitors variation in model parameters in response to intersubject/intrasubject variation and glycemic disturbances is used. Statistical monitoring techniques are developed to monitor predicted glucose concentrations and generate hypoglycemia alarms.

Result:
The proposed algorithm is used to provide *early* (30 min in advance) hypoglycemia (and hyperglycemia) alarms. Alarm systems developed are tested using simulators and patient data. Both alarm systems based on CGM measurements and alarm systems using CGM and armband data provide good hypoglycemia monitoring.

Conclusion:
The linear low-order models developed are easy to identify and update, which make them good candidates for early hypoglycemia/hyperglycemia alarms. The RLS and the change detection methods proposed enable the dynamic adaptation of the models to intersubject/intrasubject variation and glycemic disturbances.

Pen Needle Preference

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Objective:
Controversy and confusion exist regarding appropriate needle length for injecting insulin in patients with diabetes, specifically in those who are obese and using large doses of insulin. The goal of this study was to evaluate patient satisfaction and efficacy of treatment, as determined by hemoglobin A1c levels, when using a 5 mm pen needle compared with an 8 mm pen needle.

Method:
The experiment was a substudy of a glycemic control trial of patients with type 2 diabetes. Individuals in the group had a mean weight of 98.25 kg, and greater than 50% of these individuals took at least one insulin injection daily greater than 41 U. Over the course of the 6-month trial, 66 patients used an 8 mm needle for the first 3 months of the study and a 5 mm needle for the last 3 months. At the conclusion of the 6-month trial, questions were posed in order to identify preference of specific needle attributes.

Result:
Analysis of the questionnaire revealed patients preference of the 5 mm needle over the 8 mm needle. Satisfaction scores regarding comfort and ease of use were higher for the 5 mm needle. The study revealed that the overall preference for the 5 mm needle was 41.80%, while the 8 mm needle was preferred by 27.87% of the population. The 5 mm needle was equally effective at maintaining glycemic control as the 8 mm needle, as indicated by patients' consistent hemoglobin A1c values.

Conclusion:
The study revealed that patients using pen needles for insulin injection preferred the 5 mm needle to the 8 mm needle. The shorter needle was more comfortable, easier to use, and equally as effective at delivering insulin and managing blood sugar as compared with the 8 mm needle.

Designing a Diabetes Telemedicine System

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Objective:
People with diabetes from rural or isolated population areas (small islands) where a doctor is not available should still have access to diabetes medical advice daily.

Method:
A platform-independent Web software application gives both doctors and diabetes patients access to an online system from personal computers and mobile phones. Both doctors and diabetes patients are registered in the online system. Diabetes patients log in to the system by entering their username and password, then they add their glucose values, the insulin type and units they use, and their comments. Doctors log in to the system to see which diabetes patients have posted data, to access the data, see the glucose values and insulin type and units, and read the comments. The doctors then provide feedback and suggestions to the diabetes patients. Finally the diabetes patients log in and read the feedback from the doctors and are able to reply to doctor feedback.

Result:
This Web software application could work under one health organization umbrella, from the department of health or from volunteer doctors. It requires at least one kind of Internet connection to be available (dial-up is nice). No software installation is required.

Conclusion:
Advantages of this Web software applications are: diabetes patients may have daily access to medical advice, there is no social exclusion, the online system is accessible from everywhere, the process is simple, no software installation is required, and the phenomenon of depression may be reduced.

Exterior Artificial Pancreas (Project)

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Objective:
The aim is to develop a pump-size exterior artificial pancreas that will keep glucose between 120 and 150 mg/dl.

Method:
The whole project is based on the premise that we should already know how much one insulin unit can lower glucose, and how much one glucagon unit increase glucose. For glucose levels lower than 120 mg/dl, the pump uses glucagons; for glucose levels higher than 150 mg/dl, it uses insulin. The pump checks the glucose automatically every 8 min. The pump (which uses software decision) will choose between insulin or glucagons based on an internal database table with prerequisite glucose values, and the insulin or glucagon units required for each glucose value (adaptive database table for each diabetes patient). The pump (software) is able to choose how many insulin or glucagon units it should use (not based on what the diabetes patient will eat, but based on the current glucose level received from the sensor located in human body by needle and sensor as one piece). The insulin should have an 8 min duration and works instantly.

Result:
Because a glucose level of 120 mg/dl is considered secure for the diabetes patient (there is time to prevent major hypoglycemia), this value was chosen as the lowest allowed glucose level. This should keep glucose close to normal values.

Conclusion:
This project offers patients with diabetes freedom from insulin injections, prevention of hypoglycemia, and emergency test runs. It is ideal for all ages. Endocrinologists will have the software to adapt the internal database table of the pump to the needs of each patient. More information on this artificial pancreas project is available at Web site: *http://www.eap-project.dom.gr.*

Self-Monitoring of Hemoglobin A1c

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Objective:
The aim was to develop a software application that is able to approximate hemoglobin A1c (HbA1c) without a blood sample, useful for people who are checking their glucose three to six times daily.

Method:
The software application, Diabetes Management V1.2, is able to guess HbA1c. First of all, the patient with diabetes should check glucose three to six times daily. Second, the patient should add up all the glucose results of the past 90 days and then open the diabetes management application to enter the sum (one number). The program will divide this number by 90, which represents the past 90 days, and then divide the result by 4, which represents the average times per day that the diabetes patient checks their glucose. Then this number is compared by internal table with glucose values and possible HbA1c levels.

Result:
I have tested the software application Diabetes Management V1.2 and asked diabetes patients in forums to use this software application and take the regular HbA1c test with blood. People who checked both gave me these results: program 6.1% and regular test 6.4% and program 6.0% and regular test: 6.3%.

Conclusion:
Diabetes Management V1.2 is able to guess HbA1c, is unable to substitute the original HbA1c test with blood, but is able to give to diabetes patients an idea about their approximate HbA1c to let them know whether they need to adjust their medication. Diabetes patients found this program useful, and they upload it at *http://diabetes-management.software.informer.com.*

Effective Diabetes Management via New Affordable Patient-Friendly Tool

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Objective:
Most insulin users do not achieve optimal glycemic control [hemoglobin A1c (A1C) < 7%] and are thereby susceptible to complications. An abundance of clinical trials have shown that frequent insulin dosage titration is a key for successful outcome. Unfortunately, implementation of such a paradigm has been hindered by a lack of medical expertise, inadequate reimbursement, and fear of hypoglycemia. We hypothesized that the Diabetes Insulin Guidance System (DIGS), which automatically adjusts patients' insulin dosage between clinic appointments, would improve glycemic control.

Method:
We recruited insulin-treated patients with suboptimal glycemic control in a 16-week trial. Patients were divided into three groups: (i) type 1 diabetes treated with basal-bolus insulin therapy, incorporating carbohydrate counting; (ii) type 2 diabetes with basal-bolus therapy; and (iii) type 2 diabetes with biphasic insulin. Following a 4-week run-in period, glucose readings reported in diaries were processed weekly by DIGS software for 12 weeks and its insulin dosage recommendations were communicated to patients. Efficacy was assessed by reduction in weekly mean glucose and safety by frequency of hypoglycemia.

Result:
Forty-six patients were recruited and 8 withdrew. During the run-in period, weekly mean glucose was stable at 174 mg/dl (±37). During the following 12 weeks, weekly recommendations made by DIGS resulted in progressive improvement in weekly mean glucose to 163 mg/dl (±35); $p < .03$. Patient A1C decreased from 8.4% (±0.8) to 7.9% (±0.9); $p < .05$. Concomitantly, frequency of hypoglycemia decreased by 25%. No severe hypoglycemia was reported. In only 3 out of 1734 instances, the study team overrode the DIGS recommendations.

Conclusion:
This novel report showed that insulin dosage titrated by software (DIGS) resulted in effective and safe therapy. Incorporating a glucose sensor on the DIGS platform may lead to improved outcomes through better usage of insulin and glucose tests and may reduce patient and care provider effort.

Effect of Infusion Set Age on Pharmacokinetic and Pharmacodynamic Profiles of Injected Rapid-Acting Insulin Analogs Using the InsuPatch Device

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Objective:
Continuous subcutaneous insulin infusion (CSII) is a common therapy. Studies with CSII have shown better glucose control along with increased quality of life. Continuous subcutaneous insulin infusion involves insertion of a catheter into the subcutaneous adipose tissue (SAT), which inevitably induces tissue trauma. Studies have shown an increase in inflammatory process at the insertion site, which may limit long-term use of that site. Currently, subjects are advised to change infusion sites every 2–3 days. On the other hand, it was shown that increased inflammation at the infusion site may result in increased local blood flow, which may result in a change in the pharmacodynamics (PDs) and pharmacokinetics (PKs) of infused insulin.

The InsuPatch device is intended to accelerate insulin absorption into the blood system by applying local heat to the SAT where insulin is infused. The applied local heat increases local blood flow, which enables faster insulin absorption. In this study, we have tested the effect of the infusion site age on PK and PD profiles of infused insulin with and without the use of the InsuPatch device.

Methods:
The effect of the infusion site age on rapid-acting insulin PKs and postprandial glucose levels was tested in a meal tolerance test procedure. The test was performed on day 1 and day 3 since infusion site replacement and was repeated twice with and without activation of the InsuPatch device.

Results:
Day 3 PK profile was found to be faster compared with day 1 PK profile. Using the InsuPatch device was found to accelerate insulin PK profiles on both days while reducing variability.

Conclusions:
These results suggest that the InsuPatch device can reduce insulin PK variability where changes in local blood perfusion are expected.

A Comparison of Users and Nonusers of Real-Time Continuous Glucose Monitoring with Type 1 Diabetes in the Type 1 Diabetes Exchange

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Background:
We compared characteristics of patients with type 1 diabetes mellitus (T1DM) who are continuous glucose monitoring (CGM) users and nonusers in the T1D Exchange clinic registry.

Methods:
At >60 U.S.-based clinics, data were collected through questionnaire completion by participants with T1DM, of whom 5708 were <18 years old (median age 12 years) and 5255 were ≥18 years old (median age 35 years). Continuous glucose monitoring use, defined as self-reported use in the past 30 days and medical record confirmation of current use, was reported by 148 (2.6%) of <18 year olds (minimum age 1.7 years old) and 577 (11.0%) of ≥18 year olds (maximum age 80 years old).

Results:
An insulin pump was being used by 80% of the 577 adult CGM users versus 56% of the 4678 adult nonusers and by 87% versus 49% of the 148 pediatric CGM users and the 5560 nonusers, respectively ($p < .001$). Adult CGM users were more likely to be white non-Hispanic than nonusers ($p < .001$). The CGM users in both age groups were more likely to have higher family income level and higher education level (of parents for pediatric participants) than nonusers ($p < .01$). Mean hemoglobin A1c (HbA1c) was 7.2% versus 7.9% in adult CGM users versus nonusers and 7.7% versus 8.5% in pediatric CGM users versus nonusers ($p < .001$, adjusted for pump use). Median CGM use in the prior 30 days was 28 days in adult and 23.5 days in pediatric participants, and median number of meter glucose checks were five and six per day, respectively.

Conclusions:
In both adults and children, CGM users are more likely than non-CGM users to be using an insulin pump, to have lower mean HbA1c levels, and to be of higher socioeconomic status.

Interim Analysis of an In-Clinic, Randomized, Crossover Study to Assess Efficacy of the Low Glucose Suspend Feature of the Paradigm Veo System with Hypoglycemic Induction from Exercise

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Background:
The Paradigm Veo system (Medtronic MiniMed Inc., Northridge, CA) with low glucose suspend (LGS) suspends insulin for 2 h after sensor glucose reaches a threshold (40–110 mg/dl) set by patient/provider. An interim analysis of a study designed to assess efficacy in reducing hypoglycemia after exercise was performed.

Method:
Type 1 pump therapy subjects were studied twice (LGS on; LGS off), in random order, after fasting overnight and exercising until the plasma glucose was ≤85 mg/dl. The LGS activated when the sensor glucose (calibrated by subjects using an Ultra home glucose meter) reached ≤70 mg/dl; all other analyses were done with Yellow Springs Instrument (YSI) plasma glucose readings. A 4 h observation period occurred after the YSI glucose reached <70 mg/dl; if the full 4 h period was not reached, the last observation carried forward was applied. The study was terminated if a subject had hypoglycemic symptoms, had YSI readings <50 mg/dl, or did not reach <70 mg/dl.

Result:
Thirty subjects, 22–58 years (60% male), had a mean body mass index of 27.3 ± 4.6 kg/m^2 and hemoglobin A1c of 7.8 ± 0.6%. Because of a carryover effect (p value = .017), only data from the first induction experiment was used for analysis. Mean duration of time with YSI readings ≥50 and <70 mg/dl was 91.6 min (LGS on) versus 191.6 min (LGS off; p = .003). The mean glucose nadir was 61.9 mg/dl (LGS on) versus 56.7 mg/dl (LGS off). Based on all induction experiments, there were 12 with YSI readings <50 mg/dl (4 LGS on; 8 LGS off), and after 4 h of observation, mean YSI reading was 90.3 mg/dl (LGS on) and 62.9 mg/dl (LGS off). No ketoacidosis was observed.

Conclusion:
These data suggest that LGS significantly reduces the duration of hypoglycemia and does not result in clinically significant hyperglycemia.

Detecting Insulin Infusion Set Failure

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Background:
Insulin infusion set failures (IISFs) can cause high blood glucose (BG) levels, diabetic ketoacidosis, and/or shorten insulin pump wear. This work introduces a real-time IISF detection algorithm that monitored continuous glucose monitor (CGM) readings and commanded insulin to generate a binary user alert.

Methods:
The method constructs dynamic models with both nominal and zero insulin effect. It evaluates how well the models predict the CGM readings and how strongly the necessary state estimates conflict with basic assumptions. This avoids misinterpretation of an IISF as additional meals, a positive BG rate of change, or an increasing CGM bias. Two simulated scenarios provide validation: (a) an IISF at midnight after three daytime meals and 9 h before breakfast and (b) an IISF at noon, 3 h after breakfast and 1 h before lunch. We also studied performance with explicit meal announcements.

Results:
Without meal announcement, this method detected 8 of 10 midnight IISFs and 10 of 10 noon IISFs, with 9 and 0 false positives, respectively. The average time to detection and BG level at detection was 6 h 47 min and 286 mg/dl for midnight IISFs, and 3 h 21 min and 273 mg/dl for noon IISFs. With meal announcement, these results improve to 100%, 6 false positives, 5 h 52 min, and 202 mg/dl for midnight IISFs and 100%, 0 false positives, 2 h 36 min, and 245 mg/dl for noon IISFs.

Conclusions:
Our method successfully distinguishes the similar effects of IISFs and meals. Naturally, higher performance is achieved during the daytime with high insulin activity than nighttime with low insulin rates. Performance is always improved by explicit meal announcements. The method can detect IISFs with few false positives, potentially reducing hyperglycemic risk, diabetic ketoacidosis, and increasing pump wear duration.

Probabilistic Blood Glucose Prediction with Meal Estimation, Anticipation, and Announcement

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Background:
The timing and size of meals significantly impacts blood glucose levels, requiring appropriate consideration in prediction and control. In contrast to isolated meal detectors, we present an integrated probabilistic framework with multiple benefits. Meal estimation increasingly adjusts predictions as confidence increases. Known meal patterns allow anticipation by increasing prior probabilities of meals without committing if meals do not occur. Similarly meal announcements are integrated with implicit safeguards for false announcements.

Method:
We formulated a seven-state linear model (glucose x2, continuous glucose monitoring bias, insulin x2, meal x2). Multiple distinct instances of this model, differing by meal start times, were weighted by prior probabilities of the start times and by their fit to the sensor data. The combined prediction is the weighted sum of the individual model predictions. New models were instantiated as future start times become relevant; low probability and functionally redundant models were removed. Meal patterns and announcements altered the expectation of future meals and thus the predictions. The predictions also generated prediction uncertainty for use by nonstandard controllers.

Result:
We validated against a single Kalman filter implementation that estimates meals using one instance of the base model. Including meal anticipation improved the 1/3 h daytime prediction accuracy by 17/38% tested on 22 days of clinical data. Averaging the error in the 2 h around a meal, the improvements were 30% from meal anticipation and 57% from meal announcement, tested on 100 isolated, simulated meals. Additionally, the accuracy of the uncertainty estimates improved markedly for all cases.

Conclusion:
This method provides an integrated method for probabilistic detection and estimation of meals that integrates both meal anticipation and announcement. It significantly improves prediction accuracy and estimation of the prediction uncertainty.

Development of a Synthetic, Closed-Cycle Sensing System for an Implantable Glucose Sensor

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Background:
There have been numerous efforts over the past several decades to build an *in vivo* glucose sensor. Our strategy for successful device development is based on a consideration of all the critical components and how they relate to the system as a whole, with a primary focus on a closed-cycle glucose sensing system built from stable, synthetic components.

Method:
Demonstration of the self-contained chemical sensing system required construction of two component libraries: (1) the competitive agent/signaling component, which is a dendrimer–boronic acid (DBA) construct, and (2) the glucose competitive binding environment, which consists of an immobilized monosaccharide mimic (iDIOL). The interaction of glucose, the signaling component, and the immobilized binding environment in a microarray format was used to demonstrate a glucose proportional signal response.

Result:
Response curves for multiple DBA conjugates with selected iDIOLs, with the DBA:iDIOL pairs having a range of relative affinities for glucose, were generated in both reference buffer and a fractionated plasma matrix. Glucose response curves were observed that gave minimum detection limit and slope (I50) of 20 and 100 mg/dl, respectively, with a working range of 10–600 mg/dl glucose. Comparably, when the sensing system was exposed to plasma matrix, the minimum response limit and I50 were unchanged while the working range was slightly reduced to 20–400 mg/dl, indicating that the sensing system is selective for glucose in the presence of physiological matrix.

Conclusion:
A glucose sensing system construction from stable, synthetic components has been successfully developed. The sensing system was constructed of components that competitively interact with glucose to produce a proportionate response to physiologically relevant glucose levels in biologically relevant matrices.

Redundant Sensors Improve Detection of Hypoglycemia

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Objective:
Hypoglycemia is a barrier to optimal glucose control in the treatment of diabetes. Hypoglycemia can be detected by glucose sensors, but sensor accuracy in this range is suboptimal. We sought to better understand whether using multiple sensors would improve detection of hypoglycemia and overall sensor accuracy.

Method:
Sensor data from two studies were included for a total of 34 adult subjects with type 1 diabetes who participated in 65 studies. In 36 studies (9 h in length), subjects wore two pairs of Dexcom SEVEN PLUS sensors, one pair on each side of their abdomen. Sensors were calibrated once at the start. In 29 studies (28 h), subjects wore two Dexcom SEVEN PLUS sensors calibrated every 6 h. Venous blood was drawn every 10–15 min for measurement of glucose. Hypoglycemia was defined as venous blood glucose < 70 mg/dl, and the threshold of sensor detection was <85 mg/dl.

Result:
Averaging the values from a pair of sensors significantly improved detection of hypoglycemia compared with a single randomly selected sensor (sensitivity 95.1% versus 82.9%, specificity 94.8% versus 93.4%). Averaging also significantly reduced large errors versus a single sensor (0.6 ± 0.2% versus 1.4 ± 0.8% of values ≥50% from reference, $p < .01$). Overall accuracy was improved with averaging compared with a single sensor (mean absolute difference 11.9 ± 1.0 versus 15.3 ± 1.5 mg/dl, $p < .01$, and mean absolute relative difference 12.2 ± 0.6% versus 14.7 ± 0.8%, $p < .001$). Use of a voting scheme and sensor selection based on the lowest error at the time of calibration did not improve accuracy.

Conclusion:
When two sensors are used simultaneously, sensor averaging improves detection of hypoglycemia and sensor accuracy. This finding is important for detecting hypoglycemia in an artificial pancreas system.

Is Continuous Glucose Monitoring a Better Option in Patients with Beta Thalassemia Major?

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Background:
Impaired glucose tolerance (IGT) and insulin-dependent diabetes are common complications in beta thalassemia major (TM) due to transfusion-related iron deposition in the liver and pancreas. The prevalence of diabetes in this population is reported to be as high as 24%. Routine measurements of hemoglobin A1c (HbA1c) and oral glucose tolerance tests (OGTTs) are commonly used in screening these patients. We present here a case series of three patients with TM who had grossly abnormal OGTTs but completely normal blood glucose levels on continuous glucose monitoring.

Case Series:
A 49-year-old female with TM had IGT since 2007. Routine screening revealed a HbA1c of 7.7% and an OGTT in 2009 showed progression to diabetes despite having been on metformin.

A 38-year-old female with TM had IGT since 2000. She had an OGTT in 2010 that was consistent with diabetes (HbA1c 7.9%). Use of Prandin, metformin, and glimepiride were attempted but had to be discontinued because of hypoglycemia.

A 39-year-old male had IGT since 2008 and was started on Metformin. An OGTT in 2010 showed progression to diabetes (HbA1c 7.3%).

All three patients had normal capillary blood glucose monitoring at home, discrepant with the testing. Hence a blinded, 3-day continuous glucose sensor was performed.

Results:
The sensor data revealed normal glucose values throughout the study, with no significant glucose excursions.

Conclusion:
Oral glucose tolerance tests are poorly reproducible and, in our case, were inconsistent with capillary blood glucose readings. Hemoglobin A1c values in those receiving chronic transfusions are known to be unreliable. Our case study demonstrates that continuous glucose sensors offer a potential "real-time" and possibly more accurate alternative of assessing blood glucose in TM.

Needle-Implantable Platform for Continuous Glucose Monitoring Using Photovoltaic Powering and Optical Communication

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Background:
We present the design, simulation, and fabrication of miniaturized needle-implantable sensor chip architecture for continuous glucose monitoring. The implantable sensor chip consists of an amperometric glucose sensor that interfaces a potentiostat, a photovoltaic powering source, a signal-processing unit that generates a series of digital pulses (whose frequency is proportional to the glucose level), and an optical transmitter (operating at 1.3 μm) that wirelessly relays the output data to an external proximity communicator unit. The solar cells are powered by 650 nm light-emitting diodes (LEDs), which are located in the proximity communication unit. This unit also hosts a photodiode and associated circuits that convert incoming optical pulses into glucose levels that are displayed or transmitted to a physician's office.

Method:
Circuitry employed in this system was fabricated by MOSIS foundry using a standard 0.35 μm complementary metal oxide semiconductor (CMOS) process. Fabricated circuits were interfaced *in vitro* and *in vivo*, with miniaturized glucose sensors incorporating flavoenzyme glucose oxidase as the sensing methodology.

Result:
We successfully demonstrated *in vitro* testing with the fabricated circuits, completely powered by solar cells, interfacing with amperometric glucose sensors and transmitted via a 1300 nm LED, received and processed with LabVIEW. We have also shown the successful generation of voltage pulses when light from an external 850 nm laser is incident on the on-chip photodiode link used to drive the mode select block that selects a desired function.

Conclusion:
In conclusion, we have successfully demonstrated the concept of a continuous glucose sensing platform using CMOS circuitry along with optical powering and communication links, paving the way for a low-power continuous monitoring system for diabetes patients.

Development of an Actor–Critic-Based Control Algorithm for Insulin Infusion in Individuals with Type 1 Diabetes

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Objective:
An adaptive controller-based on the Actor–Critic (AC) learning algorithm is developed to be used for the artificial pancreas concept. The robustness of the proposed controller is investigated *in silico* in terms of subject variability and carbohydrate (CHO) estimation inaccuracies.

Method:
The proposed AC-based controller provides individualized insulin infusion rates through adaptation and optimization of the control policy over time based on continuous interaction with the system under control. Actor–Critic has been evaluated *in silico* using the University of Virginia type 1 diabetes simulator for 28 patients (10 adults, 10 adolescents, and 8 children). The protocol included 12 trial days under a four-meal daily scenario. The cases of accurate meal estimation as well as underestimation/overestimation of CHO content of the order of 25% have been investigated.

Result:
In silico evaluation has shown 100% prevention of hypoglycemia and very low risks for severe hypoglycemia (low blood glucose index from 0.01 to 0.36) for all subjects, even under meal estimation inaccuracies. Times spent in euglycemia in cases of accurate, underestimation of, and overestimation of CHO content were 81%, 69%, and 86%, respectively, for adults; 80%, 74%, and 85%, respectively, for adolescents; and 82%, 73%, and 88%, respectively, for children. Further investigation is needed for efficient prevention of postprandial hyperglycemia while open issues related to the learning procedure design are addressed.

Conclusion:
A novel AC-based control algorithm has been developed and evaluated *in silico*. The proposed method seems to be able to compensate for the interpatient and intrapatient variability as well as for potentially misleading information to move toward an improved and individualized glucose control.

Zone Model Predictive Control: A Robust Design Based on A Priori Patient Information

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Background:
The robust performance of the artificial pancreas (AP) control design is one of the fundamental requirements of a closed-loop system. The underlying requirement is the ability to regulate glucose concentrations to the near-normal range under real-life events while providing a simple design method to tailor the AP system to individual clinical characteristics. The system is required to function under the following conditions: (a) minimal or no meal information, (b) extended periods of missing sensor information, (c) unreported continuous glucose monitor calibration, and (d) quick start with minimal lead time.

Method:
The robust design of the control algorithm was evaluated on historical clinical data and 100 *in silico* subjects from the Food and Drug Administration-accepted University of Virginia/Padova metabolic simulator facing two unannounced meals of 50 and 40 g of carbohydrates and an overnight period. The core algorithm is a zone model predictive control algorithm that is based on a control-relevant *a priori* model that utilizes personalized clinical information and the confidence level for the clinical information (safety factor). A parallel safety system to detect and prevent hypoglycemia was included.

Result:
The control design was evaluated with a safety factor of 1.25–2 and a 24 h protocol with two unannounced meals. Under the most aggressive settings (safety factor = 1.25), the glucose range was 75–311 mg/dl with a mean 3 h postprandial glucose of 191 and 178 mg/dl, respectively. Percentage of time in the 70–180 mg/dl range was 97% overnight and 81% overall. The safety system was activated only five times, and no hypoglycemic events occurred as defined by blood glucose < 70 mg/dl.

Conclusion:
A comprehensive AP design is presented that can safely regulate glycemia under real-life events based on a clinically oriented design and readily obtained dynamic models.

New Formulations of Linjeta with Improved Tolerability Have Rapid Onset of Action in Diabetic Miniature Swine

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Objective:
Linjeta is a formulation of recombinant human insulin (RHI), ethylenediaminetetraacetic acid, and citric acid, which has an ultra-rapid onset of action in man when compared with RHI and insulin lispro. Previous clinical studies have shown an association with local injection site discomfort following subcutaneous (sc) administration of Linjeta. Clinical studies have demonstrated that formulations BIOD-102 and BIOD-103 were improved with respect to tolerability but required further refinement to optimize the pharmacokinetic (PK) profile. The aim of the present study was to evaluate the PK and pharmacodynamic (PD) properties in the diabetic swine model of two new formulations, BIOD-105 and BIOD-107, predicted to be associated with improved toleration in man.

Method:
Six to eight diabetic miniature swine were given a sc dose (0.25 U/kg) of Linjeta, BIOD-105, or BIOD-107. Immediately following dosing, the swine were fed 500 g of their normal diet. Plasma insulin and blood glucose were measured from -30 to 480 min postdose by an enzyme-linked immunosorbent assay method and using a YSI glucose analyzer, respectively. The rate of insulin absorption was calculated as the slope of individual absorption profiles (μU/ml/min). The time to 20 mg/dl glucose reduction from baseline was estimated by linear regression.

Result:
Absorption rates [μU/ml/min ± standard error of the mean (SEM)] were 6.4 ± 1.4, 6.0 ± 1.9, and 5.2 ± 0.9 for Linjeta, BIOD-105, and BIOD-107, respectively. Times to 20 mg/dl glucose reduction (min ± SEM) were 7.0 ± 1.2, 8.6 ± 0.8, and 5.5 ± 0.9 for Linjeta, BIOD-105, and BIOD-107, respectively. No statistical differences were noted between the formulations on the PK and PD parameters.

Conclusion:
BIOD-105 and BIOD-107, predicted to have improved injection site toleration in man, have insulin absorption rates and glucose responses in diabetic miniature swine comparable to the ultra-rapid prandial insulin profile of Linjeta.

A Fully Implantable Wireless Optical Spectroscopy System for Glucose Sensing

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Background:
An implantable wireless sensor platform with an integrated spectroscopy interface has been developed that enables long-term *in vivo* insulin sensitivity factor glucose measurements when integrated with a fluorescent, glucose-responsive copolymer. This battery-free sensor system can be fully implanted under the dermis and queried by an external host system for on-demand and continuous glucose measurements.

Method:
A ferrite substrate that functions as part of the antenna serves as the base for the multichip module assembly process. The encasement of the sensor acts as a wave guide and enables the two band-pass-filtered photodiodes and an onboard light-emitting diode to serve as the spectroscopic transducer for the glucose-sensing hydrogel. The optical signal is processed through a mixed-signal application-specific integrated circuit that frequency encodes the optical and temperature information and telemeters the data to the host system using backscatter modulation through an inductive link.

Result:
This sensor system wirelessly transmits frequency-encoded optical and temperature information transcutaneously. This sensor measures changes in photodiode current that are less than 1 nA and have a temperature resolution below 0.2 °C. Configuring this system with a fluorescent, glucose-responsive copolymer and utilizing temperature compensation allows the system to wirelessly detect changes of less than 1000 ppm in the fluorescent signal.

Conclusion:
This system has demonstrated full capability to provide long-term functionality to remotely monitor spectroscopic signals *in vivo*. Integrating the optical and radio frequency circuitry enables a swollen grain-of-rice-sized implant that is suitable for subdermis implantation. This fully implantable sensing system, when coupled with a glucose-responsive fluorescent hydrogel, has demonstrated accurate glucose measurement in a 3-month nonhuman primate trial and produced clinical results that indicate stability for durations greater than 6 months.

New Metric to Assess Glucose Predictors and Identify Glucose Models

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Background:
The mean square error (MSE) metric is normally used for assessing glucose predictors and for identifying glucose models. However, this metric, by treating equally hypo and hyper errors, may not be the most appropriate given the different clinical impact of these two types of errors.

Here we propose a new cost function that overcomes this limitation and which can be used for several scopes, e.g., used for assessing quality of glucose predictors and identifying glucose models.

Method:
The MSE is modified with a Clark-error-grid-inspired penalty function, which penalizes overestimation in hypoglycemia and underestimation in hyperglycemia. The new metric is therefore called hypo and hyper penalized mean square error (hhMSE). hhMSE retains sensitivity of MSE and inherits some of its important mathematical features; in particular, it has no local minimum, simplifying the optimization. This makes it suitable also for model identification purposes.

Result:
hhMSE sensitivity to different accuracy, precision, and distortion in glucose predictions is proven by means of three experiments, designed *ad hoc*. As an illustrative example, two realistic prediction profiles are also presented. Visual inspection suggests that the first one is clinically preferable, but MSE selects the second. On the contrary, the hhMSE correctly selects the first one.

Moreover, as shown through an extensive simulation study, models identified minimizing the new cost function are more accurate in potentially harmful situations (hypoglycemia and hyperglycemia) than those obtained by MSE.

Conclusion:
hhMSE is effective in assessing the accuracy of a predicted glucose profile in a therapeutic context and can be used in place of MSE in model identification to obtain models whose accuracy is better in both hypoglycemic/hyperglycemic regions.

Hidden Markov Models for Improving Accuracy in Real-Time Glucose Monitoring

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Background:
Electrochemical glucose biosensors inserted into subcutaneous fat tissue allow for nearly continuous monitoring of electrical current generated by blood glucose molecules. In principle, this provides a means for real-time monitoring of blood glucose density, which is essential for managing diabetes. Calibration algorithms must be developed and employed in order to accurately convert sensor readings to blood glucose density.

Methods:
One hundred thirty-seven subjects were monitored for approximately 6 months on average while using an electrochemical glucose biosensor. Sensor information was stored every 5 min, along with blood glucose density predictions derived from an existing reference calibration algorithm, which was in use roughly 5 years ago. Additionally, finger stick blood glucose density measurements were taken approximately every 6 h. Using data from the first 50 subjects, we developed novel calibration algorithms that incorporate various important features of the sensor data and are derived from hidden Markov models (HMMs). These algorithms were then applied to the remaining 87 subjects, and their performance (in terms of mean absolute relative difference) was compared with that of the reference algorithm.

Results:
The newly developed HMM-based algorithms were found to consistently outperform the reference calibration algorithm by 1.1–1.6%. Preliminary evidence suggests that the HMM-based algorithms may be utilized for effectively identifying hypoglycemia and hyperglycemia within a subject.

Conclusions:
The HMM-based calibration algorithms discussed here seem to offer substantial improvements over the reference calibration algorithm. Additionally, the HMM-based algorithms seem promising when compared with other proposed calibration algorithms.

Utilization of a Bolus Calculator Feature in Multiple Daily Injection Therapy: Example of the ACCU-CHEK Aviva Expert System

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Objective:
Adjusting prandial insulin dosage is one of the greatest challenges in multiple daily injection (MDI) therapy. A bolus calculator feature has been proven helpful in estimating prandial insulin doses. The ACCU-CHEK Aviva Expert system, with an integrated bolus calculator, has the potential to help patients on MDI therapy. In order to evaluate utilization of this innovative system, we performed a survey on use of the ACCU-CHEK Aviva Expert system.

Method:
Patients treated with insulin were recruited from selected centers. After receiving education, patients used the ACCU-CHEK Aviva Expert system for 4 weeks. Afterward, both patients and health care professionals were asked to complete separate, specially designed evaluation questionnaires.

Result:
Two hundred seventy-four patients from 90 centers have evaluated the ACCU-CHEK Aviva Expert system; 93.8% of patients have used a bolus calculator feature; 66.1% of the patients reported to have achieved target glucose values more frequently while using the ACCU-CHEK Aviva Expert system. Approximately 90% of patients reported simplified bolus calculation and more confidence after using the ACCU-CHEK Aviva Expert system. There was a highly significant association between patient's assessment regarding frequency of reaching target blood glucose values and perceived simplified bolus calculation and also between reliability of bolus calculation and frequency of reaching target blood glucose values. A total of 96.7% of health care professionals have agreed that poorly controlled patients on MDI therapy would benefit the most from utilization of the ACCU-CHEK Aviva Expert system. Investment versus benefit ratio was estimated as balanced.

Conclusion:
This survey shows that utilization of the bolus calculator feature of the ACCU-CHEK Aviva Expert system can be beneficial for patients on MDI therapy, giving them more confidence and reliability and therefore helping them to achieve individual therapeutic goals.

Validation and Implementation of Low-Cost Dynamic Insulin Sensitivity Tests

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Background:
Insulin sensitivity (IS) tests can provide important information for type 2 diabetes risk assessment and investigations of metabolism or prediabetes. Our group previously presented the dynamic insulin sensitivity and secretion test (DISST) and the real-time quick dynamic insulin sensitivity and secretion test (DISTq) as low-cost, low-burden, and accurate alternatives to established tests. The DISST provides concurrent IS and endogenous insulin secretion metrics, the DISTq does not require insulin or C-peptide assays for IS identification but can return an immediate result.

This study validates the DISST and DISTq in comparison with the euglycemic hyperinsulinemic clamp (EHC).

Method:
Fifty participants [10 with body mass index (BMI) > 30; 10 with BMI > 25 and < 30; and 5 with BMI < 25 of each gender] underwent the EHC and DISST. The DISST protocol requires five samples from a 30 min protocol similar to the insulin-modified intravenous glucose tolerance test. Data from the DISST protocol was sufficient to identify IS using both the DISST and DISTq parameter identification methods and endogenous insulin secretion from the DISST.

Result:
DISST and DISTq IS values correlated well to the EHC ($R = 0.81$ and $R = 0.76$, respectively) and each other ($R = 0.84$). endogenous insulin secretion values obtained during the DISST showed clinically relevant distinctions between participants and clearly differentiated the beta-cell function of impaired glucose tolerant participants who had the same EHC IS. Participant acceptance of the protocol was high with very minor reported adverse effects.

Conclusion:
Both DISST and DISTq correlated well against the EHC compared with most established IS tests. The DISST can better differentiate patients, as it provides endogenous insulin secretion metrics that the EHC does not. A computer program makes uptake and use of the model-based DISST and DISTq tests straightforward for clinicians and researchers.

Estimation of Hypoglycemic Risks: Foundation for a Decision Support Algorithm

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Background:
A graph ("control grid") of median glucose versus glycemic variability in the low range may be effective in understanding a patient's risk of hypoglycemia and hyperglycemia. Also, it may serve as a framework to guide treatment actions that must balance these risks. This analysis describes the development of the control grid and its potential application.

Methods:
A model of the rate of hypoglycemia episodes as a function of median glucose and low-range variability (median minus 10th percentile) was developed using 20 days of masked continuous glucose monitoring (CGM) data from 66 people ("training set") with type 1 and type 2 diabetes treated with insulin. The model was then evaluated with a set of masked CGM data from 36 additional people ("test set"). An episode of hypoglycemia was defined as consecutive glucose values below 60 mg/dl for 30 min, 50 mg/dl for 20 min, or 40 mg/dl for 10 min.

Results:
The training set data suggested an exponential model, with fit:

$$\text{HypoRate} = 250\exp[0.06 \times (\text{LowRange Variability}) - 0.05 \times (\text{Median})]$$

When evaluated against the test set, the model performed well in predicting rates of hypoglycemia ($R^2 = 0.80$).

Conclusions:
The combination of median glucose and variability in the low range indicates a potentially useful model for estimating risks of hypoglycemia events and excessive glucose exposure. Selection of a target median glucose (for example, 154 mg/dl = 7.0% hemoglobin A1c) and an acceptable rate of hypoglycemia (for example, two episodes per month) creates three major "zones" of glucose control: A = above hypoglycemia risk line, below median target; B = above hypoglycemia risk line, above median target; and C = below hypoglycemia risk line. These zones may have utility in automatically guiding patient intervention for safely managing glycemia.

Human Pilot Study of the Fluorescence Affinity Sensor for Continuous Glucose Monitoring in Patients with Diabetes

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Background:
A pilot study in type 1 and type 2 diabetes subjects was performed to assess performance, safety, and comfort level of the fluorescence affinity sensor (FAS)—a minimally invasive device—for continuous glucose monitoring in subcutaneous tissue.

Methods:
A first-generation FAS device was subcutaneously implanted in the abdomen in 12 subjects with diabetes, and its acute performance to excursions in blood sugar was monitored over 4 h. After a warm-up time of 1 h, subjects with fasting blood glucose levels of less than 200 mg/dl received a glucose bolus of 75 g/liter dextrose by oral administration. Capillary blood glucose samples were obtained from the fingertip. The FAS data were retrospectively evaluated by linear least squares regression analysis and by error grid method. Comfort levels during insertion, operation, and sensor removal were scored by the subjects.

Results:
After retrospective calibration of 17 sensors tested in 12 subjects, error grid analysis showed 98% of the paired values in zones A and B, and 1% of the data pairs fell in the clinically unacceptable zones C and D, respectively. The mean absolute relative error between sensor signal and capillary blood glucose was 9.8% [standard deviation (SD) = 6.4%], and the average correlation coefficient (R) was 0.82 (SD = 0.26). Average "warm-up" time for the FAS readings to correlate with glucose readings was approximately 1 h. Pain levels during insertion, operation, and removal were very acceptable.

Conclusions:
The FAS performance achieved in this pilot study demonstrates feasibility of the fluorescence affinity technology to determine blood sugar excursions accurately and safely under acute dynamic conditions in humans with type 1 and type 2 diabetes. The short warm-up of approximately 1 h is of advantage. Further studies are warranted to validate FAS performance under chronic *in vivo* conditions.

Measuring Glucose Calibration Changes during Foreign Body Reaction Manipulation with Dexamethasone-Infused Microdialysis Probes

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Background:
A common problem with all implanted glucose sensors is overcoming the foreign body reaction (FBR) consequences to the long-term accuracy and stability of the device. Previous work with microdialysis sampling coupled with dexamethasone infusion showed differences in glucose concentrations collected or a possible change in calibration. In this work, we present the use of the *in vivo* microdialysis sampling calibration technique called zero net flux (ZNF) to calibrate the dialysis probe during dexamethasone infusions to modulate the FBR.

Methods:
Microdialysis probes (CMA/20, polyethersulfone membrane, 100 kDa molecular weight cutoff with 10 mm length) were used for all experiments. A colorimetric method (510 nm) based on glucose oxidase was used to measure glucose concentrations. *In vitro* ZNF experiments were performed by infusing 0, 2.5, 4, 5.5, and 7 mM glucose concentrations through the probe immersed in a 4 mM glucose solution. A plot of the difference between the inlet and outlet concentrations versus the inlet concentrations is used to get the point of ZNF. The slope of this line is also the dialysis probe calibration.

Microdialysis probes were implanted into the dorsal subcutaneous tissue of male Sprague Dawley rats (275–325 g). These probes were infused with 200 μg/ml of dexamethasone-21-phosphate. Controls versus dexamethasone-treated animals were compared at 0, 3, 5, and 7 days postimplantation for differences in calibration.

Result:
Using the *in vitro* ZNF method at 3 μl/min, microdialysis probe calibration was found to be approximately 50% and had a 95% accuracy measuring glucose concentration outside of the probe.

Conclusion:
The *in vitro* ZNF experiment demonstrates that the ZNF technique can potentially be used *in vivo* to calibrate the probe and measure tissue glucose levels.

Lens Autofluorescence as an Indicator of Diabetes

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Background:
The scientific literature has shown that blue-green lens autofluorescence increases with age. This literature also indicates that people with diabetes have greater lens autofluorescence compared with that seen in age-matched people without diabetes. Therefore, measurement of lens autofluorescence may be a useful means to establish whether an individual may have diabetes. If a person is found to have an elevated lens autofluorescence and further testing shows that they have diabetes, this individual may start appropriate therapy earlier than if they had not been tested. Initiating proper therapy earlier may lead to a diminishment in the costly and painful complications of the disease.

Method:
A prototype instrument to measure blue-green lens fluorescence has been developed, and an initial study was performed to show that persons with diabetes (PWDs) have an elevated lens autofluorescence compared with persons without diabetes. A total of 40 PWDs and 61 individuals without diabetes were tested and the data analyzed to measure the sensitivity and specificity of lens autofluorescence as an indicator of diabetes.

Results:
Testing and data analysis yielded 86% sensitivity and 85% specificity for determining whether an individual did or did not have diabetes. This data compares very well with other methods, e.g., fasting plasma glucose sensitivity/specificity = 64%/77% and hemoglobin A1c sensitivity/specificity = 65%/98% for screening for diabetes.

Conclusion:
These initial test results will be further expanded and assessed to determine the effectiveness of measuring lens autofluorescence as a means of screening for diabetes. Having a simple, noninvasive diabetes screening test will ideally lead to the earlier diagnosis and treatment of the disease, which will, in turn, hopefully lessen the pain and cost of these complications. In addition, such a system will add the ophthalmologist and optometrist to the other health care practitioners concerned with identifying and treating individuals with diabetes. Many more individuals have an annual eye exam than have a blood test for diabetes.

Transforming Health Care Delivery: The Diabetes Patient as an Overseen Resource in Diagnostic Testing

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Objective:
The objective of the study was to test whether patients are capable of carrying out complicated and advanced tests by themselves in their home, thereby liberating hospital resources for other uses. The test chosen was examination for cardiovascular autonomic neuropathy (CAN) using a portable diagnostic device, Vagus. Another objective was to investigate time and financial expenditure and effects on organization and structure of health care delivery to diabetes patients.

Method:
Hospital investigations for CAN were via instruction of the patient in general practice transferred to be carried out in the home of the patient. Ten diabetes patients (6 males and 4 females) were selected and introduced to the device by their general practitioner or nurse and assigned to self-examine in the home morning and evening for 3 days. Time and financial expenditure was recorded. Effects on health care structure and organization were described.

Result:
All patients were able to carry out the complicated hospital tests in their homes with no external assistance at any time. Accumulated costs of performing the test in the home of the patient was considerably lower as compared with the hospital setting. All hospital efforts ceased. General practices spent a relatively smaller number of (more inexpensive) hours on instructing the patient. The patients were performing the tests themselves at no cost. Figures for expenditure will be presented.

Conclusion:
Patients with diabetes remain overlooked as contributors to health care delivery (to themselves). General practices were able to implement testing in the patients' home at a very limited cost, and patients were able to perform a traditionally hospital-based investigation by themselves with no further assistance. Patient-centered care enhanced individual empowerment overall.

Evaluation of the Safety and Efficacy of Two Oral Insulin Formulations in Healthy Volunteers

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Objective:
Orally administered drugs face challenges all along the gastrointestinal tract, which affects their bioavailability and effectiveness. Successful management of the natural impediments to the uptake of oral insulin promises to revolutionize diabetes care through allowance for early intervention and increased glycemic control. To this end, Oramed Pharmaceuticals Ltd., developer of oral drug delivery solutions, tested the safety and efficacy of its oral insulin (ORMD-0801) preparation in attempt to monitor and further optimize its pharmacodynamics.

Method:
In a single-blind, two-period study, two ORMD-0801 formulations, differing only in their emulsifier content, were administered to 10 fasting, healthy volunteers on two independent visits. Subjects were monitored for 5 h thereafter for safety evaluations as well as determination of blood insulin, glucose, and C-peptide levels.

Result:
No adverse events were reported throughout the study. Tested oral insulin preparations yielded similar plasma insulin responses, which peaked (C_{max}: 8.4–11.3 mU/ml) at approximately 1.5 h post-treatment. In parallel, while overall C-peptide behavior was identical, reaching a minimum at ~5 h post-treatment, the mean C_{min} value registered after treatment with formulation F130 was 27% lower than that which followed formulation F130GT treatment ($p = .04$). Similar blood glucose concentration profiles were recorded following either treatment; however, formulation F130 induced significantly greater glucose reductions when compared with F130GT, with a two-fold increase in the mean area above the curve.

Conclusion:
The emulsifying agent content and ratio of the tested formulations impacted glucose, insulin, and C-peptide concentrations, where formulation F130 was more effective than formulation F130GT. Integration of these findings toward further refinement of oral insulin preparations will upgrade the clinical capacities and therapeutic potential of ORMD-0801.

Overnight Automated Closed-Loop Insulin Delivery Initiated in the Early or Late Evening in Young People with Type 1 Diabetes

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Background:
We evaluated overnight automated closed loop (CL) and the influence of timing of CL initiation in young people with type 1 diabetes mellitus (T1DM).

Method:
A randomized crossover study compared overnight glucose control achieved by automated CL started at the time of an evening meal or at bedtime. Eight young people with T1DM on insulin pump treatment (male, 4; age, 14.3 ± 1.7 years; body mass index, 20.8 ± 2.8 kg/m^2; duration of diabetes, 7.9 ± 2.8 years; total daily insulin dose, 0.9 ± 0.2 U/kg/day; hemoglobin A1c, 8.2 ± 1.3%; mean ± standard deviation) were studied on two occasions at a clinical research facility. Standardized self-selected evening meal (70 ± 11 g carbohydrates) and snack (22 ± 4 g carbohydrates) accompanied by prandial insulin boluses were given at 18:00 at 21:00, respectively. In random order, automated CL started at 18:00 or 21:00 and ran until 08:00 the next day. Basal insulin delivery was automatically adjusted by a model predictive control algorithm based on real-time continuous glucose monitor readings. Plasma glucose was measured every 15 min to assess CL performance.

Result:
Plasma glucose levels were within the target range of 3.9–8.0 mmol/liter for 82% (59%, 98%) of time when CL started at 18:00 and 64% (48%,70%) when started at 21:00 [median (interquartile range), p = .04, Wilcoxon test]. Time spent within 3.9–10 mmol/liter [87% (77%, 100%) versus 81% (74%, 88%), p = not significant (NS)], above 10 mmol/liter [8% (0%, 17%) versus 13% (3%, 23%), p = NS], or below 3.9 mmol/liter [0% (0%, 7%) versus 0% (0%, 8%), p = NS] did not differ between the two occasions. Mean overnight glucose (6.7 ± 0.8 versus 7.6 ± 0.7 mmol/liter) was also similar. Insulin infusion rates were higher when CL started at 21:00 (0.9 ± 0.4 versus 0.8 ± 0.4 U/h, p = .01, paired t-test).

Conclusion:
Automated CL delivery can be applied safely to control glucose levels overnight in young people with T1DM. Tighter glucose levels may be achieved with an earlier time of CL initiation.

Long-Term Comparison of the Injection Force of the Disposable Insulin Pens SoloSTAR, FlexPen, and KwikPen

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Objective:
For patients with limited hand dexterity, e.g., elderly people or young children, a lower injection force may facilitate insulin therapy. Three of the leading disposable insulin pens for injecting insulin analogs are SoloSTAR (SS; insulin glargine), FlexPen (FP; insulin detemir), and KwikPen (KP; insulin lispro). The aim of this study was to monitor the injection force of these three pens over a 16-month period and to confirm findings from a previous injection force study that did not have a time component.

Method:
Twenty pens of each device were purchased from a local pharmacy at 4-month intervals from July 2009 to November 2010. Measurements were performed five separate times over this 16-month period (July, November, March, July, and November). After priming, injection force was measured at the maximum dose level (60 U for FP and KP and 80 U for SS) and at a constant volume flow speed of 6 U/s using a Zwick tensile meter. The SS and KP were tested with BD Micro-Fine (31 G 0.25 × 5 mm) needles and the FP with NovoFine (31 G 0.25 × 6 mm) needles.

Results:
Mean plateau injection force for the SS, FP, and KP ranged from 6.3 to 8.0, 9.6 to 10.5, and 7.1 to 8.6 N, respectively. Mean maximum injection force ranged from 8.1 to 10.3, 12.2 to 13.6, and 8.9 to 13.2 N, respectively. Mean plateau and maximum injection forces were consistently greater for the FP than for the SS or KP. Differences between the FP and SS were statistically significant.

Conclusion:
The injection force required to inject a maximum dose of insulin was consistently less with the SS and KP than with the FP.

Improving Overnight Safety Monitoring in Patients with Type 1 Diabetes: A Method to Detect Failures of the Glucose-Sensor–Insulin-Pump System

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Objective:
New sensors for real-time continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (CSII) pumps have opened new scenarios for type 1 diabetes treatment. However, possible failures of either CGM sensors or CSII pumps expose diabetes patients to potentially severe risks, especially overnight. In this contribution, we present a method to detect in real time possible overnight failures of the sensor–pump system by simultaneously using CGM and CSII pump data.

Method:
The failure-detection method consists of four main steps: identification of a model, personalized on the patient, describing the relationship between glucose measured by CGM and insulin injected by the CSII pump; use of a model-based Kalman filter estimator to obtain a real-time statistical prediction of the future glucose level; comparison of glucose predictions and future CGM samples; and generation of a failure alert if CGM samples are not consistent with the predicted values.

Result:
The method was tested on a Monte Carlo simulation created by using the University of Virginia/Padova simulator. Three types of failures have been simulated: spikes, loss of sensitivity of glucose sensors, and failures in insulin delivery by the pump. Results show that the method is able to correctly generate alerts for all kind of failures, with a very limited number of false negatives and a number of false positives lower than 10%.

Conclusion:
The proposed failure-detection method performed satisfactorily on simulated data. This first preliminary study evidenced, however, how CGM failures seem more easily detectable than CSII pump failures, because of the delay in subcutaneous insulin absorption and action.

A Self-Powered Glucose Sensor Suitable for Fully Implanted Operation

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Objective:
Fully implanted continuous glucose sensors offer possible advantages in convenience and accuracy compared with transcutaneous sensors, but their development has been thwarted by several factors, notably, the large size required for a long-term power source. A self-powered glucose sensor (SPS), with no attached battery, can reduce size substantially. However, SPSs reported to date suffer from both nonlinear response and poor stability. Our objective was to fashion a SPS with a robust and linear response for use in a fully implanted glucose sensor.

Method:
A SPS was constructed from (1) a 0.1 mm^2 anode based on an osmium-based redox polymer cross-linked to either glucose oxidase or flavin adenine dinucleotide-dependent glucose dehydrogenase, (2) a 0.3 mm^2 platinized carbon cathode, and (3) an intervening resistor (approximately 5 MΩ). Both electrodes were overlaid with a poly(vinylpyridine)-based biocompatible membrane.

Result:
When the SPS was tested *in vitro* (glucose from 20–500 mg/dl), it spontaneously produced nA-range currents without an attached power source. In fact, the performance of the SPS and FreeStyle Navigator were identical under most conditions, with similar sensitivity (0.6 nA/mM), response time (2 min), stability (decay less than 0.1%/h), and response to electrochemical interferents. The SPS exhibited a linear response at oxygen concentrations as low as 0.5%.

In addition, 20 human subjects wore both FreeStyle Navigator (n = 39) and a transcutaneous self-powered sensor (n = 39) simultaneously for 5 days. Results were comparable both for Clark grid (in zone A SPS = 84.3% and Navigator = 85.8%) and for mean absolute relative difference (SPS = 12.1%, Navigator = 10.8%).

Conclusion:
A compact SPS, constructed from the combination of (1) a directly mediated, low potential glucose oxidizing anode and (2) a suitable O_2-reducing cathode is a promising candidate for fully implanted operation.

Accurate Glycemic Control Using a Stochastic Target (STAR) Framework

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Background:
Accurate glycemic control (AGC) has proven difficult due to excessive hypoglycemia risk. Stochastic TARgeted (STAR) glycemic control forecasts changes in insulin sensitivity to calculate a range of glycemic outcomes for an insulin intervention, creating a risk framework to increase safety and performance.

We aim to create a new protocol with improved safety from hypoglycemia and reduced clinical burden using virtual trials, prior to clinical pilot trials.

Method:
Clinically validated virtual trials were run on 371 virtual patients (39,841 h) from the Systolic Blood Pressure Intervention Trial (SPRINT) AGC cohort. Model forecasts target control to a clinically specified glycemic range (80 to 145 mg/dl). Robustness to measurement error limit insulin increases to +2 U/h (max 6 U/h bolus and 3 U/h infusion) and nutrition changes to ±30% (between 30% and 100% of American College of Chest Physicians goal) per intervention. Measurement intervals of 2–3 h were used when predicted 5th and/or 95th percentile blood glucose (BG) were within target range. Performance was compared with clinical SPRINT and measured as time within glycemic bands and safety assessed by patients with severe (BG < 40 mg/dl) and moderate (BG < 72 mg/dl) hypoglycemia.

Results:
Severe hypoglycemia was reduced from 14 patients (clinical SPRINT data) to 5 with a simultaneous 23% workload reduction from 26,646 BG measurements to 20,591. Moderate hypoglycemia was reduced from 2.89% to 1.33%. Whole-cohort percentage BG in 80–145 mg/dl was 90.6% (86.0% for SPRINT), and enteral nutrition was increased overall by 21% in median amount. Limiting measurement intervals to every 2 h (as in SPRINT) reduced severe hypoglycemia to two patients, reduced moderate hypoglycemia to 0.99%, and increased percentage BG in 80–145 mg/dl to 91.5%.

Conclusions:
Safe AGC that also reduces clinical effort is achieved using stochastic forecasting of potential patient variation. Initial pilot clinical trials are successful and ongoing.

Glycemic Control Protocol Comparison Using Virtual Trials

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Background:
Several accurate glycemic control (AGC) protocols for critical care patients exist, but making comparisons has proven difficult. This study uses clinically validated virtual patient methods to compare safety and performance for several published AGC protocols.

Method:
Clinically validated virtual trials were run on 371 patients (39,481 h, 26,646 measurements) created from the Systolic Blood Pressure Intervention Trial (SPRINT) AGC cohort. For protocols that do not modulate feed rates, enteral nutrition was held at 100% of American College of Chest Physicians goal (25 kcal/kg/day) when the patients were clinically fed, and parenteral nutrition rates were matched to clinical data. Performance was defined as percentage blood glucose (BG) within glycemic bands and BG measurement frequency. Safety was defined as the incidence of severe (number of patients with BG < 40 mg/dl) and moderate (percentage BG < 72 mg/dl) hypoglycemia. Clinical data from SPRINT was also compared.

Results:
Clinical SPRINT performance data matched resimulated SPRINT with 86% versus 86% BG in 80–145 mg/dl, 2.00% versus 2.07% BG above 180 mg/dl, and 7.83% versus 7.29% BG below 72 mg/dl, with 14 measurements (over 8 patients) of BG < 40 mg/dl. Yale results were 83.5%, 3.20%, and 5.18%, with 6 severe hypoglycemic patients, using 37,961 measurements (23.0/day). Glucontrol had 75.2%, 3.70%, and 9.45%; 52 cases; and 26,199 measurements (15.8/day). Braithwaite had 84.2%, 3.00%, and 4.22%; 19 cases; and 24,396 measurements (14.8/day). The Stochastic targeted (STAR) model-based method had 90.6%, 1.67%, and 1.33%; 5 cases; and 20,591 measurements (12.3/day).

Conclusions:
Virtual trials provided an effective comparison across protocols with different target bands/values and different clinical cohorts. The model-based STAR protocol provided the best management of patient variability, yielding the best performance and safety.

Assessment of Subclinical Diabetic Autonomic Neuropathy in Outpatient Clinics Using a Point-of-Care Device: The DAN Study

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Objective:
Subclinical diabetic cardiovascular autonomic neuropathy (CAN) is as a surrogate marker of micro-angiopathic complications, and the presence of asymptomatic CAN may develop before other late complications. The aims of this study were to evaluate (1) the prevalence of subclinical autonomic neuropathy in a large cohort of diabetes patients and (2) the association between CAN and other risk markers.

Method:
The DAN Study is a Danish multicenter study focusing on diabetic autonomic neuropathy. Six hundred sixty-four patients, 378 type 1 and 286 type 2 diabetes patients, were tested for CAN during a period of 1 year. Patients were recruited and tested during normal visits to one of four university hospital outpatient clinics. Cardiovascular autonomic neuropathy was defined as at least two abnormal cardiovascular reflex tests (valsalva, response to standing, and deep breathing). In order to describe possible associations, multivariate analysis with CAN as the dependent variable was performed.

Results:
Besides heart rate and age multiple ordinal logistic regression analyses revealed significant associations between CAN and other risk factors in the two populations. In type 1 diabetes patients, CAN was associated with microalbuminuria ($p = 0.015$), macroalbuminuria ($p = 0.005$), and proliferative retinopathy ($p = 0.021$). Among type 2 diabetes patients, CAN was associated with high pulse pressure ($p < 0.001$) and body mass index above 35 kg/m^2 ($p = 0.025$).

Conclusion:
Our results indicate that different pathophysiological mechanisms may account for the development of CAN in type 1 and type 2 diabetes. Cardiovascular autonomic neuropathy remains an underdiagnosed and undertreated diabetic late complication, considerably influencing the quality of life and the somatic health of patients with diabetes. Patients may therefore suffer this condition unnoticed, as they have not been diagnosed.

A Technological and Clinical Feasibility Study: Testing for Diabetic Autonomic Neuropathy in General Practice and in a Home Setting

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Objective:
Diabetic cardiovascular autonomic neuropathy (CAN) is associated with the development of a number of late complications in both type 1 and type 2 diabetes patients. Testing for CAN is scarcely available in hospitals and even less so in private practices, and nonexistent in private homes, despite described benefits of diagnosing CAN early. The aims of this study were to evaluate (1) the clinical robustness of CAN testing outside of hospitals and (2) the feasibility of CAN testing outside of hospitals.

Method:
Ten diabetes patients (6 males and 4 females) were recruited from their general practitioner. Participants underwent in-practice testing for CAN before and after home monitoring using a handheld electrocardiogram device (Vagus, Medicus Engineering Ltd.). For 3 consecutive days, self-monitoring was performed at home [resting electrocardiogram (5 min), expiration:inspiration ratio, 30:15 ratio, Valsalva]. All data were stored electronically in the device for subsequent analysis. The intraindividual and interindividual reproducibility was determined by coefficient of variation (CV) and the reproducibility coefficient (RC).

Result:
All patients were capable of performing home testing, and data were satisfactory. The correlation between self-monitoring and in-practice testing for CAN were high in all cardiovascular reflex tests. Subclinical autonomic dysfunction was present in 3 out of 10 patients. Reproducibility was high in all measures, with RC ranging from 87–96% and CV ranging from 2–4%.

Conclusion:
This study is the first to demonstrate that patient self-monitoring of cardiac autonomic function at home is feasible in a group of diabetes patients. The correlation between repeated measurements in hospital and between self-monitoring and hospital testing were high in all cardiovascular reflex tests.

System Accuracy Evaluation of Three Blood Glucose Monitoring Systems According to European International Organization for Standardization Standard 15197

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Objective:
The aim of this study was to verify whether systems for self-monitoring of blood glucose (SMBG) comply with accuracy requirements indicated by the European International Organization for Standardization (EN ISO) standard 15197. This standard states minimum accuracy limits, which must be met by a SMBG system in order to obtain a European Conformity (CE) label. However, more restrictive limits are currently being discussed.

Method:
In this study, three CE-labeled SMBG systems (ACCU-CHEK Aviva, ACCU-CHEK Mobile, and ACCU-CHEK Performa) were evaluated for system accuracy according to EN ISO 15197. Two devices of each system were used to perform SMBG measurements on 100 capillary blood samples adhering to a defined distribution of glucose concentrations. Reference measurements were performed with the hexokinase method, the manufacturer's measurement method.

Results:
Reference glucose concentrations of the test samples ranged from ~20 to ~600 mg/dl. The current EN ISO 15197 system accuracy requirements were met by all systems. The EN ISO 15197 provides additional, more restrictive limits, which, however, are not relevant for CE labeling: ±10 mg/dl for concentrations < 75 mg/dl and ±15% for concentrations ≥ 75 mg/dl. The percentage of results within these more restrictive limits were 97.5% for the ACCU-CHEK Performa system, 99% for the ACCU-CHEK Aviva system, and 99.5% for the ACCU-CHEK Mobile system.

Conclusion:
In a SMBG system accuracy evaluation, the minimum acceptable accuracy limits according to the standard EN ISO 15197 were met by all three tested systems. Even with the more restrictive limits mentioned here, all systems comply with the requirements. Accurate SMBG results can enable diabetes patients to make appropriate therapeutic decisions. However, minimum limits have to be chosen with constraints in technical implementation in mind.

Essential Steps toward a Truly Noninvasive Glucose Monitor for Home Use

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Background:
Typically, noninvasive (NI) glucose monitoring utilizes a single method for tracking physiological phenomena correlated with blood glucose. Due to the indirect nature of measurement and lack of glucose specificity, NI methods usually suffer from impaired accuracy and are particularly susceptible to interferences introduced by users' impact and varied environmental conditions. Furthermore, NI methods require calibration against a reference (invasive) device, administering additional vulnerability because of the limited accuracy of the reference device. Consequently, insusceptibility to these interferences determines reliability and accuracy of NI glucose monitors.

Method:
A multitechnology approach can be utilized to decrease errors derived from each technology separately, thereby increasing the integrated glucose reading accuracy, compared with the accuracy achieved by a single technology.

Measurement simplicity and minimal user involvement may reduce users' impact. Multisensor input promotes identification of different environmental conditions; algorithmic solution accounts for these data in the glucose result calculation. A combination of these methods was evaluated in clinical trials, divided into three groups: clinic, home simulation (HS), and home. Measurements in each group were performed by a proficient medical team and the subject at clinic/home and clinic environment, correspondingly.

Result:
Clarke error grid analysis for all groups shows over 96% of the points in the clinically accepted A+B zones. Mean absolute relative difference values are 21.4%, 25.3%, and 25.6% for the clinic, home and HS groups, respectively.

Conclusion:
Results demonstrate validity of a multisensor and multitechnology approach. Similar results in home and HS groups indicate insusceptibility to environmental conditions. However, the suggested approach is still partially limited by the users' impact, implied by slight degradation between home and clinic arms. This limitation might be reduced by algorithmic enhancement using the multisensor data.

An Artificial Intelligence Algorithm for Automatic Assessment of Physical Activity Intensity and Metabolic Type Using Multiaxial Accelerometry and Heart Rate

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Background:
We aim to automatically recognize periods with relevant physical activity (PA) based on accelerometry and heart rate measurements, assessing intensity range (sedentary/moderate/vigorous) and which metabolic mechanism (aerobic/mixed/anaerobic) predominates.

Method:
Two experiments were conducted: one in free-living conditions (~150 h, 72 sessions) and another consisting of specialized circuit training in a gymnasium (~30 h, 20 sessions). Sixteen volunteers wore an ActiTrainer multiaxial accelerometer on their hip and a Polar pulsimeter to record PA. Data were manually grouped into three standard levels (65.5% sedentary/17.6% moderate/16.9% vigorous), according to their metabolic equivalent intensity. Metabolic-type information was also registered (~17 h, 25 sessions). To extract meaningful PA patterns, we combined several classical artificial intelligence methods; time-domain statistics were computed to characterize signals, and most relevant features were selected by genetic algorithms to reduce data-space dimensionality and optimize recognition performance. Subsequently, a multilayer perceptron was trained for classification, and hidden Markov model filtering was applied to exploit temporal redundancy in consecutive intervals. Performance was evaluated by 10-fold cross validations.

Result:
We obtained 88.83 ± 1.00% accuracy for PA classification (rest/moderate/vigorous ranges) and 88.74 ± 8.30% for metabolic-type (aerobic/mixed/anaerobic) distinction. Misclassifications were brief and occurred mainly during transients.

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García-García cont. ⟶

Conclusion:
Our approach achieves an accurate PA classification, outperforming similar techniques in literature based exclusively on accelerometry since heart rate proved to supply valuable physiological information about intensity and fuel selection during exercise. Classification errors arise mostly as temporary disparities, which restricts their practical impact in realistic scenarios. Therefore, we consider our proposal suitable for ambulatory 24-h-based PA monitoring, e.g., to assess subjects' adherence to exercise programs. Furthermore, the automated distinction of metabolic mechanisms allows us to study the effects of different exercise types on glycemia and other diabetes indicators.

Improved Accuracy Using a Multisensor Continuous Glucose Monitoring System

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Objective:
Current continuous glucose monitoring systems involve the use of a single sensor that must be calibrated against a reference value at regular intervals. System accuracy is dependent upon the output of this individual sensor and may be affected by transient periods of sensor instability. Accuracy of the sensor system can be improved by comparing an array of redundant sensors within the same system. Data from a recent Enlite pivotal trial was analyzed to show that the system accuracy can be improved when data from two sensors worn by the same patient is combined into a single output.

Method:
Data were obtained from the Enlite pivotal trial where subjects wore two sensors (abdomen and back) at a time for two consecutive wears. The data were postprocessed in the following methods: (1) obtaining sensor glucose values separately for each sensor, (2) averaging the output from the two sensors, and (3) modifying the system output using a signal switching or weighing scheme based on individual sensor deviations that can be detected using diagnostic algorithms.

Results:
The overall YSI mean absolute deviation percentage for the three methods was calculated for the data set. A total of 78 pairs of sensors were analyzed.

Conclusion:
Two prototype algorithms comprising two sensor components were developed. An aggregate improvement in sensory accuracy compared with individual sensors was demonstrated. Algorithms utilizing multiple sensors may provide more reliable and accurate output compared with similar algorithms relying on a single sensor. Redundant sensing may be an important step toward achieving a nonadjunctive continuous glucose monitoring system.

Prototype Continuous Glucose Monitoring System from Medtronic

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Background:
The following describes improvements made in a prototype next-generation continuous glucose monitoring (CGM) system from Medtronic. The goal was to design a more durable sensor system with improved day 1 accuracy through better sensor startup, increased *in vivo* linearity (dynamic range), and a system where all performance aspects conform to a model of sensor behavior that is derived from *in vitro* testing. In addition, preliminary data from two potential candidates were also evaluated.

Method:
Improvement in sensor performance was achieved through chemistry and mechanical changes as well as upgrades to the device algorithm.

The chemistry was optimized to hydrate more quickly after insertion (day 1 accuracy) while maintaining its integrity. Additionally, sensor fabrication processes were refined to decrease sensor-to-sensor variability to establish a consistent model for *in vitro* behavior (durability).

Mechanical enhancements included a more user-friendly insertion device and a more effective adhesive tape to increase comfort and reduce pullouts. The device algorithm enhanced overall signal quality with an optimized noise-filtering scheme. Additionally, the calibration scheme of the device was modified to account for interstitial delay, high glycemic swings, as well as sensor *in vivo* linearity (dynamic range).

Results:
Preliminary results from a feasibility trial where two configurations containing various aspects of the design enhancements will be presented. A total of 22 subjects (all with diabetes) were tested. All data were run at minimum calibrations required by the device.

Conclusion:
Modifications to the next-generation CGM system have shown potential for improved sensor performance in day 1 accuracy, dynamic range, and durability.

Performance of the HypoMon: Transition from At-Hospital to the Home Environment

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Objective:
Nocturnal hypoglycemia is a feared complication experienced by people with type 1 diabetes mellitus (T1DM). The HypoMon (AIMEDICS P/L) is a real-time nocturnal hypoglycemia alarm that detects changes within certain physiological parameters resulting from the patient's own response to hypoglycemia. The goal of this study was to demonstrate that the performance of the HypoMon as a nocturnal hypoglycemia monitor was maintained throughout the transition from the at-hospital to the home environment.

Method:
A total of 85 T1DM patients aged between 10 and 25 years participated in this study, with 85 at-hospital night sessions and 233 at-home night sessions. Patients wore the HypoMon continuously throughout the night, with a single hypoglycemia alarm per night. Their blood glucose levels were periodically measured; the YSI glucose analyzer was used for the at-hospital group, and a CGMS device with a glucometer was used at home. All participants were monitored and observed for the natural occurrence of nocturnal hypoglycemia. The performance analysis for the at-hospital and at-home group included comparing HypoMon alarm times with confirmed hypoglycemia events.

Results:
Analysis of the at-home group (n = 233) in comparison with the at-hospital group (n = 85) demonstrated no significant reduction in the sensitivity/specificity markers. The at-home group produced a sensitivity and specificity of 70% and 74%, respectively. The at-hospital produced sensitivity/specificity of 75% and 88%, respectively. Cross-sectional analysis showed no significant difference in sensitivity between the groups for the detection of nocturnal hypoglycemia, with p = 0.301. Reduction in performance was attributed to home environmental factors and uncontrolled device use.

Conclusion:
Transitioning from the at-hospital clinical setting to the real-life home environment, the HypoMon maintained its efficacy in detecting nocturnal hypoglycemia, a step closer toward a viable device.

A New Continuous Glucose Monitoring Trend Metric: The CGM Trend Compass

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Background:
In response to a call from the Food and Drug Administration for a new trend accuracy metric, the CGM Trend Compass is proposed for the burgeoning field of continuous glucose sensing in the hospital to compare sensor glucose (SG) to reference blood glucose (BG) and their rates of change (ROCs).

Method:
The CGM Trend Compass analysis used polar coordinates of radius (BG) and angle [arctan(SG ROC/BG ROC) + 45 degrees]. Data points were segregated by magnitude of relative change [|BG ROC – SG ROC|]:< 12, 12–30, or >30 mg/dl/h. A grid was applied to define zones of accuracy and clinical relevance. Green zone is the region that SG and BG are trending in the same direction. Yellow zone was SG and BG trending oppositely, which could represent a false alert at <90 or >160 mg/dl. Red zone represents a missed alert at <90 mg/dl.

Two comparative data sets, correlated and uncorrelated, were used to verify the concept of the Trend Compass. The data were from an intensive care unit clinical trial of a new Medtronic hospital glucose sensor and compared with hourly reference BG (YSI 2300). The ROC was calculated hourly for both measurements.

Result:
The correlated data had an overall trend accuracy of 90%, no points in red zone (0%), and 3% in yellow zone. The uncorrelated data resulted in a trend accuracy of 62%, 3% in red zone, and 12% in yellow zone.

Conclusion:
The CGM Trend Compass was able to discern correlated data from uncorrelated data. Further refinement of the metric with respect to the accuracy grid will be evaluated in the future.

Evaluation of an Automatic High/Low Pattern Recognition Tool: The OneTouch Verio Pro Blood Glucose Meter

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Background:
Blood glucose (BG) monitoring systems provide information about glucose control, but identifying BG patterns is challenging, The OneTouch Verio Pro meter containing a high–low pattern recognition tool provides insights to patients on their BG trends. A clinical study was conducted to evaluate the pattern tool. A subset of this data describing the performance of the pattern tool is presented here.

Method:
A 4-week, single-arm clinical study was conducted at three U.K. clinics. Participants were self-adjusting insulin patients with type 1 or type 2 diabetes (n = 101). Participants completed daily diaries with BG results, high–low pattern messages, and insulin dosing.

Result:
On average, individual participants received 4.5 [standard deviation (SD) 1.9] pattern messages per week, with 3.6 (SD 1.8) high patterns (premeal or fasting BG >130 mg/dl) and 0.89 (SD 1.3) low patterns (BG values <70 mg/dl). Ninety-seven percent of participants received ≥1 high pattern per week, and 46% received ≥1 low pattern per week. The number of high patterns was associated with higher baseline hemoglobin A1c (A1C; p = .0062) and fasting plasma glucose (FPG; $p \leq .001$), whereas number of low patterns was associated with lower baseline A1C (p = .0008) and FPG (p = .015).

Participants found high and low pattern messages clear and easy to understand (83% and 84%, respectively). Eighty-two percent found the frequency of low pattern messages were about right, 74% of participants clicked on the pattern message every time to see the extra details describing the pattern, and 89% who viewed these details found them somewhat or very useful.

Conclusion:
The OneTouch Verio Pro System includes a novel on-device high–low pattern tool that identifies BG patterns, highlighting potential opportunities for improving glycemic control. These results further validate this pattern tool and suggest its clinical value to patients.

Thermal Threshold as an Early Indicator of Diabetic Polyneuropathy

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Objective:
Distal polyneuropathy is a common complication in diabetes, and conduction velocity and electromyography are used to study it, but these only measure the function of the thick nervous fibers. It is believed that the damage of small fibers [studied with the thermal sensation threshold (TST)] is more prevalent and occurs earlier. We compared nervous conduction velocity (NCV) versus TST, with the objective of demonstrating which of the two occurs earlier as an indicator of neuropathic damage.

Method:
We used a sample of 70 type 2 diabetes patients without symptoms of neuropathy (31 women and 39 men, average age 54 years, and an evolution of 16 ± 28 months). Thermal sensation threshold was assessed on hands, dorsum, and soles of feet. Motor NCV was assessed in median and peroneal nerves, and sensory latencies and NCV were assessed in median, ulnar, and sural nerves.

Results:
Nervous conduction velocity showed two groups: normal (n = 57) and sensory or sensory–motor polyneuropathy (n = 13). In the TST study, we found 30 cases with abnormalities, while 40 were normal. So 43% of patients had abnormal TST, while only 19% showed alterations in NCV consistent with classic diabetic polyneuropathy. Alterations in TST tended to happen before and in younger patients compared with abnormalities in NCV (52 versus 61 years old).

Conclusions:
In our study, TST shows more sensibility than NCV in the early and subclinical diagnosis of diabetic neuropathy. In addition, we believe that abnormalities of TST occur in younger patients. Moreover, age (among others) is an important factor in the severity of neuropathic damage. We support TST's usefulness for an early intervention in asymptomatic diabetes and even in impaired glucose tolerance.

Accuracy of Continuous Glucose Monitoring Enhanced Online via a Deconvolution-Based Algorithm

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Background:
Continuous glucose monitoring (CGM) requires calibration every 24–48 h because accuracy deteriorates over time. Here we test whether CGM accuracy can be enhanced using an online deconvolution-based procedure that can be used in cascade with any CGM sensor, exploiting a population model of blood glucose (BG) to interstitial glucose (IG) kinetics and some available self-monitoring of blood glucose (SMBG) samples.

Method:
Twelve subjects with type 1 diabetes were studied for 1 week. Two DexCom SEVEN PLUS CGM sensors per patient were inserted. After initial calibration, the first sensor (REF) and the second sensor (TEST) were recalibrated every 12 and 48 h, respectively. Eight CGM segments of 36 h were extracted. The deconvolution-based online-enhancement algorithm was applied to TEST signals. An estimate of the BG signal from CGM was obtained via regularized deconvolution with a BG-to-IG kinetics model and regressed to SMBG. Regression parameters were applied to the CGM signals to obtain an enhanced (ENH) signal.

Results:
Mean [± standard deviation (SD)] root mean squared error (RMSE) between all available SMBG samples in the considered segment and CGM was 29.3 ± 13.4 and 66.3 ± 49.9 mg/dl for REF and TEST, respectively. The ENH segments, obtained from TEST segments, yielded a RMSE of 22.3 ± 4.9 mg/dl. Comparing ENH with TEST signals, a three-fold reduction of RMSE is achieved. Moreover, RMSE is lower for ENH than for REF signals, with REF sensors calibrated three times in the 36 h segments versus ENH sensors calibrated once.

Conclusion:
Calibration as suggested by manufacturers does not necessarily guarantee optimal sensor accuracy, even if performed rather frequently. The proposed deconvolution-based algorithm can be used to enhance CGM accuracy in real time.

Parsimonious Description of Glucose Variability Investigated by a Sparse Principal Component Analysis Approach

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Background:
Dozens of different indexes have been proposed to explain glucose variability and control. Redundancy is expected to be present among many of them. In this work, by using sparse principal component analysis (PCA), we investigate which indexes better capture the information on glucose variability.

Methods:
Thirty-six variability and control indexes, comprising mean- and standard deviation (SD)-based measurements (e.g., Mr, J indexes), control indexes (e.g., percentage on target), indexes based on the transformation of the glucose scale (e.g., low blood glucose, high blood glucose indexes), and indexes based on the dynamic risk (DR) concept (e.g., 95% confidence ellipse area), were evaluated on continuous glucose monitoring (CGM) signals collected within the DIAdvisor project (*www.diadvisor.eu*). Sparse PCA was then applied for computing their principal components (PCs), i.e., a linear combination of a limited number of indexes summarizing most of the information within them.

Results:
More than 90% of the total variance of the original 36 indexes can be explained by only five components by standard PCA. Sparse PCA allows an easy interpretation of the first two principal components. The first component comprises information about mean and SD, while the second summarizes indexes related to the first time derivative (e.g., the weighted center of derivatives distribution evaluated in the DR space).

Conclusion:
Many of the glucose variability indexes determined from CGM signals are correlated, and their relative usefulness in the interpretation of the glucose variability is often unclear. Starting from 36 indexes, PCA indicates that only five principal components are able to explain 90% of variability. Sparse PCA shows that indexes directly related to the first time derivative of the signal such as DR-based indexes are of crucial importance because they are complementary to mean and SD measures.

A Retrospective Comparison of a Computer-Guided Glucose Management System versus a Standard Insulin Algorithm in a Teaching Hospital

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Objective:
The goal of this analysis was to compare a standard insulin algorithm for continuous intravenous (IV) insulin infusion to a computer-guided glucose management system to determine which method leads to the most rapid achievement of target blood glucose levels with the least hypoglycemia.

Method:
The hospital's database identified 27 patients from seven intermediate care nursing units on continuous IV insulin infusions, rate adjusted by a standard insulin algorithm (group A) during a one-month period. During that month, IV insulin infusions based on a computer-guided glucose management system were used for 53 patients on three intensive care units (group B1) and 17 patients on two intermediate care units (group B2). Data were collected on initial finger stick blood sugar (FSBS), time to target of 140 mg/dl, FSBS after 4 h, number of FSBSs < 70 mg/dl, and number of FSBSs > 200 mg/dl.

Result:
Group A patients had a higher average initial FSBS (409.74 versus 282.17 mg/dl in group B1 and 203.95 mg/dl in group B2), an intermediate average time to reach target (5.3 versus 6.6 h in group B1 versus 4.56 h in group B2), and a higher average FSBS after 4 h (206.63 versus 135.69 mg/dl in group B1 and 129.49 mg/dl in group B2). The percentage of low FSBS (<70 mg/dl) were comparable (0.98% versus 0.93% in group B1 and 1.2% in group B2). The percentage of high FSBS (>200 mg/dl) were higher in group A (10.97% versus 8.8% in group B1 and 8.2% in group B2).

Conclusion:
Compared with a standard insulin algorithm, continuous IV insulin infusion delivered by a computer-guided glucose management system achieves glucose control more promptly without a higher risk of hypoglycemia.

Design of the Health Monitoring System for the Artificial Pancreas: Low Glucose Prediction Module

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Objective:
The artificial pancreas is a high-risk device requiring several safety layers to ensure the health of the user and the proper condition of the device. The health monitoring system (HMS) is a process monitoring module designed to work in conjunction with the artificial pancreas control algorithm or as part of a continuous glucose monitoring (CGM) system. The HMS operates as a parallel, separate safety system that automatically relays information to the user and physician.

Method:
The low glucose prediction (LGP) submodule of the HMS predicts hypoglycemia and recommends consumption of rescue carbohydrates. The LGP is robust to real-life situations by preprocessing for missing data, sensor inaccuracy, and calibration. The Food and Drug Administration-accepted University of Virginia/Padova metabolic simulator was used to simulate an overbolus with the LGP operating in parallel. The robustness of the system was tested using clinical data.

Result:
The LGP submodule was executed on 10 *in silico* subjects following manual therapy with an overbolus equivalent to a bolus for a 65 g carbohydrate meal: 15% of readings were below 70 mg/dl without intervention, decreasing to 3% with intervention. Activation of the LGP was demonstrated with a visual and audible alarm and with short message service and multimedia message service to cell phones with different carriers. Clinical data consisting of 490 days of DexCom SEVEN data were also evaluated. Data gaps were present in 7% of the data, and there were approximately 1000 sensor calibrations. There were 2.1 false positive alarms per day, and 81% of hypoglycemic events were predicted within 1 h.

Conclusion:
The HMS is a versatile tool for use in CGM and the future artificial pancreas as a separate, parallel safety module with several submodules that can be used to detect and alleviate or prevent adverse events.

Monitoring the Normal Use Temperatures of Pumped Insulin

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Objective:
Temperature profiles of insulin pump reservoirs were analyzed during normal wear conditions across multiple seasons. This information is useful for establishing the appropriate stability and storage conditions for device evaluation because temperature effects have previously been shown to influence device performance.

Method:
Thermocouples in reservoirs filled with insulin diluent were loaded in infusion pumps worn by volunteers, and temperatures were recorded during the course of normal daily activities. Reservoir and ambient environmental temperature data and activity levels were logged during the months of February (winter), April (spring), and August (summer). Each seasonal data set comprised approximately 15 days of wear from 3–5 volunteers.

Result:
Reservoir temperature profiles were typically higher than ambient temperatures, likely due to heat transfer from the wearer when the pump is placed close to the body. The maximum and minimum observed reservoir temperatures were 36.8 °C (summer) and 16.5 °C (winter), respectively. The average reservoir temperature remained close to 30 °C throughout the study. Averaging across all seasonal data sets, the reservoir temperature remained between 25 and 37 °C more than 90% of the time. Temperatures cycled repeatedly within a day, with an average of 7 ± 2 fluctuations > 3 °C per day, with >80% of cycles between 25 and 37 °C.

Conclusion:
These results indicate that normal insulin temperature conditions fluctuate between 25 and 37 °C regardless of seasonal variations, with environmental controls and body temperature helping to maintain this range. However, temperature cycling occurs multiple times per day within this range and should also be considered when examining device performance.

In Silico Validation of a Bio-Inspired Glucose Controller

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Background:
Bio-inspired approaches for solving medical problems have been motivated by the belief that evolved biology optimizes efficacy and efficiency. Replicating the functionality of human physiology may lead to a system with greater function. In this work, a recently developed glucose controller based on a mathematical model of pancreatic β-cell physiology is validated using the 100 adult and 100 adolescent type 1 diabetes mellitus virtual populations accepted by the U.S. Food and Drug Administration (FDA).

Method:
Two versions of the controller were tested, both with meal announcement but one with premeal bolus and the other without premeal bolus. However, the premeal bolus version was tested using a non-FDA-accepted population. The *in silico* tests were carried out by the Epsilon Group (University of Virginia). An already published meal protocol was used for this purpose

Result:
For the adult population without premeal bolus, mean blood glucose was 125 mg/dl [standard deviation (SD) 12 mg/dl] with 92.8% time in target (70–180 mg/dl), no severe hypoglycemia, and 0.44% of time <70 mg/dl. Results for the adult population with premeal bolus were superior with mean glucose 118 mg/dl (SD 9 mg/dl), 97.8% time in target, and 0.22% time <70 mg/dl. Results with the adolescent population followed the same pattern, with mean blood glucose of 133 mg/dl and slightly improved control noted with premeal bolus.

Conclusion:
Both versions of the controller showed very good glycemic control over the two virtual populations. Despite the FDA-accepted and non-FDA-accepted populations being statistically very similar, the results are not wholly comparable. Nevertheless, the premeal bolus version was found to result in slightly better glucose control compared with the version without premeal bolus.

Insulin Bolus Calculator Based on Case-Based Reasoning

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Background:
Most commercially available insulin pumps include a bolus calculator feature. The clinical benefit of using insulin bolus calculators has been demonstrated, but their performance remains suboptimal and their utilization has yet to be extended to people on multiple dose injection regimes. To achieve a significant improvement in glycemic control, these systems require initial tuning and continuous follow-up by an expert team. In this work, we present a new insulin bolus calculator based on case-based reasoning (CBR), a consolidated artificial intelligence technique, which solves newly encountered problems by applying the solutions learned from solving previous problems. Case-based reasoning provides more flexibility and adaptability than the rule-based approach used by current bolus calculators, making it ideal for the uncertainties and variability seen in diabetes.

Method:
A proprietary algorithm incorporating the full CBR cycle (retrieve, reuse, revise, and retain) was implemented. The algorithm is initialized with the subject's standard bolus therapy or with a subject-specific case memory from retrospective clinical data. The CBR algorithm was evaluated *in silico* using the 10 adult subjects of the commercial version of the Food and Drug Administration-accepted type 1 diabetes simulator (University of Virginia). The default bolus therapy from the simulator was compared with the CBR algorithm. A 1-month scenario, with realistic variability in meal timing and carbohydrate, was used.

Result:
With the CBR algorithm, a reduction of 10 mg/dl in mean blood glucose concentration was achieved without an increase in hypoglycemia events.

Conclusion:
Case-based reasoning is a viable approach for insulin bolus recommendation, requiring less initial tuning and ongoing maintenance than current bolus calculators. The proposed algorithm is currently being integrated in a telemedicine platform, and the whole system will be clinically validated in the near future.

Prospective Noninvasive Glucose Measurement Using a Wearable Raman Spectrometer

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Background:
Raman spectroscopy provides highly structured molecular information that, when combined with appropriate analysis, can discriminate glucose from other interfering substances in the human body. Our goal was to develop a practical, noninvasive continuous glucose monitor using this technology.

Methods:
We developed a universal calibration in the course of an 8-week, human subject trial (N = 65). The data collection was conducted at Mills-Peninsula Health Services Diabetes Research Institute. The resulting calibration is used to make prospective measurements on additional test subjects who were not in the calibration trial. Prospective measurements were performed on type 1 and type 2 diabetes patients and subjects without diabetes who were measured either as presented or during an oral glucose challenge. The reference measurements were a YSI blood analyzer for the calibration and a OneTouch Ultra finger stick for the prospective measurements.

Results:
Prospective measurement results are presented on an independent test population (N = 5 and 409 measurements), none of whom are in the calibration data. For this set, the mean absolute relative difference was 19.8%/12.2%/30.7% (mean, minimum, maximum), which improved to 9.3%/1.7%/14.1% following a two-point calibration. On the Parkes consensus error grid, 54% were in the A range and 46% in the B range, with no points in the C, D, or E ranges. With a two-point calibration, this improved to 86%/14% in A/B, respectively. The correlation coefficient for the aggregate data set was 0.85.

Conclusion:
We have demonstrated a noninvasive glucose monitor with a universal calibration in a pilot study. Incorporation of an additional two-point calibration provides better accuracy. Prospective measurements yield 100% of points in the A and B regions of the consensus error grid, and the data have a correlation coefficient of 0.85. These results have been obtained with engineering prototypes; further data collection with advanced generation devices is ongoing.

Miniaturized Differential Affinity Sensors for Continuous Glucose Monitoring

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Objective:
We present miniaturized differential glucose sensors based on affinity binding between glucose and a biocompatible, synthetic polymer. The sensors possess excellent resistance to environmental disturbances and allow wireless measurements of glucose concentrations within interstitial fluid in subcutaneous tissue for long-term, stable continuous glucose monitoring (CGM).

Method:
The sensors are constructed using microelectronic mechanical system (MEMS) technology and exploit poly(N-hydroxyethyl acrylamide)-*ran*-3-acrylamidophenylboronic acid (PHEAA-*ran*-PAAPBA), a biocompatible glucose-binding polymer with excellent specificity, reversibility, and stability. Two sensing approaches have been investigated that respectively use a pair of magnetically actuated diaphragms or perforated electrodes to differentially measure the glucose-binding-induced changes in the viscosity or permittivity of PHEAA-*ran*-PAAPBA with respect to a reference glucose-unresponsive polymer.

Result:
In vitro and *in vivo* characterization of the MEMS affinity sensors have been performed at physiologically relevant glucose concentrations (30 to 500 mg/dl). The sensors exhibited time constants of approximately 2–3 min upon glucose concentration changes and demonstrated excellent stability and reversibility. The drift of the differential sensors was 50 times smaller than those in single-channel measurements, indicating the sensors' ability for common mode cancellation of environmental disturbances. Preliminary animal experiments using the devices with laboratory mice showed that the sensors' output closely followed the commercial glucose meter readings. The measurement accuracy was assessed by Clarke error grids. It was observed that up to 95% of measurement points from the devices were located in zone A and 5% in zone B, suggesting that the sensors can potentially allow highly accurate CGM applications.

Conclusion:
The miniaturized MEMS sensors explore differential measurements of affinity glucose recognition. *In vitro* and *in vivo* testing demonstrated excellent sensitivity, repeatability, reversibility, and stability, indicating that the devices hold the potential to enable long-term and reliable CGM applications.

Employing Insulin Information to Improve Glucose Sensor Accuracy

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Background:
Insulin therapy development relies on the improved accuracy of the glucose measurement signal for potential nonadjunctive use of the continuous glucose monitor (CGM) to make treatment decisions. Specifically, a certain level of accuracy is necessary in the hypoglycemic range, where sensor performance is generally the worst. The need for ensuring the accuracy of the sensor serves a purpose not only in a potential nonadjunctive use setting, but also in assisting patients and families in day-to-day decision making and in stand-alone safety systems where alarms are generated based on CGM values and trends.

Method:
Our method focuses *for the first time* on the signal from the insulin pump as a source of information to improve the accuracy of the CGM. The method consists of three basic steps: (1) blood glucose (BG) state estimation, (2) BG state projection a short time period ahead to account for CGM lag, and (3) *weighting* of the BG state estimate against the CGM signal.

Result:
We test the algorithm in two scenarios designed to induce high glucose variability: (1) repeated correction bolus delivery and (2) skipped meal. *In silico* results indicate reduction in mean absolute relative difference (MARD) by 3.5% and 3.6% in the hypoglycemic range and increase continuous glucose error grid analysis percentage within the A zone by 6.8% and 2.2% over the full glycemic range for scenarios 1 and 2, respectively. *In vivo* results demonstrate the use of the algorithm to flag erroneous sensor measurements and significantly reduce MARD by 1.96% (alpha = .05) when flagged sensor data are removed.

Conclusion:
We introduce an algorithm that can provide more accurate glucose information and a measure of glucose sensor credibility to the user. The algorithm can additionally be employed as a real-time data source for making insulin therapy treatment decisions.

Initial Intensive Care Unit Clinical Results Using Specialized Relative Insulin and Nutrition Tables to Guide Insulin Infusions in a Hungarian Medical Intensive Care Unit

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Objective:
Our objective is to report the initial clinical results and glycemic control using the Specialized Relative Insulin and Nutrition Tables (SPRINT) protocol at an independent intensive care unit (ICU), with modifications to modulate only insulin infusions.

Method:
The SPRINT protocol was used for 10 adult ICU patients (615 h) at Kálmán Pándy Hospital (Gyula, Hungary) as part of a clinical practice assessment. SPRINT insulin recommendations were administered via constant infusion rather than bolus delivery. Nutrition was administered per local protocol (parenteral nutrition weaned to enteral nutrition) and reduced in total per SPRINT protocol when required and clinically approved. Measurement was every 1 to 2 hours per protocol. Glycemic performance is assessed by percentage of (hourly resampled) blood glucose (BG) measurements in glycemic bands for the cohort and per patient. Safety is assessed by numbers of patients with BG < 2.2 mmol/liter (severe) and 3.5 mmol/liter (moderate). Clinical effort is assessed by measurements per day. Results are median (interquartile range) as appropriate.

Results:
There were 428 measurements over 615 h of control (16.7 measurements/day), which is similar to clinical SPRINT results (16/day). Per-patient hours of control were 56 (46–75) h. Initial per-patient BG was 10.5 (8.6–11.5) mmol/liter. All 10 patients (100%) reached 6.1 mmol/liter in 7.5 (1.5–9.0) h. Cohort BG was 6.6 (5.6–7.7) mmol/liter, with 48.8%, 61.8%, and 81.0% of BG in the 4.0–6.5, 4.0–7.0, and 4.0–8.0 mol/liter bands, respectively. Per patient, the percentages of time in these bands were 54.2% (32.5–68.5%), 63.8% (42.6–83.7%), and 85.5% (70.0–92.6%), respectively. No patients had BG < 2.2 mmol/liter, and two had one BG < 3.5 mmol/liter. Percentage of BG < 4.0 mmol/liter was 1.6%.

Illyés cont. ⟶

Illyés cont. ⟶

These results were achieved using 3.0 (3.0–5.0) U/h of insulin with 7.4 (4.0–10.8) g/h of dextrose administration (all sources) for the cohort. Per-patient median insulin administration was 3.0 (3.0–3.0) U/h and 6.3 (1.3– -9.7) g/h dextrose. Higher carbohydrate nutrition than in SPRINT protocol is offset by slightly higher insulin administration.

Conclusion:
The glycemic performance shows that the SPRINT protocol to guide insulin infusions provided very good glycemic control in initial pilot testing, with no severe hypoglycemia. The overall design of the protocol generalized well, with good compliance and outcomes across geographically distinct clinical units, patients, and clinical practice.

Trueness of the Comparison Method in Scandinavian Evaluation of Laboratory Equipment for Primary Health Care's Evaluations of Instruments for Self-Monitoring of Blood Glucose

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Background:
Scandinavian Evaluation of Laboratory Equipment for Primary Health Care (SKUP; *www.skup.nu*) is a Scandinavian cooperation for evaluation of near patient laboratory equipment. A SKUP evaluation provides objective and supplier-independent information about analytical quality and user-friendliness and includes the intended users' examination. We examined if the comparison method used in SKUP evaluations of instruments for self-monitoring of blood glucose (SMBG) gives true glucose values.

Method:
SKUP uses a hospital method for quantitative determination of glucose in human serum and plasma as the selected comparison method in the evaluation of SMBG devices. The method is a photometric enzymatic method utilizing hexokinase and glucose-6-phosphate dehydrogenase enzymes. The method is implemented on Architect *ci*8200 System from Abbott Laboratories and has been used by the SKUP in 12 evaluations of SMBG devices. The comparison method must show traceability to an internationally accepted reference standard. In order to demonstrate the trueness of the comparison method, SKUP uses the Standard Reference Material (SRM 965a, 965b) from the National Institute of Standards and Technology (NIST). The trueness is confirmed by analyzing two levels of freshly frozen human serum controls with target values determined by an isotope-dilution gas chromatography/mass spectrometry method at a reference laboratory in Belgium (Laboratory for Analytical Chemistry, University of Gent).

Jacobsen cont. ⟶

Jacobsen cont. ⟶

Result:
The trueness of the glucose comparison method is shown with use of SRM 965 from the NIST and freshly frozen human serum controls. The mean deviation (bias) of each of the 12 SMBG devices from the comparison method will be illustrated in a figure.

Conclusion:
The trueness of the selected comparison method in SKUP glucose evaluations is good.

Comparative Dose-to-Dose Variability Analysis of Insulin Pumps

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Objective:
A comparison of the Animas OneTouch Ping (OTP) and Insulet OmniPod insulin pumps was performed to quantify dose variability per delivery and averaged dose delivered over a time window.

Method:
Insulin pumps were tested for flow accuracy using a time-stamped microgravimetric system. Flow rates were set at 0.500 U/h and tested for a period of 20 h. At this basal rate, the OTP delivers half the insulin twice as often per dose (0.025 U, 3 min) than OmniPod (0.05 U, 6 min). Several thousand individual doses for each pump were measured on several pumps. The dose error was calculated and the data analyzed to determine the number of doses outside accuracy thresholds of ±5% to ±50%.

Result:
The OTP showed significantly better accuracy per individual delivery than the OmniPod insulin pump. In particular, for threshold accuracy of ±5%, ±20%, and ±50%, the OTP delivered 58%, 98%, and 100% doses within target. In contrast, for the same thresholds accuracy, the OmniPod delivered 17%, 60%, and 83% within target.

Conclusion:
The OTP demonstrated significantly better accuracy per delivery than the OmniPod. One might expect there would have been more dose-to-dose variability and less accuracy with a pump that has smaller volume increments, as smaller dose volumes are more difficult to deliver given the mechanical constraints of the system. However, the results demonstrate otherwise. Large dose-to-dose variations of insulin on a long-term basis may have a significant clinical impact. As we look forward toward artificial pancreas systems, the need for minimal dose variability and increased dose accuracy is heightened. Further research on the clinical relevance of this finding is warranted.

Observation of the Incretin Effect in Critically Ill Patients

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Background:
The impact of endogenous insulin secretion and its interaction with type of feeding [enteral (EN) or parenteral] in glycemic control protocols is unknown. This study examines whether there is any evidence for an EN-driven incretin effect.

Method:
Model-based insulin sensitivity (S_I) was identified for 52 patients on the Specialized Relative Insulin and Nutrition Tables glycemic control during transitions off EN (ON/OFF) and back on to EN (OFF/ON). There was a minimum 10 h before ON/OFF, 7 h with EN off, and 5+ h after OFF/ON. Increased modeled S_I after the OFF/ON transition or decreased S_I after ON/OFF implies an incretin effect. Patients with diagnosed diabetes were not included.

Result:
Patients exhibited a -36% (interquartile range [IQR] -82% to 24%; $p = .05$) reduction after the ON/OFF transition and a median 32% (IQR -5% to 53%; $p = .001$) maximum rise in measured S_I after the OFF/ON transition. Blood glucose was stable during the transitions with median shifts of -2% and -3% after the ON/OFF and OFF/ON boundaries, respectively. However, 32% of patients exhibited increased S_I at the OFF/ON boundary, and 37% exhibited reduced S_I at the ON/OFF boundary. The latter results are likely due to changes in patient condition over the 5–8 h considered outweighing this effect.

Conclusion:
The results show that a majority of patients exhibited results indicating the existence of an incretin effect. The impact was stronger for the OFF/ON transition, indicating that this effect may be blunted by long-term continuous EN infusions. These results provide the data to design conclusive studies as well as to inform glycemic control protocol development.

Electroencephalogram-Based Real-Time Hypoglycemia Detection

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Objective:
Hypoglycemia-associated acute changes in the electroencephalogram (EEG) precede severe cognitive impairment in type 1 diabetes mellitus (T1DM). We have recently established that these changes can be detected both during daytime and during sleep by an automated multiparameter algorithm. Our aim is to develop a hypoglycemia sensor for diabetes patients with hypoglycemia unawareness. The initial results of real-time hypoglycemia detection during everyday activities are presented.

Methods:
Patients with T1DM and hypoglycemia unawareness were studied during insulin-induced hypoglycemia and during 1 month of out-of-hospital observation. Continuous EEG was recorded from a miniaturized EEG recorder consisting of a small implant and an external device that powers the implant, conducts real-time EEG analysis, and alarms in case of hypoglycemia. Continuous glucose monitoring (CGM) and hypoglycemia registration were performed. After initial individual calibration, no further calibration was needed.

Results:
The study is ongoing. So far, all patients have developed characteristic EEG changes during induced hypoglycemia. In the out-of-hospital studies, EEG-based hypoglycemia alarms were given at CGM values between 2.2 and 4 mmol/liter. During these events, the patients were cognitively intact and able to correct hypoglycemia by carbohydrate ingestion. Thus no events of severe hypoglycemia have occurred so far. The full data set, including EEG recordings, alarms, CGM data, and hypoglycemia registration, will be presented.

Conclusion:
A sensitive hypoglycemia sensor is required in a closed-loop insulin delivery system and could be based on a technique that is different from the glucose monitor. We propose an EEG-based hypoglycemia sensor either as a stand-alone hypoglycemia alarm device or as a backup in a closed-loop system.

Treatment Compliance to Diabetes Care: A Cross-Sectional Study from Pakistan

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Objective:
Diabetes is increasing worldwide, and the treatment of type 2 diabetes is based on lifestyle modification and pharmacological therapy. The objective of this study was to assess current treatment patterns, treatment compliance, and reasons for noncompliance for patients with type 2 diabetes in Pakistan.

Methodology:
A cross-sectional study was conducted to collect data through structured interviews based on a pretested questionnaire. A total of 211 patients (46% males and 54% females) ages 25 years and over were randomly selected for the study from a population of patients attending five primary care diabetes centers throughout Karachi. Information was collected on sociodemographic characteristics, diabetes duration, and compliance to physician advice.

Results:
Overall, median age for male subjects was 53 years, significantly older ($p = .008$) than females (46 years). The mean duration of diabetes among respondents was 9.2 ± 3.8 years. Of the total, the majority of patients were treated with oral medication (61%). Only 27% reported full compliance as per their physician's advice for timely medication, routine exercise, timely laboratory investigation, and follow-up for next visit. Approximately 45% of the subjects were taking medication for diabetes-related complications. Lack of financial resources, knowledge and supportive services, and fear of needles were the main reasons for noncompliance. We also found that people with low literacy levels were less likely to manage their condition effectively compared with people with higher educational levels ($p < .001$).

Conclusion:
Both physicians and patients should attempt to improve compliance to diabetes treatment, which could lead to better disease management. Based on the findings, a public health intervention/information campaign is needed to change behaviors of diabetes patients. Further, physicians can educate patients by identifying potential risks of noncompliance and educating them accordingly.

Development of an Internet-Based Glucose Management System for Glucose Control of Pregnant Women

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Objectives:
Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first detection during pregnancy. The rise in blood glucose level during a pregnancy period increases obstetrical complications between fetus and mother, and it also increases probability of neonatal obesity and diabetes. Therefore, education on diabetes, life management, and insulin doses regulation should be done comprehensively in daily life. However, palliative outpatient services do not sufficiently address all these factors. In order to find a solution, we analyzed the effects using an information-technology-based glucose monitoring system (IBGMS) for GDM patients and medical doctors.

Methods:
A total of 268 Korean women with GDM who delivered from November 2008 to June 2010 were screened. The patients who used the IBGMS were assigned to the intervention group (n = 117) and those who did not use it were assigned to the control group (n = 151). Using their medical records, we analyzed the differences between the two groups.

Results:
The intervention group that used the IBGMS had a higher rate to inject insulin right after being diagnosed with GDM compared with the control group (43.6% versus 10.1%; $p < .001$). It seems that the control group, which did not have much control over blood glucose, eagerly wanted to use the IBGMS. Nevertheless, there were no differences between groups in birth weights and number of preterm labors and macrosomia (>4000 g). In the intervention group, the percentage of macrosomia was 2.8%, and this result was better than previous studies. More subjects are needed in order to yield much more useful statistical results.

Conclusions:
The Internet is used worldwide as a communication tool, and this IBGMS program will be very effective in that it regulates blood glucose with an Internet-based blood glucose regulator, and it will increase patients' satisfaction. By actively using the program, comprehensive regulation for GDM patients can be possible.

Role of Interleukin 1/Interleukin 1 Receptor Antagonist in Long-Term Continuous Glucose Monitoring *in Vivo*

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Background:
Tissue reactions such as inflammation are known to negatively impact glucose sensor function *in vivo*, i.e. biofouling. The powerful pro-inflammatory cytokine interleukin-1Beta (IL-1B) is regulated *in vivo* by the anti-inflammatory antagonist known as interleukin -1 receptor antagonist (IL-1ra). Utilizing IL-1ra transgenic mice, we have recently demonstrated that deficiency of the IL-1ra significantly compromises glucose sensor function during the first 7 days post-sensor implantation *in vivo* when compared with IL-1ra overexpressing or normal mice.

Research Design and Methods:
To investigate the role of IL-1ra in long-term (28 days) glucose sensor function *in vivo*, we compared sensor function in transgenic mice that overexpress IL-1ra designated IL-1ra overexpressing (B6.Cg-Tg*(IL1rn)1Dih/J*) or are deficient in IL-1ra designated IL-1ra knockout (B6.129S-*IL1rn*^{tm1Dih}*/J*) with mice that have normal levels of IL-1ra (C57BL/6).

Results:
Our studies demonstrated that overexpression of IL-1ra, i.e., IL-1ra overexpressing mice, had less inflammation at the site of sensor implantation as well as showed significantly better sensor functionality when compared with IL-1ra knockout mice.

Conclusion:
These data not only directly support our hypothesis that the IL-1 family of cytokines and antagonists play a critical role in controlling tissue reactions and sensor function *in vivo*, but also suggest that local control of IL-1/IL-1ra will likely positively impact tissue reactions and extend sensor function *in vivo*.

Targeted Glycemic Control Following Total Pancreatectomy: A Challenging Goal

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Background:
The impact of pancreatogenic diabetes following total pancreatectomy is not well characterized. We hypothesize that our current hospital-based system of glycemic management is inadequate to address regulatory needs of patients following total pancreatectomy.

Method:
Patients who underwent radical total pancreatectomy (TP) between 2005 and 2010 (n = 13) were compared with an age-matched cohort (n = 13) who underwent radical pancreaticoduodenectomy (RP; "Whipple"). Glycemic control was described relative to a targeted range of 80–150 mg/dl. Postoperative course and outcome was evaluated and then compared between groups.

Results:
Median age, comorbidities, and preoperative nutritional status were similar between groups. Average intensive care unit (TP 3.8 days; RP 1.5 days) and hospital length of stay (TP 23.2 days; RP 10.1 days) were longer in TP patients. Mean postoperative glycemic levels were higher following TP [150.8 mg/dl, standard deviation (SD) 62.7] as compared with RP (134.2 mg/dl, SD 30.3). The proportion of patient glucose values outside the targeted range (80–150 mg/dl) was higher in TP (51%) compared with RP (28%). The proportion of critical hypoglycemia (<70 mg/dl) was 4% in TP versus 1% in RP. The proportion of critical hyperglycemia (>350 mg/dl) was minimal in both TP (1%) and RP (0.6%). The incidence of delayed gastric emptying (DGE) was higher following TP (n = 8/18 versus n = 1/13). Among those with DGE, the majority (n = 6/9) had poor postoperative glycemic control (>50% values outside 80–150 mg/dl range), and 5/6 of those with DGE underwent TP. The incidence of postoperative infection was similar between groups (TP n = 6; RP n = 5).

Conclusion:
Targeted glycemic control following TP is difficult to achieve. Glucose dysregulation contributes to complications and may prolong hospital stay. Emerging technologies, including continuous monitoring and closed-loop systems, may have dramatic and positive impacts in this patient population.

A Video Game Teaching Tool for the Prevention of Type 2 Diabetes and Obesity in Children and Young Adults

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Objective:
The risk of acquiring type 2 diabetes is greater than one in three in the general U.S. population. Obesity and glucose intolerance in childhood has been shown to be strongly associated with increased rates of premature death. The purpose of this study was to see if diabetes education in conjunction with a video game could help modify youths' attitudes toward nutrition, obesity, and diabetes prevention.

Method:
An informational questionnaire was given to 12 healthy volunteers aged 9–29 years. This consisted of facts regarding carbohydrates, fat, and diabetes interspersed with 10 test questions. This was followed by a Web-browser-based video game called "Carb Wars," which features various high-carbohydrate/low-fiber foods such as doughnuts and white bread parachuting onto city buildings. The player is to stop the invasion and preserve the buildings. The game play was followed by a survey regarding attitudes toward carbohydrates, exercise, and diabetes.

Results:
Only 33% reported generally eating a healthy diet, 75% reported being generally physically active, and 50% reported eating a high-fiber/low-sugar diet. After completing the educational material and game, 83% reported wanting to exercise more and 92% wanted to eat a healthy diet; 100% reported wanting to avoid diabetes.

Conclusion:
A video game teaching tool is an effective method for influencing the attitudes of children and young adults toward obesity and diabetes prevention.

Robust Performance of Closed-Loop Control Design Based on Insulin Pharmacokinetics/Pharmacodynamics

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Background:
People with type 1 diabetes mellitus are required to administer exogenous insulin to regulate blood glucose concentration. Currently, a variety of insulin formulations with different pharmacokinetics (PK)/pharmacodynamics (PD) are available, and others are being developed for insulin therapy. Closed-loop system robustness/performance largely depends on the PK/PD of insulin formulation. Thus one of the main design questions of a closed-loop system is the following: What is the robustness/performance tradeoff expected from different PK/PD of insulin-formulations?

Method:
We developed a research platform to investigate the robustness/performance of closed-loop systems based on different insulin formulations. A PK model of different insulin formulations was developed and incorporated into the University of Virginia/Padova Food and Drug Administration-accepted metabolic simulator. The insulin model time constant (τ_{PK}) can be adjusted to represent different insulin formulations from long-acting insulin to rapid-acting and ultra-rapid-acting formulations. A proportional-integral-derivative controller was designed based on the PK/PD model of insulin formulations and the metabolic simulator using Internal Model Control methodology. Robustness/performance of the controller was analyzed for a range of insulin formulations on 10 *in silico* subjects following a 75 g carbohydrate unannounced meal protocol.

Result:
Analysis shows that the controller can achieve better performance using faster-absorbing insulin formulations without losing robustness or increasing hypoglycemia. Average maximum blood glucose concentration decreased by 11 mg/dl per 25 min decrease of τ_{PK}, and the average duration in the hyperglycemia (>180 mg/dl) decreased by 0.6 h per 25 min decrease of τ_{PK}. No hypoglycemia (<60 mg/dl) was observed for the different insulin formulations.

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Conclusion:
These results suggest that the research platform enables analysis of the robustness/performance of closed-loop systems using different insulin formulations. In the future, the research platform can assist in development of new insulin formulations that would result in superior closed-loop glucose regulation with minimal hyperglycemia or hypoglycemia.

Performance Evaluation of a Novel Blood Glucose Monitoring System

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Objective:
A blood glucose monitoring system (BGMS) with a new generation of blood glucose sensors that utilize the flavin adenine dinucleotide-glucose dehydrogenase enzyme and a proprietary mediator is currently in development. The current study evaluated the accuracy and precision of the novel BGMS compared with the ACCU-CHEK Aviva and OneTouch Verio systems.

Method:
This clinical trial enrolled 110 subjects aged ≥18 years with type 1 or type 2 diabetes. Health care providers tested capillary finger stick samples using the novel BGMS and the ACCU-CHEK Aviva and OneTouch Verio systems (single tests each). All meter results were compared with results from the same fingertip blood tested on the local reference analyzer. Accuracy assessment was based on the proposed change to the International Organization for Standardization (ISO) 15197:2003 (section 7) guidelines: percentage of results within ±15 mg/dl of the reference result for samples with glucose concentrations <100 mg/dl and ±15% for samples with glucose concentrations ≥100 mg/dl. Parkes consensus error grid analysis was used to determine clinical accuracy.

Result:
The novel BGMS achieved 100% accuracy based on the proposed ISO 15197 standard; the ACCU-CHEK Aviva and OneTouch Verio systems achieved 98.2% and 96.4% accuracy, respectively. Regression analyses demonstrated strong correlation between all meter and reference results (adjusted R^2 > 98% for all regressions). An analysis of variance showed that the Verio system had significantly greater differences in meter results versus reference results than the novel BGMS or the Aviva system, which did not differ significantly from each other. Parkes consensus error grid analysis showed 100% of results for the novel BGMS were within zone A.

Conclusion:
Performance of the novel BGMS met proposed ISO 15197 accuracy standards.

Telemedical Diabetes Consultations Significantly Reduce Total Treatment Costs without Compromising the Quality of Care: Results from the Svendborg Telemedical Diabetes Project

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Background:
The increasing number of patients with diabetes poses a major challenge for the health care system, including the foreseen shortage of highly qualified medical professionals. One instrument to meet these challenges and, at the same time, reduce treatment costs could be the use of telemedicine. Health Optimum, launched in 2004, is a telemedical project designed to investigate if telemedicine can deliver health care across distances within regions of Europe. As a result, patients with diabetes on the island of Aeroe (~7000 inhabitants) are now offered expert health care that they could otherwise only receive at the larger hospital on the mainland. The present study examines the impact of our telemedical service on essential diabetes parameters and cost-effectiveness.

Method:
Telemedical diabetes consultations were carried out with the patient and nurse specialist placed in a consultation room on Aeroe in audiovisual communication with the physician placed in the hospital on the mainland. An adjustable video camera with zoom function can be directed by the physician. Electronic patient record and a Web-based quality-monitoring diabetes database were used, including automatic capture of retinal photos.

Result:
Patients living on Aeroe with known or recently discovered diabetes were referred to telemedical consultation. Inclusion criteria for the present study were at least 6 months of telemedical control with a minimum of two visits and two hemoglobin A1c (HbA1c) values. Results were compared with data from the Danish National Diabetes Registry (NIP). Data are given in medians. In total, 24 type 1 diabetes mellitus (T1DM) patients, age 66 years, diabetes duration 17.5 years, body mass

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index 25.4 kg/m^2, and 47 type 2 diabetes mellitus (T2DM) patients, 66 years, 12.0 years, 31.0 kg/m^2, were included. Hemoglobin A1c before/after telemedicine was 8.6% versus 8.1% in T1DM patients and 8.1% versus 7.1% in T2DM patients (in T2DM, $p < .002$ versus before and $p < .005$ versus the NIP). The NIP values for HbA1c were 8.0% and 7.6% for T1DM and T2DM patients, respectively. Blood pressure and lipid values were comparable with the NIP. Preliminary economic analysis showed a significant reduction in total costs based on (1) a 6 h reduction in transportation time, (2) reduced absence from regular job (30% of patients were full-time employed), (3) reduced public spending on transportation of patients, (4) less use of physician working hours related to diabetes consultations, and (5) improved diabetes control.

Conclusion:
In conclusion, telemedical consultation for remote outpatient diabetes control is feasible, and the interdisciplinary interventions secured a high quality in essential diabetes parameters. The results were also highly cost-effective due to a positive impact on several economic parameters. A comprehensive economic analysis of the service is ongoing.

Evaluation of Glycometabolism by Continuous Glucose Monitoring System in First-Degree Relatives of Chinese Patients with Type 2 Diabetes Mellitus

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Background:
The characteristics of glycemic stability in the first-degree relatives of Chinese patients with type 2 diabetes mellitus (T2DM) were investigated by continuous glucose monitoring system (CGMS).

Methods:
The clinical and glycometabolic status of 32 first-degree relatives (FDRs) of T2DM patients and 38 age- and gender-matched controls were estimated by oral glucose tolerance test (OGTT) and CGMS. Mean blood glucose (MBG), standard deviation of mean blood glucose (SDBG), mean of daily differences (MODD), and mean amplitude of glycemic excursions (MAGE) were obtained from CGMS software or calculated by the specific program; the clinical and biochemical markers, including blood glucose, serum lipids profile, body fat distribution, and serum insulin, were assayed. Insulin sensitivity and resistance were assessed by homeostatic model assessment of beta-cell function (HOMA-B), homeostatic model assessment of insulin resistance (HOMA-IR), $\Delta I_{30}/\Delta G_{30}$, and modified beta-cell function index (MBCI).

Result:
There were no significant differences between the FDRs and controls at the levels of serum glucose in OGTT, MBG, SDBG, and MODD. However, the MAGE was significantly higher in FDRs (2.61 ± 0.57 versus 2.15 ± 0.64 mmol/liter, $p < .05$). It also showed that MBCI of the FDR group was lower than the control group [37.82 (15.61 ~ 60.23) versus 18.98 (15.92~56.95), $p < .05$], and there were no significant differences on serum lipids profile, body fat distribution, HOMA-B, HOMA-IR, and $\Delta I_{30}/\Delta G_{30}$ between the two groups.

Conclusion:
The results showed that the excursions of blood glucose were serious in FDRs of Chinese patients with T2DM, which suggests that CGMS is more sensitive to discover this change than OGTT.

Mathematical Model of Glucose Dynamics with Application to Improve Sensor Accuracy

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Objective:
Medtronic's continuous glucose monitoring system (CGMS) estimates a patient's blood glucose (BG) by measuring interstitial fluid (ISF) glucose concentration. However, the physiological time delay between BG and ISF glucose can affect sensor performance. The objective of this study was to investigate ISF BG dynamics with a mathematical model and to improve sensor accuracy.

Method:
Medtronic Guardian real-time CGMS was used to collect ISF glucose values while YSI 2700 was used to collect BG values as reference. A glucose dynamics model was built to simulate the time delay between BG and ISF glucose. The delays were simulated in various scenarios such as the regions of high BG and low BG and the regions of high rate of change (ROC) and low ROC of glucose. Furthermore, to better simulate real sensor signals, other parameters were also put into the model. Among these were delays from the device, offset currents from the device, and offset current contributed by the biological environment. Experimental data were used to validate the model as well as determine the value or varying range of each parameter. A calibration algorithm based on the model was developed to estimate and compensate for the delays and offsets to improve sensor accuracy.

Result:
The experimental data matched well with the model simulation results. With dynamic estimation and compensation for delay and offset, sensor accuracy was improved by approximately 20%, especially for hypoglycemic and hyperglycemic event detection, where, in some cases, it was greatly improved.

Conclusion:
Delays and offsets can greatly affect sensor performance and should be compensated for during the signal calibration. The model proved to be an effective tool for simulation of *in vivo* sensor signals.

Evaluation of a Next-Generation Durable Insulin Pen with Memory Function among People with Diabetes and Health Care Professionals

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Objectives:
Our objective was to evaluate usability and preference for durable insulin pens among people with diabetes (PwD) and health care professionals (HCPs) by comparing NovoPen 5 (NP5), a next-generation insulin pen with memory function, with HumaPen MEMOIR (HPM), HumaPen LUXURA (HPL), and ClikSTAR (CS).

Methods:
This crossover multicenter usability study recruited 278 insulin-pen-experienced adults with type 1 or type 2 diabetes and 102 HCPs treating PwD in China, Germany, and the United Kingdom. Participants evaluated all four pens in randomized order by performing handling and usability tasks related to everyday use during a face-to-face interview. Tasks, pens, and preference were rated by completing a questionnaire comprising rating and open-ended questions.

Results:
Overall, NP5 was selected as the most preferred pen by 51% of participants compared with HPM (22%, $p < .01$), HPL (12%, $p < .01$), and CS (15%, $p < .01$). In general, all pens received similar ratings for handling and usability tasks. Participants preferred the design of NP5 (appearance, length, and robustness). Memory function (last dose with NP5 versus 16 last doses with HPM) was rated equally by PwD and HCPs, but 54% of PwD rated NP5 as very easy to learn to use versus 22% for HPM ($p < .01$), and significantly more HCPs found it very easy to teach others versus HPM. Significantly more PwD (64%) gave NP5 the highest rating of "very confident for managing daily insulin injections" versus HPM (43%, $p < .01$), HPL (49%, $p < .01$), and CS (45%, $p < .01$).

Conclusion:
NovoPen 5 was preferred to other durable insulin pens by more than half of PwD and HCPs. The main preference drivers were design, memory function, and ease of learning/teaching. Most PwD would be very confident in using NP5 for everyday management of their diabetes.

Does Device Make a Difference? A Real-World Study of Switching from Vial to Disposable Pen among an Employee Population with Type 2 Diabetes Mellitus Who Were Treated with Insulin Glargine

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Background:
We evaluated the outcomes of switching from vial to disposable pen among U.S. patients with type 2 diabetes mellitus (T2DM) treated with insulin glargine.

Method:
The MarketScan Commercial database, containing health care claims for U.S. employees and dependents from ~100 payers, was used to identify T2DM patients aged 18–64 years treated with insulin glargine vial or disposable pen from 2007–2009. Patients switching to disposable pen after ≥2 prior vial usages were identified as the pen switcher cohort, with the first pen usage as the index event. Patients continuing to use only insulin glargine vial after ≥2 vial usages were identified as the vial continuer cohort, with a vial claim subsequent to the second vial usage randomly assigned as the index event. All patients had continuous health plan coverage for 6 months before (baseline period) and 1 year after the index date (follow-up period). Propensity score matching 1:1 was used to balance the baseline characteristics of the cohorts.

Result:
The study included 5782 matched patients (n = 2891 each cohort, mean age 51 years, 50% female). During the 1-year follow-up, pen switchers were more persistent (70.0% versus 55.6%, $p < .0001$) and adherent (adjusted medication possession ratio: 0.79 versus 0.75, $p < .0001$) than vial continuers on overall insulin glargine use. Hypoglycemia rates were similar (10.3% versus 10.1%, $p = .76$). Pen switchers incurred similar total health care costs as vial continuers ($20,894 versus $21,573, respectively, $p = .525$), despite higher diabetes medication costs ($3424 versus $2897, $p < .0001$).

Lin cont. ⟶

Lin cont. ⟶

Conclusion:
This study indicated that, among the employee T2DM population treated with insulin glargine, switching from vial to disposable pen may lead to better adherence and persistence in insulin glargine treatment without increase in total health care cost.

Outcomes of Initiating Insulin Glargine Therapy with Disposable Pen or Vial among Patients with Type 2 Diabetes in a U.S. Managed Care Health Plan

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Background:
We evaluated the differences in outcomes when initiating insulin glargine (IG) via disposable pen versus vial in type 2 diabetes mellitus (T2DM) patients in a national managed care plan.

Method:
This retrospective study included insulin-naïve adult T2DM patients in a national managed care plan who had continuous health plan coverage for 6 months before (baseline) and 1 year after (follow-up) IG pen or IG vial initiation. The two groups were matched on observed characteristics using 1:1 propensity score matching. Study outcomes included treatment persistence and adherence, hypoglycemia-related events, health care utilization/costs, and hemoglobin A1c (A1C).

Result:
A total of 4348 patients (mean age 55.5, 43% women) were included (n = 2174 in each group), and there was no significant difference in baseline characteristics. During follow-up, IG pen users, compared with IG vial users, were more persistent (45.6% versus 38.2%, $p < .001$) and adherent (adjusted medication possession ratio 0.68 versus 0.64, $p < .001$), with lower average daily dose (28.8 versus 31.0 U/day, $p = .009$) and fewer hypoglycemia-related events, either overall (6.5 versus 9.3%, $p < .001$) or hospitalization-associated (0.3% versus 1.1%, $p = .002$). They were less likely to be hospitalized (22.1% versus 25.8%, $p = .004$) but had more endocrinologist visits (30.7% versus 25.3%, $p < .001$) and similar total health care costs (pen $38,202 versus vial $40,957, $p = .290$) despite higher diabetes medication cost ($2936 versus $2582, $p < .001$). In the subgroup of patients with A1C data available (IG pen: n = 228; IG vial: n = 194), follow-up A1C was lower for IG pen (8.05 versus 8.37, $p = .056$), but the reduction was not statistically different (-1.07 versus -0.90, $p = .41$).

Lin cont. ⟶

Lin cont. ⟶

Conclusion:
This study suggests that initiating IG with a pen, instead of vial/syringe, may be associated with increased treatment adherence and persistence and thereby better clinical outcomes, without increasing overall health care costs.

Diabetes Connected Health Evaluation

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Background:
We determined patient and provider engagement on a Web-based diabetes self- management portal and its association with clinical outcomes.

Method:
Patient engagement was determined by number of blood glucose readings and uploads, and provider engagement was determined by number of logins to the Web portal. Clinical outcomes were determined by change in hemoglobin A1c (HbA1c) over 1 year in the program.

Result:
A total of 166 patients were enrolled in Diabetes Connect (DC). Of these, 98 (~62%) engaged (at least one upload per month) within 2 months; 43% were never active. Engaged patients consistently uploaded 10–20 blood glucose readings/upload, 2–3 times/month. Less than half remained active after 7 months.

The 67 patients with available clinical outcomes were, on average, 60 years old (standard deviation: 11.9), were 64% male, and had started insulin within the past 3 years. Patients engaged in DC had average HbA1c change of 1.5 gm%, while inactive patients had a HbA1c change of 0.4 gm% ($p < .03$). Patients with better outcomes (HbA1c change of greater than 0.8 gm%) typically took less than 10 days to engage, while patients with worse outcomes (increase in HbA1c) took an average of 65 days to upload. Patients with more engaged providers had a better HbA1c change (1.39 versus 0.87 for practices with average provider logins of 74 versus 30).

Conclusion:
Outcomes in a collaborative Web-based diabetes self-management tool are impacted positively by their consistent engagement in the program. Patients who engage early and remain active longer have better clinical outcomes than unengaged patients. Patients who had positive outcomes uploaded consistently over time. Also, patients with engaged providers are more engaged in the program, leading to better clinical outcomes.

Improved Performance with Enlite Sensor Electrode Layout

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Background:
Numerous benefits were realized with the European Conformity marking of the Enlite sensor. These improvements were the result of modifications to the electrochemical, chemical, and mechanical components of the sensor system. One major improvement to the Enlite sensor was an optimized layout of the flexible electrode array.

Method:
In the Enlite sensor, the aspect ratio, proximity, and depth were adjusted to improve sensor performance over legacy configurations. These modifications, in conjunction with chemistry and mechanical modifications, improved sensor hydration, stability, and overall responsiveness. In the Enlite configuration, the nonsensing electrode was partially included within the dermis. Bridging both the dermal and subcutaneous layers allowed a sensing electrode area equivalent to the Sof-Sensor in a 70% smaller volumetric implant. Enlite sensor performance was measured in numerous human feasibility clinical studies. Accuracy metrics, along with measurements provided by the MiniLink glucose sensor transmitter, were gathered for each of the studies.

Results:
Improvements in sensor performance were seen in the Enlite pivotal trial. Overall mean absolute difference of the Enlite sensor was 14.1%. Furthermore, there were no instances of delayed startup or artificial sensor restarts during the first 4 h of patient data. Finally, the sensitivity of Enlite exceeded that of the Sof-Sensor, which was a requirement specific to the diagnostic algorithms used by the Paradigm RT and Revel sensor-augmented insulin pumping systems. Many of the accuracy improvements in Enlite were attributed to electrode layout optimization.

Conclusion:
Modifications to the electrode layout from Sof-Sensor to Enlite yielded improvements in sensor accuracy, reliability, and the speed of hydration following implantation.

GlucoMen Day: Microdialysis-Based Approach for Intravenous Continuous Glucose Monitoring in Critical Care Settings

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Background:
GlucoMen Day (GMD) is a continuous glucose monitor (CGM) from A. Menarini Diagnostics, and its clinical performance has been validated through several clinical trials. Unlike needle-type CGMs, the microdialytic platform of GMD has shown the potential to operate in both interstitial fluid and intravenous compartments, thus appearing as an ideal candidate for use in critical care settings. This work presents important steps forward in assessing the performance of the device prior to moving to the challenging intensive care unit (ICU) environment. Specific tests were designed to emphasize point and trend accuracy of the system, ability to detect severe hypoglycemic events, and robustness against drug interference.

Method:
GlucoMen Day disposable kits integrating the microdialysis probe MicroEye (Probe Scientific, UK) and a device that allows generation of controlled and rapid glycemic excursions using circulating whole human blood were used during a 3-day test. Interference testing was performed as recommended by the EP7-A2 guideline (Clinical and Laboratory Standards Institute, 2005), using blood samples spiked with endogenous and exogenous chemicals.

Result:
Glycemic excursions as rapid as 3.8 mg/dl/min were generated within the 7–180 mg/dl range. Using just one calibration point/day, 99% of the data pairs fell within the A+B zones of the Clarke error grid. Mean absolute error and mean absolute rate deviation were 9.4 mg/dl and 0.44 mg/dl/min, respectively. None of the tested chemicals (including ascorbic, uric, and salicylic acids; acetaminophen; and dopamine) biased the GMD signal by more than ±15%.

Conclusion:
Accurate and real-time measurement of glucose directly in whole blood and with negligible time lag have been demonstrated *ex vivo*. The substantial immunity to therapeutic/toxic levels of common drugs represents an additional feature for a system that could find application in ICU settings.

Continuous Glucose Monitoring Accuracy Assessed at Home Is Seemingly Better than When Assessed at the Clinical Research Center

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Background:
We investigated whether continuous glucose monitor (CGM) accuracy determined at home differs from accuracy determined at the clinical research center (CRC).

Method:
Twelve patients used the Dexcom SEVEN PLUS CGM for 7 days, calibrated twice daily. Patients performed ≥6 capillary blood measurements (CBMs) per day while at home. On day 3, 4 or 5 patients completed a 24 h CRC admission during which blood was sampled for plasma glucose (YSI). The CGM data were compared with YSI and CBM values. Outcome measures included the mean absolute relative difference (MARD) and Clarke error grid analysis.

Result:
During CRC admission, the MARD of CGM versus YSI glucose values was 19.2% (n = 509), significantly higher than 16.8% at home (n = 611; p = .004). In the hypoglycemic range, MARD was 23.9% at the CRC (n = 26), not significantly different from 41.6% at home (n = 39; p = .269). Also in the euglycemic range, CRC MARD at 18.4% (n = 368) and home MARD at 14.7% (n = 454) were not significantly different (p = .197). In the hyperglycemic range, CRC MARD at 20.3% (n = 115) was significantly higher than home MARD at 11.2% (n = 118; p = .001). Clarke error grid analysis showed no significant difference in the distribution of data pairs (CRC versus home: 67.0% and 71.5% in zone A, 28.7% and 26.4% in zone B, 1.2% and 0.3% in zone C, 2.4% and 1.5% in zone D, and 0.8% and 0.3% in zone E; overall p = .317).

Conclusion:
Continuous glucose monitor accuracy determined from the MARD using CBM at home appeared better than when using YSI measurements in the CRC. Testing CGM accuracy under standardized conditions in the CRC provides valuable information in addition to home testing. The observed difference is probably mainly due to the higher sampling rate of paired values feasible only in the CRC.

Evaluation of Different Cleaning Agents on the Glucose-Oxidase-Based Nova StatStrip Xpress Glucose Meters

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Objective:
Glucose-oxidase-based glucose meters have been reported to be susceptible to interference by hydrogen-peroxide-containing cleaning agents. The objective of this study was to evaluate the effect of two cleaning agents on the performance of the Nova StatStrip Xpress glucose meter.

Method:
The performance of five Nova StatStrip Xpress glucose meters was determined before and after cleaning the devices with either CaviWipes (14.3% isopropanol and 0.23% diisobutyl-phenoxy-ethoxyethyl dimethyl benzyl ammonium chloride) or Accel (0.5% hydrogen peroxide) wipes. Three replicate glucose measurements were conducted before cleaning the devices, immediately after cleaning, and then 1 and 2 min post-cleaning. Analysis was sequentially completed for five different meters. Results were analyzed by a two-way analysis of variance (Analyze-it software).

Results:
No clinical (<0.3 mmol/liter) or statistical ($p > .05$) differences in glucose concentration were detected when the Nova StatStrip Xpress glucose meters were cleaned with either CaviWipes or Accel cleaning wipes and measured immediately or 1 or 2 min post-cleaning. No clinically significant difference in glucose concentration was detected between meters (<0.3 mmol/liter).

Conclusion:
The glucose oxidase amperometric-based Nova StatStrip Xpress glucose meters are not susceptible to interference from CaviWipes or Accel cleaning agents. Differences observed between meters were anticipated due to glycolysis.

A Robust Mathematical Model for Diabetes Education

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Objective:
The purpose of our study was to develop a diabetes simulator to help patients with diabetes to manage their disease better. The core of the simulator is a mathematical model that calculates temporal glucose and insulin profiles corresponding to known inputs (food, medication). We present preliminary results of this model for healthy people and for people with type 1 diabetes mellitus (T1DM).

Method:
Our model is based on the combination/modification of existing literature models, using three main compartments (gut, plasma, interstitium) modeled by integral–differential equations. For these compartments, we evaluated inflows and outflows of glucose and insulin. First, the model was developed for a healthy person; next it was extended to include insulin injections and oral antidiabetic drugs to model diabetes. The parameters of the healthy person model were determined using glucose and insulin profiles taken from literature. The parameters of the T1DM model are determined using continuous glucose monitoring data and insulin profiles acquired by the Amsterdam Medical Center.

Result:
The output of our healthy person model represents glucose and insulin profiles in the same range as expected from measurements, clinical practice, and literature. The model for T1DM patients gives high glucose values and zero insulin if no insulin injection is simulated. The inclusion of insulin injections effectively lowers the output glucose profile and heightens the insulin profile, corresponding to real-life values.

Conclusion:
Our results look promising and, in general, output glucose and insulin graphs are in the range expected from clinical practice. Additional data need to be acquired that can be used for the validation of the T1DM model.

GlucoMen Day Continuous Glucose Monitor: Assessment of Safety and Accuracy Performance in Patients with Type 1 Diabetes

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Objective:
The aim of the present study was to assess the accuracy performance of GlucoMen Day (GMD), the new microdialysis-based continuous glucose monitoring (CGM) system from A. Menarini Diagnostics (Florence, Italy), in patients with type 1 diabetes mellitus (T1DM).

Method:
Twenty T1DM subjects (9 female, age 41 ± 11 years, diabetes duration 21 ± 10 years, body mass index 24.4 ± 3.0 kg/m^2, hemoglobin A1c 7.6% ± 0.7%) were implanted with GMD and monitored for 100 h periods alternating in-patient visits (around meal/insulin challenges) and home study phases. During in-patient visits, arterialized venous blood samples were withdrawn and analyzed with a Super GL analyzer; patients were also instructed to collect capillary reference glucose measurements several times per day using a study-specific glucometer. The CGM signal was calibrated to capillary reference data, two calibration points for the first study day and one calibration point per day for the remaining study period.

Result:
One subject was withdrawn from the study because of a problem identified in the monitoring setup; accordingly, it was excluded from data analysis. A total of 1678 h of useful CGM profiles were collected (mean per patient duration 88 ± 15 h), along with 843 capillary and 349 venous reference glucose data. A total of 98.6% of the CGM/reference data pairs fell within the A+B zones of the Clarke error grid analysis. Median absolute relative error and median absolute rate deviation were 10.5% and 0.81 mg/dl/min, respectively.

Conclusion:
The microdialysis-based GMD system confirmed its ability to track rapid changes in the patients' glycemia, ranging from the hypoglycemic to the hyperglycemic range. The accuracy and reliability of GMD guarantee high-quality CGM profiles, particularly suitable for evaluating indices of glycemic variability and glycemic control.

Automated Screen for Excessive Glycemic Variability Using Continuous Glucose Monitoring Data

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Objective:
There is a growing awareness that not all risks for diabetes complications are adequately assessed by hemoglobin A1c (HbA1c) alone. In particular, excessive glycemic variability, which contributes to oxidative stress linked to long-term vascular diabetic complications, is not detected by HbA1c. This study aims to provide an automated screen for excessive glycemic variability that could be routinely applied to continuous glucose monitoring (CGM) data. An automated test that routinely assesses glycemic variability could augment HbA1c as a clinical measure of overall glucose control.

Method:
Four hundred daily CGM plots, for nine patients with type 1 diabetes on insulin pump therapy, were rated by two physicians as exhibiting excessive glycemic variability or not. The 262 plots with agreed upon ratings were used as input to three machine learning (ML) algorithms: naïve Bayes, multilayer perceptron, and support vector machine. *In silica* experiments were run using each ML algorithm with either raw or smoothed CGM data and different combinations of 11 descriptive input features. Ten-fold cross validation was used to evaluate the performance of each developed classifier.

Result:
The best automated classifier matched physician ratings 93.8% of the time, with a sensitivity of 86.6%, specificity of 96.6%, and area under the receiver operating characteristic curve of 0.95. This was a multilayer perceptron using smoothed CGM data and the following features: distance traveled, roundness ratio, direction codes, mean amplitude of glycemic excursion, and standard deviation.

Conclusion:
A ML classifier, using CGM data, could potentially be used to routinely screen patients for excessive glycemic variability. Greater accuracy could be achieved by training ML algorithms on additional CGM plots rated by multiple diabetes specialists.

GlucoCare IGC System: A Software-Based Decision Support System Designed to Enhance Clinical Trials in Intensive Glycemic Control

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Background:
After Van den Berghe's initial study suggested a benefit to maintaining tight glycemic control in the critically ill, subsequent randomized studies have been unable to confirm these results. One difference between the studies may be that Van den Berghe's was a single-center study in a well-trained unit. This is in contrast to the multicenter randomized trials that have failed to confirm her results. Importantly, none of the trials reported on adherence rates to the protocols that could play a significant role in determining benefit and the incidence of severe hypoglycemia.

Method:
The GlucoCare IGC System (GlucoCare) is a software program designed to facilitate incorporation of any insulin protocol into the system and to run on a hospital's existing servers or through the "cloud." The system can run several protocols simultaneously. GlucoCare allows personnel to override and/or stop the protocol if indicated, but all deviations are clearly documented within the system itself. Thus protocol adherence is documented in real time.

Results:
Seven protocols have been coded into GlucoCare (e.g., Yale, Portland, Bode/Davidson, NICE-SUGAR). Food and Drug Administration approval was achieved for the Yale protocols (90–120 and 100–140 mg/dl targets) in August 2008. Clinical use of GlucoCare began in January 2009. To date, the care of nearly 1000 patients with >25,000 glucose readings have been directed by GlucoCare with an incidence of <40 mg/dl (2.2 mmol/liter) of 0% of patients. Mean blood glucose achieved was approximately 122 mg/dl (6.8 mmol/liter). Time to target range varied from 1.8–7.4 h, depending on the population.

Conclusion:
GlucoCare is a proven-effective insulin-dosing calculator uniquely designed to facilitate clinical trials, and its use may enhance the effectiveness of clinical trials in intensive glycemic control.

Glymera (PB1023): A Novel Glucagon-Like Peptide-1 Analog Dose Dependently Reduces Meal-Challenge-Induced Glucose Exposure Following a Single Subcutaneous Dose

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Background:
Glymera is a 636 amino acid polypeptide of glucagon-like peptide-1 (~5% of molecular weight) genetically fused to a physiologically inert repeating peptide polymeric expressed in *Escherichia coli*. Glymera retains potency similar to native peptide and is formulated as a liquid for subcutaneous administration. This study assessed single-dose safety, tolerability, pharmacokinetics (PKs) and pharmacodynamics (PDs) in adults with type 2 diabetes.

Method:
Subjects treated with one or two oral antidiabetic drugs (OADs) discontinued their OADs during a minimum 2-week run-in period. Subjects were randomized (double-blind) to either placebo or PB1023 (1:3) in each cohort. Following a baseline liquid mixed meal tolerance test (MMTT), subjects were dosed. Cohorts were staggered in time and safety, and PKs and PDs were reviewed before escalation through doses 0.1, 0.3, 0.9, 1.35, and 2.0 mg/kg.

Results:
Glymera was well tolerated with no dose-related trends in the type and severity of reported adverse events at escalating doses. Two subjects (9%) treated with active study drug reported mild nausea, with one event of vomiting at exposures approximately 2–3-fold higher than what is needed to elicit a significant PD effect. The PK parameters showed Glymera to have a slow flat absorption profile with a sustained duration of exposure in a therapeutic range to support once-weekly dosing. Fasting plasma glucose average days 1–7 change from baseline days at -2–0 showed dose response with a difference from placebo of -53 mg/dl at the dose 0.9 mg/kg, close to maximal effect. Day 2 MMTT glucose area under the curve (0–240 min) demonstrated a consistent dose response, with an ED50 at 0.35 mg/kg in Emax modeling.

Conclusion:
In conclusion, Glymera has properties that support further development as a once-weekly dose.

Use of Fuzzy Logic Controller in a Closed-Loop Artificial Pancreas

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Objective:
We evaluate the effectiveness of a fully automated system using a fuzzy logic (FL) controller in a 24 h clinical research center setting. We wished to determine whether this system could (1) correct an elevated blood glucose, (2) control the fasting state and diurnal variation, (3) control the glycemic response to a small meal (30 g carbohydrate), and (4) control the glycemic response to a larger meal (60 g carbohydrate).

Method:
A FL controller was used to direct insulin delivery to adult type 1 diabetes patients. We used the Artificial Pancreas System developed by University of California, Santa Barbara, and Sansum Diabetes Research Institute, an OmniPod pump, and Dexcom SEVEN PLUS sensors. The study began at 8:00 PM. Subjects began with glucose values of 205 and 196 mg/dl. There were then four periods of 6 h, each corresponding to each of the aims. There was no premeal priming boluses, nurse or physician data entry, or modifications. The controller algorithm was initialized using only the patient's total daily insulin.

Result:
Two of 20 planned adult subjects have completed the study to date. The average blood sugar value over a 24 h period for the two subjects was 166 mg/dl. The average blood sugar values for the four 6 h periods are correction of elevated glucose, 197 mg/dl; fasting and diurnal variation, 126 mg/dl; 30 g meal, 144 mg/dl; and 60 g meal, 192 mg/dl. The low blood glucose index and high blood glucose index values were 0.30 and 6.04, respectively. There were no hypoglycemic events.

Conclusion:
These preliminary data indicate that a FL controller may provide effective regulation of blood sugar with only the entry of a patient's total daily insulin.

Calibrating Noninvasive Glucose Monitors: Facts and Factors

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Objective:
Noninvasive (NI) glucose monitoring, based on tracking physiological phenomena correlated with blood glucose (BG), is an indirect measurement of tissue parameters. These parameters are "translated" into glucose values by calibration performed with a reference (invasive) device. The reference's accuracy directly impacts the validity of NI readings. Calibration minimizes the effect of the individual quasi-stable factors such as tissue thickness and structure and sets the baseline for physiological change detection. It is only valid as long as the quasi-stable factors remain unaltered; therefore, recalibration is required periodically. Intervals between recalibrations, calibration length and complexity, number of finger sticks, and choice of reference device strongly affect a NI device's usability and utilization.

Method:
Although partially solved by calibration, accuracy of indirect measurement from tissue, instead of blood, remains limited due to tissue blood lag time. A NI reading from highly perfused tissue, with lag time as in the reference reading location, may reduce inconsistency with BG.

Selecting homogenous and stable tissue can lengthen recalibration intervals, as well as facilitate sensor placing at a repeatable location. An adequate algorithmic solution may minimize calibration complexity. Clinical trials, performed on the earlobe, with ~2 h calibration procedure (six invasive points), were conducted to validate the approach.

Result:
During a full month, weekly analysis of degradation in accuracy level as a function of elapsed time from calibration was evaluated on 110 subjects (2699 data points). Mean absolute relative difference values for each week were 22.5% ± 0.7%.

Conclusion:
Combining these methods enhances the feasibility of simple, less frequent calibration, leading to enhanced user adherence and motivation for use. It is believed that long intervals between recalibrations are essential for a NI device to become a useful home-based self-monitoring of BG solution for diabetes patients.

Use of Diabetes Self-Management Technology Impacts Glucose Variability in Type 1 Diabetes Mellitus

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Objective:
Our aim was to analyze the effect of subjects' use of diabetes self-management technologies (DSMT), specifically, the OmniPod insulin pump (OmniPod) and the Dexcom SEVEN PLUS continuous glucose monitor (Dexcom), on glucose variability (GV) in adults with type 1 diabetes mellitus.

Methods:
Fifty-five subjects equipped with OmniPod insulin management systems (Insulet, Bedford, MA) and Dexcom SEVEN PLUS monitors (Dexcom, San Diego, CA) were observed for 4–6 weeks. Glucose variability was assessed at the onset and end of the study using the average daily risk range (ADRR). Subjects were classified as high risk (ADRR > 30) or low/moderate risk based on their initial GV assessment and further stratified by DSMT usage: intensive—reported DexCom values for ≥75% of the trial period and ≥4 OmniPod behavioral tags daily for ≥75% of the trial—and nonintensive.

Results:
Low/moderate-risk subjects had a marginally higher intensive DSMT use than high-risk subjects (72% versus 67%, respectively). In the high-risk group, use of DSMT, regardless of intensity, reduces GV (intensive 60% versus non-intensive 53%). But in low/moderate-risk patients, intensive DSMT use was associated with a higher proportion of subjects with improved ADRR (38% versus 20%, respectively).

Conclusions:
Our preliminary results suggest that use of DSMT (regardless of intensity) is highly beneficial in individuals with high GV, i.e., high risk for both hypoglycemia and hyperglycemia. Low-risk individuals proved more resistant to the benefits of DSMT, and only intense use led to further improvement in GV.

Noninvasive Thermo-Optic Glucose Monitor

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Background:
We utilized thermo-optic sensing technology to monitor glucose noninvasively.

Method:
A change in blood glucose concentration modifies the intensity distribution of near-infrared light scattered by the human skin. When the intensity profile of back-scattered light (i.e., light intensity versus depth) is acquired at two temperatures, one can accurately determine the glucose concentration in the interstitial fluid. This method combines optical coherence tomography (OCT) with thermal modulation of the skin surface. In contrast to prior attempts to measure glucose using light scattering, with or without thermal modulation, this approach (a) uses OCT to dynamically identify a particular skin layer where the measurement is performed and (b) eliminates confounding tissue interferences through a differential measurement at two temperatures.

Results:
This method was tested on both healthy individuals and diabetes patients both in-house and through a blind study at the University of Massachusetts. The range of glucose concentration measured was 80–430 mg/dl. The noninvasive test results versus commercial test strips readings were plotted on Clarke error grid with >80% in the A region and ~20% in the B region.

Conclusion:
Preliminary results obtained exhibit excellent correlation with blood glucose levels measured by standard methods over a clinically relevant range. Thermo-optic measurements appear to be unaffected by tissue interference.

A Counter-Regulation Model in Type 1 Diabetes

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Background:
Mathematically describing hypoglycemic events is crucial to simulating glucose dynamics in type 1 diabetes mellitus (T1DM) and thus enabling reliable testing of closed-loop control algorithms. The objective of the study is thus to develop a model of glucose kinetics during hypoglycemia and a model of glucagon secretion and kinetics in T1DM subjects.

Method:
The model of glucose kinetics in hypoglycemia is based on the glucose minimal model but assumes that insulin sensitivity is increased when glucose plasma concentrations fall below basal value based on the risk function.

The glucagon model assumes that kinetics are described with a single compartment model and that secretion is regulated by plasma insulin, plasma glucose concentration, and its rate of change under a certain threshold. The models were tested on a data set of 20 T1DM subjects (age 38 ± 12 years; height 174 ± 10 cm; weight 78 ± 12 kg) who underwent a hyperinsulinemic euglycemic and hypoglycemic clamp, where hypoglycemia is induced at a descending rate of 1 mg/dl/min until 50 mg/dl glucose value is reached.

Result:
The model of glucose kinetics in hypoglycemia coupled with the glucagon kinetics and secretion model accurately describes glucose and glucagon plasma concentrations during induced hypoglycemia in T1DM subjects. All the models provide precise estimates of the parameters.

Conclusion:
A counter-regulation model in T1DM has been successfully developed that allows us to properly describe blood glucose and glucagon plasma concentration during hypoglycemia in T1DM subjects.

MIMURA V Dimension Healing on Pico-Nonchemical Technology

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Objective:
The aim is to convert MIMURA into a H2O cluster of colloidal mineral metals with nitrogen, carbon, toxin, bacteria, and virus in a cell mitochondria of healing deoxyribonucleic acid (DNA)/ribonucleic acid (RNA) of adenosine-5'-triphosphate, apoptosis, immunity, and memory-tip to resolve metabolic failure of body cells of all internal organs, blood (red corpuscle, lymph in leukocyte, plasma), vessels, and tissue systemization. All diseases are caused by oxygen deficit and diabetes, and cardiac and cancer diseases by cellular oxygen deficit means the positive electron energy deficit on quantum physics dynamic. Diabetes is a standard bearer of oxygen deficit on insulin that shall cause incurable diseases. H2O of hydrogen for oxygen combined with natural positive energy on Earth shall sympathize with colloidal minerals, vitamins in amino-protein of mitochondria. As a result, processing proteins at amino acid constructs dimensions of phosphoric acid, D-glucose, adenine-thymine/guanine-cytosine bases, alpha helix, and beta sheet. Integrated DNA/RNA/P53, synthesis enzymes-hormones, noradrenalin and serotonin in nervous PC12, alpha wave and spirit, glycol-CD4/CD8, helper T, embryonic stem cells, and extracellular matrix shall have high-voltage energy against virus, bacteria, free radical, cancer DNA RAS21, toxin, depression, and atomic nucleus at negative energy under nature principle.

Method:
Subjects are given MIMURA (M) energy water: 1~1.5 liter/day for quality of life, drink/cook/take a bath. Quality is much oxygen, nonoxidization, non-free radical, nanocluster, hardness CaCO3/Mg over 50% down for melt-soft, colloidal minerals and NO3/SO4 compound, low surface tension, high penetration, high electric conduction, self-destruction of bacteria and virus, air infective protection, ammonia resolution, smell methane volatilization, pH for low, ion radiation. Subjects were given Super ATORU (S) liquid: 40~60 cc/day. Morning/evening, subjects have huge oxygen and colloid minerals energy in a nano-tornado cluster of low pH.

Result:
After M for 3 months, diabetes with hypertension, atopy, kidney stone, menstrual dark, hemoglobin A1c 6.7–5.8%, skin normal, stone melt, blood fresh color, and no pain. After M and S for 4 months,

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(1) before human immunodeficiency virus/RNA 373,455/ml CD4 148 after 20 days and 186,915/ml CD4 62 and healing for healthy fat; (2) cancer (brain glioblastoma multiforme stage 3) with diabetes, after 2 months restrain and stop tumor expand and decrease for recovery with refresh hair and skin; (3) diabetes with hypertension and cardiac and kidney diseases and much neutral fat, before glycogen 270 after 2 months 110 for healthy recovery; and (4) myocardial and cerebral infarction, cancer (breast/womb/stomach), leukemia, hepatitis, vertebra carries, articular rheumatism, arthritis, neuralgia, Alzheimer, and alcoholic since 1997 research and development on clinical tests.

Conclusion:
MIMURA and S would be able to extend the average of healthy lifespan for the 22nd century's hope.

Use of a Unique System to Transmit Home-Based Monitoring of Glucose and Blood Pressure Compared with Usual Diabetes Care Management

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Objective:
We sought to determine whether patients using a home-based diabetes telemetry device (TELE) to transmit blood glucose and blood pressure readings have better outcomes after 6 months than usual-care managed patients (CNTL).

Methods:
We randomized 259 adult patients with type 2 diabetes [hemoglobin A1c (HbA1c) = 7.5–10.5%] to TELE or CNTL for nurse management with current Kaiser clinical protocol. For the TELE group, glucose (OneTouch Ultra) and blood pressure readings were transmitted using serial cable and weight was transmitted wirelessly to the Samsung device. We evaluated self-efficacy using the diabetes management self-efficacy scale for type 2 diabetes (DMSES).

Results:
A total of 199 patients (TELE = 105, CNTL = 92) completed the 6-month program. Baseline age (CNTL 56.4 versus TELE 54.8), gender (female: CNTL 40% versus TELE 37%), and body mass index (CNTL 35.5 versus TELE 34.8) were similar in both groups. There were no baseline differences in systolic blood pressure (CNTL 127.3 versus TELE 129), low-density lipoprotein (LDL) cholesterol (CNTL 88.4 versus TELE 90.9), fructosamine (CNTL 324 versus TELE 315.6), HbA1c (CNTL 9.2% versus TELE 9.4%), or self-efficacy score. Minimal changes in systolic blood pressure (CNTL -3.2 versus TELE -6.3 mm Hg) and fructosamine (-59.4 versus -54.9) were observed at 6 weeks. Low-density lipoprotein decreased more at 6 weeks (-2.4 versus -12.6). Over 6 months, LDL decreased 5.4 mg/dl in CNTL versus 17.1 mg/dl in TELE subjects (p = .045). Hemoglobin A1c decreased 1.8% versus 2.0% over 6 months.

Conclusions:
In patients with type 2 diabetes and excellent prior control of blood pressure and LDL, the use of a unique telemetric device to download information was associated with improved control of LDL. Glycemic control as assessed by HbA1c improved significantly over 6 months of care management with or without the device.

Prevalence of Diabetic Complications in Rural Tamil Nadu Using Telemedicine: The Chunampet Rural Diabetes Project

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Objective:
This study was initiated to estimate the prevalence of diabetes and its complications in rural Tamil Nadu using telemedicine.

Method:
The Chunampet Rural Diabetes Project is an ongoing project initiated in a cluster of 42 villages in and around Chunampet village in Kancheepuram district in Tamil Nadu in South India. A mobile telemedicine van fitted with a digital retinal camera, biothesiometry, Doppler, electrocardiogram (ECG), and laboratory facilities went around all the villages screening for diabetes and associated complications. Capillary fasting blood glucose (FBG) testing was done using a handheld glucometer to screen for diabetes. Subjects with FBG levels > 100 mg/dl (>5.6 mmol/liter) underwent a 75 g oral glucose tolerance test using a venous plasma sample. High-resolution retinal images from the telemedicine van were transmitted to the main diabetes center located at Chennai through the satellite connectivity. Through video conferencing, the ophthalmologist provided online consultations with the persons with diabetes.

Result:
Of the 27,014 adults aged ≥ 20 years in the 42 villages, 23,308 subjects (86.5%) were screened for diabetes. Of the 1763 individuals who were found to have diabetes (1556 individuals with self-reported diabetes and 207 with newly detected diabetes), diabetic retinopathy was detected in 313/1737 subjects with gradable photographs (18.0%). Diabetic neuropathy defined as vibratory perception threshold of the great toe ≥ 20 V using biothesiometry was present in 298/1001 subjects (29.8%). Peripheral vascular disease defined as ankle-brachial index <0.9 was seen in 76/1001 subjects who underwent Doppler studies (7.6%). Coronary artery disease (CAD) based on medical history of CAD and/or Minnesota coding of ECGs was seen in 119/772 subjects (15.4%).

Conclusion:
This is the first study on prevalence of diabetic complications from rural India using a telemedicine facility.

Health-Related Quality of Life in Patients with Type 1 Diabetes

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Objective:
Considering the importance of quality of life (QOL) that could be affected in chronic diseases, including diabetes, this study was conducted to evaluate health-related QOL in patients with type 1 diabetes (T1DM).

Method:
A total of 150 T1DM patients were enrolled from Institute Endocrinology and Metabolism in this cross-sectional study. A QOL questionnaire validated for assessment of QOL in people with T1DM in Iran was used. The questionnaire included 20 questions in five areas of social relationships, emotions, daily activity, academic performance, and treatment.

Result:
Mean age of the subjects and duration of disease were 22.14 ± 6.84 and 8.97 ± 7.14 years, respectively. The mean score for general QOL was 70.70 ± 13.95 in men and 67.27 ± 11.87 in women. There was no significant difference in general QOL between men and women. However, in the treatment area, QOL in men (65.64 ± 16.65) was higher than women ($p < .05$). General QOL was significantly correlated with duration of diabetes and type of insulin. In patients who have been treated with insulin analogs, general QOL and areas of emotions, social relationships, academic performance, and treatment were better.

Conclusion:
This was the first study to determine QOL in patients with T1DM in Iran. Comprehensive diabetes care, including mental health counseling and structured patient education programs, might improve QOL in this group of people.

Real-Time Blood Glucose Management and Alert System

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Objective:
Control of blood glucose levels can significantly reduce the risk of developing diabetes-related complications, improve patients' quality of life, and cut down costs on medical expenditures. The value of blood glucose data gathered by current glucose meters can be greatly enhanced if these data can be immediately transmitted to, stored in, and analyzed by a remote data management system.

Method:
The WM System by Wireless Medical connects a glucose meter with a Web-based management system that provides instant alerts. This allows for automatic, ongoing, and real-time management of blood glucose levels by caregivers, relatives of patients, and health care professionals. The glucose meter device is integrated with an embedded cellular connectivity module that provides a data channel between the glucose meter and the Web-based management system. The WM management system analyzes the accumulated data and generates alerts in case of missing or out-of-target glucose levels. Alert settings, such as alert addressee and alert media, can be easily modified by the caregiver as well as by the patient.

We tested the integrated WM device with 20 subjects with diabetes. Their mean age was 42 years. All 20 subjects owned a mobile phone. Each subject measured a simulated blood glucose level using a control solution glucose meter device twice, and the two data points of simulated blood glucose levels per subject were transmitted to the Web-based management system. Subjects were asked to compare between use of control solution and standard blood glucose monitor not enabled for automatic wireless data transmission.

Result:
One hundred percent of the 40 data points were transmitted accurately to a secure subject-individualized dedicated Web site, within no more than 60 s per blood glucose data point following display of the blood glucose level on the monitor screen. Within 120 s of display of each simulated blood glucose value on the monitor screen, 100% of the 20 subjects received a notification to their mobile phone that their data points (two per subject) had been uploaded. One hundred percent of the alerts generated by the simulated data were submitted within 120 s and in-line with the individualized preconfigured alert settings. In addition, all 20 subjects reported that the use of the WM System did not pose additional complexities to their current blood glucose test procedure.

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Conclusion:
Our WM meter uploaded data accurately and within 1 min to a secure server in 100% of 20 subjects with diabetes. Proper alerts were generated in 100% of the relevant measurements and submitted according to the preconfigured alert settings. The integrated connectivity of the blood glucose meters with the management system ensured a reliable transmission of blood glucose data, real-time analysis of the glucose data, and generation and submission of alerts in case of missing or out-of-target blood glucose levels—without negatively affecting current usage patterns.

Sitagliptin Reduces Microalbuminuria in Patients with Type 2 Diabetes Mellitus

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Objective:
Sitagliptin, a dipeptidyl peptidase-4 inhibitor, is a newly developed oral hypoglycemic agent. Its efficacy for the management of diabetic kidney is known in animal models but remains unproven in humans. The aim of this study was to study the effect of sitagliptin on microalbuminuria patients with type 2 diabetes mellitus (T2DM).

Method:
Sixty patients with T2DM [age 20–80 years, hemoglobin A1c (HbA1c) > 8.4%] were enrolled and randomized to patients taking sitagliptin 50 mg once a day and other drugs (metformin, glinide, or α-glucosidase inhibitor). We evaluated at baseline and after 3 months following parameters of body weight, blood pressure, HbA1c, fasting plasma glucose, fasting plasma insulin, C-peptide immunoreactivity, homeostatic model assessment of insulin resistance, homeostatic model assessment of beta-cell function (HOMA-β), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, triglycerides, and microalbuminuria. The primary outcome of the study was changes in microalbuminuria at 3 months, and the secondary outcome was HbA1c and LDL-C at 3 months.

Result:
(1) Sitagliptin significantly reduced microalbuminuria within 3 months, whose changes were marked in patients with a higher amount of microalbuminuria. (2) There was no significant correlation between decrease of microalbuminuria and improvement of glucose metabolism, lipid metabolism, and blood pressure. (3) A significant decrease of HbA1c was obtained in both groups without any significant differences between the two groups. Fasting plasma glucose was decreased only in the sitagliptin group. Fasting plasma insulin was not changed in both groups. Homeostatic model assessment of insulin resistance was decreased significantly, and HOMA-β values were increased in the sitagliptin group. (4) Sitagliptin significantly reduced LDL-C. (5) Body weight and blood pressure were not changed in both groups.

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Conclusion:
These results suggest that sitagliptin improved not only glucose and lipid metabolism but also albuminuria at 3 months of treatment in patients with T2DM. The mechanism of reduced microalbumin might be a direct effect as well as a yet undetermined factor caused by an increase in active glucagon-like peptide-1, despite the blood pressure, body weight, and glucose metabolism.

Glucose-Responsive Fluorescent Copolymer Material for a Long-Term, Fully Implantable Sensor

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Background:
A fluorescent glucose-sensing copolymer material that can be integrated with a wireless optical spectroscopy interface and enable a long-term fully implantable glucose sensor has been developed. This biocompatible and stable polymer, grafted onto the surface of our miniaturized optical sensor platform, allows for the direct measurement of interstitial fluid glucose after subcutaneous implantation. Herein, we describe the chemical structure, glucose sensing mechanism, and *in vitro* and *in vivo* performance of this material.

Method:
Glucose-sensing copolymer materials were characterized *in vitro* on a spectrofluorophotometer and *in vivo* by merging the polymer with our miniaturized wireless optical interface. *In vitro* and *in vivo* testing focused on signal response, stability, interference, and biocompatibility.

Result:
In vivo longevity was demonstrated in animal and human clinical trials. *In vitro* performance was evaluated in pH 7.4 phosphate-buffered saline at 37 °C. The glucose-sensing copolymer material shows a large fluorescent response to glucose over a wide range of concentrations, with a dissociation constant of ~400 mg/dl and a response time (t90) of less than 5 min. No other monosaccharides or disaccharides interfere over clinically relevant concentrations. Biocompatibility tests were completed in accordance with International Organization for Standardization 10993 guidelines.

Conclusion:
This biocompatible polymer provides the responsivity, selectivity, and stability required for interstitial glucose measurements. Merging this material with a wireless interface system has enabled accurate *in vivo* glucose measurement from subcutaneously implanted sensors during a 3-month nonhuman primate trial. Preliminary human clinical results indicate stability for durations greater than 6 months.

Improved Consistency of Pharmacokinetic and Glucodynamic Responses Using Recombinant Human Hyaluronidase Pretreatment with Continuous Subcutaneous Insulin Infusion in Type 1 Diabetes Mellitus

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Objective:
Rapid analogs delivered by continuous subcutaneous insulin infusion (CSII) exhibit variable insulin pharmacokinetic (PK)/glucodynamic (GD) profiles as infusion sets age. This study compares recombinant human hyaluronidase (rHuPH20) pretreatment followed by CSII using NovoLog to NovoLog alone on insulin PK/GD over infusion set life.

Method:
Subjects with type 1 diabetes mellitus who use CSII were recruited to a randomized two-way crossover inpatient study. New infusion sets were placed, and rHuPH20 (150 U in 1.0 ml) or sham injection was rapidly infused. After 2, 26, and 74 h of basal infusion, a bolus of 0.15 U/kg of NovoLog was followed by a 6 h euglycemic clamp study. Subjects were readmitted 5–14 days later for repeat study using the other treatment condition.

Results:
Interim data with NovoLog alone showed systematic variability in insulin PK/GD profiles, as previously observed. Onset of action (early $t_{50\%}$) progressively fell over 72 h of infusion set use from 58–21 min ($p = .007$) and duration of action from 186–140 min ($p < .0001$).

With rHuPH20 pretreatment, both PK and GD maintained a consistent ultrafast profile. Relative to NovoLog alone, rHuPH20 pretreatment followed by 2 h of infusion set use accelerated the onset of action (-35 min, $p = .01$) and shortened the duration of action (-34 min, $p = .001$). Over the infusion set life, this ultrafast profile remained consistent, with an onset of action from 24–35 min ($p \geq .2$) and duration of action from 139–152 min ($p \geq .2$). Thus variability in these parameters over time was reduced from 37 to 11 min for onset and 46 to 13 min for duration of action.

Conclusion:
Pretreatment with rHuPH20 provided a consistent ultrafast PK/GD profile over infusion set life and greatly reduced the PK and GD variability observed for rapid-acting analog alone across infusion set life.

Clinical Feasibility Study of a Transdermal Optical Fiber Glucose Sensor

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Objective:
Current continuous glucose monitoring systems (CGMSs) exhibit a rather short lifetime. We present *in vitro* and *in vivo* data of a novel CGMS (FiberSense) with improved duration of action based on a fluorescent biosensor placed on the tip of a 500 µm polymeric optical fiber.

Method:
In vitro investigations were performed in a flow cell either under stepwise glucose concentration variation or employing varying glucose concentration gradients (up to ±4 mg/dl/min). *In vivo* FiberSense was inserted perpendicular to the subcutaneous abdominal tissue in four patients and compared with a commercially available CGMS simultaneously placed on the contralateral body area. Fluorescence was measured using a self-developed personal-computer-driven two-channel photometer.

Result:
Under *in vitro* conditions, sensor resolution was as good as (2.6 ± 0.5 mg/dl). In a 26.5 h experiment (9426 records), blood glucose changes were modeled in a range of 50 to 450 mg/dl glucose with various glucose slopes. Measured glucose concentrations showed no significant deviation from defined concentrations reflected by mean absolute relative difference of 7.9% (99.8% within limits of International Organization for Standardization 15197). The calibration was based on independent stepwise glucose concentration response data of the same sensor. FiberSense was clinically well tolerated during 14 days of wearing time, without any complications or signs of inflammation at the insertion site. Early results clearly showed proper functionality of our CGMS sensor during this time period.

Conclusion:
The present clinical feasibility study proves the capability of FiberSense to replace current CGMSs, with the possibility to extend wearing time up to 21 days.

New Optical Method for Blood Glucose Self-Monitoring

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Objective:
Many noninvasive blood glucose monitoring technologies try to replace conventional finger sticking. So far, all approaches have failed because of insufficient accuracy and/or long-term instability. The new concept to overcome these drawbacks is based on a glucose-specific biosensor placed under the conjunctiva of the eye, an ideal place for blood glucose monitoring. Replacement is scheduled once per year. Data are presented proving the short- and long-term feasibility of this new blood glucose self-monitoring approach.

Method:
Small hydrogel disks with an embedded biochemical sensor were inserted below the conjunctiva of 22 insulin-dependent diabetes patients (two cohorts, 12 and 10 patients) under local anesthesia. Disks were optically interrogated by the patients with a small handheld fluorescence photometer over a period of up to 180 days. Data were taken during glucose challenge conditions and compared against capillary blood glucose (laboratory method).

Result:
In a first cohort, the mean absolute relative difference (MARD) was 6.9% in the first week. A total of 97.4% of combined data points were within the limits of International Organization for Standardization 15197 (100% in combined zones A and B of consensus error grid). In a second cohort with a modified sensor, MARD was 7.7% in the first week, increasing to 12.6% after 180 days (still 100% in zones A and B of consensus error grid). The minimally invasive insertion was painless and simple, implants were well tolerated at all times, and measurements were fast and easy (approximately 10 s).

Conclusion:
Clinical results impressively show the new technology's potential to replace finger sticking for blood glucose measuring. The accuracy could be largely maintained over a period of 180 days. After insert placement, the method allows convenient, frequent, noninvasive measurements.

Determination of Dexterity and Cognitive Function Greatly Deviates from Self-Assessment in Patients with Type 1 and Type 2 Diabetes Mellitus

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Background:
Insulin-treated patients perform complex treatment activities during their daily routine, such as blood glucose measurements or insulin injections. The goal of this study was to compare the patients' self-assessment of their dexterity skills with the results of validated dexterity and cognitive function tests [Jepsen–Taylor hand function test (JHFT) and the number connection test].

Methods:
The JHFT consists of seven subtests, of which at least four need to be passed to be considered "not impaired." Also, neuropathy was assessed by means of heat, cold, pain, and vibration perception threshold determination (Medoc TSA 2001). We enrolled 90 patients (36 females, 54 males) from four different groups: (A) 15 type 1 with clinically suspected dexterity impairment [age 60 ± 9 years; hemoglobin A1c (HbA1c) 6.9% ± 0.7%; body mass index (BMI) 26.8 ± 4.1 kg/m^2]; (B) 30 type 2 with clinically suspected dexterity impairment (age 61 ± 10 years; HbA1c 7.5% ± 1.2%; BMI 36.3 ± 7.4 kg/m^2); (C) 30 type 1 or type 2 with visual impairment (age 64 ± 6 years; HbA1c 7.3% ± 1.0% ; BMI 32.5 ± 6.9 kg/m^2), and (D) 15 type 1 or type 2 without any other concomitant condition (control group; age 64 ± 5 years; HbA1c 7.0% ± 1.0%; BMI 30.5 ± 5.5 kg/m^2).

Results and Discussion:
There were no major pathological findings in the neuropathy and cognitive function tests. Patient self-assessment revealed that all, but two patients from group B, considered themselves to have no dexterity impairment. When performing the JHFT with the dominant hand (normal age-related reference score 5.5 s), all but the control group showed significant dexterity impairment in the mean JHFT score (A, 6.8 ± 3.2 s; B, 6.8 ± 3.2 s; C, 6.5 ± 3.8 s; D, 5.8 ± 3.8 s, $p < .05$ versus all other groups). All patients from A and B, 33% from C, and 0% from D had impaired dexterity according to the individual JHFT criteria.

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Conclusion:
Impairment of dexterity (independent from neuropathy or cognitive function) was more frequent than what the patients actually expected. It may be worthwhile to consider these findings when developing new diagnostic or therapeutic devices for patients with diabetes mellitus, as it may affect their individual performance with (and their preference for) a particular device.

Effects of Human Serum on Free and Encapsulated Porcine Islets: An *in Vitro* Study

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Background:
We tested the effect of human serum, both fresh and heat-inactivated, on free and microencapsulated adult porcine islets (APIs) and neonatal porcine islets (NPIs).

Method:
Studies were performed with wild-type (WT) APIs and WT and Galactose-α1,3-Galactose (Gal)-negative (ve) NPIs. Islets were encapsulated in low-viscosity high-mannuronic-acid (LVM) alginate gelled with barium (Ba) or calcium-gelled alginate coated with poly-L-lysine (PLL) and a final layer of dilute alginate-poly-l-lysine-alginate (APA). Free and encapsulated islets were incubated in the following media: a 50:50 mixture of M199 medium and fresh human serum, a 50:50 mixture of M199 medium and heat-inactivated human serum, and M199 medium with 10% porcine serum. At 4 days postincubation, islet viability was evaluated by calcein AM/ethidium bromide and confocal microscopy and insulin secretion by enzyme-linked immunosorbent assay.

Results:
Incubation in M199 medium plus human fresh serum resulted in death of free APIs and free WT and Gal-ve NPIs but not of APIs or NPIs encapsulated in LVM-Ba or APA beads. When free and encapsulated APIs and NPIs were incubated in the presence of medium plus heat-inactivated human serum or medium with 10% porcine serum, no significant cell death occurred.

Conclusion:
LVM-Ba and APA encapsulation systems protect APIs and WT/Gal-ve NPIs from the effects of human serum under *in vitro* culture conditions. Results also indicate that immune recognition of NPIs does not occur via the Gal epitope only.

Effects of Hypoxia on Free and Encapsulated Adult Porcine Islets: An *in Vitro* Study

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Background:
We tested the effect of hypoxia on free and microencapsulated adult porcine islets (APIs).

Method:
Studies were performed with APIs free and encapsulated in low-viscosity high-mannuronic-acid (LVM) alginate gelled with barium (Ba). Free and encapsulated APIs were incubated in M199 medium with 10% porcine serum for up to 6 days under normoxic (100% air saturation or 21% oxygen) and hypoxic conditions. Hypoxia (0.3–5% air saturation or 0.063–1.05% oxygen) was established by pumping a gas mixture comprised of 95% N_2+5% CO_2 into a chamber, which was kept on an orbital shaker in a CO_2 incubator. At different time points, islet viability was evaluated by calcein AM/ethidium bromide and confocal microscopy and insulin secretion by enzyme-linked immunosorbent assay.

Results:
When cultured for 6 days under normoxic conditions, free and encapsulated APIs exhibited no significant changes in size or shape and islet viability remained stable. In contrast, free APIs cultured under hypoxic conditions for 1 day began to disaggregate, and islet viability decreased. Disaggregation continued with time and became most severe by day 6, with apparent lysis of many cells. However, when APIs were encapsulated in LVM-Ba and incubated under hypoxic conditions, there was minimal, if any, disaggregation, with the difference from free APIs being most pronounced on day 6.

Conclusion:
Under hypoxic conditions, free APIs exhibited disaggregation with lysis by day 6. Encapsulation of APIs in LVM-Ba helped them tolerate hypoxia, as the islets maintained their integrity and viability for up to 6 days.

Rate of Occurrence and Risk Factors for Development of Hypoglycemia during Treatment Intensification in Type 2 Diabetes Mellitus

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Background:
Fear of hypoglycemia may inhibit diabetes treatment intensification (TI). The Structured Testing Program study, a prospective, cluster-randomized, multicentered clinical trial, showed significant glycemic improvement after TI based on structured self-monitoring of blood glucose (SMBG) in 483 poorly controlled [hemoglobin A1c (HbA1c) ≥ 7.5%] type 2 diabetes mellitus (T2DM) patients.

Method:
Patients in the intervention group (STG) used the ACCU-CHEK 360° View blood glucose analysis system (tool) to collect seven-point glucose profiles for three consecutive days at multiple visits. We analyzed risk for developing hypoglycemia and rate of occurrence in the STG patients. The SMBG values (n = 19,270) were collected from all tools (n = 991) completed by STG patients. Hypoglycemia was defined as any blood glucose value ≤ 80 mg/dl. At study end, risk factors for hypoglycemia were calculated, drug interactions were determined with MICROMEDEX interactions check, and timing of hypoglycemia was explored.

Results:
Hypoglycemia rate over one year was 2.4% (n = 470) with 3.6% (n = 17) of all hypoglycemia events < 50 mg/dl. The rate at the study start was 1.4% (n = 65) and increased significantly (p < .0001) to 3.8% (n = 128) at study end. Most hypoglycemia occurred before lunch (25.5%). Significant independent risk factors for hypoglycemia included age > 65 years, diabetes duration ≥ 10 years, HbA1c < 7.0%, HbA1c < 6.5%, elevated triglycerides, and drug interactions that specifically indicated increased risk of hypoglycemia. Hemoglobin A1c reduction > 1.0% and medication class were not independent risk factors for hypoglycemia.

Conclusion:
Treatment intensification facilitates improved glycemic control but with increased hypoglycemia risk. Use of TI and presence of risk factors increases the need to monitor for hypoglycemia. Structured SMBG may aid in the detection and/or prevention of hypoglycemia in T2DM patients undergoing TI.

Retrospective Analysis of Events Preceding Low Glucose Suspend Activation in Pediatric Subjects on the Paradigm Veo System

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Objective:
The Paradigm Veo system (Medtronic MiniMed Inc., Northridge, CA) with low glucose suspend (LGS) halts insulin delivery for ≤2 h when sensor glucose values reach a predetermined threshold (40–110 mg/dl). CareLink Pro 3.0 Episode Summary describes occurrences from a list of 22 events within the 3 h preceding hypoglycemic/hyperglycemic episodes. This algorithm was applied to CareLink data to analyze occurrences of 12 events within the 3 h preceding LGS activation in pediatric subjects (<16 years).

Method:
Data from pediatric Veo users in 2010 (1100 subjects; 563 male) totaling 37,042 patient days (75% with LGS on) were extracted from the CareLink database. Events occurring up to 3 h before each of 28,489 LGS activations were retrospectively analyzed with the Episode Summary algorithm and compared by night (10:00 PM–8:00 AM) versus day (8:00 AM–10:00 PM) and by <2 h versus 2 h duration.

Result:
Rapid negative rate of change (–ROC; ≤–2mg/dl/min; 47.63%) and hyperglycemia (30.61%) most frequently preceded nighttime LGS; daytime LGS was most commonly preceded by –ROC (61.33%), food bolus (FB) with Bolus Wizard (43.19%), and hyperglycemia (≥180 mg/dl; 41.23%). Low glucose suspend lasting <2 h versus 2 h showed a higher mean percentage preceded by FB ($p < .0001$), hyperglycemia ($p = .0008$), and –ROC ($p = .0014$). Nighttime LGS lasting <2 h versus 2 h showed a higher mean percentage preceded by bolus with –ROC ($p < .0001$) and FB ($p = .0004$). Daytime LGS lasting <2 h versus 2 h showed a higher mean percentage preceded by bolus with –ROC (≤–1.5 mg/dl/min; $p = .0361$); manual bolus more commonly preceded daytime LGS lasting 2 h than <2 h ($p = .0023$).

Conclusion:
Use of CareLink Pro 3.0 Episode Summary algorithm allows analysis of events preceding LGS and can help identify pediatric behaviors that may contribute to hypoglycemia.

Comparison of Insertion Force and Assessment of Pain during Insertion between a Single-Needle and a Dual-Needle Transcutaneous Device

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Objective:
New approaches in diabetes management, such as bihormonal therapy or use of devices that incorporate both insulin delivery and glucose measuring elements in one transcutaneously inserted device, require commencing of devices that have more than a single insertion needle. The objective of this study was to investigate the difference in forces needed to insert single-needle and dual-needle subcutaneous devices and how it relates to pain perceived by the patient.

Method:
A load cell was used to collect the insertion force data for single-needle and dual-needle insertions into a moistened circular chamois material, which was used as a skin substitute. Various depth offsets of the dual needle were tested, and the peak insertion forces were measured.

Next, a blinded, randomized study was conducted by inserting single-needle (control) and dual-needle depth offset devices into the lower back of 17 subjects. Subjects' pain level evaluation was assessed using a numeric pain rating scale (scale of 0–10).

Result:
Analysis showed that offsetting the needles in depth resulted in lower insertion forces over inserting both needles at the same vertical distance, 0.888 ± 0.186 and 1.181 ± 0.205 lb peak force, respectively (n = 59).

In the pain study, for both single-needle and dual-needle devices, the pain level never exceeded "mild" (0–3 on numerical pain scale). Additionally, there was not a statistically significant difference in pain level during insertion of the single-needle and dual-needle configurations.

Conclusion:
For a dual-needle transcutaneous device, a lower insertion force was observed for needles that were depth offset. Insertion pain caused by single-needle and dual-needle devices was comparable.

Ten Years' Experience with Specific Analytical Quality Specifications for Self-Monitoring of Blood Glucose Devices in Norway

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Background:
Norway established a national system with analytical quality specifications for the reimbursement of self-monitoring of blood glucose (SMBG) strips in 2002. This implies that SMBG devices have to be evaluated according to a protocol that involves approximately 100 diabetes patients.

Method:
The evaluations are standardized and should be performed independently of the manufacturer. Analytical requirements apply for health care professionals (target ± 20%) as well as for lay users (target ± 25%). At concentrations < 4.2 mmol/liter, allowable deviations are ±0.83 and ±1.0 mmol/liter, respectively.

Results:
The 17 standardized evaluations show that the analytical quality improved from 2002 to 2005 and has been rather constant onward. The national system has limited the number of different types of SMBG strips, and at the moment, there are 15 test strips on the market, a decrease from 21 in 2002. In 2002, it was a mix of whole blood and plasma glucose test strips, but now all test strips report plasma glucose results. Forty-eight applications for reimbursement of European Conformity (CE)-marked test strips have been considered: 23 applications for completely new test strips, 17 for new versions, and 8 for parallel imported test strips. Seventy-four percent (17) of the new test strips satisfy the quality specifications, and 26% (6) do not. An important reason for this might be the requirement for independent evaluations that is not necessary for CE-marking. Distributors selling SMBG strips that do not meet the requirements never do apply for reimbursement. None of the 11 SMBG systems that do not meet the International Organization for Standardization 15197 requirements in an independent study of 27 CE-marked SMBG systems have ever been on the Norwegian market.

Conclusion:
Preventing SMBG systems with poor analytical quality from coming into the market is an important effect of the Norwegian system.

Progressive Improvements in Continuous Glucose Monitoring Algorithms

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Background:
In continuous glucose monitoring, the algorithms used to calculate glucose and detect faults play an important role in improving sensor performance. Medtronic currently has two real-time algorithms available, and a third prototype version is currently in development. This analysis examined the performance of these algorithms.

Method:
Sensor data were taken from the recent Enlite Adult Pivotal Trial and reprocessed using each algorithm. While each subject in the trial typically took four finger stick readings per day, only two readings per day were using in this reprocessed analysis. Accuracy metrics were calculated by comparing the finger stick reading that occurred within 5 min.

The calculated metrics include day 1 mean absolute relative deviation (MARD), overall MARD, and the percentage of accurate points, as defined by International Organization for Standardization 15197 (0–75mg/dl). The hypothetical calibration error alarms were also noted during reprocessing.

Results:
The results show accuracy has improved with each generation. In the prototype algorithm, the fault detection has improved, resulting in fewer calibration alarms, but more of these alarms result in ending the sensor to maintain accuracy.

Conclusion:
These results show encouraging progress in developing better algorithms that are more accurate and have better fault detection.

Strategies that Work for Glucose Control in the Community Hospital

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Objective:
The objective of this project was to develop a glycemic management system that could improve care of persons with preexisting diabetes when they are admitted to our 400-bed California community hospital for treatment of acute illnesses. Diabetes is best managed as a chronic illness, and acutely ill diabetes patients are subjected to physiological stressors that require careful glycemic management.

Method:
The Northridge Hospital Medical Center (NHMC) interdisciplinary diabetes committee designed and implemented evidence-based practices, including: a teaching campaign for nurses and patients on timing insulin injections with meals; introducing carbohydrate counting with carbohydrate-to-insulin ratios; initiating preprinted basal–bolus order forms for all insulin orders; identifying diabetes patients on the census board and meal trays; introducing insulin pump policy on all units; including patient input on insulin dosing and carbohydrate counting in insulin injection policy; amending pharmacy policy on the use of secretagogues and correction insulin as redundant; eliminating premixed insulin from the formulary; eliminating hour of sleep coverage if not specifically endorsed by prescriber; and adding to standardized orders a midsleep blood glucose check without coverage for the most vulnerable.

Result:
Currently, house-wide hypoglycemia (<70 mg/dl) is less than 3% with less than 1% in the intensive care unit and hyperglycemia (>250 mg/dl) is 30%. Laboratory limitations prevented collection of preintervention data, but anecdotal reports suggest improvement.

Conclusion:
The NHMC has achieved effective glycemic management of acutely ill patients with preexisting diabetes that is supported by a hospital-wide plan that overcame barriers of resistance to practice changes, physician unfamiliarity with basal/bolus dosing, fears of hypoglycemia, nurses' limited knowledge, and patients' physiological instability.

A Simulation Tool for Validating Inpatient Glucose Management

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Objective:
The objective of this study was to develop and validate a simulation environment for testing inpatient glucose management algorithms.

Method:
A subset of 6773 patients was randomly identified from data collected during the clinical application of EndoTool software at 61 hospitals. The mean length of stay per patient was 1.95 ± 2.49 days, and the mean number of glucose samples per patient was 33.72 ± 40.06. The patient population had the following demographics: the mean weight was 89.49 ± 45.63 kg; the mean age was 60.63 ± 18.36 years; 61.46% of the patients were male; 34.07%, 13.72%, and 52.21% were type 1, type 2, and nondiabetic, respectively. Virtual patients, each representing the glucose/insulin dynamics and changes in insulin sensitivity through time of a specific patient, were developed on the basis of the selected clinical data. The set of models was then used to simulate glucose control with EndoTool glucose management software.

Result:
Virtual patients were evaluated to determine how closely they matched (or fit) the original data and were able to predict glucose levels 60 min in advance. Mean error in the fit was 0.21% ± 0.29%, and prediction error was 5.29% ± 10.15%. Additionally, a cross-validation study was performed on two independent data sets, each using a different EndoTool software configuration (target glucose range 95–135 versus 130–160 mg/dl). The results indicate that virtual patients developed from one set of data can predict the glucose distribution of another independent data set.

Conclusion:
The simulation environment accurately represents and predicts the clinically observed inpatient glucose management in the intensive care unit; therefore, it provides a safe environment to evaluate EndoTool software enhancements as new forms of treatment become available and target glucose ranges in different subpopulations change.

Ambulance-Requiring Hypoglycemia in a Population-Based Nondiabetic Cohort

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Background:
We evaluated the prevalence, etiology, and outcomes of hypoglycemia associated with emergency medical service (EMS) among patients with no diabetes mellitus (non-DM).

Methods:
We retrieved all Gold Cross ambulance calls among non-DM patients with blood glucose < 70 mg/dl in Olmsted County between January 1, 2003, and December 31, 2009, and reviewed medical records.

Results:
A total of 131 patients made 142 EMS calls, age 51 ± 19 years, 54% females. Duration of follow-up was 1.28 (interquartile range 0.13–2.70) years. Causes of hypoglycemia were critical illness in 42 (32%) patients, alcohol and polysubstance use in 36 (27.5%), insulinoma/bariatric surgery in 10 (8%), poor oral intake due to different factors in 7 (5%), and multiple factors in 36 (27.5%). Patients with alcohol and polysubstance abuse were younger (p = .002). Ten patients made repeated calls, 17 patients had 19 hypoglycemia predisposing comorbidities (adrenal deficiency in 2, end-stage renal disease in 11, and chronic liver disease in 7), and 35 patients were on medications associated with hypoglycemia (34 on beta blocker and 1 on pentamidine). Repeated calls and emergency room transportation were similar between different etiologies (p = .28 and p = .67, respectively). Hospitalization varied across the etiologies, with lowest among the multiple-factor-related hypoglycemia (p = .01); however, duration of hospitalization was similar (p = .67). Thirty-seven patients died, and age-adjusted mortality varied across the hypoglycemia causes (p < .001) with highest among critically ill. Cancer caused the highest number of deaths (19%), while one death was due to hypoglycemia.

Conclusions:
Hypoglycemia associated with EMS in non-DM patients is not uncommon. Critical illness, multifactorial causes, and alcohol and polysubstance abuse are common causes. Hospitalization and mortality was higher with critical illnesses. A critical clinical pathway for such patients has the potential to improve outcomes.

Decision Theory Enables Self-Treatment "Reengineering" in Type 1 Diabetes Mellitus

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Objective:
Decision theory provides a systematic approach to engineering design and control under uncertainty. Perceiving insulin self-treatment in type 1 diabetes mellitus as an optimization problem with significant uncertainties, it is of interest to know whether the tools of decision theory can be applied to reach treatment objectives.

Method:
Thirty-four systems engineering graduate students, all taking the elective course SYS6014 (Decision Analysis) at the University of Virginia, received a specially crafted type 1 diabetes simulator that presents the metabolically significant events that a patient could experience throughout the day. The simulator requires the user to make decisions about self-monitoring of blood glucose sampling, insulin basal rate adjustments, and meal and correction boluses, all subject to poorly calibrated conventional therapy parameters, sensor errors, inaccurate estimates of carbohydrate content in meals, and the possibility of meals being skipped or unacknowledged. The students were asked to devise a self-treatment strategy based on their experience with the simulator and were then asked to apply their strategies in a scenario with a prescribed (but unknown) set of meals for 14 simulated days.

Result:
The students were evaluated in terms of percentage of time spent in 70–180 mg/dl (PERCENT_EUG) and below 70 mg/dl (PERCENT_HYPO). Median (mean, standard deviation) PERCENT_EUG was 77.18% (76.48,14.01), whereas median (mean, standard deviation) PERCENT_HYPO was 0.00% (2.67,4.61). In contrast, the patient's initial basal rate profile and mealtime insulin strategy resulted in PERCENT_EUG = 50.45% and PERCENT_HYPO = 0.00%.

Conclusion:
The SYS6014 students, most of whom had no prior experience with diabetes, managed to achieve a high level of control with minimal time spent in hypoglycemia, suggesting that engineering methods that explicitly model and confront the uncertainties of self-treatment may be a path to improved outcomes.

Accurate Glycemic Control in Critically Ill Patients: The Stochastic Targeted Framework

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Background:
Stochastic Targeted (STAR) is a model-based, adaptive, patient-specific accurate glycemic control (AGC) framework, customizable to clinically specified glycemic targets, control approaches, and clinical resources. This work compares two STAR pilot trials with different control approaches (insulin only versus insulin + nutrition) to results of the model-derived Systolic Blood Pressure Intervention Trial (SPRINT).

Method:
Pilot trials were performed at the Centre Hospitalier Universitaires (Liege, Belgium) targeting 100–140 mg/dl using insulin only (SB) and Christchurch Hospital (New Zealand) targeting 80–120 mg/dl using insulin + nutrition control (SNZ). The SB trials were 24 h long, and the SNZ trials were for entire patient stay. Measurements and interventions were every 1–3 h. Insulin rates were limited to 8 U/h. Results are compared with those from SPRINT, which targeted 72–110 mg/dl and measured every 1–2 h.

Result:
There were 660 h of control with 402 measurements for SNZ and 194 h with 91 measurements for SB. Median [interquartile range (IQR)] SNZ blood glucose (BG) is 108 (94–122) mg/dl with 76% and 90% of BG in the 72–125 and 72–145 mg/dl bands, respectively, and no severe hypoglycemia. Median (IQR) SB BG is 134 (117–151) mg/dl with 35% and 65% of BG in the 72–125 and 72–145 mg/dl bands, respectively, and no severe hypoglycemia. Results of SB are skewed slightly higher by the 24 h trial length. Moderate hypoglycemia (BG < 72 mg/dl) was 4.5% for SNZ and 1.1% for SB. In comparison, with over 40,000 h (371 patients), SPRINT BG was 104 (90–119) mg/dl with 79% and 88% of BG in the 72–125 and 72–145 mg/dl bands, respectively, and ~2% of patients experiencing severe hypoglycemia (BG < 40 mg/dl).

Conclusion:
Pilot clinical trials demonstrate that STAR provides flexible and customizable AGC to desired target levels and compares well with a proven model-derived AGC protocol.

Does Intensive Insulin Therapy Reduce the Severity of Organ Failure?

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Background:
Organ failure is a common complication associated with increased mortality in intensive care unit patients. Increased mortality is also associated with hyperglycemia and glycemic variability. This research evaluated the impact of intensive therapy versus conventional insulin therapy on organ failures.

Method:
Daily sequential organ failure assessment (SOFA) score was used to assess organ failure, and glycemic control quality was measured by cumulative time in a 4.0–7.0 mmol/liter band, evaluated daily. Glycemic variability was assessed by a glycemic lability index, defined per day. These metrics are evaluated for 704 patients with sufficient data in the multicenter GluControl study, where patients were randomized to intensive insulin therapy [IIT; blood glucose (BG) target 4.4–6.1 mmol/liter] or conventional insulin therapy (CIT; BG target, 7.8–10.0 mmol/liter). The SOFA score improvement is measured by the percentage of patients with SOFA ≤ 5 on a given day. Patients in both groups were matched for age, sex, diagnosis, and severity of illness (Acute Physiology and Chronic Health Evaluation II score; $p > .15$).

Result:
Blood glucose levels differed between the IIT group and the CIT group ($p < .05$), as expected. Initial and maximum SOFA scores are equivalent ($p > .3$). Intensive insulin therapy and CIT showed no difference ($p > .1$) in the percentage of patients with SOFA ≤ 5 over days 1–10 and no effective change in value over days 1–7. Glycemic variability was much higher for the IIT group than the CIT group on all days and statistically significant on days 1–8 ($p < .05$) and several further days.

Conclusion:
Intensive insulin therapy was unable to mitigate organ failure in two cohorts randomized to different glycemic targets. Intensive insulin therapy provided better but not tighter control, with higher variability and more hypoglycemia than CIT, which may have been a causative factor, compared with other studies that were successful in reducing organ failure.

Glucose Sensor Initialization

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Background:
In electrochemical sensing, the application of sequential voltage pulses (referred to as initialization) at the start of sensor use has shown to improve sensor startup and accelerate sensor stabilization. Various initialization sequences are being investigated that are aimed toward reducing the amount of time necessary for a sensor to stabilize and operate linearly within the physiological range after insertion.

Method:
Improvements in sensor startup are being explored *in vitro* through pulsing sequence optimization. Metrics being used to evaluate efficacy of an initialization sequence are (1) stability time, the amount of time for the sensor rate of change to be <0.2 mg/dl/min for 45 min during the first 2.5 h of sensor life; (2) difference in sensor glucose (SG) pairing, in mg/dl, how much the SG varies when paired with a reference glucose reading at 40 versus 90 min; and (3) linearity, how linear the sensor is within the first 2.5–5 h.

Results:
A significant improvement in sensor startup at 100 mg/dl glucose is noted *in vitro* through the use of initialization. Experimenting with different sequences can allow for improvements in sensor stability and linearity. Such improvements can translate to a sensor that can be more responsive and accurate sooner after patient insertion.

Conclusion:
Research is continuing on improving the time to sensor stability through initialization. *In vitro* data support the opportunity for improving sensor startup and stability *in vivo*.

Microengineered Electrodes for Glucose Sensing

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Objective:
The objective of this study was to investigate the effect of electrode morphology and roughness uniformity on glucose sensing performance. Electrode size, shape, and roughness play vital roles on the target analyte (glucose, H_2O_2) flux dynamics, and oxidation. Sensor hydration and H_2O_2 flux can be improved, which benefits sensor startup, response time, and signal-to-noise ratio.

Method:
Computer simulation software was used to analyze current density distribution over the surface of the sensing electrode. Flux of glucose and H_2O_2 was modeled using different electrode shapes. To translate computer simulation to experiments, an excimer 193 nm wavelength laser was used to modify the surface of the electrode, either by generating microholes or by ablating electroplated material from the electrode surface.

Results:
In computer simulation, a three-dimensional model was built for electrodes with microholes. Glucose gradient, H_2O_2 concentrations, and flux were simulated. Flux of H_2O_2 was highest around microhole edges. Glucose concentration was highest at microholes. *In vitro*, electrodes with increasing micro-hole density (drilled before chemistry layer) displayed higher signals. When the microholes were drilled following the application of glucose-sensitive chemistries, slightly lower signal with increasing microhole density was observed. *In vivo*, non-negative effects were observed for electrodes with microholes. In general, these electrodes displayed an average of 4 nA of higher current during the first 2 h of sensor operation.

Conclusion:
Computer simulations correlated with *in vitro* results. Microholes improved H_2O_2 flux, which helped increasing sensor signal *in vivo*. Reducing edge roughness has a high potential of improving sensor performance in terms of reducing variability and drift.

Mobile-Based Architecture for an Insulin Dosing Decision Support System

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Background:
Recent developments in mobile technologies and real-time continuous glucose monitoring (RT-CGM) have opened the door to a new era of telemedicine systems for diabetes management. We present a smart-phone-based platform that connects to a commercial RT-CGM and integrates an insulin dosing recommendation algorithm based on case-based reasoning (CBR), an artificial intelligence technique that solves newly encountered problems by applying solutions learned from solving similar problems in the past.

Method:
We have developed a discrete PCB-based system that acquires continuous glucose measurements from a RT-CGM sensor through proprietary electronic instrumentation and communicates wired or wireless with a smart phone. Additional data required for insulin dosing recommendation algorithm (e.g., meal ingestion, physical activity) are obtained through mobile graphical user interfaces (GUIs) especially designed for this purpose. Each time an insulin dose is required, the smart phone sends these data to a Web server that contains the CBR algorithm and a patient-specific database with historical data. Once the insulin recommendation has been calculated, it is sent back to the smart phone. The system also provides expert GUIs for data visualization and supervision.

Result:
The sensor instrumentation has been successfully tested *in vitro*, and its wireless communication with the smart phone has been implemented using a low-power radio. The CBR algorithm has already been *in silico* validated and is currently being integrated into the platform. Additionally, the smart phone in-built accelerometer will be incorporated into the system to allow estimation of physical activity of the subject. The whole system is to be clinically validated.

Conclusion:
The developed smart-phone-based platform can support any type of decision support system for diabetes management but can also be seen as a platform for a future artificial pancreas.

Is Diabetes-Related Peer Review Obsolete?

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Objective:
Our objective is to develop the Telemedicine and Advanced Technology Research Center (TATRC) within the U.S. Army Medical Research and Materiel Command to promote convergence science and support innovation through activist management that transcends peer review systems using iterative team building and convergence strategies with diabetes as a model.

Method:
A unique management strategy was put in place and evaluated for outcomes in diabetes as a protean model for the wider medical endeavor.

Result:
The TATRC's diabetes portfolio encompasses research relating to decision tools, monitoring technologies, personalized health, and treatments. Program examples include (1) an Internet-based My Care Team (MCT) deployed into diverse clinical environments to evaluate how a clinical information system can be integrated into existing diabetes management programs (the results from the deployed system analyses show that MCT contributed to positive health outcomes for people with diabetes) and (2) a new initiative with industry and academia to test the hypothesis that amplified autologous brown fat implants can facilitate weight management and maintenance.

Conclusion:
The TATRC provides an alternative to the 20th century peer review model designed for 19th century academic structures. Such a model appears compatible with 21st century research and economics, emphasizing convergence science, partnerships of academia, industry, and multiple federal agencies. Transition strategies to facilitate disruptive innovation transition to sustainability through state and global funding sources and markets are being developed.

BGStar Is Highly Accurate in a Clinical Setting

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Background and Aims:
Blood glucose meters for patient self-measurement need to comply with the accuracy standards as set forth in the International Organization for Standardization (ISO) 15197 guideline. This study was performed to investigate the accuracy of blood glucose readings with the new blood glucose meter BGStar (sanofi-aventis) in comparison with four other competitive devices (ACCU-CHEK Aviva, FreeStyle Freedom Lite, Contour, and OneTouch Ultra2) at different blood glucose ranges in a clinical setting with healthy subjects and with patients with type 1 and type 2 diabetes. BGStar and iBGStar are employing dynamic electrochemistry.

Method:
The study was performed with 106 participants [53 female, 53 male, age (mean ± standard deviation) 46 ± 16 years, 32 type 1 patients, 34 type 2 patients, and 40 healthy subjects). Two devices from each type and strips from two different production lots were used for glucose assessment. Spontaneous glucose measurements and glucose or insulin interventions under medical supervision were used to perform measurements in the different glucose ranges in accordance with ISO 15197 requirements. As allowed by the regulations, sample values <50 and >400 mg/dl were prepared by laboratory manipulations. The YSI glucose analyzer (glucose oxidase method) served as standardized reference method.

Result:
For all devices, there was a very close correlation of the glucose results with the results of the YSI reference method. The correlation coefficient was $r = 0.995$ for BGStar (Aviva 0.995, Freedom Lite 0.990, Contour 0.993, and Ultra2 0.990). The error grid analysis revealed 100% of the readings to be within the clinically acceptable areas A+B with BGStar (100 + 0), Aviva (97 + 3), and Contour (97 + 3) and 99.5% with Freedom Lite (98 + 1.5) and Ultra2 (97.5 + 2).

Conclusion:
This study demonstrated a high accuracy for BGStar and the competitive blood glucose meters in a clinical setting, demonstrating that they represent the current state-of-the-art technology for blood glucose testing in clinical practice.

Determination of Hematocrit Interference in Blood Samples Derived from Patients with Different Blood Glucose Concentrations

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Background:
Hematocrit (HCT) interference is usually tested in a laboratory setting with one blood sample of sufficient volume to artificially prepare the test samples containing different glucose levels and different HCT concentrations. The laboratory manipulations necessary to prepare these samples, however, may have an impact on the performance of some device technologies and may lead to deviating results from the performance in clinical practice. We had tested HCT interference as stated previously. The purpose of this trial was to modify the protocol by using blood samples from patients with clinically different blood glucose levels so that laboratory manipulation was reduced to achieve different HCT levels only.

Method:
Blood was freshly drawn from five patients with different blood glucose levels (2.8, 5.6, 8.3, 13.9, and 19.4 mmol/liter) and immediately manipulated to contain five different HCT concentrations (35%, 40%, 45%, 50%, and 55%).

Each sample was measured three times with each blood glucose testing device (ACCU-CHEK Aviva and Aviva Nano, BGStar, Breeze2, Contour, OneTouch Ultra2 and Verio, FreeStyle Freedom Lite, Precision Xceed, GlucoCard G+, GlucoMen LX, and MediTouch), and the deviation versus the YSI glucose analyzer was determined. For each device, the largest deviation in both directions was identified and added to obtain the impact of HCT on the results. The mean values of the two low and the three high glucose levels were calculated. A value below 15 mg/dl (low glucose levels) or 10% (high glucose levels) was considered to represent noninterference by HCT on the device performance.

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Results:
Less than half of the devices were shown to be unaffected by HCT, including BGStar (7.2 mg/dl, 7.3%), Contour (10.8 mg/dl, 4.6%), OneTouch Verio (10.8 mg/dl, 5.2%), GlucoCard G+ (12.6 mg/dl, 7.0%), and GlucoMen LX (7.2 mg/dl, 5.1%), while the other devices showed pronounced interference at least at one of the two glucose ranges ACCU-CHECK Aviva (12.6 mg/dl, 10.7%) and Aviva Nano (7.2 mg/dl, 10.5%), Breeze2 (3.6 mg/dl, 30.2%), OneTouch Ultra2 (12.6 mg/dl, 25.6%), FreeStyle Freedom Lite (9.0 mg/dl, 11.0%), Precision Xceed (16.2 mg/dl, 15.3%), and MediTouch (19.8 mg/dl, 28.0%).

Conclusion:
The results of this trial with less sample manipulation requirements (HCT only) confirmed the results of a previous examination with more manipulation requirements (HCT and glucose). The same devices (BGStar, Contour, OneTouch Verio, and GlucoCard G+) showed HCT stability as seen in the previous laboratory trial. Only GlucoMen LX performed better in this actual study. Artificial sample manipulation may have an impact on accuracy meter results but seem to be less important when evaluating HCT interference.

Evaluation of the Intra-Assay Precision and Accuracy of Blood Glucose Meters for Patient Self-Testing

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Background and Aims:
Blood glucose (BG) meters for patient self-measurement need to be as accurate and precise as possible to allow for most optimal treatment efficacy in daily practice. This study was performed to evaluate the intra-assay precision and accuracy of several BG meters in a laboratory setting (BGStar, iBGStar, AccuChek Aviva and Aviva Nano, BREEZE 2 and Contour, GLUCOCARD G+, GlucoMen LX and GM, OneTouch Ultra 2 and Verio Pro, MediTouch, Precision Xceed, and FreeStyle Freedom Lite).

Materials and Methods:
The study was performed with blood samples from five patients with different BG concentrations (42, 84, 121, 207, and 320 mg/dl). The samples were tested 10 times with 10 devices from each type (=500 measurements/device type). The coefficient of variation (CV) was calculated for each glucose level, and the mean CV served for benchmark comparison between the devices. Accuracy was evaluated by calculating the mean absolute relative deviation from the YSI glucose analyzer.

Result:
All tested devices performed well in the intra-assay precision testing experiment, with precision results between 3% and 5%, except FreeStyle Freedom Lite, MediTouch, GlucoMen LX, and Precision Xceed. The accuracy testing achieved mean deviations < 7% for the majority of devices, with the exception of GLUCOCARD, GlucoMen LX, MediTouch, and OneTouch Ultra 2.

Conclusion:
This study demonstrates that an intra-assay precision of 3–5% and a system accuracy <7% is currently achievable by most of the state-of-the-art BG meters for patient self-testing.

Hematocrit Influences Glucose Determination by Self-Measurement Devices with Few Exceptions

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Background:
Hematocrit (HCT) interference is a known phenomenon for many blood glucose measurement technologies. High HCT levels can lead to false low glucose readings and vice versa. One way to correct for these potential deviations is to apply the dynamic electrochemistry method, which is used, e.g., in the new BGStar meter (sanofi-aventis). The purpose of this laboratory investigation was to assess the potential influence of HCT variations on a variety of blood glucose meters applying different measurement technologies.

Method:
Venous heparinized blood was immediately aliquoted after draw and manipulated to contain three different blood glucose concentrations (80, 155, and 310 mg/dl) and five different HCT levels (25%, 37%, 45%, 52%, and 60%). After careful oxygenation to normal blood oxygen pressure, each of the resulting 15 different samples was measured 8 times with the following devices: BGStar, Bayer Contour, ACCU-CHEK Aviva and Aviva Nano, Bayer BREEZE 2, Precision Xceed, OneTouch Ultra 2 and Verio, FreeStyle Freedom Lite, GlucoMen GM, and StatStrip (point-of-care device [POC]). cobas (Roche Diagnostics) served as laboratory reference method. Stability to HCT influence was assumed, when less than 10% bias occurred between the highest and lowest HCT levels, when analyzing the mean deviations for the three different glucose concentrations.

Results:
The StatStrip device (POC) is known to measure and correct for HCT, which resulted in only 2% bias. Only three of the investigated self-test meters also showed a stable performance in this investigation: BGStar (8%), Bayer Contour (6%), and OneTouch Verio (6%). All other meters failed this test: FreeStyle Freedom Lite (16%), ACCU-CHEK Aviva (23%) and Aviva Nano (18%), Bayer BREEZE 2 (36%), OneTouch Ultra 2 (34%), Precision Xceed (34%), and GlucoMen GM (31%).

Conclusions:
Hematocrit variations can occur frequently in daily routine (e.g., due to exercise, stay in mountains, or hemodialysis). Our results may encourage use of meters with stable performance under these conditions. Dynamic electrochemistry as used in the BGStar device (sanofi-aventis) appears to be an effective technology to correct for potential HCT influence on the meter results.

Impact of Oral Antidiabetic Drugs on a Biomarker Panel Concept for Treatment Selection and Monitoring in Patients with Type 2 Diabetes

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Background:
Recent outcome studies (the Action to Control Cardiovascular Risk in Diabetes, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, and the Veterans Affairs Diabetes Trial) have demonstrated that an isolated focus on treatment of hyperglycemia/hemoglobin A1c (HbA1c) is not sufficient to decrease excess cardiovascular mortality in patients with type 2 diabetes. To understand these results and to develop new treatment strategies, we sought to elucidate the impact of antidiabetic drugs on the components of the underlying pathophysiology of the disease.

Method:
The BEVAIR concept provides a panel of biomarkers indicating the degree of severity of □-cell dysfunction (intact proinsulin), visceral adipose tissue activity (adiponectin), insulin resistance (homeostatic model assessment), and chronic systemic vascular inflammation (high-sensitivity C-reactive protein). We investigated the impact of different antidiabetic drugs on the BEVAIR biomarker panel, body weight, and hypoglycemia with data derived from more than 40 epidemiological and interventional clinical trials performed by IKFE from 2002 to 2009 with a total of approximately 20,000 patients.

Results:
All antidiabetic drugs lowered glucose and HbA1c. However, after correction for the glucose-lowering effects, very different actions were observed on the underlying disease components. The effects of insulin were ambivalent and dependent on the type and time-action profile, disease stage, and degree of insulin resistance.

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Conclusions:
Our results indicate that a combination of lifestyle changes with several modern antidiabetic drugs (e.g., pioglitazone + glucagon-like peptide-1) or very early use of insulin may be more effective in addressing chronic systemic inflammation and atherosclerosis than the treatment combinations used in the outcome studies mentioned earlier. However, appropriately designed outcome trials are required to prove whether these biomarker-derived suggestions can translate into an improved macrovascular outcome in patients with type 2 diabetes.

Impact of Pioglitazone/Glargine versus Metformin/Glargine on Laboratory Biomarkers of □-Cell Dysfunction, Insulin Resistance, and Chronic Systemic Inflammation

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Background:
A common approach to starting insulin therapy in patients with type 2 diabetes is the addition of basal insulin to the existing oral therapy. The goal of this analysis of the PIOcomb study was to investigate the impact of 6 months of therapy with pioglitazone plus insulin glargine in comparison with metformin plus insulin glargine treatment and to triple therapy on glycemic control [hemoglobin A1c (HbA1c)] and on the BEVAIR biomarker panel for insulin sensitivity and beta-cell function (intact proinsulin), endocrine visceral lipid tissue activity (adiponectin), and chronic systemic inflammation (high-sensitivity C-reactive protein).

Method:
A total of 121 patients participated in the prospective double-blind study (47 women, 74 men, aged 63 ± 8 years, disease duration of 11.1 ± 6.2 years, body mass index of 32.2 ± 5.3 kg/m², HbA1c of 7.3% ± 0.5%). They received an optimized and individualized insulin regimen with insulin glargine (titration) and were randomized to additional therapy with pioglitazone (2 × 15 mg/day) or metformin (2 × 850 mg/day) or a combination of both drugs.

Results:
There was no difference in the number of hypoglycemic episodes between the treatment arms. A reduction in intact proinsulin indicating reduced □-cell stress was seen with all treatments and may be related to the insulin glargine therapy. Reduced endocrine activity of the visceral lipid tissue and reduced chronic systemic inflammation was seen only in the pioglitazone treatment groups.

Conclusions:
Addition of metformin and/or pioglitazone to a basal insulin therapy with insulin glargine provided stable metabolic control in all cases. A significant improvement in insulin resistance and cardiometabolic syndrome, as indicated by related biomarkers (BEVAIR panel), was seen in the treatment arms with pioglitazone only.

Impact of Strip Filling on the Performance of Glucose Meters for Patient Self-Testing

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Background and Aims:
The accuracy of blood glucose readings is dependent on the use of the devices and strips in strict accordance with the respective instructions for use. This includes completely filling the strips with sufficient blood sample volume. Many devices have built-in filling checks and are supposed to display an error message in case of incomplete filling. In a worst-case scenario, incomplete strip filling does not result in an error message, but does result in a wrong reading, potentially leading to wrong treatment decisions. This laboratory investigation was performed to test the performance of 31 commercially available devices in the event of incomplete strip filling.

Materials and Methods:
Samples with two different glucose levels (60–90 and 300–350 mg/dl) were used to generate three different sample volumes: 0.20 µl (below any required volume), 0.32 µl (borderline volume), and 1.20 µl (sufficient volume for all tested devices). After a point-of-care reference measurement (StatStrip, Nova Biomedical), the strip was filled with the respective volume and the response of the meter was documented. Each experiment was performed six times with two different devices (i.e., 72 determinations/meter type). Correct meter reaction was defined as either an error message indicating incomplete filling or a correct reading (±20% compared with reference reading).

Results:
Four meters showed 100% correct performance [ACCU-CHEK Compact Plus and Mobile (Roche), OneTouch Verio (LifeScan), and BGStar and iBGStar (sanofi-aventis)]. The majority of the meters (17) had up to 10% of wrong reactions [Precision Xceed and Xtra and FreeStyle Lite and Freedom Lite (Abbott); GLUCOCARD+ and GlucoMen GM (Menarini); Contour, Contour USB, and BREEZE 2 (Bayer); OneTouch Easy, Ultra 2, and UltraSmart (LifeScan); Wellion Dialog and Premium (MedTrust); FINETOUCH (TERUMO); ACCU-CHEK Aviva (Roche); and GlucoTalk (Axis-Shield)]. A total of 10–20% wrong reactions were seen with OneTouch Vita (LifeScan), ACCU-CHEK Aviva Nano (Roche), Omnitest plus (B. Braun), and AlphaCheck (Progen). More than 20% wrong reactions were obtained with Pura (Ypsomed), GLUCOCARD X and GlucoMen LX (Menarini), Ascensia Elite (Bayer), and MediTouch (Medisana).

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Conclusion:
This study showed that the majority of commercially available blood glucose meters and strips may occasionally display a pronouncedly incorrect reading in case of incomplete strip filling. It underlines the importance of training patients regarding the requirement of complete strip filling when performing blood glucose self-monitoring.

Assessment of Hepatic Insulin Extraction from a Meal Test

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Objective:
Assessment of hepatic insulin extraction (HE) in normal life conditions is fundamental for understanding glucose regulation in healthy, prediabetic, and type 2 diabetic subjects. A model to estimate HE from a meal tolerance test (MTT) has been proposed by Campioni and colleagues, which, however, simply represents HE time course as a piecewise linear function. The aim of this study was to develop a mechanistic physiological model accounting for HE.

Methods:
The model is based on the oral C-peptide minimal model, which describes pancreatic insulin secretion; a two-compartment model describing C-peptide kinetics; and a single-compartment model describing insulin kinetics. Suppression of HE is assumed to be linearly dependent on both plasma and delayed insulin concentrations. Indices of hepatic extraction and insulin control on it are derived from model parameters. The model was tested on 204 normal subjects (117 males and 87 females, age = 55.5 ± 1.5 years, body mass index = 26.6 ± 0.2 kg/m^2, body surface area = 1.90 ± 0.01m^2) who underwent a MTT (1 ± 0.02 g/kg of carbohydrates, 45% carbohydrate, 15% protein, 40% fat) and frequent plasma sampling to measure plasma glucose, insulin, and C-peptide concentrations.

Results:
The model accurately predicts plasma insulin and C-peptide time courses and provides precise estimates of parameters, which also well correlate with those derived with the Campioni and colleagues model. Akaike information criterion also indicates that the new model is more parsimonious than the Campioni and colleagues model.

Conclusions:
A new physiological and parsimonious model has been proposed that enables estimation of HE from a MTT and provides an index that quantifies the control of insulin on this process.

Interim Safety Assessment of Glycemic Control with the GLUCOSAFE System after Traumatic Brain Injury or Subarachnoid Hemorrhage

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Objective:
Our objective was to conduct an interim safety assessment of a computerized model-based glycemic control decision support system (GLUCOSAFE) using variable insulin and nutrition administration compared with usual management of glucose performed in the absence of formal protocols.

Method:
We completed a randomized controlled trial in a Danish intensive care unit. Twelve consecutive hyperglycemic adults with traumatic brain injury or subarachnoid hemorrhage were included. A blood glucose sample was drawn every 2 h. For patients in the intervention group, insulin dosage and feeding rates were recommended by GLUCOSAFE. Data collection stopped after 96 h or due to transfer to another department, resumed oral feeding, or death.

Result:
Six patients were randomized into each group [intervention: body mass index (BMI) 27.6 ± 3.9 kg/m^2, SAPS2 35.2 ± 13.7; controls: BMI 30.2 ± 7.2 kg/m^2, SAPS2 41.5 ± 14.2]. In the GLUCOSAFE group, 79% of measured glucose values were in the 4–8 mmol/liter band (controls, 53%) and 23% of measurements were in the 4–6.1 mmol/liter band (controls, 11%). Total median glucose was 7.1 mmol/liter (controls, 8 mmol/liter), with an interquartile range of 6.3–7.9 mmol/liter (controls, 7–9.1 mmol/liter). The lowest measured value was 4.2 mmol/liter (controls, 4.0 mmol/liter). All GLUCOSAFE patients reached the 4–6.1 mmol/liter band (controls, 5 of 6 patients). Nutrition advice by GLUCOSAFE resulted in continuous feeding rates that were, on average, 97% ± 4.5% of the calculated basal metabolic rate (controls, 127% ± 10.2%). Mean insulin infusion rates were comparable: GLUCOSAFE, 0.058 ± 0.030 U/h/kg; controls, 0.059 ± 0.044 U/h/kg.

Nurses used GLUCOSAFE without help. More than 90% of records had been entered correctly and on time, and 95% of the systems recommendations were accepted as decisions for treatment.

Conclusion:
GLUCOSAFE effectively reduces blood glucose in intensive care unit patients after traumatic brain injury and subarachnoid hemorrhage and is safe to use in clinical practice.

Onset of Insulin Absorption Following Pump Administration of BIOD-105 and BIOD-107 Compared with Insulin Lispro

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Objective:
More rapid absorption of insulin following pump administration could enable a better match of insulin delivery to postprandial glucose peaks. BIOD-105 and BIOD-107 are two improved recombinant-human-insulin-based formulations projected to have an ultrarapid onset of action in man. The objective of this study was to compare key absorption parameters following pump bolus administration of BIOD-105, BIOD-107, and insulin lispro (IL; Humalog) to diabetic miniature swine.

Method:
Five miniature diabetic swine were suited with an Animas OneTouch Ping pump filled with IL, BIOD-105, or BIOD-107. A continuous basal infusion at a rate of 0.3 U/h was initiated 30 min prior to a morning bolus dose of 0.1 U/kg followed by a meal. Plasma was sampled at multiple time points from -30 to 360 min relative to insulin bolus administration. Plasma insulin was measured by enzyme-linked immunosorbent assay method; plasma glucose was measured with a YSI glucose analyzer.

Result:
The time to half-maximal plasma insulin concentration (T_{ins}50% early) was 27.9 ± 6.9 min for IL, 15.9 ± 5.2 min for BIOD-105, and 4.7 ± 1.9 min for BIOD-107 ($p < .05$ versus IL). The pharmacodynamic effect, as measured by a drop in glucose, was consistent with the early insulin peak.

Conclusion:
In addition to prandial doses of insulin, patients using pumps often make adjustments to their insulin delivery rate to keep in the normal glycemic range. Faster absorption of insulin from the catheter site should enable better control of plasma glucose levels. BIOD-105 and BIOD-107 are more rapidly absorbed than IL following pump administration, providing the potential for more precise timing of insulin bolus delivery with a meal and between meal doses to keep the patient in the normal glycemic range.

eCONSULTA: An Integrated Diabetes Care Model (Specialist–Primary) Based On Video Consulting

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Objective:
Communication between primary care and specialists is often unidirectional and inadequate. Most consultations suggest patient referral to the hospital even for low-complexity entities due to suboptimal information. The main objective of our project is to improve communication between general practitioners (GPs) and diabetologists using information technologies in order to optimize the resources and the quality of care.

Methods:
We have designed and developed a new video consulting system for real-time communication between primary care and diabetologists. The eCONSULTA system has been integrated in the electronic health record (EHR) system currently in use by GPs in Catalonia, where users have to be previously authenticated, and it is available in a restricted Internet-based network that communicates the involved health care centers. The eCONSULTA is based on free video conference software (OpenMeetings) that has been complemented with additional functionalities such as a virtual waiting room that possess some tools devoted to minimizing waiting time. During the videoconference session, users can access the patient EHR and additional tools to share documents, to draw in a board, and to interchange messages through a chat.

Results:
A feasibility pilot study has been conducted involving 15 GPs in five different primary care centers and 1 diabetologist. The specialist and GPs were equipped with a standard Webcam (microphone built in) and a brief user guide. Minor technical problems were detected and solved. Eight minutes was considered as the most appropriate time duration. The results of the satisfaction questionnaires will be presented at the meeting.

Conclusion:
A video consulting system integrated in the EHR application seems to be a good way to offer integrated (specialist–primary) diabetes care.

Accuracy and Acceptability of the Enlite 6-Day Glucose Sensor in Pediatric Subjects with Type 1 Diabetes

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Objective:
Accuracy and acceptability of the next-generation, 6-day subcutaneous glucose sensor (Enlite) were evaluated in a pediatric cohort (≤17 years).

Method:
Eighty of 83 subjects (44 male), mean age 12.5 ± 2.8 years and mean hemoglobin A1c 8.2% ± 1.1% (5.5–11.5%), completed a prospective study with Guardian REAL-Time, MiniLink transmitter, and Enlite sensor (Medtronic MiniMed Inc., Northridge, CA) for two 7-day periods; calibration was recommended four times/day. Pediatric sensor accuracy was assessed using paired self-monitored blood glucose (SMBG) sensor values with a prespecified mean agreement rate within 20% and compared with sensor accuracy in the adult Enlite study. Child/parent questionnaires using a Likert-type scale (1–7) were analyzed to assess satisfaction.

Result:
From 3843 paired SMBG sensor values in the pediatric cohort, the Enlite sensor had mean absolute relative difference (ARD) of 16.3%, median ARD of 11.9%, and 95.5% of points within the A+B zones of the Clarke error grid. Adult paired SMBG sensor values (n = 8243) had mean ARD of 16.0%, median ARD of 11.7%, and 95.4% of points within the A+B zones of the Clarke error grid. Mean agreement rates between pediatric [71.8%; 95% confidence interval (CI), 0.697, 0.739] and adult (71.7%; 95% CI, 0.696, 0.739) cohorts were not significantly different (p = .3126). Greater than 95% of children/parents were satisfied with ease of calibration, use of inserter device and retractable needle, and glucose trending display; ≥95% did not fear sensor insertion and agreed the device was easy to use, consistent, and comfortable to wear. Ninety-one percent of children/parents would recommend this continuous glucose monitoring system.

Conclusion:
The 6-day Enlite sensor was accurate in pediatric subjects; no significant difference in sensor accuracy was observed between adults and children. Child/parent satisfaction was very high. The Enlite sensor should improve pediatric continuous glucose monitoring adherence.

Pancreatic Insulin Secretion in Critically Ill Patients

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Objective:
Glucose–insulin pharmacokinetic–pharmacodynamic (PK–PD) models can be used for improved glycemic control of critically ill patients. A key component of glucose–insulin PK–PD models is pancreatic insulin secretion. There are limited data in the literature quantifying insulin secretion in critically ill patients at physiologic levels. This study creates a model pancreatic insulin secretion in critically ill patients to improve glucose–insulin system modeling.

Method:
Nineteen patients from the Christchurch Hospital intensive care unit enrolled in a prospective clinical trial studying sepsis, and each had arterial blood samples assayed for insulin and C-peptide. Two sets of four samples were taken from each patient, with each set collected over 60 min. Blood glucose (BG) data were collected with a bedside glucometer. C-peptide data were deconvolved using the model of van Cauter and colleagues to determine prehepatic insulin secretion rates (Uen). Data from literature suggested a maximum secretion rate of 16 U/h. A minimum rate of 1 U/h was also adopted. There were no patients diagnosed with type 1 diabetes mellitus (T1DM).

Result:
Regression analysis indicated endogenous secretion could be modeled as a function of BG only. There was clear separation of secretion levels between normal glucose tolerant (NGT) and impaired glucose tolerant (IGT) patients. Hence, Uen was modeled as a constrained linear function of BG (in mmol/liter) for NGT and IGT patients separately with R^2 = 0.55 and 0.58, respectively. For NGT patients, Uen = 16.5 × BG - 62.4, constrained to 16.7– 266.7 mU/min, and for IGT patients, Uen = 6.2 × BG - 40.2, constrained to 16.7– 266.7 mU/min.

Conclusion:
This work presents a simple model of pancreatic insulin secretion in critically ill patients based on clinical data. The model is a function of BG level and glucose tolerance status and can be easily incorporated into glucose–insulin PK–PD models.

Edge-Plane Microwire Electrodes for High-Sensitivity Glucose Detection

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Background:
The promise of implantable glucose sensors for continuous glucose monitoring is often undermined by the critical requirement of device miniaturization that inadvertently degrades sensor performance in terms of sensitivity and selectivity. We present a novel configuration of electrochemical glucose sensors that affords the much needed sensor miniaturization while maintaining high sensor performance.

Methods:
The glucose sensor is grown at the "edge plane" of a 25 μm gold wire and is based on first-generation Clark-type enzymatic detection of glucose. Electrochemical rebuilding of the gold surface and subsequent decoration of platinum nanoparticles was performed on the "edge plane" working electrode (WE) to enhance sensor performance *via* increases in electroactive surface area and electrocatalytic activity.

Results:
Owing to the close distance between the working, reference, and counter electrodes, edge plane microsensors afforded minimal iR drop, three-dimensional diffusion for effective glucose mass transfer, as well as microelectrode behavior. This, together with electrochemical rebuilding and Pt nanoparticle decoration on the WE, resulted in a six-fold improvement in sensitivity ($1.2\ mAmM^{-1}cm^{-2}$) over previous reports. In addition, these sensors exhibited low operation potential (0.3 V), high selectivity (more than 95%) against redox interferences, an apparent Michaelis–Menten constant of 75 mM of glucose, and limit of glucose detection as low as 3 μM. Efficacy of these devices in laboratory animals is currently under investigation.

Conclusions:
Edge plane glucose sensors, in addition to being synergistic with our miniaturized ($0.5 \times 0.5 \times 5\ mm^3$) implantable sensor platform (under development) also afford the ease to attain and scale up the production, thereby rendering them an ideal vehicle for advanced biosensor research.

A Cluster-Randomized Trial of a Mobile Phone Behavioral Intervention for Blood Glucose Control: Primary and Secondary Outcomes

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Objective:
Our aim was to test whether adding mobile phone application coaching and patient/provider Web portals to community primary care compared with standard diabetes management would reduce glycated hemoglobin levels in patients with type 2 diabetes, differing by patient-reported secondary outcomes.

Research Design and Methods:
This cluster-randomized clinical trial of mobile phone diabetes management randomly assigned 26 primary care practices to one of three stepped-treatment groups or a control group (usual care). One hundred sixty-three patients were enrolled/included in analysis. The primary outcome was change in glycated hemoglobin levels over a 1-year treatment period. Secondary outcomes were changes in patient-reported diabetes symptoms, diabetes distress, depression, and other clinical (blood pressure) and laboratory (lipid) values. Maximum treatment was a mobile and Web-based self-management patient coaching system and provider decision support. Patients received automated educational and behavioral messaging in response to individually analyzed blood glucose values, diabetes medications, and lifestyle behaviors communicated by mobile phone. Providers received quarterly reports summarizing patients' glycemic control, diabetes medication management, lifestyle behaviors, and evidence-based treatment options.

Results:
Mean declines in glycated hemoglobin were 1.9% in the maximum treatment group and 0.7% in the usual care group ($p < .001$) over 12 months. Appreciable differences were not observed between groups for patient-reported diabetes distress, depression, diabetes symptoms, or blood pressure and lipid levels (all $p > .05$). Diabetes distress subscales will be presented in detail.

Quinn cont. ⟶

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Conclusions:
The combination of behavioral mobile coaching system with blood glucose data, lifestyle behaviors, and patient self-management data analyzed and presented with evidence-based guidelines to providers substantially reduced glycated hemoglobin levels over 1 year. Patient-reported outcomes were not specific to intervention behaviors, limiting explanation of how change in clinical outcomes was achieved.

Automated Decision Support Tool Improves Clinicians' Ability to Accurately Interpret and Act on Structured Self-Monitoring of Blood Glucose Data

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Objective:
Our aim was to develop an automated decision support tool (DST) that analyzes self-monitoring of blood glucose (SMBG) data from the ACCU-CHEK 360° View tool, a form used to document seven-point glucose profiles obtained on 3 consecutive days. The DST outputs a printed report that identifies the primary glycemic abnormality, helps to identify the potential causes of the abnormality, and recommends appropriate therapeutic options.

Method:
This study evaluated the impact of the DST on clinicians' ability to identify glycemic abnormalities in SMBG data and choose appropriate therapy options. In this prospective, randomized, controlled, multicenter study, 288 clinicians (39.6% family practice physicians, 37.9% internal medicine physicians, and 22.6% nurse practitioners) were randomized into four groups: structured SMBG alone (STG; $n = 72$); structured SMBG with DST (DST; $n = 72$); structured SMBG with educational DVD (DVD; $n = 72$); and structured SMBG with the DST and educational DVD (DST+DVD; $n = 72$). Clinicians were asked to analyze 30 clinical cases, identify the primary glycemic abnormality, and choose an appropriate therapy option.

Results:
A total of 222 clinicians completed all 30 patient cases with no major protocol deviations. Significantly more DST+DVD clinicians (86%) correctly identified the primary glycemic abnormalities than STG (51%; $p < .0001$), DST (77%; $p < .05$), and DVD (72%) clinicians. The DST (55%) and DVD (58%) clinicians performed on par with DST+DVD (60%) clinicians and significantly better than STG (45%) clinicians (all $p < .0001$) in identifying appropriate therapy changes in response to glycemic abnormalities.

Rees cont. ⟶

Rees cont. ⟶

Conclusion:
Recent studies have demonstrated improved clinical efficacy of structured SMBG when combined with clinician education. Automated decision support technology can be equally as effective as clinician education, while combining both approaches significantly improves clinicians' ability to accurately interpret and act on structured SMBG data.

Practicality and Accuracy of a Continuous Glucose Monitor in a Rodent Model

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Objective:
We aimed to demonstrate the practicality and accuracy of the continuous glucose monitor (CGM) in a rodent model compared with standard, invasive measurements of glucose estimation.

Method:
We studied six male (three young, two old Sprague Dawley rats and one Zucker rat) for an average of 4 days using iPro CGM (Medtronic MiniMed, Inc.). In addition to the CGM, a group of animals (n = 3) had intravascular catheters placed for measurement of glucose in plasma and whole blood using an Analox GM9 glucose analyzer (Analox Instruments, UK) and OneTouch Ultra glucometer, respectively. In the other group (n = 3), glucose was estimated repeatedly by tail vein sampling using a OneTouch Ultra glucometer. Samples were also obtained during a glucose tolerance test (intraperitoneal). The blood glucose readings from the CGM were compared with plasma, whole blood, and tail blood for each time point, with an average of 30 time points per animal. Data were analyzed using Pearson's coefficient of correlation.

Results:
Glucose levels varied between 87 and 450 mg. The CGM results correlated significantly with whole blood glucose estimation from intravascular catheter [r = 0.79 (p < .0001), r = 0.8 (p < .0001), and r = 0.98 (p < .0001)] in each of the three animals. Glucose from tail blood correlated with r = 0.8 (p < .0001), r = 0.6 (p = .01), and r = 0.99 (p < .0001), with no lag. In general, plasma glucose levels correlated poorly with the other three glucose measures.

Conclusion:
A CGM is easy, reliable, and correlates significantly with standard methods of glucose estimation. A CGM provides an alternative to stressful and invasive glucose monitoring in rodents and may serve as a valuable substitute to acquire vast, accurate data in a noninvasive way.

Subjects with Type 2 Diabetes Mellitus Reported the Victoza Pen Was Easy to Use

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Objective:
Liraglutide (Victoza, Novo Nordisk A/S) is a once-daily glucagon-like peptide-1 receptor agonist indicated for adult type 2 diabetes mellitus (T2DM). It is administered by subcutaneous injection using the Victoza pen, a multidose, disposable, prefilled pen. Study objectives were to evaluate subjects' ability to correctly use the Victoza pen for the first time and subject-reported ease of handling.

Method:
In this U.S. randomized, multicenter, open-label study, 43 insulin-naïve, literate adult subjects (18–75 years) with T2DM currently treated with ≥1 oral antidiabetic drug and/or exenatide were randomized to one of three dose groups: 0.6, 1.2, and 1.8 mg. Subjects read the instructions for use, prepared the pen for injection, and injected their assigned dose into a test pillow. Observers recorded whether the subject successfully completed each task and if they required clarification (yes/no). Subjects completed a 17-item usability questionnaire and rated how easy it was to perform each task and to learn to use the pen. Questionnaire items were rated from 1 (very difficult/most negative score) to 4 (very easy/most positive score).

Result:
As assessed by the observers, the majority of the 43 randomized subjects successfully attached the needle (86%), made a drop appear at the end of the needle (98%), and dialed (86%) and injected (93%) the requested dose. Mean usability questionnaire scores pertaining to ease of preparing the pen, routine pen use, delivering the required dose, and pushing the activation button were ≥3.6 across all dose groups. Subjects rated the instructions for use as being easy to understand (≥3.5).

Conclusion:
Subjects with T2DM who read the instructions for use were able to correctly use the Victoza pen for the first time with relative ease.

Retrospective Evaluation of Medtronic's Next-Generation Subcutaneous Glucose Sensor

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Background:
Professional continuous glucose monitoring (CGM) can be utilized by health care professionals (HCPs) to help make therapy adjustments for type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational patients. iPro2, Medtronic's next-generation professional CGM system, will deliver the same accuracy as the previous system while reducing HCP burden to setup, download, and interpret data. Using an iPro2, HCPs can acquire sensor glucose data with minimal patient training and obtain critical trending data. To further advance professional CGM, Medtronic has developed the next-generation Enlite sensor for use in conjunction with iPro2 to improve the accuracy and sensor lifetime of the reports.

Method:
Data obtained from a prospective clinical trial was postprocessed through the Medtronic retrospective algorithm. A total of 63 T1DM and T2DM subjects each wore two Enlite sensors (one in the abdomen and one in the buttock) over a period of 7 days. Performance was evaluated against capillary blood glucose values obtained from a OneTouch UltraLink (LifeScan Inc., Milpitas, CA) meter.

Results:
The mean absolute relative difference was 10.58%, and 98.12% of meter reference values were within the Clarke A and B zones when used with the iPro2 system. The average lifetime of the 252 sensors was over 6.6 days.

Conclusion:
Medtronic's next-generation professional CGM system used with the Enlite sensor yields accurate sensor readings and extended sensor lifetime while improving comfort and usability. Data obtained using the next-generation system can be used to analyze glucose trends effectively and make therapy adjustments.

Effect of Insulin Feedback Algorithm on Closed-Loop Blood Glucose Control

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Background:
Closed-loop (CL) insulin delivery systems utilizing proportional-integral-derivative (PID) controllers have demonstrated susceptibility to late postprandial hypoglycemia due to time delays between insulin delivery and blood glucose response. Insulin feedback (IFB) modifications to the PID algorithm have been introduced to mitigate this risk. We examined the effect of IFB incorporated into a PID CL system on blood glucose control.

Method:
Using the Medtronic ePID CL system, subjects were studied for 24 h on PID control and for 24 h during a separate admission with PID + IFB. Target glucose was 120 mg/dl; meals were served at 8:00 AM, 1:00 PM, and 6:00 PM and were identical for both study days. No premeal manual boluses were given. Reference blood glucose excursions, defined as incremental glucose rise from premeal to peak, and incremental postprandial blood glucose area under the curve (AUC; 0–5 h) were compared between conditions. Results are reported as mean ± standard deviation.

Result:
Among four subjects (two female, 15.7–27.8 years, hemoglobin A1c 7.5% ± 0.9%), PID + IFB control resulted in higher mean blood glucose levels compared with PID alone (153 ± 54 versus 133 ± 56 mg/dl, $p < .0001$). Incremental postmeal glycemic excursions (114 ± 28 versus 114 ± 47 mg/dl) and AUCs (285 ± 102 versus 255 ± 129 mg/dl/h) were similar under both conditions (p = not significant). Total insulin delivery averaged 57 ± 20 U with PID versus 45 ± 13 U with PID + IFB ($p = .18$). Notably, eight episodes of hypoglycemia (blood glucose < 60 mg/dl) occurred during PID control versus none during PID + IFB.

Conclusion:
Insulin feedback markedly reduced the occurrence of hypoglycemia in patients under CL PID control without increasing meal-related glucose excursions, but at the expense of higher average blood glucose levels. The prevention of postprandial hypoglycemia with PID + IFB suggests that this algorithm may allow for lower target glucose selection and improved overall glycemic control.

Relationship between Meal Size and Blood Glucose Excursions during Closed-Loop Control

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Background:
Current closed-loop (CL) systems have been unable to normalize postprandial blood glucose (BG) levels effectively, particularly after high-carbohydrate meals. We utilized a proportional-integral-derivative (PID) controller with insulin feedback (IFB) under varying conditions to examine the relationship between meal carbohydrate content and corresponding BG excursions.

Method:
Using the Medtronic ePID system, eight subjects [four female, age 15 ± 28 years, hemoglobin A1c (A1C) 7.5% ± 0.7%] were studied for 24 h on full CL control and again for 24 h on full CL control plus 30 mcg premeal doses of pramlintide. These data were compared with 12 subjects (5 female, age 12 ± 26 years, A1C 7.4% ± 0.6%) who underwent 48 h of "hybrid" CL control with manual premeal "priming" boluses of 0.05 U/kg administered at the time of the meal. Target glucose for all conditions was set at 120 mg/dl. Reference BG excursions, defined as incremental glucose rise from premeal to peak, were compared between conditions; results are reported as mean ± standard deviation.

Result:
A weak, positive correlation was observed between carbohydrate content and BG excursion (R^2 = 0.276, p = .0084) under control conditions but not in pramlintide (R^2 = 0.0384, p = .359) or premeal priming bolus (R^2 = 0.00241, p = .682) conditions. Mean meal carbohydrate content was similar among conditions (84 ± 26, 84 ± 26, and 93 ± 24 g, respectively, p = not significant); prandial BG excursions were significantly lower in the pramlintide versus control condition (87 ± 42 versus 113 ± 32 mg/dl, p = .006) but only modestly lower in the priming bolus condition (96 ± 50, p = not significant).

Conclusion:
Under PID + IFB control, the correlation between meal carbohydrate content and BG excursion suggests that system performance is influenced by meal composition. The use of pramlintide or premeal priming may mitigate this sensitivity to changes in meal carbohydrate content but might require larger premeal boluses.

Personalized Decision Support in Routine Diabetes Care: A 3-Year Update

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Objective:
It was the aim of this study to evaluate the medical outcome of personalized decision support in routine diabetes care after 3 years of running a patient-focused decision support system.

Method:
The German health insurance fund BBK Gesundheit launched the Diabetiva program in April 2007. Diabetiva offers continuous glucose monitoring (CGM) and personalized decision support generated by the Karlsburg Diabetes Management System KADIS. The Diabetiva timeline includes annual CGM followed by generating KADIS-based decision support for therapy optimization and quarterly check-up of hemoglobin A1c (A1C). Patients with two CGM readings were retrospective analyzed for acceptance of the KADIS-based decision support using a questionnaire, and the outcome was evaluated according to A1C as primary outcome parameter.

Results:
After running Diabetiva for 36 months, 869 insured diabetes patients (95.4% type 2) were enrolled and had received 2607 CGM readings. Patients were cared for by 616 general practitioners and 44 diabetes specialists. Approximately 75% of physicians accepted KADIS as personalized decision support to optimize diabetes therapy of their patients. Logistic regression revealed that KADIS acceptance and outcome depended on A1C at baseline ($p < .01$). General practitioner or diabetes specialist, age, onset of diabetes, and type of diabetes or diabetes therapy had no significant influence on acceptance or outcome parameters. If KADIS-based decision support was accepted, A1C could be significantly decreased overall by -0.5% ($p < .01$), whereas A1C at baseline <6.5 decreased by -0.1%, 6.5–7.5 by -0.3%, and >7.5% by -1.5%. If KADIS was refused, the impact of Diabetiva was completely diminished: overall increase of A1c by +0.40% (A1C at baseline <6.5, +0.5%; 6.5–7.5, +0.3%; >7.5%, 0.1%), $p < .05$.

Conclusion:
Personalized decision support is well accepted by physicians. The acceptance rate is related to A1C at baseline. Personalized decision support in combination with CGM significantly improves outcome parameters in routine diabetes care.

Noninvasive Evaluation of the Peritoneal Oxygen Environment in Animals with Encapsulated Pancreatic Islet Implants

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Objective:
Islets encapsulated in biocompatible materials for immune protection have the potential to restore glycemic control in diabetic animals and potentially humans. The peritoneal cavity is often used as an implantation site, as it can be easily accessed and accommodate such implants. However, implant failure generally occurs after various periods of time. The objectives of this study were to assess whether hypoxia is a contributing factor toward implant failure and to evaluate whether the implant itself affects the host physiology at the implantation site.

Method:
We established a method that utilizes ^{19}F nuclear magnetic resonance spectroscopy, with perfluoro-15-crown-5-ether (PFCE) as an oxygen concentration marker, to measure dissolved oxygen (DO) concentration noninvasively at the implantation milieu. Alginate capsules containing PFCE were co-implanted with encapsulated adult porcine islets (APIs) in the peritoneal cavity of streptozotocin-induced diabetic mice. Both the peritoneal DO and implant functionality, as assessed through the glycemic state of the mice, were monitored for 60 days. Constructs were then explanted and evaluated for integrity, cell viability, and functionality.

Result:
Implantation of encapsulated APIs reversed diabetes in mice. The peritoneal DO was low (~0.07 mM), and implantation of APIs reduced it further toward severely hypoxic levels (~0.02 mM). Explanted APIs were viable and functional, indicating that the metabolically active implant contributed toward the decrease in peritoneal DO. Recruited host cells at the implantation site could have also contributed to the decrease in DO.

Conclusion:
Implantation of encapsulated APIs significantly reduces the peritoneal DO in mice. However, islets function and restore glycemia under these conditions. Hence, hypoxia does not appear to be a major contributor of islet failure; however, its full effect remains to be determined.

Uptake of an Internet-Based Patient Portal and Ethnic and Educational Disparities: The Diabetes Study of Northern California (DISTANCE)

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Background:
We investigated uptake of an Internet-based patient portal by race/ethnicity and educational attainment.

Methods:
We measured the frequency of requesting a password for the patient portal, which represents intent to use the patient portal and indicates some computer access between January 2006 and December 2009, among an English-speaking adult, continuously insured population with diabetes receiving care in an integrated health maintenance organization.

Results:
We studied 11,921 ethnically diverse participants with varying educational attainment. Overall, intent to use the patient portal (i.e., requesting a password) increased markedly over the observation period across all educational levels and race/ethnicities, from 1427 (12%) of participants in 2006 to 4466 (37%) in 2009. In 2006, 9% of those with less than a high school degree requested a password, compared with 13% of those with a college degree or higher ($p < .001$). In 2009, 32% with less than a high school degree had requested a password compared with 39% with a college degree or more ($p < .001$). Similarly, in 2006, there were small race/ethnic differences in intent to use the patient portal, with African American, Filipino, and Latino participants least likely and Asian and white participants most likely to request a password. Relative differences narrowed over time for all ethnic groups. Absolute differences also narrowed, except among African Americans. In 2009, whites were most likely and African Americans least likely to request a password (40% versus 34%, $p = .001$).

Conclusions:
Expanded computer/Internet access, training in patient portal use, and cultural/educational tailoring may be required for patient-facing electronic health records to be harnessed as a means to reduce disparities.

Transdermal Metformin for the Treatment of Type 2 Diabetes: A Case Series

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Objective:
Oral metformin is considered a cornerstone of treatment in type 2 diabetes mellitus and can also be used in conditions such as prediabetes and polycystic ovarian syndrome. Studies show that 20% of patients taking metformin have a side effect, with at least 5% of those patients discontinuing the medication due to the side effects. Transdermal metformin holds the potential to be an effective alternative treatment modality in patients with insulin resistance who are unable to tolerate the oral preparation. The purpose of this study is to determine if transdermal absorption allows the medication to avoid the gastrointestinal side effects that frequently warrant discontinuation of oral metformin.

Methods:
For this study, participants were chosen based on a history of metformin intolerance who were clinically determined to gain benefit from continued metformin treatment. The participants are being followed for up to one year at which point charts will be retrospectively reviewed for occurrence of side effect, general tolerability, and efficacy.

Results:
Preliminary results show that transdermal metformin has the capability to decrease blood glucose levels and hemoglobin A1c levels with a 90% reduction in dosage.

Conclusion:
Transdermal metformin is a novel and effective use for the treatment of type 2 diabetes. One advantage of using transdermal metformin is its ability to bypass the gastrointestinal system while being systemically absorbed. Anecdotal evidence suggests that another benefit of transdermal metformin is a 90% decrease in dosage from the oral preparation. The significant decrease in dose leads to the implication that transdermal metformin could be used in hepatic and renal failure patients as well as decrease the incidence of vitamin B12 deficiency associated with diabetic peripheral neuropathy.

Food Recognition Based on Computer Vision Technologies

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Objective:
The scope of the current work was to define the optimal architecture of a computer-vision-based system for automated food recognition from images. This task is the first step prior to estimation of included carbohydrates (CHOs).

Method:
A visual data set of approximately 12,000 color images of food from different Web sources and with different lighting conditions were collected. The images were grouped into two main categories based on their CHO content (CHO versus non-CHO). The CHO images were further grouped into the main representative meals, namely pasta, pizza, bread, potatoes, and salad, while the non-CHO images were grouped into egg, rice, fish, and meat, thus resulting in a total of nine classes.

Two different approaches have been developed and evaluated. The first one consists of a multiclass classifier (MC), solving the one-versus-all problem. In other words, the MC recognizes the type of the food among the nine classes. The second approach is a hierarchical classification (HC) scheme, where the system first recognizes if the image belongs to CHO or non-CHO and then proceeds to the food recognition.

Result:
The preliminary results have shown that the MC approach is able to recognize the food on a plate with a mean accuracy of 60% in the evaluation visual data set, while the HC scheme has a mean accuracy of 75%.

Conclusion:
The feasibility study has shown that a HC scheme seems to be more appropriate in such a complex problem. The promising results indicate that computer vision approaches might be a useful tool for diabetes patients during CHO counting.

Estimation of Insulin Sensitivity from Continuous Glucose Monitoring and Subcutaneous Insulin Delivery in Type 1 Diabetes

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Objective:
The use of continuous glucose monitoring (CGM) devices and subcutaneous insulin pumps for diabetes management has greatly increased since 2000. It would be interesting to power data analysis, e.g., by estimating insulin sensitivity by using these data.

The objective of this study was to propose a new index of insulin sensitivity ($S_I^{CGM\&P}$) calculated from CGM data and subcutaneous insulin pump that is easily derivable for patients with type 1 diabetes mellitus (T1DM) in normal life conditions.

Method:
The database consists of 12 T1DM subjects studied three times (at breakfast, lunch, and dinner) with a standard mixed meal test wearing both a subcutaneous insulin pump and a CGM device. Blood samples were drawn for measurement of plasma glucose and insulin concentrations, which were used to estimate insulin sensitivity with the oral glucose minimal model, here considered as reference (S_I^{ref}).

$S_I^{CGM\&P}$ was calculated with a formula that takes into account the area under CGM trace and total amount of infused insulin. $S_I^{CGM\&P}$ was compared with S_I^{ref} to assess its validity.

Result:
$S_I^{CGM\&P}$ correlated well with the S_I^{ref} ($r = 0.72$; $p < .01$). In addition, the daily pattern of the new index is similar to the reference index S_I^{ref}.

Conclusion:
A new approach to estimate insulin sensitivity from CGM and infusion rate of subcutaneous insulin pump is proposed, which appears to be closely associated with insulin sensitivity derived from plasma measurements and oral glucose minimal model. The new index is thus usable to assess insulin sensitivity in T1DM patients in normal life conditions.

Glycemic Levels in Critically Ill Patients: Is Normoglycemia and Low Variability Associated with Improved Outcomes?

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Background:
There is ongoing debate about the benefits of tight glycemic control (TGC) and the link between blood glucose levels and the outcome of critically ill patients. The association between cumulative time in band and odds ratio (OR) of living was assessed in this study.

Method:
Clinical blood glucose measurements from 310 critically ill patients who stayed in the intensive care unit (ICU) for at least 5 days, regardless of whether they received TGC, were used. Cumulative time in a 4–7 mmol/liter band (CTIB) was calculated for each patient and day. Patients were stratified into two groups: CTIB ≥ 70% and CTIB < 70%. Odds ratios (number lived / number died = OR) based on hospital outcome were calculated for both groups, as well as the overall cohort for comparison.

Result:
Overall cohort OR = 2.6 (28.1% mortality). At the end of day 1, OR = 3.1 for CTIB ≥ 70% patients and OR = 2.3 for CTIB < 70% patients. By day 5, OR = 4.4 and 1.6 for these groups, respectively. Days in between were stratified between these two values for each group and centered about the cohort value. Considering 784 patients with 24+ h of ICU stay, OR = 2.6 on day 1 and 4.4 on day 5 for CTIB ≥ 70% and 2.6 and 1.6 for CTIB < 70%. Hence the results are relatively independent of length of stay and patients leaving the ICU.

Conclusion:
The results show that, irrespective of glycemic control protocols, normoglycemia measured by CTIB ≥ 70% is associated with higher odds of living, and these odds increase for each day of stay through day 5. These results thus provide guidelines for the target glycemia and variability that might be required for effective TGC.

Sensitivity of Recalibrated Continuous Glucose Monitor Data

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Objective:
Continuous glucose monitors (CGMs) are increasingly used in research settings to examine glucose metabolism in newborn babies. Accuracy of these devices depends on calibration blood glucose (BG) measurements entered into the CGM. The potential impact of variations in timing and accuracy of reference calibration measurements on CGM output were assessed.

Method:
Clinical CGM data from 50 neonates (~228 days) and blood-gas analyzer reference BG measurements were used. Normally distributed [standard deviation (SD) 2%, 5%, or 10%] random errors were added to reference BG concentrations, and random timing lags up to +25 min simulated delays in registering calibration BG with the CGM. The CGM trace was recalculated 1000× in a Monte Carlo analysis using randomly modified calibration measurements. Uncertainty in each CGM measurement was defined as the range (mmol/liter) of that measurement over the 1000 runs.

Result:
Considering only reference BG measurement error, median CGM uncertainty across the cohort varied from 0.5 mmol/liter for SD 2% to 2.4 mmol/liter for SD 10%. Considering only timing lags, uncertainty was less than 0.18 mmol/liter (75% of time) but reaches 3 mmol/liter or more, depending on local rate of change of glucose. Combining both BG measurement error and timing lag effectively adds these uncertainties.

Conclusion:
Reference BG measurement error causes an almost uniform uncertainty band around the "no error" CGM trace. The level of uncertainty depends upon the reference sensor accuracy. The effect of timing lags is highly dependent on the local rate of change of glucose, with high rates of change causing very large uncertainties. Clinically, timing lags should be minimized for highly variable situations (e.g., brittle diabetes patients or postprandial measurements) to reduce uncertainty.

Transdermal Exenatide Delivery in Patients with Type 2 Diabetes: Pharmacokinetic and Pharmacodynamic Evaluation

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Objective:
Exenatide, an incretin mimetic administered twice daily (BID) via subcutaneous (SC) injection, improves glycemic control, often with associated weight reduction. This double-blind, placebo controlled, three-period, three-treatment study evaluated the pharmacokinetics and pharmacodynamics of exenatide transdermal patch (TDP), placebo TDP, and exenatide SC injection in patients with type 2 diabetes mellitus (T2DM).

Method:
Exenatide, a 4 kDa peptide, was delivered transdermally through micropores in the stratum corneum in patients with T2DM (eight male/three female; age 48 ± 13 years; body mass index 32.5 ± 3.8 kg/m^2; hemoglobin A1c 7.96% ± 1.01%; fasting plasma glucose 168.7 ± 65.7 mg/dl; diabetes duration 6 ± 3 years; mean ± standard deviation). On separate days, subjects received exenatide TDP (1.9 mg, 3 cm^2), placebo TDP, or exenatide SC (10 mcg BID). Meals were given 3, 7, and 13 h after TDP application, and the patch was removed after 24 h. Subcutaneous exenatide was administered before the breakfast and dinner meals. Blood samples were collected for plasma exenatide and glucose concentrations throughout the study.

Result:
With exenatide TDP, mean peak concentrations of 301 pg/ml were achieved at 19 h and minimal efficacious concentrations (>50 pg/ml) were maintained for 21 h. Significant reduction in postprandial glucose was observed mainly after lunch and dinner when the exenatide plasma concentrations were at therapeutic levels. Glucose area under the curve (0–24 h) was reduced by 31.6% for exenatide TDP compared with placebo. Exenatide TDP was generally well tolerated, with no serious adverse events (AEs) or hypoglycemic events. The most frequent AEs with exenatide TDP were nausea, headache, and vomiting.

Conclusion:
These data showed that exenatide administered by the transdermal route resulted in sustained therapeutic plasma exenatide concentrations and postprandial glucose lowering in patients with T2DM.

Continuous Subcutaneous Insulin Infusion and Multiple Daily Insulin Injections: An Impact Study

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Background:
We studied the relative sociocultural, lifestyle, and diabetes management impact of continuous subcutaneous insulin infusion (CSII) and multiple daily insulin injections (MDII) for intensive diabetes management (IDM) on patients and their significant others (SOs).

Methods:
Sociotechnical systems theory and the life patterns model framed the study. We created four survey instruments (MDII/CSII; patient/SO) to study type 1/type 2 diabetes patients using MDII or CSII. Consented patients and SOs completed surveys to capture demographic characteristics, patient/SO perceptions of CSII/MDII impact on life patterns, patient perceptions about disease management impact, and overall perceptions of management satisfaction and lifestyle impact.

Results:
Cronbach's alpha for the instruments was >0.90. Patient/SO surveys exhibited significant ($p < .001$) differences between CSII and MDII patients' satisfaction with treatment method impact on disease management and lifestyle. The SOs did not score CSII higher on either parameter than they scored MDII. Only treatment method and age group of dependent variables examined (treatment method, diabetes type, income, race, education, gender, employment status, living circumstance, age, existing health insurance) and interactions (treatment method/age, method/gender, method/income, method/insurance, method/education) had an effect. Patient age was positively associated with *both* disease management *and* lifestyle impact for *both* CSII *and* MDII. An inverse relationship between satisfaction and lifestyle and patient education impact was suggested.

Conclusions:
Patients perceive greater satisfaction with CSII impact on disease management and lifestyle than MDII. Neither age nor education level are contraindications for CSII. Neither diabetes type, age, gender, race, education, income, health insurance, nor living circumstance is a predictor of the recommended insulin administration method for IDM. Clinicians should recognize that, while both MDII and CSII are potential methodologies IDM, CSII exhibits greater patient satisfaction regarding disease management and lifestyle impact.

Can Blood Glucose Drops during Exercise Be Predicted from Heart Rate Data?

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Objective:
Cardiac exercise often poses a hypoglycemic-inducing event for diabetes patients. For the purpose of glucose prediction in such circumstances, a model describing the relationship between elevated heart rate level and blood glucose drops was addressed.

Method:
The relationship was modeled by an autoregressive model with external input, and the model parameters were identified by the least-squares method.

Result:
Twenty-nine type 1 patients [age 45 (22–68) years, body mass index 24.7 (19.5–32.8) kg/m^2, hemoglobin A1c 7.8 (5.6–9.8)%] participated in a stationary bike exercise trial with effort held constant at intensity corresponding to the calculated ventilatory threshold +15%. Patients were equipped with a continuous glucose monitoring (CGM) and heart rate (HR) monitoring system and given a standardized breakfast (42 g carbohydrates) 2 h in advance of the physical test, with no or reduced bolus doses. In total, only 13 data sets could be evaluated due to hardware malfunctions, mainly related to the HR monitoring system. Using the patient-specific data, model parameters were identified for each patient. Using these models, expected glucose drops were calculated from each patient's HR data and compared with the collected CGM data, which was regarded as a proxy of blood glucose level. Stationary HR level was established as mean HR level 1 h before the test. The prediction error had a small bias (2.3 ± 7.8 mg/dl) and small root mean square error (7.7 ± 4.6 mg/dl).

Conclusion:
The study is small, and no cross-validation data are available, but the study indicates that there is a statistically significant relationship between elevated HR level and glucose drop during exercise.

Transdermal Insulin Application System with Dissolving Microneedles

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Background:
To increase user-friendliness, a dissolving microneedle (MN) application system has been developed, where 225–300 insulin loaded MNs were formed on a tablet that was attached to an application system. The whole system is provided as a product packaged in protein tyrosine phosphatase (PTP). By removing the heat-sealed sheet, the system covered with a PTP layer is put on the skin. By pressing with a hand, insulin MNs were inserted into the skin. To evaluate the system, the effect of the collision speed on the penetration depth of microneedles were studied with rat and human skins, and the hypoglycemic effects of the MNs having the optimized insulin-loaded space length were studied in an *in vivo* rat experiment.

Method:
The system containing an insulin MN array chip made of a chondroitin sulfate/dextran mixture as the base was applied to the rat and human skins supplied by NPO, Human and Animal Bridging Research Organization, Tokyo, with different collision speeds, 0.8–4.0 m/s (force, 8–40 N) followed by second pressure, 0.5–2.5 N, for 1 to 5 min. The penetration depth of the MNs was estimated by the difference of the MN lengths before and after application. Two kinds of MNs, where insulin was loaded at the acral portion of MNs of which mean length was 181 ± 4 and 210 ± 4 μm, were prepared. Insulin contents were measured by high-performance liquid chromatography method. The MNs were attached to the application system and applied to the abdominal skin of shaved rats. After administration, plasma glucose levels were measured for 5 h. Relative pharmacological availability (RPA) of insulin was determined by comparing the area above the plasma glucose level versus time curves obtained after subcutaneous injection of insulin solution, 1.0 U. Fluorescein isothiocyanate insulin was formulated into MNs, and the delivery site and diffusion rate in the rat skin was studied microscopically.

Result:
The penetration depth of MNs into the skin was dependent on the collision speed of the MNs. As the collision speed increased from 0.8–4.0 m/s, the penetration depth increased from 20 to 70 μm. As the second pressure increased from 0.5 to 2.5 N, penetration depth increased to 200 μm. There was no

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significant difference in the penetration depth between rat and human skins nor between *in vivo* and *in vitro* rat experiments. Insulin contents of the two MNs, of which the length of insulin-loaded space was 181 and 210 μm, were 1.58 ± 0.03 and 1.72 ± 0.13 U, respectively. From the pharmacodynamic study, they showed RPAs of 98.1% ± 0.8% and 98.1% ± 3.1%, respectively. Histological study suggested that there was no irritation on the rat skin. Fluorescence microscopic experiment showed that the MNs dissolved in the inserted epidermal site of the skin within 1 min after administration, and thereafter fluorescence diffused in both horizontal and vertical directions of the skin within 1 h.

Conclusion:
A dissolving MN application system showed high RPA of insulin after percutaneous administration to the rat skin and was found to be a useful transdermal drug delivery system for insulin with high safety, because MNs were made of water-soluble thread-forming polymer, chondroitin sulfate, and dextran that have been used as pharmaceuticals for the injection therapy of arthritis and peripheral circulatory disturbances of patients with head injury.

Which Japanese Patients with Type 1 Diabetes Would Benefit from Continuous Subcutaneous Insulin Infusion?

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Background:
The Diabetes Control and Complications Trial demonstrated that continuous subcutaneous insulin infusion (CSII) effectively delayed the onset and slowed the progression of diabetic microvascular complications in patients with type 1 diabetes mellitus (T1DM). We attempted to determine which Japanese patients with T1DM were appropriate candidates for CSII.

Method:
Twenty-eight patients (10 men, 18 women) with T1DM who were on CSII for 3 months were enrolled in the retrospective study. Median (25–75 percentiles) age was 37.0 (28.0–46.5) years. Median hemoglobin A1c (HbA1c) values at introduction of CSII and after 3 months were 8.15% and 7.65%, respectively, with a median difference between baseline and 3 months of 0.55%. We divided the patients into two groups of 14 patients each: a CSII effective group with a change in baseline HbA1c greater than the median and a CSII ineffective group with a change less than the median. Statistical analysis was performed by using the Mann–Whitney test.

Results:
We found that the median baseline HbA1c in the CSII effective group (8.65%) was significantly higher than that of the CSII ineffective group (7.80%; $p = .017$).

Conclusion:
Our results suggest that Japanese patients with T1DM who have poor glycemic control should try CSII to improve their HbA1c.

Safety Profile of Finesse Insulin Bolus Patch Compared with Pen/Syringe Delivery Devices in Adults with Diabetes Mellitus

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Background:
We compared the safety profile of the Finesse insulin bolus patch with pen/syringe to deliver prandial insulin for glycemic control in adults with diabetes on multiple daily insulin treatment. Subjects continued their usual basal insulin.

Method:
Thirty-eight 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 pen/syringe devices [55% pen, 45% syringe]). During the study, subjects followed their previously prescribed insulin regimen. Subjects self-monitored their blood glucose 4–7 times daily. They also examined the Finesse cannula insertion or pen/syringe injection sites as instructed. These safety data were collected throughout the study.

Results:
No significant difference between Finesse and pen/syringe devices were observed for differences in the rate of biochemical hypoglycemia (<70 mg/dl) per 30 days (mean ± standard error; Finesse 9.9 ± 1.4 versus pen/syringe 9.8 ± 1.4, $p = .971$) or the rate of hyperglycemia (>180 mg/dl; Finesse 59.1 ± 4.4 versus pen/syringe 54.2 ± 4.3, $p = .134$), indicating that Finesse did not overdeliver or underdeliver insulin doses. There were no episodes of severe hypoglycemia in either the Finesse or the pen/syringe phase. There were no differences in the cannula insertion site compared with injection site reactions. There were no clinically relevant device-related adverse events (AEs) for Finesse compared with pen/syringe devices. Twelve subjects (32%) reported 21 AEs (half during the Finesse phase and half during injection phase; primarily upper respiratory infection and cough). There was 1 serious AE during the pen/syringe phase (acute pancreatitis) and 1 serious AE during the Finesse phase (acute bronchitis), both unrelated to delivery device used.

Conclusion:
Overall, Finesse insulin bolus patch had good safety results. The safety profile of Finesse and the pen/syringe devices were comparable.

A Retrospective Comparative Audit Investigating the Glycemic Control Implemented in Two Intensive Care Units

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Background:
Critically ill patients experience stress-induced hyperglycemia. Glycemic control therapy (GCT) is administered to control patients' glycemic levels and reduce the incidence of infection, myocardial infarctions, and organ failure. However, many factors influence the effectiveness of glycemic control.

Methods:
A retrospective audit was carried out on patients' case notes in intensive care units (ICUs) in the East Midlands, UK, to examine which GCT was implemented and its effectiveness. This method prevents the study outcomes from being swayed toward any particular direction, because GCT has already taken place, and to reduce selection bias, the most recent available case notes were selected.

Results:
Different glycemic control protocols were being implemented in each hospital setting, despite both belonging to the same ICU network. It was found in most incidences that, regardless of age, diabetes status, or current diagnosis, patients were administered the same sliding scale insulin (SSI), and medications were not taken into account. Results also indicated that some medical staff adapted hospital titration regimens and that Actrapid was the only insulin used for SSI.

A new glycemic range was also discovered; 85.2% (n = 109) of patients (across hospitals A and B) receiving GCT were not controlled in hypoglycemia, normoglycemia, or hyperglycemia. They had mean average blood glycemic levels between 5.7 and 9.9 mmol/liter, described as medioglycemia.

Conclusion:
To overall improve glycemic control and increase effectiveness and safety of practice for patients, a new comprehensive guideline needs to be developed for glycemic control. This needs to include recommendations on how to adapt the titration regimen to individuals, taking into account their age, diabetes status, diagnosis, and medications.

Automated Insulin Infusion and Blood Glucose Regulation with an Adaptive Multivariable Model-Based Control System

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Objective:
The objective of this work was to develop subject-specific models that can capture a subject's daily glucose variations, predict his/her future glucose excursions, and automate insulin infusion by using model-based closed-loop control. 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 used 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 and control algorithms.

Method:
The subject-specific glucose prediction model was developed using measurements from a glucose sensor and physiological signals from a multisensor armband. The frequent data from the sensors were analyzed by time-series methods. Adaptive system identification consists of an online parameter identification using the weighted recursive least squares (RLS) method and a change detection method that monitors variation in model parameters. It estimates model parameters that enable the adaptation of the model to intersubject/intrasubject variation and glycemic disturbances. Generalized predictive control methods were used to determine insulin infusion flow rates.

Result:
The control algorithms based only on glucose measurement information were tested by using simulators. The multivariable control systems were tested in clinical studies. Errors in glucose concentration predictions were reduced with additional information from the armband when compared with predictions done solely on glucose measurements. Both control approaches were successful in regulating glucose concentrations in response to various meal and exercise disturbances.

Conclusion:
Models developed are linear, low order, and easy to identify, which make them a good candidate for closing the loop with an automated insulin pump. The RLS and the change detection methods enable the dynamic adaptation of the models to intersubject/intrasubject variation and glycemic disturbances.

Retrospective Analysis of Events Preceding Low Glucose Suspend Activation in Adult Subjects on the Paradigm Veo System

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Background:
The Paradigm Veo system (Medtronic MiniMed Inc., Northridge, CA) with low glucose suspend (LGS) halts insulin delivery for ≤2 h when sensor glucose values reach a predetermined threshold (40–110 mg/dl). The CareLink Pro 3.0 episode summary analyzes the occurrence of 22 potential events that could occur in the 3 h preceding hypoglycemia/hyperglycemia. An analysis using the episode summary algorithm was performed to describe the occurrence of 12 events within the 3 h preceding LGS activation.

Method:
Data from adult Veo users (age ≥16 years) in 2010 were obtained from the CareLink database. Data from 2494 patients (1307 female) totaling 73,579 patient days (72.49% with LGS on) were collected and retrospectively analyzed using the episode summary algorithm; 47,783 LGS activations were analyzed by night (10:00 PM–8:00 AM) versus day (8:00 AM–10:00 PM) and by those lasting 2 versus <2 h.

Result:
Rapid negative rate-of-change (-ROC; ≤-2.0 mg/dl/min; 47.27%), hyperglycemia (≥180 mg/dl; 31.06%), and food bolus with Bolus Wizard (25.31%) most commonly preceded LGS. Two-hour LGS at night was preceded most commonly by -ROC (42.06%), hyperglycemia (28.83%), and bolus with -ROC (≤-1.5 mg/dl/min; 13.92%) and during the day by -ROC (51.35%), hyperglycemia (37.92%), and manual bolus (28.96%). Two-hour LGS versus <2 h LGS at night showed a higher mean percentage preceded by hyperglycemia (28.83% versus 25.06%; $p = .0051$). Two-hour LGS versus <2 h LGS during the day showed a higher mean percentage preceded by manual bolus (28.96% versus 20.56%; $p = .0116$) and hyperglycemia (37.92% versus 33.33%; $p = .0042$).

Conclusion:
Use of the CareLink Pro 3.0 episode summary algorithm allows analysis of events preceding LGS and can help identify patient behaviors that might contribute to hypoglycemia.

Incorporating Nonlinear Response to Hypoglycemia into the Type 1 Diabetes Simulator

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Background:
In 2008, we introduced a computer simulator of type 1 diabetes mellitus (T1DM) equipped with 100 in silico adults, 100 adolescents, and 100 children, which was accepted by the Food and Drug Administration as a substitute for preclinical trials of certain insulin treatments, including closed-loop algorithms. The major claim of the simulator was that, for any person with T1DM, there would be one or more simulated "subjects" with similar metabolic response. We now enhance this claim by matching the distribution of simulated subjects to the observed population distribution, particularly in terms of frequency of hypoglycemia.

Method:
The model of glucose kinetics in hypoglycemia included in the simulator has been modified by introducing the risk function in the insulin-dependent utilization, which makes the virtual subjects more sensitive to insulin, when glucose levels fall.

The database considered in the study consists of 24 T1DM subjects who received dinner (70.7 ± 3.3 g of carbohydrates) and breakfast (52.9 ± 0.1 g of carbohydrates) in two occasions (open- and closed-loop), for a total of 96 postmeal traces.

Measured plasma glucose profiles were compared with those simulated in 100 *in silico* adults, and continuous glucose error grid analysis (CG-EGA) was used to assess clinical validity of the model.

Result:
With the introduced modification, the frequency of hypoglycemia episodes predicted by the simulator reflects that observed during clinical trials. In addition, CG-EGA proves the clinical validity of the model (percentage in A+B zone: 94.6% in hypoglycemia, 98.6% in euglycemia, 94.1% in hyperglycemia).

Conclusion:
The updated distribution of virtual subjects included in the T1DM simulator is representative of real T1DM populations observed in clinical trials, thereby providing the opportunity for *in silico* population-based trials.

Noninvasive Glucose Measurement: On the Way to Specific Glucose Values

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Background:
At present, there is no instrument capable of measuring glucose of a diabetes patient in a noninvasive way. We are currently developing a measuring system based on mid-infrared (MIR) spectroscopy that offers high specificity for glucose.

Method:
Our method combines the high energy emitted by tunable quantum cascade lasers (QCLs) in the MIR in the spectral range of the glucose fingerprint (approximately 8–10 μm) with photoacoustic (PA) detection. Studies applying a limited number of MIR wavelengths have previously shown the feasibility of this approach. This approach accounts for the problems related to skin glucose measurement, such as low penetration depth for the optical energy in the MIR, quantitative determination absorption, and measuring tissue glucose instead of blood glucose.

Result:
In addition to previous feasibility studies using 2–4 QCL wavelengths in the MIR, the introduction of a broadband tunable QCL resulted in a significant improvement of glucose prediction and a more reliable and easy data acquisition. Analysis of the data does not require significant data processing, because the signals indicating the specific absorption of glucose can be used. The correlation between blood glucose as reference and photoacoustic glucose signals is continuously improved and has meanwhile reached a correlation coefficient of >0.8.

Conclusion:
Our data show that pulsed MIR laser radiation induces PA signals that yield reliable information about the glucose level and its changes and trends in the tissue. The results suggest that these are signals specific for glucose. The technology presented will lead to the development of an easy-to-use noninvasive glucometer.

Comparative Evaluation of BodyMedia Armband Glucose Estimates and Continuous Glucose Monitor Estimates

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Objective:
The objective of this study was to compare the performance of BodyMedia's armband-based noninvasive sensor model with continuous glucose measurement sensors (CGMSs) during both restful conditions (oral glucose tolerance test [OGTT] protocol) and motion-based physical activity in patients with type 2 diabetes mellitus (T2DM).

Method:
This study collected noninvasive multisensor data from BodyMedia armbands, obtained continuous glucose values using Medtronic CGMS, and measured glucose values (used as ground truth) from an automated plasma oxidase glucose analyzer simultaneously. The data have been collected for 21 T2DM subjects. The armband measures acceleration, heat flow from the body, skin temperature, electrocardiogram, and galvanic skin and has been shown in previous studies to accurately predict energy expenditure, heart rate, and heart rate variability. Data for each subject was collected during (1) a restful OGTT protocol, and during (2) a treadmill protocol under controlled conditions. Models were developed for each protocol for predicting plasma glucose values from the armband data. The models were developed and evaluated using by-subject cross validation.

Result:
For the OGTT protocol, with respect to plasma glucose values, average absolute error (AAE) for armband estimated glucose values was 37.2 mg/dl (23%), whereas the AAE for CGMS was 46.1 mg/dl (36%). For the treadmill protocol, with respect to plasma glucose values, AAE for armband estimated glucose values was 13.3 mg/dl (10.7%), whereas AAE for CGMS was 46.1 mg/dl (36%). Armband estimated glucose values had better correlation (0.704 OGTT, 0.955 treadmill) with the plasma glucose values than CGMS (0.422 OGTT, 0.824 treadmill).

Conclusion:
Preliminary results suggest that the armband may be capable of estimating plasma glucose levels for both restful and physically active periods and performs well compared with the CGMS results.

A Small Peptide Treatment to Prevent and Reverse Hyperglycemic Onset in NOD Mice

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Objective:
Treatments for type 1 diabetes mellitus (T1DM) are varied, ranging from antibodies to control inflammatory cytokines or to induce regulatory T cells, steroids to control inflammation, and potentially tolerogenic peptides to induce immune anergy. Still no "cure" exists. The objective was to create a small peptide that could interfere with the CD40–CD154 proinflammatory axis and potentially affect the disease process in T1DM.

Methods:
We described a subset of T cells that express CD40 (Th40) and that proved highly diabetogenic in the NOD model of T1DM. Th40 cells are drastically expanded in human T1DM subjects compared with T2DM or nonautoimmune control subjects and respond to a panel of diabetes-associated antigens. Based on the known interaction site of CD40 and CD154, a series of peptides corresponding to the CD154 hot spot region was designed and tested in prediabetic NOD mice.

Results:
NOD mice (78 total) injected with a 15-mer peptide demonstrated 100% protection from developing T1DM, and 80% of new-onset diabetic NOD mice (12 total) reversed hyperglycemia, recovering significant beta-cell mass. The 6-mer and 24-mer peptides were unable to protect NOD mice. A 13-mer peptide was also efficacious at preventing (8 out of 10 mice) and reversing (2 out of 2 mice) hyperglycemia. Unlike antibody treatments, the peptides only affected Th40 cells, with immune cell types in treated animals remaining normal.

Conclusions:
A specific small peptide binds directly to Th40 cells, prevents diabetes onset, and, in new-onset mice, reverses hyperglycemia. This suggests an exciting new treatment option for T1DM.

DialBetics: Smartphone-Based Self-Management for Patients with Type 2 Diabetes

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Objective:
The purpose of the study was (1) to develop a partially automated system to interpret patients' data—with interactive communication of findings—achieving diabetes management without increasing the physician's workload, and (2) to evaluate the potential role of the system in diabetes self-management among patients with type 2 diabetes (T2DM).

Method:
This semicomputerized system, DialBetics, is composed of three modules. (1) Data transmission: patients' data, measured at home, are sent to the hospital server twice daily by Bluetooth. Body weight, blood pressure, and blood glucose are measured before breakfast; blood pressure, pedometer count, and blood glucose are measured at bedtime. (2) Evaluation: transmitted data are automatically evaluated following the Japan Diabetes Society guideline's targeted values. DialBetics determines if each reading satisfies guideline requirements then sends the data-evaluation results and apposite questions on diet and exercise to each patient's smart phone. (3) Communication: the patient's voice message about diet and exercise in response to DialBetics is converted to text and matched with text in the DialBetics database. Advice on lifestyle modification, matched to the patient's answer, is sent by email.

Nine non-insulin-treated T2DM recruits utilized the system for 1 month then were evaluated to see if diabetes control was improved by change of hemoglobin A1c (HbA1c).

Result:
Baseline mean ± standard deviation (SD) age was 61.3 ± 9.6 years, body mass index 25.4 ± 4.6 kg/m^2, and HbA1c 6.4% ± 0.8%. Patients' data measurement rate at home was 97.6% ± 0.06%. Mean HbA1c significantly decreased after 1 month of follow-up (mean ± SD; 6.2% ± 0.8%, p = .04). All subjects were satisfied with DialBetics, finding advice on lifestyle modification especially helpful.

Conclusion:
DialBetics may lead to better control of diabetes, improving patient self-management—without significantly increasing health professionals' workloads. More studies are needed for further development.

Effect of Implant Size on the Foreign Body Response to Implantable Biosensors

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Background:
We performed an investigation of the effect of implant size on the foreign body response to subcutaneous (SC) implantable sensors used for continuous glucose monitoring. We have previously reported controlling the foreign body response through application of dexamethasone-eluting sensor coatings. However, in this study, no coatings were applied in order to first determine the effect of implant size alone.

Methods:
Three dummy sensors (0.35 × 3, 0.5 × 5, and 0.75 × 7 mm^2 polished silicon chips) were implanted into the interscapular SC tissue of rats using 16 and18 G needles. Tissue response was determined through serial sacrifice to investigate acute (day 3) and chronic (days 7, 14, and 28) inflammation as well as fibrosis. A histopathologic evaluation of excised tissue samples from the implantation site was conducted. Hematoxylin and eosin staining was used.

Results:
Histological examination of excised tissue revealed that the smaller needle size did not affect the extent of acute inflammation. The acute inflammatory response was similar for all three sensor sizes. However, the extent of chronic inflammation and the progress of fibrotic deposition were affected by the dummy sensor size: the smaller the size, the lesser the extent of chronic inflammation and the slower the rate of fibrotic deposition around the implants.

Conclusions:
For the implant sizes investigated, implant size did not affect the acute inflammatory response, which is related to the initial tissue trauma. However, implant size did affect the chronic inflammatory response where the continual presence of the implant has a dominant role. Based on these results, follow-up studies will titrate the dexamethasone dose required in our coatings for different-sized sensors. In addition, the implant size range will be extended.

User Acceptability and Perceived Benefits of New Reports in CareLink Pro 3.0

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Objective:
CareLink Pro therapy management software for diabetes organizes data from insulin pumps, continuous glucose monitoring (CGM) devices, and blood glucose meters for health care providers. CareLink Pro 3.0 offers two additional reports: therapy management dashboard (displays sensor glucose, pump settings, hypoglycemia/hyperglycemia patterns, and pump/sensor statistics) and episode summary (describes occurrences from a list of 22 events within the 3 h preceding hypoglycemic/hyperglycemic episodes). User acceptance and product benefits of CareLink Pro 3.0 were assessed.

Method:
Nine investigators assessed CareLink Pro 3.0 in two areas: product acceptability and value/benefits for managing sensor-augmented insulin pumps (SAPs). Investigators received training, uploaded patients' insulin pumps into CareLink Pro 3.0, and reviewed CareLink reports. Responses were collected via a questionnaire at 30 and 120 days, containing qualitative and scaled questions with a Likert-type scale (1–7). Overall acceptance was defined as ≥75% of average responses ≥4. Product value and benefits were assessed separately using yes or no responses.

Result:
The new reports met predefined criteria for acceptability in all categories at 30 and 120 days. At the end of the study, 100% of investigators agreed the new reports helped identify key information, obtained additional value from CGM, and were of value in clinical practice; 88.9% agreed they would help identify causes of hypoglycemic/hyperglycemic episodes, lead to appropriate therapy adjustments, and increase confidence that adjustments were supported; 77.8% thought the program could help educate patients to support their self-management; and 66.7% thought it would help simplify routine office appointments.

Conclusion:
CareLink Pro 3.0 was acceptable in all studied areas. These findings suggest that expanded therapy management software will be of value in helping patients achieve clinical outcomes.

Toward Extended Operation of a Closed-Loop System: Halogen-Based Design of a Rapid-Acting and Ultra-Stable U-500 Insulin Formulation

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Background:
Performance and convenience of insulin pumps and closed-loop systems could be enhanced by insulin reservoirs capable of 2-week operation between refills. To avoid an increase in reservoir size, an ideal insulin analog formulation for use in such a device would be (a) capable to concentration of U-500 without loss of rapid pharmacokinetics, (b) resistant to aggregation and hence occlusion of the reservoir or catheter, and (c) ultra-stable to chemical or physical degradation.

Method:
To develop such an ultra-stable and rapid-acting insulin analog as a U-500 formulation, we sought to exploit an expanded genetic code whereby the physicochemical properties of the insulin molecule may be modified by nonstandard amino acid modifications. A model was provided by insulin lispro, the active component of Humalog. Computer-based screening of potential halogen-modified aromatic rings at the dimer interface of the zinc insulin hexamer was undertaken based on a combination of quantum-mechanical simulations (QM; as implemented in Q-Chem) and molecular mechanics (MM; as implemented in Chemistry at Harvard Molecular Mechanics). Guided by such QM/MM calculations, multiple analogs were synthesized for testing of activity, stability, and solubility.

Results:
This pipeline yielded two analogs of potential interest. Their potency, pharmacokinetics, and pharmaco-dynamics were further characterized after subcutaneous injection in anesthetized adolescent Yorkshire pigs (body mass 25–30 kg), with preliminary results showing faster onset than and equivalent length of action to U-100 Humalog.

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Conclusion:
These studies demonstrate that nonstandard genetic engineering based on general principles of quantum chemistry may be applied to develop an ideal U-500 pump insulin formulation to extend the operating time of a closed-loop system.

Dietary Fat Increases Glucose Levels and Insulin Requirements in Type 1 Diabetes: Application of Closed-Loop Insulin Delivery with Controlled Macronutrient Intake to Derive Improved Bolus Algorithms for Open-Loop Diabetes Management

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Background:
Although there is strong evidence indicating that free fatty acids (FFAs) can impair insulin sensitivity, the implications of FFA-induced insulin resistance for the treatment of type 1 diabetes mellitus (T1DM) have not been rigorously investigated. We hypothesized that meals with the *same* carbohydrate content, but *different* fat content, would require different insulin dosages to maintain postprandial glucose control.

Method:
We used a crossover study design comparing closed-loop (CL) control following a high-fat dinner (HFD) versus a low-fat dinner (LFD) to examine the effect of dietary fat on glucose control and insulin requirements. Subjects with T1DM underwent two 18 h periods (dinner, overnight, breakfast) of CL using a proportional-integral-derivative algorithm. Diet was prepared in a metabolic kitchen and was isocaloric with carefully controlled macronutrient content. The dinner meals had identical carbohydrate and protein content but different fat content (10 versus 60 g, LFD versus HFD, respectively).

Results:
Interim analysis of five subjects (age 59 ± 4 years, hemoglobin A1c 7.0% ± 0.9%, total daily insulin dose 0.5 ± 0.3 U/kg) indicated that the HFD required more insulin coverage than the LFD (15.2 ± 7.5 versus 10.3 ± 4.7 U; $p = .01$) and, despite the additional insulin, had more postprandial hyperglycemia (area under the curve above 180 mg/dl = 55.8 ± 8.2 versus 33.3 ± 4.8 g/dl/min; $p = .0003$). Calculated insulin-to-carbohydrate ratio decreased from 1:13 ± 3 to 1:9 ± 3 U/g (LFD versus HFD, respectively; $p = .02$).

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Conclusion:
These findings (1) highlight the limitations of the current carbohydrate-counting-based approach to meal-time bolus dose calculation and (2) suggest a potential role for dietary fat restriction as a strategy to optimize glucose control. Further modeling analysis of the insulin data should allow us to develop improved insulin dosing algorithms for open-loop management of high-fat meals.

Fibrillation of Fast-Acting Insulin Analogs

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Objective:
Aggregation of insulin into insoluble fibrils (fibrillation) may lead to complications for diabetes patients such as reduced insulin potency and occlusion of delivery devices. Fibrillation of regular insulin has been well described, but little is known about fibrillation of fast-acting insulin analogs. These analogs have amino acid substitutions that lead to faster absorption and response. This work investigates the intrinsic fibrillation potential of the fast-acting analogs in the absence of formulation excipients.

Methods:
The insulin analogs were transferred from the formulation buffers to phosphate-buffered saline using desalting columns. This buffer exchange removed formulation excipients that may inhibit fibrillation. The resulting solutions were agitated with heating to promote fibrillation. Samples were intermittently removed, and the extent of fibrillation was determined by measuring thioflavine T fluorescence, turbidity, insoluble insulin mass, and soluble insulin concentration. Resulting fibrils were imaged by electron microscopy. Studies were also carried out in 96-well plates with automated turbidity measurements to measure the lag times and fibrillation rates.

Results:
The fast-acting insulin analogs form fibrils upon extended heating and agitation, as demonstrated by increases in thioflavine T fluorescence, turbidity, and insoluble protein mass and by decreases in soluble insulin. Electron microscopy shows short fibrils arranged in dense mats. Kinetic analysis shows that glulisine and lispro take longer to form fibrils than aspart and that all three analogs are more stable than human insulin.

Conclusions:
This is the first study to compare the fibrillation of the three fast-acting insulin analogs. The results show different fibrillation potentials based on intrinsic molecular structure without the formulation excipients that are critical for maintaining insulin stability. Understanding fibrillation potential is critical for evaluating insulin stability and device compatibility.

Glucose Management Advice in a Smartphone Application

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Objective:
Our objective is to provide all type 1 diabetes patients with individualized help with their glucose management. By making the bolus advice [regarding meal carbohydrate content, preprandial blood glucose (BG), and bolus on board] pump users receive from "wizards" available to multiple daily injection (MDI) users and going beyond that, we aim to provide help for all by: (1) establishing an optimal, *fasting* basal MDI regimen, or adapting multiple pump basal rates, minimizing the effort needed; (2) modifying the bolus dose for the imperfect basal insulin action profile in MDI; (3) calculating the optimal meal time delay, utilizing meal content and preprandial BG; and (4) evaluating postprandial BG to determine and report the actual carbohydrate content of the meal and the bolus dose that should have been taken (if that dose was much higher than what *was* taken, the needed supplement; and if the bolus taken was so large that hypoglycemia is predicted, how much carbohydrate should be eaten to restore normal BG and how much time remains to eat it).

Method:
Physiologic model parameters are fit to patients during setup. In the process, we learn patients' insulin sensitivity, carbohydrate-to-insulin ratio, and the shape of their bolus-on-board curve.

These models and parameters are used to calculate and deliver the advice outlined earlier, with the patient's phone's timer alarm and graphic data display used for informative interaction with the patient.

Result:
Users get optimized basal insulin. Users get bolus advice incorporating individualized bolus on board. Postprandial model predictive control corrects for any bolus error, including that leading to hypoglycemia, which is thereby prevented.

Conclusion:
Model-based advice, implemented on a smartphone already carried by type 1 patients, can give them feedback about meal content and fix any bolus errors, thereby minimizing hemoglobin A1c without hypoglycemia and helping patients learn how to estimate food content.

Using Ubiquitous Glucose Meters for Portable Quantification of a Wide Range of Nonglucose Targets

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Background:
Developing a portable monitoring device for rapid, onsite, quantitative detection of a broad range of targets for diabetes and other patients has long been a sought-after goal, because such a device can revolutionize personal health care. Despite the huge promise and many years of investigation, only a limited number of such devices are commercially available to the public. Perhaps the most successful example is the personal glucose meter (PGM), which is available at stores everywhere. However, the glucose monitor can only detect a single target of blood glucose. Herein, we report a novel and general methodology that uses a commercially available PGM as a portable meter to detect a wide range of targets beyond glucose.

Method:
The method is based on the target-induced release of invertase from a functional-deoxyribonucleic acid (DNA)-invertase conjugate. The released invertase converts sucrose, which is inert to the PGM, into PGM-detectable glucose. The enzymatic turnovers by the invertase also allows conversion of low concentrations of targets (such as in nanomolar or picomolar) into millimolar levels of glucose for PGM detection.

Result:
We have demonstrated a general method to use PGMs to detect nonglucose targets, ranging from recreational drugs such as cocaine to important biological cofactors such as adenosine and from disease markers such as interferon-gamma for tuberculosis to toxic metal ions such as uranium.

Conclusion:
Given the wide availability of PGMs to the public and the characteristics of functional DNAs to recognize many targets, the method demonstrated here can be applied to detect of a wide range of other targets and has the potential to change medical diagnostics for the public at home and in the field.

Integration of Sensor and Radio on a Contact Lens for Tear Glucose Measurement

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Objective:
Our objective is to develop a platform for noninvasive and continuous measurement of glucose from the surface of the eye in the form of a contact lens. The contact lens will be worn comfortably by the patient in a fashion similar to conventional contact lenses. The integrated sensors measure tear glucose and report the result wirelessly through a custom-designed radio chip that is also integrated on the contact lens. It has the potential benefit of replacing needle-based devices for some patients with diabetes.

Method:
The contact lens was built on a polymer substrate and composed of communication circuitry, metal interconnects, a biosensor module, and an antenna. An external antenna transmits radio frequency power to the lens and simultaneously harvests a frequency signal from the sensor. The sensor is based on electrochemical detection and features three microfabricated electrodes. A layer of titania/glucose oxidase was deposited on the sensor to provide selectivity and sensitivity. The communication circuitry consists of a regulator, a rectifier, modulation, and readout circuitry. We present a prototype of an integrated contact lens, together with preliminary measurement results.

Result:
By collecting the backscatter signal frequency at different glucose concentrations, we measured the results. They show good linearity ($R = 0.9913$) over the range of normal tear concentration (0.1–0.6 mM), and the sensitivity is around 400 Hz/mM.

Conclusion:
We have demonstrated the construction and testing of a contact lens wirelessly detecting tear glucose level in sample solutions. The integrated contact lens could be the next-generation device to monitor body glucose levels in a wireless, noninvasive, continuous way. Future improvements include protein-fouling protection, biocompatible encapsulation, and low noise interface.

Polymerized Crystalline Colloidal Array Blood Glucose Sensor Material

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Background:
Maintaining blood glucose within a normal range of 80–110 mg/dl, referred to as tight glycemic control, reduces intensive care unit morbidity and mortality by 42%. Maintenance requires an automated accurate continuous glucose monitor. Key is a glucose sensing material capable of continuous accurate measurement of glucose in blood.

Method:
We developed a colorimetric blood glucose sensor material, a polymerized crystalline colloidal array (PCCA) that diffracts light, with the wavelength of reflected light related to glucose concentration. The sensor material will be protectively placed at the tip of an optode catheter suitable for positioning in a blood vessel.

Result:
The sensor material is suitable for body fluids. It is an acrylamide hydrogel containing a self-organized, highly ordered array of polystyrene spheres ~150 nm in diameter that diffracts light, with its wavelength a function of array spacing. A boronic acid (BA) internally bonded to the hydrogel structure can reversibly bind to glucose. Each glucose molecule can bind two BA molecules, causing the hydrogel to shrink, consequently reducing array spacing. Thus wavelength blue shifts as glucose concentration increases. The spheres are highly regular, having the very high surface charge needed for ordering. Molding technique reduces forces on the spheres that can lead to array irregularities. Processes to convert the PCCA to a sensor have been studied to determine parameters to produce required response. The material responds linearly over the blood glucose range, producing an ~200 nm wavelength blue shift.

Conclusion:
The work has produced a PCCA sensor material that can measure blood glucose concentration. Its colorimetric response to glucose is measurable. Potentially, the material can be attached to the tip of a fiber optic.

Nanostructure-Laden Lens Sensor for Noninvasive Glucose Monitoring

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Background and Objective:
Decades of research on tear glucose demonstrates that tear fluid can be used for glucose level diagnosis. Unfortunately, very few suitable devices are able to overcome the challenges of tear sample collection and detection simultaneously. The goal of our research project was to develop a noninvasive diagnostic tool for monitoring physiological glucose in tears by applying a nanostructure-laden contact lens.

Methods:
A nanostructured optical probe incorporated with hydrogel lens materials was developed through a two-step photopolymerization. The nanostructured optical probe was assembled by the luminescent resonance energy transfer (RET) labeled bioassay for conjugating glucose molecules. Both luminescent intensity (*I*) and the shift of RET as a function of the concentration of aqueous glucose (0.01~10 mM) were investigated through a fluorospectrometer.

Results:
The advantages of hydrogel-based lens sensors lie in their porous structures, which makes the sensor act as an analyte reservoir. Furthermore, the nanostructured optical probe has a higher sensitive reaction with aqueous glucose. The color change before and after adding 10 μl of glucose (0.05 mM) on the lens sensor is detected less than 2 min at microscale. The linear relation of the *I*(donor)/*I*(acceptor) and the concentration of glucose is found. Furthermore, the shift of the λ(donor)/ λ(acceptor) is related to the concentration of glucose. In addition, signal processing algorithms have been used to obtain the pixels from the resulting matrix. It is found that the device is able to detect a small amount of aqueous glucose in 0.01–10 mM. Furthermore, the *in vitro* cytotoxicity study shows the device is biocompatible.

Conclusion:
The disposable and noninvasive biosensor for detecting tear glucose may provide an alternative method to help patients manage the disease conveniently.

Glucose Rate Change Evaluation by Continuous Glucose Monitoring in Adult and Pediatric Populations

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Background:
One of the unique features of continuous glucose monitoring (CGM) devices is their ability to measure the glucose rate of change every few minutes. This abstract provides the glucose rate-of-change values measured by a prototype fourth-generation Dexcom CGM device in both an adult and a pediatric population with type 1 diabetes.

Method:
The data were generated from two separate clinical trials of a prototype fourth-generation CGM device. For the pediatric trial, 72 youths ages 6–17 years were studied at three U.S. centers. For the adult trial, 60 adult subjects (>18 years) at four U.S. centers were enrolled. This analysis includes glucose rate of change during the home use in day 5 and day 6 only. The data were broken down by day, 7:00 AM–10:00 PM, versus night, 10:00 PM–7:00 AM.

Results:
The average glucose rate of change for the adult subjects and the pediatric subjects are 0.83 ± 0.72 and 0.85 ± 0.88 mg/dl/min, respectively, and are not significantly different ($p = .13$). However, significantly higher glucose rate change during the day time (from 7:00 AM–10:00 PM) was observed in pediatric group than the adult group (1.00 ± 1.00 versus 0.86 ± 0.77 mg/dl/min, respectively, $p < .001$). On the other hand, the pediatric group has a slightly lower glucose rate change during the night time (from 10:00 PM–7:00 AM) than the adult group (0.53 ± 0.51 versus 0.63 ± 0.69 mg/dl/min, respectively, $p < .001$). Furthermore, significantly more fast glucose rate-of-change values (> ±4mg/dl/min) were observed in pediatric subjects (0.98% of overall data set) than in adult subjects (0.32% of overall data set).

Conclusion:
Overall, the pediatric population has a relatively similar glucose rate of change as the adult population.

Technology for Next-Generation Diabetes Monitoring: A Molecular Recognizer System

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Objective:
The aim was to establish a method to develop a molecular recognizer system, which can be used to selectively and specifically detect glucose, glycated hemoglobin, lactate, uric acid, cholesterol, or other molecules related to diabetes metabolism without using any biological recognition elements such as a glucose oxidase.

Method:
The method used is making a selective molecular recognition site for each of those target molecules or proteins related to diabetes metabolism (21).

Result:
The resulting molecular recognizer system should be able to monitor all the key diabetes metabolite element changes at the same time. The system can be used a couple of hundred times without losing its recognition ability. The calibration range of the system for glucose was from μM to M. This feature makes it a good candidate for noninvasive continuous glucose monitoring, as well as acting as part of an artificial pancreas. The molecular recognizers for molecules other than glucose related to diabetes metabolites are under investigation.

Conclusion:
The application of this state-of-the-art technology to diabetes monitoring will change the traditional diabetes monitoring industry, research, as well as other clinic analysis. It will provide a complete overview of diabetes metabolism and enable doctors and patients with diabetes to really control diabetes.

Clinical Performance of the Insulin Infusion Set InsuPatch: Reduced Blood Glucose Excursion after Local Heating of the Skin

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Objective:
The objective of this study was to investigate the effect of a local skin-heating device on postprandial blood glucose (BG) levels of patients who ate differently composed meals.

Method:
Twenty-four subjects with type 1 diabetes on continuous subcutaneous insulin infusion (10 male, 14 female, age 43.5 ± 11.3 years, diabetes duration 18.3 ± 10.5 years, hemoglobin A1c 7.4% ± 0.8%) were included in this study. After an in-house visit (data presented previously), subjects' participated in a home-use phase of 14 days with use of InsuPatch and 14 days without. On days 12 and 13 of the two 14-day periods, the subjects ate meals, which could be chosen freely by the subjects but had to be identical on all four days. The impact of local skin heating on BG levels was measured using the normalized area under the curve (AUC) 0–120 min of BG above baseline.

Result:
A reduction of BG during the home-use phase was observed, which was similar to the reduction during the in-house visit. The AUC after breakfast during home use was, for $n = 33$ meal pairs, 64.9 ± 62.1 versus 57.1 ± 68.1 mg/dl (not heated versus heated [relative change $\Delta = 12.0\%$]) and during in-house was, for $n = 42$ meal pairs, 66.4 ± 32.8 versus 56.8 ± 34.0 mg/dl ($\Delta = 14.5\%$, $p < .05$). The AUC after dinner during home use was, for $n = 32$ meal pairs, 23.8 ± 45.2 versus 13.6 ± 46.1 mg/dl ($\Delta = 42.9\%$) and during in-house was, for $n = 38$ meal pairs, 30.8 ± 31.0 versus 18.4 ± 23.9 mg/dl ($\Delta = 40.3\%$, $p < .05$). Apart from two skin reactions and two abrasions, the device was well tolerated.

Conclusion:
The study showed a positive effect of local skin heating on postprandial BG after breakfast and dinner, which was similar to the observed results during the in-house visit. Still, the home use results did not show statistical significance due to the large variability. The device was well tolerated, and its capabilities during use at home should be investigated in a larger-scale study.