Abstracts

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Achieving Tight Glycemic Control in Critically Ill Children Requires Individualized Insulin Infusion Rates

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Introduction:
Adult studies have demonstrated that tight glycemic control improves morbidity and mortality in critically ill patients. Prospective trials of euglycemia in critically ill children are needed but pose significant challenges, including finding safe and effective insulin infusion rates to use in a population whose insulin sensitivity is poorly understood.

Methods:
Thirty-two consecutive patients aged below 3 years were enrolled in a trial of tight glycemic control following cardiopulmonary bypass surgery. Fifteen patients were randomized to the intervention (glycemic control) condition. Blood glucose concentrations were monitored by subcutaneous continuous glucose monitoring and a bedside glucometer. Insulin infusion rates were calculated by a computer algorithm with a target blood glucose concentration of 95 mg/dl. Glucose concentrations between 70 and 110 mg/dl were considered normoglycemic.

Results:
Thirteen of 15 patients assigned to the intervention required continuous insulin infusion to maintain blood glucose within the target range. They received insulin for a median 55.0% of their acute intensive care unit course (27.0–93.8%) and were normoglycemic for a median 61.1% of that period (0–97.7%). Thirteen patients achieved normoglycemia within a median of 1.1 hours postoperation (0–14.87). Mean infusion rates ranged from 0.008 to 0.043 units/kg/hr with a median of 0.023 units/kg/hr. Maximum infusion rates ranged from 0.029 to 0.174 units/kg/hr with a median of 0.057 units/kg/hr. The mean insulin infusion rate was negatively correlated with percentage of time spent in the normoglycemic range ($R = -0.86$, $p < 0.01$).

Conclusions:
Critically ill postoperative cardiac surgical pediatric patients require widely varying amounts of insulin to achieve glycemic control. Euglycemia interventions in this population should be responsive to differences in insulin sensitivity between patients as well as changes in an individual's insulin sensitivity over the course of their illness.

Multicenter Study of Noninvasive Glucose Monitoring

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Background:
A truly noninvasive glucose sensing device could revolutionize diabetes treatment by leading to improved compliance with recommended glucose levels, thus reducing the short- and long-term complications and cost of diabetes. The purpose of this study is to validate a new calibration method of the fully noninvasive NBM device (OrSense Ltd.) for continuous blood glucose monitoring in type 1 and 2 diabetes subjects.

Methods:
A multicenter study has been launched to validate the new calibration method of the NBM device. A clinical study was performed in the first center to quantify the *in vivo* performance of the NBM device. A total of 29 patients with type 1 (n = 18) and type 2 (n = 11) diabetes were enrolled in the clinical study. Hemoglobin A1c levels ranged from 6.2 to 10.5. Subject wore the NBM sensor for 12–15 hours per day and participated in 2.0 ± 1.2 sessions, yielding a total of 61 sessions. Accuracy was assessed by comparing NBM data with paired self-monitoring blood glucose meter readings.

Results:
The first segment of the clinical trial produced a total of 1297 paired glucose values (NBM vs reference). In the paired data set, the reference glucose range was 40–430 mg/dl. The median relative absolute difference was 12.1%, and a Clarke error grid analysis showed that 95.1% of the measurements fell within the clinically acceptable A + B regions (zone A, 66.1% and zone B, 29.0%).

Conclusion:
This study substantiates the potential use of OrSense's NBM device as a noninvasive sensor for continuous blood glucose evaluation. The device was comfortable for subjects, safe, and well tolerated.

Instruction Time, Intuitiveness, and Patient Acceptance of a Prefilled and a Reusable Insulin Delivery Device

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Introduction:
This study investigated the intuitiveness, instruction time, and handling of the Levemir® FlexPen® (Novo Nordisk A/S) compared to the OptiClik® insulin pen with glargine cartridges (sanofi-aventis).

Methods:
The study was performed as a randomized, open-label, crossover handling test on two groups of insulin device naive Japanese type 2 diabetes patients (age 61.9 ± 12.3, 57% males). One group was instructed (n = 29) in each device according to the device manual, and another group (n = 32) was asked to operate the devices without prior instruction as an indication of the intuitiveness of the device and subsequently instructed properly.

Results:
The instruction time was shorter for the FlexPen ($p < 0.001$) and it was objectively more intuitive to use ($p < 0.01$) than the OptiClik. Nevertheless, with either device, few patients in the intuitiveness group felt confident in injecting prior to being instructed (FlexPen: 31%, OptiClik: 15%). No patients in the instruction group found the FlexPen difficult to learn (0%), whereas 45% of patients found the OptiClik difficult or very difficult to learn ($p < 0.001$). The FlexPen was evaluated as the simplest pen to use (82% vs 11%) ($p < 0.001$), and patients found it easier to inject with the FlexPen compared to the OptiClik (62% vs 13%) ($p < 0.001$). The FlexPen was evaluated as more convenient than the OptiClik (70% vs 16%) ($p < 0.001$); overall, more patients trusted the FlexPen for delivering insulin injections ($p < 0.01$). More patients preferred using the FlexPen ($p < 0.001$) compared to the OptiClik (82% vs 13%).

Conclusions:
These findings highlighted the importance of instructing patients in the correct use of devices for the patients to be confident in performing injections. In this study, the Levemir FlexPen was found to be quicker to teach, simpler to use, and more trusted by diabetes patients.

Lantus® SoloStar® and Apidra® SoloStar® Pen Colors Contribute to the Differentiation by Users with Normal Vision and by Users with Impaired Color Vision

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Introduction:
SoloStar® (sanofi-aventis, Paris, France) is a new prefilled insulin pen device for the administration of once-daily basal insulin glargine (Lantus® SoloStar®) or prandial insulin glulisine (Apidra® SoloStar®). Confusing basal and bolus insulin pens could have significant consequences, including serious adverse events; therefore, it is essential that both pens can be identified and differentiated correctly. In order to support correct pen identification, Lantus SoloStar and Apidra SoloStar colors must be sensitive to all patients, including those with color vision deficiencies.

Methods:
The color differentiation assessment focused on three color dimensions: hue (perceptual quality of light of different wavelengths), saturation ("purity" of a hue), and brightness (the relative lightness or darkness of a color from 0% black to 100% white). In order to assess each colored feature, the pen body, sticker, and injection button were assessed and scored separately. Scores for each component were totaled. A minimum combined score of six points was judged as providing sufficient color differentiation.

Results:
For the pen body, sticker, and injection button, a maximum component combination of nine points was scored. The colors of Lantus SoloStar and Apidra SoloStar were assessed as sufficiently differentiated under various lighting conditions for users with normal color vision and for those with a range of color vision deficiencies. Additionally, the sticker text was sufficiently differentiated from background color, with Lantus and Apidra brand and generic names clearly labeled on each pen.

Conclusion:
The ability to differentiate insulin pens irrespective of user color vision status minimizes the risk of administering the wrong treatment and consequential adverse events. Results demonstrate that pen body, sticker, and injection button color choices for Lantus SoloStar and Apidra SoloStar differ sufficiently.

Affinity-Based Turbidity Sensor for Glucose Monitoring by Optical Coherence Tomography: Toward the Development of an Implantable Glucose Sensor

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Design:
In this novel sensor, analyte concentration-dependent changes induced in the degree of optical turbidity of the sensing element can be monitored accurately by optical coherence tomography (OCT), an interferometric technique. To demonstrate proof of concept, we engineered a sensor for monitoring glucose concentrations that enabled us to quantitatively monitor the glucose-specific changes induced in bulk scattering (turbidity) of the sensor. The mechanism of modulation of bulk turbidity in the sensor is based on glucose-specific affinity binding of concanavalin A (ConA) to pendant glucose residues of macroporous hydrogel particles. The sensor consists of a glucose-sensitive compartment, which contains a suspension of macroporous hydrogel particles and the glucose-specific lectin ConA that alter the optical scattering of the sensor as a function of glucose concentration, and a glucose-insensitive compartment. The backside of both sensor compartments supports a reflective layer. Determination of glucose levels is facilitated by ratiometric signal analysis of the reflections measured from the reflective layers of both glucose-sensitive and glucose-insensitive sensor sections.

Methods:
Turbidity changes in sensor suspensions were measured *in vitro* at 750 nm. OCT was employed in *in vitro* and *in vivo* experiments for measuring the diffuse reflectivity of sensors in response to glucose concentrations. Blood samples were collected from an anesthetized pig on which a modified glucose tolerance test over a period of 4 hours was performed. Measurements of sensor performance under skin were conducted in anesthetized guinea pig.

Results:
The affinity-based modulation of the scattering coefficient was enhanced significantly by optimizing particle size, particle size distribution, and ConA concentration. Successful operation of the sensor was demonstrated under *in vitro* conditions where excellent reversibility and stability (160 days) of prototype sensors with a good overall response over the physiological glucose concentration range (2.5 to 20 m*M*) were observed. Furthermore, to assess the feasibility of the novel sensor for glucose determination in body fluids, it was demonstrable that the response of the sensor to physiological glucose changes could be measured in plasma and full blood as well as under skin tissue (thickness of 500 μm) of an anesthetized guinea pig.

Conclusion:
We demonstrated a novel sensing paradigm for continuous glucose monitoring that relies on detection of a reversible change in optical scattering because of competitive affinity binding. We showed that the sensor exhibits a highly specific optical response as a function of changes in glucose concentration *in vitro* and *in vivo* when monitored by OCT. This new sensor can potentially be engineered to be used as an implantable sensor for *in vivo* through-skin optical monitoring of glucose.

Guardian® Real-Time Monitoring in Management of Pregnancy Complicated by Type 1 Diabetes

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Introduction:
Despite many advances in diabetes therapy, high maternal and perinatal morbidity still exist. Glucose variation is a result of diabetic and obstetric complications during pregnancy complicated by type 1 diabetes. Optimal blood glucose sugar is necessary for guaranteeing the best outcomes. Guardian® real-time monitoring lowers hemoglobin A1c levels and reduces hypo- and hyperglycemic periods during the day. We present a pilot study that compares two groups of pregnant women with type 1 diabetes. We compared glycemic control and the percentage of hypoglycemic and hyperglycemic periods during assessing time in two groups. The first used finger stick glucose monitoring only, where results were checked with a continuous glucose monitoring system (CGMS) gold system. The second used Guardian real-time monitoring.

Methods:
Number of patients: 22 pregnant women
16 used finger stick glucose monitoring and CGMS
6 used Guardian real-time glucose monitoring
Retrospective chart review with pair samples

Results:
No differences were observed in perinatal outcomes and in gynecologic/obstetric complications during pregnancy in both groups. The percentage of hypoglycemia was lower in the group using real-time monitoring ($p < 0.05$), and the percentage of hyperglycemia was higher in the group using real-time monitoring ($p < 0.05$). Regardless, there were no significant discrepancies in metabolic control in the first, second, and third parts of pregnancy.

Conclusions:
Using Guardian real-time glucose monitoring resulted in a restriction in blood glucose variation and there was less time spent in hypoglycemia, but a longer time in hyperglycemia. Despite previous results, there were no differences in metabolic control. It seems to be better for women and developing fetuses to have less hypoglycemia and tight metabolic control.

Significance of Minor Subfractions of Hemoglobin Resolved by the Improved Bio-Rad Variant II Hemoglobin A1c Method

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Introduction:
An improved version of the Variant II hemoglobin A1c (HbA1c) method is able to chromatographically resolve additional minor fractions of hemoglobin (P3 and P4). Earlier studies characterized minor peaks eluting in the region between A1c and Ao and found that these peaks can be elevated in cases of uremia or poor glycemic control. Elevation of these peaks may also provide an indication that the specimen has been stored at an elevated temperature prior to analysis. The purpose of this study was to determine reference ranges for the P3 and P4 components resolved by the VII HbA1c method; determine correlations with labile A1c, HbA1c, and CHb; and investigate the effect of specimen storage conditions on P3, P4, and HbA1c.

Methods:
A total of 2861 specimens were analyzed with the VII HbA1c method to determine a reference range for each of the minor hemoglobins and to assess the correlation between the minor hemoglobin components and the labile A1c, HbA1c, and CHb peaks. A stability study was performed on fresh clinical specimens to determine the response of the P3 and P4 peaks to different storage conditions.

Results:
The reference ranges for P3 and P4 were determined to be 2.18 to 6.49 and 1.62 to 4.55, respectively. Correlation of P3 and P4 with HbA1c, LA1c, and CHb peaks ranged from weak to moderately strong. The combined level of minor components in the P3/P4 region increases with storage time at elevated temperatures. HbA1c results were not significantly impacted by the storage conditions studied.

Conclusion:
The quantitative levels of P3 and P4 provide a means for identifying specimens stored at elevated temperatures outside of recommended storage conditions for the assay.

Assessing Diabetic Retinopathy Using Telemedicine Technology among a Rural South Indian Diabetic Population

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Objective:
This study detected and graded diabetic retinopathy (DR) in rural south Indian type 2 diabetic subjects using telemedicine as a novel tool.

Methods:
Using a questionnaire, 970 subjects were identified to have type 2 diabetes in 43 villages of the Kancheepuram district, south India. Four field digital retinal photographs were done using a nonmydriatic Topcon camera (TRC-NW200) fitted in a telemedicine mobile unit. The images obtained were sent via the V-sat (provided by Indian Space Research Organization Bangalore) using a system CYPACS client to the base center at Chennai. Retinal images were assessed by ophthalmologists using a Dicom viewer. DR was graded using the Early Treatment Diabetic Retinopathy Study. Final consultation was done by an ophthalmologist at Chennai with the patient seated in a mobile unit at Kancheepuram.

Results:
Of the total 970 self-reported diabetic subjects, 239 subjects were photographed. Fifty-four (22.6%) subjects had DR, which included 26 (10.9%) with nonproliferative DR, 21 (8.8%) with diabetic macular edema, and 7 (2.9%) with proliferative DR. Subjects identified with sight threatening DR were advised treatment at the main center.

Conclusions:
Using telemedicine technology, the prevalence of DR was 22.6% in a south Indian rural population enabling eye care in rural area.

Noninvasive Continuous Monitoring of Glucose Concentration using Raman Spectroscopy: Results of a Glucose Clamp Study

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We previously reported initial results from our testing of a Raman spectroscopic device (RSD) that measures glucose noninvasively in the skin (Diabetes Technology Meeting 2006). Motivated by the early success of this approach, a glucose clamp study was performed on a group of adult patients with type 1 diabetes mellitus. A total of 10 subjects were studied by inducing three distinct glycemic states: "hypoglycemic" range: 80 mg/dl, mid- "euglycemic" range: 150, 170, or 190 mg/dl, and a high "hyperglycemic" range: 270 mg/dl. During the glucose clamp procedure, the subject's blood glucose levels were monitored every 10 minutes with the RSD and concurrently using the Yellow Strings Instrument, 2300 Stat Plus and/or a Food and Drug Administration (FDA) approved commercial home blood glucose monitor. Test subjects then returned for a subsequent visit and their blood glucose levels were measured with both the RSD and an FDA-approved commercial blood glucose monitor and compared to the previous results. During this subsequent visit, no attempt was made to manipulate or control the test subjects' glucose levels.

The RSD was able to predict measured glucose levels well within clinically acceptable errors throughout the entire range of the studied glucose levels. It is important to note that with respect to patient comfort, there was not a single incident or complaint related to the noninvasive device or measurement procedure. In addition, the RSD continues to yield new insights into metabolic physiology as well as novel structural information, with important implications for developmental physiology, aging and general health. The RSD promises to be a platform technology that will likely be applied to a broad set of clinically relevant diagnostic questions (including those that do not require continuous measurement) with a strong impact on therapeutic intervention.

Poly(lactic-co-glycolic acid)/Polyvinyl Alcohol Hydrogel Composites for Long-Term Inflammation Control on Subcutaneous Implantation of Biosensor

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Introduction:
A novel, biocompatible composite coating for implantable medical devices that effectively controls negative tissue reactions at the device–tissue interface has been developed. This coating allows the development of totally implantable, wireless glucose sensors for long-term continuous monitoring, which will eventually enable the development of an artificial pancreas. We have demonstrated the functionality of this coating for a period of 3 months: (1) controlling acute and chronic inflammation, (2) preventing fibrosis, and (3) inducing neoangiogenesis at the implant site.

Methods:
Composites were fabricated in 18-gauge needles using poly(lactic-co-glycolic acid) (PLGA) microsphere/polyvinyl alcohol (PVA) (5%, w/w) dispersions (three freeze/thaw cycles, –20°C/24°C and implanted in rat subcutaneous tissue. Pharmacodynamic effects were evaluated by histopathological examination of excised tissue sections (stained with hematoxylin and eosin).

Results:
Composites releasing dexamethasone for 3 months controlled acute and chronic inflammation as well as fibrosis, whereas control composites showed an intense acute inflammatory phase (1 week) followed by a granulomatous reaction that worsened over the 3-month period. Continuous release of dexamethasone was necessary, as otherwise a delayed inflammatory response occurred. Based on *in vitro* and *in vivo* release testing and histopathological data, we have developed strategies to control inflammation and fibrosis, as well as to promote neoangiogenesis for any desired sensor lifetime. Composites containing vascular endothelial growth factor, platelet-derived growth factor, and dexamethasone induce the formation of mature blood vessels at the sensor implant site for adequate analyte supply.

Conclusions:
PLGA microsphere/PVA hydrogel composite coatings achieve localized delivery of tissue response modifiers, avoiding systemic side effects and effectively controlling the tissue reaction at low dose. These composites offer an innovative solution to make continuous metabolic monitoring feasible using totally implantable biosensors.

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A Comparative Trial with an Experimental 4-mm Needle versus a 6-mm NovoFine® with Regard to Anatomical Deposition of Sterile Air and Backflow of Test Medium to Skin Surface in Lean Children and Adults with Diabetes

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Background:
Lean diabetes mellitus patients may unintentionally inject insulin intramuscularly, which may cause differences in insulin absorption and may, in turn, increase the risk of hypoglycemia. Therefore, it is of major importance to secure correct insulin deposition in the subcutaneous tissue.

Objectives:
This study detected tissue deposition of a simulated insulin bolus (sterile air) injected with a 4- or 6-mm needle in lean children and adults with diabetes mellitus and evaluated simulated insulin leakage (test medium) to the skin surface.

Patients and Methods:
Twenty-eight lean children (19 males) and 34 lean adults (25 males) received two injections of 300 µl sterile air at the abdomen and thighs with a NovoPen® 3 using experimental 4- and 6-mm NovoFine® needles, respectively. The needles were inserted perpendicular to the cutis without a skin fold. Tissue deposition of the air was detected by ultrasound. Backflow of test medium was evaluated injecting volumes of test medium corresponding to 10 and 40 IU insulin.

Results:
All women and girls were injected subcutaneously with a 4-mm needle except for four girls who were injected intramuscularly in the abdomen. Two boys and two men were injected intramuscularly at the thigh with a 4-mm needle. None of the subjects were injected intradermally. Leakage to the skin surface was minimal and not different between the two needle lengths.

Conclusion:
A perpendicular injecting technique with a 4-mm needle without an elevated skin fold can be used in lean adults and in most lean children at the thigh. Insulin leakage to the skin surface is minimal and independent of whether injecting with a 4- or a 6-mm needle.

Chemical and Biological Characterization of Recombinant Human Insulin Produced in Transgenic Plants

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Introduction:
Insulin therapy is currently the primary treatment for type 1 diabetes and is frequently required in the treatment of type 2 diabetes as the disease progresses. Human insulin is presently the largest volume recombinant biopharmaceutical in the world with production levels on the order of 5 to 6 tons per year. Due to increasing incidence and earlier diagnosis of the disease, together with the advent of alternative delivery technologies, the demand for insulin is projected to increase sharply over the next 5 years to levels of more than 16 tons per year. Transgenic plants have the potential for meeting this increased demand, providing for both high-capacity and low-cost production.

Methods:
Transgenic plants expressing a recombinant insulin fusion protein were developed through *Agrobacterium*-mediated transformation of safflower seedling explants. Following extraction from transgenic seed, the insulin precursor was processed *in vitro* to generate mature human insulin. Authenticity and functionality of the plant-derived insulin were established through mass spectrometry, peptide digest, receptor binding, and insulin tolerance tests.

Results:
When analyzed by mass spectrometry, the safflower-derived insulin was found to have a mass of 5807 Da identical to that of authentic human insulin. Correct formation of disulfide bonds was demonstrated by V8 peptide digest. In competitive receptor-binding assays, safflower-derived insulin exhibited similar binding kinetics to that of pharmaceutical-grade reference standards. Pharmacodynamic equivalence was established through insulin tolerance test assays in mice.

Conclusions:
Using a variety of chemical and biological methods, we have shown that insulin produced in transgenic safflower is indistinguishable from recombinant human insulin from other sources. Together, these results validate the feasibility of SemBioSys' transgenic plant system for the large-scale manufacture of human insulin.

Using Home Telehealth Technology to Manage Diabetes

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Introduction:
More than 800,000 people with diabetes receive care from the Veterans Health Administration. Diabetes is a major cause of morbidity and the seventh leading cause of mortality in the United States. Self-management, delivery system design, and clinical information systems are key components of the chronic care model for managing patients with chronic illness. Management of chronic conditions such as diabetes has moved from traditional ambulatory settings to the patient's home. Home telehealth technology can enhance patient-centered care by gathering objective and subjective clinical data, providing education, and increasing communication between patients and their health-care providers.

Methods:
Forty-seven veterans diagnosed with diabetes living in rural Oregon were provided home telehealth equipment and were monitored daily for up to 33 months. Descriptive data distance from medical center to patient home, health-care utilization, frequency of data transmission by patient, and examples in which real-time access to data improved clinical management are described. Clinical data regarding pre/posthemoglobin A1c levels, average glucose values, and frequency of hypoglycemic events are provided. Technology usage as measured by frequency of data transmission is reported.

Results:
Descriptive and summary statistics are presented. Case illustrations highlighting clinical data and the impact of telehealth technology on triggering changes in clinical management are discussed. Information regarding telehealth technology, benefits, and integration into the Veterans Affairs electronic medical record is presented.

Conclusion:
Older patients with diabetes and other chronic health conditions readily accept telehealth technology. This technology allows for patient-centered intensive diabetes management that has not previously been possible in a rural setting. This study is limited as a single-group study design.

Adaptive Algorithm Predicting Hypoglycemia in Continuous Glucose Monitoring

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Introduction:
The timely prediction of hypoglycemia is critical for enabling (i) accurate hypoglycemia alarms in contemporary continuous glucose monitoring (CGM) and (ii) safety features (such as insulin pump shut off) in future closed-loop control systems. However, most currently employed methods rely on linear extrapolation of glucose patterns and are therefore vulnerable to a high rate of false alarms as a consequence of the inherent nonlinearity of the metabolic system, particularly in the lower glucose range.

Methods:
The proposed predictor of hypoglycemia has been developed and tested *in silico* using a computer simulator of patterns of hypoglycemia. The algorithm was then validated in a large data set containing 40-day CGM traces of 120 patients with type 1 and insulin-requiring type 2 diabetes collected in a clinical trial of the FreeStyle Navigator® (Abbott Diabetes Care, Alameda, CA).

Results:
Two predictors were tested: (i) a sliding autoregressive module analyzing 45-minute data blocks and predicting glucose 30 minutes ahead and (ii) the aforementioned combined with a self-learning module analyzing glucose patterns and creating a 24-hour personal profile of risk for hypoglycemia. *In vivo*, autoregression alone achieved a hypoglycemia detection of 85%, with minimal (<10%) false alarms. The addition of pattern recognition improved the prediction and reduced false alarms to below 5%.

Conclusions:
Optimal hypoglycemia prediction was achieved by an algorithm combining self-learning pattern recognition with predictive autoregression. Thus, utilizing adaptive methods that take advantage of accumulated information about the patient could potentially enhance hypoglycemia alarms in CGM and the safety features of closed-loop control.

Evaluation of Time Shift and Time Constant in Capillary to Interstitial Glucose Dynamics Using the FreeStyle Navigator® Blood Glucose Monitoring System

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Introduction:
This work attempted to find a simple capillary to interstitial glucose dynamics model that simultaneously identifies the best-fit parameters of a linear model with both time shift (delta) and time constant (tau). Raw sensor signal profiles (N = 115, from 58 subjects with type 1 diabetes) using the FreeStyle Navigator® system and reference blood glucose (Yellow Springs Instruments) are used. Each insertion nominally lasts 5 days, with 50 hours of YSI measurements taken every 15 minutes.

Methods:
Tau and delta are the two main parameters of interest. To account for potential changes in sensor equilibrium over time, sensitivity gain S1 and offset S0 parameters are also identified simultaneously. Because rate calculation is required, an additional filter window size parameter M is also included, resulting in a total of five parameters. A finite set of M and delta is defined. For each combination, a least-squares error fit of tau, S1, and S0 is computed. The optimal tau, S1, and S0 for each M and delta combination are evaluated using a metric based on least-squares error.

Results:
Overall, given a reasonable assumed delta, the optimal solution requires that the sum of tau and delta equals approximately 13.3 minutes. If only one parameter is used, zero delta with a 13.3-minute tau results in the best fit given data, method, and error metrics used. The supporting datum that resulted in the 13.3-minute sum has a standard deviation of 4.2 minutes.

Conclusions:
While both time shift and time constant could be used as simple representations of capillary to interstitial dynamics, a model with only a time constant provides the best fit.

Are Two New Blood Glucose Meters with Integrated Speech Accessible to Blind and Visually Impaired People?

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Introduction:
The use of compact and efficient blood glucose meters (BGMs) has revolutionized diabetes care, but people who are blind or visually impaired have not been able to take full advantage of these advances. The features of voice output, readable displays, and compact size have been lacking in BGMs, but are highly sought out by blind and visually impaired persons. The Prodigy and the Advocate by Taidoc and the SensoCard by BBI Healthcare are the first BGMs to use integrated speech. These products have been evaluated to determine how accessible they are to blind and visually impaired persons.

Methodology:
Data on the physical aspects and features and functions, including documentation and download software of the Prodigy, the Advocate, and SensoCard, were tabulated and analyzed for usability by blind and visually impaired individuals. Measurement standards from the Video Electronics Standards Association were used to determine contrast modulation and font size in the displays of the BGMs.

Results:
Preliminary observations are that these compact devices do not voice all of the information displayed on the screen and that the accompanying software used to download test results and monitor result trends are not compatible with the adaptive computer technology used by blind and visually impaired people Additionally, documentation provided is not fully accessible to blind and visually impaired persons. Display analysis awaits further investigation.

Conclusions:
While these BGMs show improved accessibility related to integrated speech technology and compact size, serious limitations were noted in software and screen readout capability. However, these problems can be remedied through changes in software, which makes fixing them readily achievable.

Tracking Glucose Excursions with a Multisensor Platform for Noninvasive Glucose Monitoring

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Introduction:
Impedance spectroscopy (IS) is a promising approach for noninvasive glucose monitoring (NIGM). However, a number of external and physiological factors can affect the measurement, and some of these factors may even be considered as generic perturbations to NIGM in general. In order to be able to compensate for such factors, a multisensor platform, including sensors for broadband IS, optical, moisture, conductance, acceleration, and temperature, has been developed.

Methods:
Blood glucose excursions were induced by an oral glucose load in four patients with type 1 diabetes [T1DM, age 40 ± 13 years; body mass index 23.9 ± 1.6 kg/m^2; duration of diabetes 20 ± 14 years; hemoglobin A1c 7.6 ± 1.0%) and four T2DM patients (60 ± 11 years; 25.9 ± 4.4 kg/m^2; 11 ± 4 years; 7.6 ± 0.5%]. In another series of experiments, the effect of drinking 3 liters of water (while blood glucose remained stable) was studied in four healthy subjects (23 ± 2 years; 22.2 ± 1.6 kg/m^2). Our multisensor platform held all sensors on one single substrate and was attached to the upper arm of the subjects by an expandable band. For data evaluation, a multiple regression analysis was performed to establish a universal model including all subjects. The models generated (a) aimed at simplicity, taking great care to avoid potential overfitting, and (b) allowed investigating the effect of excessive water intake on the dielectric characteristics and hence on the overall performance of the platform.

Results:
Using impedance parameters only, including one individual baseline parameter, glucose excursions could be tracked by our multisensor approach with an R^2 value of 0.7. Clark error grid analyses showed that 96.1% of all data points were in zone A + B, 1.2% in C, 2.7% in D, and 0% in D. Taking into account all sensor signals leads to an improvement of R^2 to 0.763.

Conclusions:
Results indicate that an improvement of noninvasive monitoring by IS can be achieved by a multisensor approach. Whether a calibration strategy of such a multisensor platform in a larger clinical setting will need to consider separate patients groups rather than a universal calibration approach remains to be seen.

Statistical Linear Prediction Using Continuous Glucose Measurements for the Predictive Detection of Hypoglycemia

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Introduction:
Hypoglycemia presents a significant risk for patients with insulin-dependent diabetes mellitus (IDDM). We propose a predictive hypoglycemia detection algorithm with explicit certainty measures to enable early corrective action.

Method:
The method uses multiple statistical linear predictions with regression windows between 5 and 75 minutes and prediction horizons of 0 to 60 minutes. These predictions also generate linear error distributions, which we mapped to nonlinear, continuous glucose monitor (CGM)-based error distributions using their averaged statistical correlation. These error distributions give confidence levels that the CGM reading will drop below a hypoglycemic threshold. We alarm if any test rises above a minimum confidence level. This level trades off the positive predictive value against warning time and missed events.

Results:
We evaluated our algorithm on 26 sets of 24-hour minutely Navigator® data of 3 to 18 year olds with IDDM from DirecNet. We postprocessed the CGM readings to remove dropouts and calibrate against finger stick measurements. Setting a low, medium, or high confidence level, the algorithm shows a valid alarm rate (positive predictive value) of 60, 74, and 100% with an average warning time of 43, 31, and 20 min while missing 0, 0, and 0% of 37 hypoglycemic events. For false alarms, CGM readings drop to 101 mg/dl, 96 mg/dl, and not applicable. Comparing against linearly interpolated finger stick readings, the results are 56, 83, and 100%; 56, 31, and 16 min; 0, 0, and 15%; and 124 mg/dl, 106 mg/dl, and not applicable, respectively.

Conclusion:
Statistical linear prediction can give significant early warning of hypoglycemic events with an explicit, tunable trade-off of longer warning times and fewer missed events versus higher valid alarm rates.

Early Detection of Hypoglycemia Combining Multiple Predictive Methods on Retrospective Clinical Continuous Glucose Monitoring Data

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Introduction:
Severe hypoglycemia is a risk factor in intensive insulin therapy for type 1 diabetes mellitus (T1DM). Real-time predictive alarms allow for corrective actions to minimize the severity of hypoglycemic events.

Method:
We combined several algorithms to alarm for impending hypoglycemia using continuous glucose monitoring (CGM) data, including statistical linear prediction, Kalman filtering, numerical prediction, and adaptive autoregression methods. A voting scheme fused the individual alarms to improve robustness. We evaluated the scheme on 26 sets of 24-hour (minute-by-minute) CGM data from 3- to 18-year-old children with T1DM involved with DirecNet. Temperature-compensated, FreeStyle Navigator® (Abbott Diabetes Care, Inc., Alameda, CA) data were complemented by finger stick, event, and meal data. We postprocessed the CGM readings to remove outliers and performed a retrospective affine calibration to finger stick data.

Results:
For a hypoglycemic threshold of 80 mg/dl, the combined algorithm had a valid alarm rate (positive predictive value) of 73% while missing 0% of hypoglycemic events (100% sensitivity). For valid alarms, the average warning time was 46 minutes (median 47 min, SD 20 min). For false alarms, glucose readings dropped to 97 mg/dl on average. The combined alarm outperformed individual algorithms, which provided positive predictive values of 76, 74, 72, and 76%, missing 0, 0, 8, and 3% of events, giving 29, 42, 54, and 40 average warning, and false alarm minima of 98, 98, 115, and 100 mg/dl, respectively. We considered alarms valid up to 60 minutes before a hypoglycemic measurement with a 5-mg/dl buffer. We ignored false alarms where mitigating events were present. Comparisons against finger stick data were hindered by infrequent measurements.

Conclusions:
The combination of different algorithms provides a robust alarm against hypoglycemia with significant warning time.

Development of the Saint Francis Hospital Critical Care Insulin Infusion Protocol

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Introduction:
It is known that subcutaneous insulin administration in the critical care area (CCA) directed by a sliding scale simply does not consistently result in glucose control required by more modern recommendations and standards of care. Intravenous regular insulin infusion has been demonstrated to lend itself well to glucose control in the critically ill patient. Given that the author is a full-time critical care physician and has experience in computer programming, it was decided to develop our own computerized insulin infusion protocol. Further, given the goal to simplify delivery of the resultant tool to the CCA bedside, it was decided to produce the tool using the Web environment.

Methods:
Original equipment included only a personal computer configured as a dynamic Web server, using open-source Unix software, placed on the Saint Francis Hospital intranet in mid-June of 2006. The application was developed day by day by J. B. Carr, with multiple daily episodes of critique and input from the CCA nursing staff. By December 2006, the application had reached a state of documented effectiveness.

Results/Data:
At this writing, glucose control in 311 patients has been managed in the CCA using this protocol to direct the rate of insulin infusion. Of bedside blood glucoses, 14,876 were performed in these patients. The mean of the first three blood glucoses of all patients was 182 mg/dl; that of the last six was 114 mg/dl. Eighty-five percent of patients were controlled to less than 140, and 70% between 80 and 119. The incidence of hypoglycemia (<60) was 00.7%.

Conclusions:
This Web-based tool is quite effective in improving glucose control and related information flow in the CCA.

Usability, Participant Acceptance, and Safety of SoloStar® in an Observational Survey in Everyday Clinical Practice

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Introduction:
SoloStar® (sanofi-aventis, Paris, France) is a new prefilled insulin pen device for the injection of insulin glargine and insulin glulisine. This is the first survey to determine the usability, participant acceptance, and safety of SoloStar in clinical practice.

Methods:
Individuals with type 1 diabetes mellitus (T1DM) or T2DM were eligible for this 3-month observational survey (supported by sanofi-aventis) conducted in Australia (November 2006–January 2007). At the start of observation, participants were given SoloStar pens containing insulin glargine, an instruction leaflet, and a toll-free help line number. Training was offered to all participants. Safety data, including product technical complaints (PTCs), were gathered from ongoing feedback given by the participant or health-care professional and by solicited interviews conducted by independent moderators at weeks 6–10.

Results:
Of 2674 people consenting to take part across 93 sites (150 health-care professionals), 2029 participated in interviews (48.9% female [mean ± standard deviation] aged 50.5 ± 16.1 years). Of the participants, 52.6% had T1DM, 16.3% had manual dexterity problems, and 15.5% had poor eyesight not corrected by glasses. At the time of interview (time to follow-up: 60.5 ± 15.7 days), 96.8% of participants were using SoloStar. Of eight PTCs investigated, seven were reported during solicited interviews and most were related to handling errors. Sixty-two participants reported 77 adverse events (injection site reactions, $n = 34$; hypoglycemia, $n = 8$; other, $n = 35$); none were related to a PTC. Most participants (95.3%) reported that they were "very satisfied" or "satisfied" with using SoloStar to inject insulin; 89.7% reported no problems with using SoloStar.

Conclusions:
In this survey of everyday clinical practice, SoloStar showed a good safety profile after exposure for 6–10 weeks and was very well accepted by participants with a low incidence of participant-reported problems during use.

Health-Associated Reference Intervals for Hemoglobin A1c generated from NHANES 1999–2002 Show High Prevalence of Elevated A1c in Older Normoglycemic Adults

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Introduction:
The U.S. National Health and Nutrition Examination Survey (NHANES) contains clinical and laboratory data on civilian noninstitutionalized individuals. NHANES 1999–2002 is a subset of the ongoing 1999–2004 NHANES and was conducted on 12,210 individuals, ages 12 years and older, who had their fasting blood drawn and analyzed in central laboratories for hematology and chemistry parameters, including high-performance liquid chromatographic glycohemoglobin (HbA1c).

Materials and Methods:
NHANES data were abstracted with Microsoft® Access™ (Redmond, WA) and analyzed with Microsoft® Excel®. To determine health-associated reference intervals, we used the following exclusion criteria: pregnancy, obesity (body mass index >30), diastolic blood pressure >100 mm Hg, positive hepatitis B or C serology, creatinine >2.5 mg/dl, and glucose >126 mg/dl. The population was separated into six categories: female non-Hispanic White (FNHW, $n = 96$), female non-Hispanic Black (FNHB, $n = 785$), female Mexican-American (FMA, $n = 1177$), male non-Hispanic White (MNHW, $n = 1816$), male non-Hispanic Black (MNHB, $n = 934$), and male Mexican-American (MMA, $n = 1279$). The population was also separated by age groupings: ages 12–14, 14–18, 18–25, 25–45, 45–65, and >65 years. Graphs of the 2.5, 5, 50, 90, 95, and 97.5 percentiles were generated for HbA1c and each age/gender/race grouping.

Results:
Graphs are available at http://www.mylaboratoryquality.com/. For individuals younger than 45, the 97.5 percentile HbA1c is uniformly under 6.0%. However, for individuals older than 45, more than 10% of normoglycemic MMA and MNHB and more than 2% of the FMA and FNHB have HbA1c >6%. HbA1c elevations are also present in older MNHW and FNHW, but to a lesser degree.

Conclusions:
On the basis of age-related HbA1c increases in the absence of hyperglycemia, the practice of screening for diabetes using HbA1c is marginalized as an acceptable clinical practice. Even setting an ideal HbA1c target of 7% for glycemic control in the elderly might be questioned.

Comparison of Average Uncertainty in High-Pressure Liquid Chromatography and Immunoassay Measurements of Hemoglobin A1c

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Introduction:
High-pressure liquid chromatography (HPLC) represents the most precise and accurate approach to measuring hemoglobin A1c (HbA1c). The most common HbA1c method is not HPLC, but a set of two assays, one for the measurement of hemoglobin and the other for an immunoassay with antibodies directed against HbA1c. This two assay combination should result in increased uncertainty in the HbA1c measurement and results in even more uncertainty in the presence of hemoglobin variants.

Materials and Methods:
Method-specific means, standard deviations, and number of laboratories reporting were obtained from participant summaries for three College of American Pathologists glycohemoglobin surveys: GH2-B (2005), GH2-A (2006), and GH2-B (2006). In all, there were nine samples, with National Glycohemoglobin Standardization Program targets ranging from 5.3 to 11.7% HbA1c. For selected methods and for certain subsets, e.g., HPLC or immunoassay methods, these statistics were analyzed with a statistical program, VFP7, to obtain a precision profile in the form of a three-parameter variance function appropriate to most immunoassays: typically, (SD)^2 =b1 + b2*mean)^J.

Results:
A total of 2282 laboratories participated in survey GH2-B. Of these, 54.6% used immunoassay and 36.5% used HPLC. Imprecision vs HbA1c concentration curves demonstrated that the "average" immunoassay intrainstrument variation was 4% compared to 3% for the average HPLC analyzer.

Conclusions:
At the target for glycemic control HbA1c concentration of 7% and with an average biological variation for HbA1c of 1.7%, the critical difference [the minimum difference required to signify a genuine change in the HbA1c concentration (two-tailed test, $P < 0.05$)] is 0.7 and 0.85% for the average HPLC and immunoassay, respectively. This increased level of uncertainty at a HbA1c of 7% is significant.

Virtual Population of Critically Ill Patients to Simulate Glucose Control in the Intensive Care Unit

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Introduction:
Critically ill patients are characterized by high inter- and intrasubject variability of insulin resistance confounding the delivery of safe, tight glycemic control (TGC) at the intensive care unit (ICU). Supported by the EC-funded CLINICIP project (IST-2002-506965) and the European Foundation for the Study of Diabetes, we are developing a model-based glucose controller for TGC and opted, as a supportive task, to create a simulation environment to tune the controller and to predict the outcome of clinical testing.

Methods:
Clinical data collected over 48 to 72 hours of TGC with a model-predictive controller at four ICUs (29 medical and 27 surgical subjects) were employed to estimate parameters of a multicompartment glucoregulatory model. Sampling from informed probability distributions, the Bayesian estimation, and the regularization approach provided, on an individual basis, 22 time-invariant parameters and one time-variant parameter, basal insulin concentration (BIC), representing the temporal variation in insulin sensitivity. The model validation process included assessment of the ability of the model to reproduce glucose control with a model-predictive control algorithm.

Results:
The model provided satisfactory fit to data in all 56 subjects. The BIC was similar in surgical and medical patients [30.9 (25.8–36.4) vs 38.1 (26.0–54.2) mU/liter, surgical vs medical; median (IQ range); P = not significant] with higher temporal variability in medical patients [standard deviation of BIC 5.3 (3.8–7.0) vs 7.2 (5.5–12.6) mU/liter; $P < 0.05$]. Comparison between clinical and simulated studies with a model-predictive controller provided identical blood glucose, SD of blood glucose, hyperglycemic index, time in target, time to target, and sampling frequency (all P = not significant) supporting model validity.

Conclusion:
Clinical data were employed to generate a virtual population of 56 critically ill patients. The virtual population was able to reproduce glucose control with a model-predictive controller. We use the virtual population extensively to improve the glucose controller that we are developing.

Closed-Loop Linear Quadratic Gaussian Control of Blood Glucose with Subcutaneous Continuous Glucose Monitoring and Insulin Infusion: *In Silico* Comparison to PID

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Introduction:
In the context of renewed interest in artificial pancreas and closed-loop glucose control, we proposed applying linear quadratic Gaussian (LQG) methodology to the SC-SC blood glucose regulation problem. We evaluated, *in silico*, subject-specific LQG control and compared it to a preexisting proportional–integral–derivative (PID) controller.

Methods:
Our LQG feedback control law is based on a linearization of the type 1 diabetes mellitus model; the controller computes insulin infusion rates to minimize squared deviations from a nominal target, including glucose concentration and basal insulin rate. A Kalman filter estimates metabolic states based on continuous glucose monitoring (CGM), and insulin infusion is computed from LQR feedback gains applied to these estimates.
The evaluation of LQG and the comparison to PID were performed in a simulation environment including physiological and technological models (e.g., CGM sensor). Ten independent repeated trials were performed on 100 silicon subjects; results are presented for four classical indices of glucose control: PERCH (percent-time BG >180 mg/dl), PERCVL (percent-time BG <70 mg/dl), LBGI, and minimum glycemia. Our simulation protocol followed Steil 2006; the LQG target was adjusted to match PID average glycemia.

Results:
On average, LQG control achieved PERCH = 17.8%, PERCVL = 0.3%, LBGI = 0.33, and minimum glycemia = 81 mg/dl. In contrast, PID control achieved slightly less time in hyperglycemia (PERCH = 14.2% $p < 0.001$) but had a much greater hypoglycemic excursion (PERCVL = 8.73% $p < 0.001$, LBGI = 2.25, $p < 0.001$, minimum glycemia = 54 mg/dl $p < 0.001$). Average glycemia was 128.2 and 128.7 mg/dl (NS $p = 0.65$) for PID and LQG, respectively.

Conclusions:
LQG control achieves tight glycemic regulation with minimum hypoglycemic events *in silico*. Overall, LQG compares favorably to PID: equal average BG and comparable maximum and lower risks of hypoglycemia. Postprandial excursions were comparable in both methods, hinting at limitations of purely reactive methods.

High Correlation between Hemoglobin A1c and Average 1- to 3-Month Interstitial Fluid Glucose Concentrations

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Introduction:
Hemoglobin A1c (HbA1c) reflects the mean plasma glucose concentration (PG) over the previous 8 to 10 weeks. PG is closely related to the glucose concentration in interstitial fluid. This study compares the HbA1c with the mean interstitial fluid glucose concentration (ISFG) measured continuously (up to 288 values per day) over the preceding 4-, 8- and 12-week periods.

Methods:
The sensor was inserted subcutaneously into the gluteal or abdominal region. Signals were transmitted wirelessly into the Paradigm® 722 insulin pump (Medtronic MiniMed, Northridge, CA). Individual sensors were functioning for 4 to 9 days. Sensor calibration was performed twice daily by means of the Hypoguard Advance glucometer. Ten people with type 1 diabetes (PWD1) aged 23–69 years, with a diabetes duration of 21.5 ± 3.5 years (mean ± SE), and treated with the Paradigm 722 insulin pump (insulin aspart) were provided with sensors over 12 weeks (three 1-month periods). Medtronic MiniMed Solutions pumps and meters software 7311 v.7.0 were used to download data from the pump into a personal computer. Mean ISFG from the first, second, and third months and HbA1c at the end of each period were analyzed by means of the statistical program SPSS v.14.0.

Results:
There was no difference in the mean number of ISFG values per person in individual months (8187 vs 7537 vs 7456). Pearson's correlations (r) were found between HbA1c and mean ISFG from each previous month (approximately 0.9 each). There was also a strong correlation ($r > 0.9$) between the final HbA1c and the mean ISFG determined for 2 and 3 previous months ($p < 0.05$).

Conclusions:
Continuous glucose monitoring appears to be a helpful tool in establishing precise relationships between HbA1c and mean ISFG. Assessment that is more detailed is in progress.

Labor-Saving Effect of the Semiautomatic Response System for Diabetes Management Based on the Internet

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In a previous study we reported on the efficacy of the Internet-based glucose monitoring system (IBGMS) on glucose control in type 2 diabetes. The IBGMS was effective for glucose control during a long-term period of 30 months, as well as a short-term period of 3 months. However, the cost for maintaining a glucose monitoring system for a long-term period is very high. The majority of the cost comes from the labor cost of physicians. In a previous long-term study using the IBGMS, we found that about 50% of the contents of messages from doctors to patients were "encouraging." From these results, we developed a decision supporting system, the semiautomatic response system for diabetes management (SARS-DM), which can help filter uploaded glucose data and differentiate between "good" and "bad." The SARS-DM can decide whether the level of glucose control is optimal or not. It can also send a response to patients directly or report to physicians. We designed a study to investigate the log-in time-saving effect of the SARS-DM. This study compared the effect of the SARS-DM to that of a previous IBGMS on the frequency of log-in and log-in times by doctors. A total of 80 patients with type 2 diabetes were enrolled and randomized to a control group (MANUAL group) who used the previous IBGMS and to an intervention group (SARS group) who used the new SARS-DM. A baseline laboratory test was performed for all enrolled patients, who used each system for 6 months. The mean frequency of recommendations by doctors was 7.7 ± 4.1 and 11.4 ± 1.6 per patient in the MANUAL and SARS groups, respectively ($p < 0.001$). The mean frequency of the log in of doctors to the system online was 9.2 ± 4.1 and 13.7 ± 3.4 per patient in the MANUAL and SARS groups, respectively ($p < 0.001$). The log-in time of doctors to the online system was 395.0 ± 961.4 and 448 ± 611.1 seconds per patient in the MANUAL and SARS groups, respectively ($p = 0.829$). The SARS-DM reduced the frequency of log-in frequency of doctors to the online system and showed a 12% reduction effect on log-in time of doctors.

Software and Hardware Implementation of an Artificial β Cell: Modular Prototype Development and Risk Management

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The quest toward an artificial β cell has been accelerating, propelled by recent technological advances in subcutaneous glucose sensors and insulin pumps. The development and clinical testing of control and related algorithms present several challenges, such as communication and data transfer between a sensor (and pump) and a computer; a human interface presenting real-time information to the physician; safety issues when an automated system is used to administer insulin to subjects; and an architecture that supports different sensors, pumps, and control algorithms. These challenges were addressed in our development of a modular artificial β-cell system. The development environment of MATLAB® (The MathWorks, Inc., Natick, MA) allowed flexible implementation of communication protocols for any sensor or pump. The system has a plug-and-play option for the control algorithm and a human interface that presents and logs data, as well as enforcing protocol safety rules and facilitating physician oversight. A novel platform for use in clinical trials and a bridge toward a portable unit were realized. This prototype encapsulates communication between the control algorithm and the pump and sensors. Its simple and clear human interface presents all the information to the physician and allows all events to be logged electronically. It also ensures subject safety by integrating interlocks, checklists, and alarms. Furthermore, the plug-and-play concept allows this artificial β-cell system to serve as a test bed for various control algorithms without regard to the specific sensors or pumps involved. The modular design of the artificial β-cell system provides a robust test bed for various sensors and pumps, as well as control and other related algorithms, such as meal detection and predictive hypoglycemia alarms.

In Silico Dynamic Simulator for Closed-Loop Control of an Artificial β Cell with Hardware in the Loop

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Introduction:
A critical step in the prototyping and development of algorithms for an artificial β cell is *in silico* testing through extensive simulations. These simulations usually involve only the software part of the controller, leaving untested the hardware elements, including the critical communication interface between the controller and the glucose sensor and insulin pump.

Methods:
We have developed a hardware-in-the-loop simulator using all the components of the clinical system, replacing the subject with a mathematical patient model. The platform is developed in MATLAB® (The MathWorks, Inc., Natick, MA). A multifunction input–output card (USB-6008, National Instruments Corp., Austin, TX) is used to convert the mathematical model's interstitial glucose level to an electrical current, which is relayed to the FreeStyle Navigator® (Abbott Diabetes Care, Inc., Alameda, CA) glucose sensor system. The sensor instrument, including calibration, is then used to provide glucose measurements to the controller. The controller calculates an infusion rate that is relayed to the insulin pump (OmniPod®, Insulet Corp., Bedford, MA), and a digital input port is used to detect when a microbolus is delivered, which is then provided to the patient model, closing the loop.

Results:
The system is unique in that it uses all of the hardware components for simulations as used in clinical trials, allowing for full-system level verification. With a detailed mathematical model, a suite of patients can be simulated under various conditions. Because all hardware is used, related limitations are automatically included.

Conclusions:
A complete artificial β-cell system testing platform was realized, allowing for the systematic analysis of monitoring and control algorithms. The system facilitates a variety of tests and challenges to the software and the component devices, minimizing the need for preclinical validation trials.

Influence of Diabetes Type and Previous Experience of Pen Devices on Acceptance and Usability of a New Pen: An Observational Survey on SoloStar® Use

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Introduction:
SoloStar® (sanofi-aventis, Paris, France) is a new prefilled insulin pen device for the administration of insulin glargine or insulin glulisine. Results of subanalyses comparing usability, participant acceptance, and safety of SoloStar in individuals with type 1/type 2 diabetes (T1DM/T2DM), with/without insulin device experience, in everyday clinical practice are reported.

Methods:
Two thousand six hundred and seventy-four individuals with T1DM/T2DM consented to participate in this 3-month observational survey (supported by sanofi-aventis) based in Australia (November 2006–January 2007). At the start of observation, participants were given SoloStar pens containing insulin glargine, an instruction leaflet, and a toll-free help line number. Training was offered to all participants. Safety data, including product technical complaints (PTCs), were gathered from ongoing feedback by the participant or health-care professional and by solicited interviews conducted by independent moderators at weeks 6–10.

Results:
Of the 2029 people participating in solicited interviews (48.9% female [mean±standard deviation] aged 50.5 ± 16.1 years), 52.6/45.6% had T1DM/T2DM; 9.6/90.4% were device naive/experienced. At interview, most participants reported that they were "very satisfied" or "satisfied" with SoloStar (T1DM vs T2DM: 95.6 vs 95.1%; device naive vs experienced: 97.4 vs 95.1%) with a very low incidence of problems reported at solicited interview regarding SoloStar use, including dialing a dose (T1DM vs T2DM: 3.3 vs 3.1%; device naive vs experienced: 3.1 vs 3.2%) or injecting (T1DM vs T2DM: 3.8 vs 5.0%; device naive vs experienced: 3.1 vs 4.3%); most were temporary because of user error and were subsequently corrected by the participant. Sixty-two participants reported 77 adverse events; none were related to a PTC.

Conclusions:
After 6–10 weeks of exposure in this observational survey, SoloStar was well accepted by participants, irrespective of diabetes type or device experience, with a low incidence of participant-reported problems during use.

Performance of the New Bayer CONTOUR® Blood Glucose Monitoring System in Neonates

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Introduction:
Health-care professionals in neonatal units face notable challenges measuring the blood glucose of their patients. Neonatal blood typically contains less glucose and has a broader hematocrit range than blood from adults. Thus, it is important that the accuracy and precision of a blood glucose monitoring system are not significantly compromised when measuring blood samples that exhibit these unique characteristics. The new Bayer CONTOUR® blood glucose monitoring system uses a flavin adenine dinucleotide – glucose dehydrogenase-based test strip chemistry. This chemistry is insensitive to oxygen and is unaffected by maltose, galactose, and other potential interfering substances. A correction electrode is used by the new CONTOUR meter to measure and compensate for hematocrit.

Methods:
A clinical evaluation of this new system was conducted at two study sites with 314 neonatal blood samples from 243 subjects. Results from the CONTOUR system were compared to results from the site laboratory glucose analyzers. Sample glucose concentrations ranged from 6 to 131 mg/dl (0.3 – 7.3 mmol/liter); hematocrits ranged from 23 to 70%.

Results:
Glucose concentrations determined using the CONTOUR system were slightly affected by hematocrit, but the CONTOUR system met ISO 15197 criteria: 95.2% of results were within ±15 mg/dl or +20% of the laboratory values. Accuracy with samples having glucose concentrations <50 mg/dl (2.8 mmol/liter) was demonstrated by 90% of results being within ±15 mg/dl (0.8 mmol/liter) of the laboratory values. CONTOUR meter results correlated well with the laboratory glucose analyzer. Regression analysis of the CONTOUR vs reference analyzers yielded the following statistics: slope = 0.90, intercept = 5.90, r = 0.92, Syx = 6.85.

Conclusions:
Results of this study demonstrate that the new Bayer CONTOUR blood glucose monitoring system provides accurate blood glucose results with neonatal blood samples.

Noninvasive Diabetes Screening: Results from a Multisite Clinical Study

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Introduction:
SCOUT DS™ is a noninvasive tool being developed for rapid, convenient screening for diabetes and prediabetes. SCOUT DS does not require blood draws or patient fasting and provides an immediate test result. Premarket SCOUT DS devices have been evaluated in a four-site clinical study involving over 850 subjects.

Methods:
Study sites were selected to provide geographic and ethnic diversity to the study population. Consented subjects received fasting plasma glucose (FPG), hemoglobin A1c, and oral glucose tolerance tests (OGTT) and were tested by SCOUT DS in both fasting and nonfasting states. Participants were either aged 45 years or older or between 18 and 44 years with two or more risk factors for diabetes.

Results:
Subjects with 2-hour OGTT values equal to or exceeding 140 mg/dl defined the positive screening class. The performances of SCOUT DS, FPG, and hemoglobin A1c were evaluated for sensitivity and specificity against this classification. Preliminary analysis of data indicates a statistically significant sensitivity advantage for SCOUT DS over both blood tests. At a common specificity of 80%, test sensitivities were 56.1, 58.2, and 71.3% for FPG, hemoglobin A1c, and SCOUT DS, respectively. Receiver operator character analysis yields area under the curve values of 74.2, 77.8, and 79.7% for FPG, hemoglobin A1c, and SCOUT DS, respectively. The intermeasurement Hoorn coefficient of variation for SCOUT DS was 5.2%. Subcohort analysis indicates that SCOUT DS performance is unaffected by fasting status or skin color.

Conclusions:
Noninvasive technology shows clinical performance advantages over both FPG and hemoglobin A1C. The combination of higher sensitivity and greater convenience—rapid results with no fasting or blood draws—makes the device well suited for opportunistic screening.

Closed-Loop Blood-Glucose Control Using Dual Subcutaneous Infusion of Insulin and Glucagon in Ambulatory Diabetic Pigs

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Introduction:
Our goal was to develop a closed-loop system for automatically regulating blood glucose (BG) in type 1 diabetes using dual subcutaneous (SC) infusion of insulin and glucagon.

Methods:
The control algorithm we have developed utilizes model-predictive control (MPC) in conjunction with a recursively adaptive empirical subject model. The MPC objective function was augmented with a formulation that keeps online track of the accumulation of SC insulin in order to simultaneously minimize the latter and avoid excessive insulin dosing. The novel algorithm was tested in ambulatory diabetic pigs, whereby a central line inserted into the vena cava was used to sample BG. The control algorithm requires only the subject's weight for initialization and operates online solely based on BG data without any feed-forward information, such as timing and carbohydrate content of meals, as well as subject's activity. We have conducted experiments in a separate study in ambulatory diabetic pigs that verified that the pharmacodynamics and stability of SC glucagon, stored at room temperature, render it a practical counterregulatory agent in the context of closed-loop BG control.

Results:
Closed-loop control results in ambulatory diabetic pigs showed successful BG regulation in the euglycemic range, with no incidences of hypoglycemia, in response to multiple successive oral carbohydrate intakes in 12- and 24-hour closed-loop control experiments. Results also demonstrated the potency of SC glucagon in staving off potential episodic hypoglycemia and revealed the control algorithm's efficacy in coping with a twofold variation in subject weights, while simultaneously overlooking erratic blood-glucose fluctuations.

Conclusions:
Results establish the plausibility and practicality of closed-loop BG control using SC insulin and glucagon infusion in type 1 diabetes.

Good Acceptance of Continuous Glucose Monitoring with GlucoDay® S: Results of a Questionnaire Survey

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Introduction:
Continuous glucose monitoring (CGM) is a means of collecting detailed data on blood glucose levels in patients with type 1 and type 2 diabetes mellitus for diagnostic or clinical purposes. The GlucoDay® S system is a medical product that, by means of a microdialysis catheter, continuously measures subcutaneous glucose at 1-second intervals over a 48-hour period. The aim of the survey was to examine the practical application of GlucoDay S using four questionnaires.

Methods:
Diabetes specialists were selected for participation. Participating centers and personnel were trained on the system by qualified experts. Data evaluation and documentation were based on questionnaires completed by physicians and/or diabetic nurses at four time points; patient evaluations were also reported.

Results:
Questionnaires were received from 148 centers documenting a total of 609 applications of the system. Participants and patients evaluated GlucoDay S positively. More detailed data, nighttime measurements, and ease of use were some of the reported advantages. The handling instructions were considered good by 80% of 139 centers. Of the participants completing the survey, 65% performed at least 11 applications and 59% were interested in continuing CGM with GlucoDay S.

Conclusions:
Continuous glucose monitoring with GlucoDay S offers improved data for diagnostic and clinical purposes. Acceptance of CGM is fairly broad in Germany, even though local health insurance companies do not yet offer reimbursement. GlucoDay S itself is easy to use and is reliable. Good adherence to this system is associated with its substantial training program. GlucoDay S provides more detailed information about individual glycemic control and is therefore an important and well-accepted diagnostic tool.

Online Noise Removal of Continuous Glucose Monitoring Data: Comparison of Filtering Techniques

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Introduction:
Continuous glucose monitoring (CGM) sensor data are noisy. To remove noise, filtering is usually employed. This work compared different online signal filtering techniques also in relation to their possibility of being tuned to an individual subject.

Methods:
Twenty-five diabetic subjects were monitored for a day, and their glucose value was measured every 3 minutes using the GlucoDay® S (Menarini, Firenze, Italy). No prefiltering was used inside the device. Each time-series was filtered using moving average (MA), hard bounding (HB), and Kalman (KF). Filter performance was assessed by looking at the smoothness of profiles and introduced delay. Smoothness was quantified through energy of the second-order derivative (ESOD). Delay was calculated as the horizontal time shift that allows minimizing the distance between the two profiles.

Results:
The MA filter led to very smooth profiles (low ESOD), but it introduced a significant delay (6 minutes on average). The HB filter introduced a minimal delay (less then 1 minute on average) and eliminated spikes, but the profile was not sufficiently smoothed (HB ESOD higher than MA). KF gave a smooth profile comparable to MA (same ESOD value) but the introduced delay was half the MA delay (3.6 minutes on average). Among these filtering techniques, only KF was adaptive, i.e., it was individually tuned.

Conclusions:
The MA filter leads to well-smoothed profiles but introduces a significant delay. Another drawback is that it is not adaptive. HB is useful in reducing spikes. KF introduces a very small delay and has the advantage of being adaptive, i.e., parameters can be tuned online easily in each patient according to statistically based smoothing criteria.

Online Time-Series Prediction Models for Continuous Glucose Monitoring Data

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Introduction:
Continuous glucose monitoring (CGM) systems can improve the management of hypo/hyperglycemic events. In particular, CGM data can be used to predict glucose levels ahead of time in order to prevent, rather than to detect, critical events. This work compared online prediction models and assessed their performance by a novel index based on the ability to predict critical events and not to create false alarms.

Methods:
Twenty-seven people with type 1 diabetes were monitored for 3 days using the FreeStyle Navigator® CGM sensor. Autoregressive (AR) from orders 1 to 5, autoregressive integrated (ARI) of order 1, and first- and second-order polynomial models were used for online prediction. To remove noise on the output signal, an online adaptive Kalman filter was implemented. Thirty- and 45-minute prediction horizons (PH) were considered. Data were weighted using a forgetting factor (FF). A novel index, called clinical performance of prediction (CPP), directly proportional to prediction irregularity (linked to false alarms) and inversely proportional to temporal gain (linked to critical events detection), was used to compare prediction models.

Results:
CPP allows choosing optimal parameters (FF and PH) for each prediction model. Comparison of CPP among prediction models suggested that an AR of order 1 performs best for this data set. The model has an average temporal gain of 16 and 17 minutes with a PH of 30 and 45 minutes, respectively.

Conclusions:
CPP allows choosing optimal parameters for a given prediction model and comparing the performance among different models. For this data set, the "best model" has a temporal gain that is sufficient to enable cautionary action to avoid hypo/hyperglycemic events. The temporal gain was similar for both PH.

Model of Intrapancreatic Network Control of Glucagon Secretion in β Cell-Deficient Diabetes

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Introduction:
Glucagon counterregulation protects against hypoglycemia, and its compromise in diabetes prevents safe control of hyperglycemia. We propose a model that views glucagon counterregulation partially as a general disinhibition phenomenon to explain the mechanisms underlying the defects in insulin-deficient diabetes. We used a network modeling strategy to analyze the glucagon axis and *in vivo* rodent experiments to verify model predictions.

Methods:
Differential equations approximated the β-cell-deficient intraislet network assuming that glucagon and glucose stimulate somatostatin, which feeds back to suppress glucagon. To provide experimental verification, we studied STZ-treated (80 mg/kg) male Wistar rats with a reduced glucagon response to hypoglycemia. Counterregulation was restored by intrapancreatic infusion of α-cell inhibitory signals (insulin/zinc, somatostatin) switched off at hypoglycemia. Frequent sampling allowed analysis of glucagon pulsatility by deconvolution.

Results:
Mathematical modeling showed that feedback interaction between α and δ cells could explain glucagon counterregulation as a pulsatile rebound secretion in response to disinhibition of the α cells. Experiments showed that intrapancreatic infusion of insulin/zinc or somatostatin can trigger pulsatile glucagon release with an average interpulse interval of 12.3 minutes (n = 5; SD = 2.4) and a half-life of 1.3 minutes (n = 5; SD = 0.3) as detected by deconvolution.

Conclusions:
This model explains some of the *in vivo* system behavior and predicts that any signal that can suppress α-cell activity may trigger pulsatile glucagon release upon disinhibition. Experiments confirmed this prediction by showing that insulin/zinc and somatostatin in STZ-treated rats can trigger pulsatile glucagon counterregulation if they are infused locally and switched off during hypoglycemia. This model can be helpful in artificial pancreas design for simulating data for testing control algorithms and exploring strategies for improving glucagon counterregulation.

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Simultaneous and Minimally Invasive Glucose and Lactate Monitoring through Reverse Iontophoresis

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Iontophoresis is a minimally invasive process that relies on both electromigration through the application of a small electrical current and electroosmosis to deliver drugs across the skin. Studies have been undertaken to examine the use of reverse iontophoresis as a method of metabolite extraction, in particular glucose and lactose, which are considered crucial to the well-being of diabetic patients and other potential patients, such as those suffering from myocardial ischemia. The work presented here focuses on the development of a prototype extraction system based on reverse iontophoresis. An *in vitro* model designed to mimic skin and internal fluid was studied to investigate the potential of using reverse iontophoresis as the basis for such a monitoring device. *In vitro* and *in vivo* work was carried out to optimize the skin contacting hydrogel to allow a maximum diffusion rate while maintaining a rigid structure capable of storing the extracted ions and molecules for later quantification. The *in vivo* trial consisted of skin hydration tests on healthy human volunteers quantified through impedance measurements over periods of up to 8 hours. The final and most critical stage of the work presented here involves an *in vivo* trial of this extraction prototype on healthy human volunteers. Results show that reverse iontophoresis increases glucose extraction threefold and lactate extraction by twofold over diffusion *in vivo.* A significant drop in skin impedance was observed during reverse iontophoresis, indicating a reduction in the protection provided by the stratum corneum; however, this drop was found to be reversible upon termination of the applied current. Outcomes of these trials indicate the viability of using reverse iontophoresis as a tool for simultaneous metabolite monitoring.

Combination of *Ex Vivo* Vascular Interface and Infrared Spectrometry for Continuous Bedside Monitoring of Blood Glucose

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

Methods:
The device consists of two main components: an extravascular μ-dialysis system and an infrared-spectrometric sensor. Continuous measurements can be carried out using biofluid sampling through the microdialysis device that is coupled to fluidics, which includes a double-lumen venous catheter in combination with whole blood dilution using a heparin solution. The diluted whole blood is transported to a flow-through dialysis cell, where the harvesting of analytes across the μ-dialysis membrane takes place at high recovery rates. The dialysate is transported continuously to the sensor. Using this setup, *ex vivo* experiments were conducted on several healthy subjects lasting up to 28 hours.

Results:
Clinical experiments have shown excellent agreement between the sensor readout and the reference blood glucose concentration values. The simultaneous assessment of dialysis recovery rates renders a reliable quantification of whole blood concentrations after taking the blood dilution into account. The method also enables simultaneous determination of metabolites (urea, lactate, and others).

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

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Continuous Glucose Monitoring Based on Whole Blood Microdialysis and Online Sensors

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Introduction:
Tight glycemic control can reduce the mortality and morbidity of critically ill patients. Therefore, it is important to enable stable and representative online glucose monitoring. In contrast to approaches relying on subcutaneous body interfaces, we have designed and tested a novel system that allows continuous glucose sensing based on extracorporeal microdialysis (MD) of whole blood. The aim of this study was to determine and evaluate the performance of the system.

Methods:
Eight healthy volunteers underwent a 30-hour investigation. Via a double-lumen catheter, blood was withdrawn continuously at a flow rate of 2 ml/h using Na-heparin as the anticoagulant. The blood–heparin mixture was microdialyzed in a planar flow-through MD unit and discarded thereafter. The dialysate was analyzed for glucose concentration using continuous enzymatic online sensor techniques and a Beckman glucose analyzer.

Results:
All 8 subjects completed the 30-hour trial successfully. The correlation between glucose concentration of dialysate and reference venous blood samples was excellent. The median coefficient of correlation between continuously withdrawn microdialyzed blood and reference blood samples using prospective one-point calibration was $r = 0.943$ [0.758; 0.966]. Clarke error grid analysis (EGA) revealed that 100% of all data pairs ($n = 526$) were in the A and B zones (A = 89.7%). Insulin titration EGA suggests that 98.9% of all data pairs are in the "acceptable treatment" area.

Conclusions:
Continuous blood withdrawal and extracorporeal MD is a promising approach to determine blood glucose reliably and safely, is stable long term, and is therefore an appropriate basis for combination with continuous online glucose sensors. Future studies include an insulin pump controlled by an eMPC algorithm to regulate type 1 diabetic patients' glucose levels in a closed-loop manner.

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The Effect of Iron Overload on Function of Pancreatic Islet Cells Releasing Insulin *in Vitro*

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Objective:
Several studies have reported an association between body iron overload and type 2 diabetes. However, so far the mechanism is not clear. The objective of this study was to observe the effect of iron overload on the function of pancreatic islet β cells releasing insulin *in vitro*.

Methods:
Pancreatic islets were isolated from normal Wistar rats. They were identified by dithizone, which make pancreatic islet cells brownish red. Islets were divided into five groups: group A, group B1, group B2, group C1, and group C2, respectively. There were 50 islets in every group. They were perfused by different fluids. Group A was the control, stimulated by 16.7 m*M* glucose fluid; group B1 was perfused with 16.7 m*M* glucose fluid, including ferric nitrilotriacetate in which the concentration of ferric was 0.05 m*M*; and group B2 was perfused with 16.7 m*M* glucose fluid in which the concentration of ferric reached 0.1 m*M*. In group C1, islet cells were incubated with culture media, including ferric (0.05 m*M*) for 5 hours, and then stimulated with 16.7 m*M* glucose fluid. In group C2, islet cells were incubated with culture media, including ferric (0.1 m*M*) for 5 hours, and then stimulated with 16.7 m*M* glucose fluid. Levels of insulin that pancreatic islets released within 40 minutes were measured. In the first 10 minutes, levels of insulin were determined every minute and were then determined every 3 minutes.

Results:
There was typically early insulin releasing responsiveness induced by 16.7 m*M* glucose stimulation in control islets, the peak value appeared at 1 minute, and the maximum of insulin was 239.89 ± 31.56 mU/liter and declined to a baseline level at 6 minutes. No peaks were found among groups B1, B2, C1, and C2. Their range of insulin value determined within 40 minutes was from 7.01 ± 1.69 to 13.54 ± 3.55 mU/liter and showed continuous microfluctuation. There are three figures that show the change of insulin value within 40 minutes in each group by different fluid stimulating. Data were shown as means ± SD. Continuous variables were compared by ANOVA. The amount of insulin released in group A was higher ($p < 0.05$) than in the other groups; however, there was no difference in the insulin value among groups B1, B2, C1, and C2 ($p > 0.05$).

Conclusion:
According to the results of this study, the function of pancreatic islets cells releasing insulin was destroyed by high-level iron, no matter whether a high concentration of ferric in fluid stimulates or the culture including over iron incubates, which is significant for the explanation of the relation between iron and diabetes.

Detection of Pharmacologically Induced Stress in Subjects with Type 1 Diabetes

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Introduction:
Stress dramatically changes glucose–insulin kinetics in subjects with type 1 diabetes (T1DM). An effective automatic control algorithm for an artificial β cell must include a monitoring component to sense these changes and consequently adapt insulin therapy accordingly.

Methods:
For each of three T1DM subjects, initial days of continuous (5-minutes) glucose data, insulin pump logs, and subject-reported meal estimates were collected in normal, ambulatory conditions. Three days of data were then collected during which the subjects were administered prednisone (60 mg/day) to mimic acute short-term stress. Additional normal days of data were collected following the stress days. Using multivariate statistical analysis, empirical models were developed for each subject from initial calibration data. The remaining *validation* data—both stress and normal days—were then compared to the models. Two standard statistical metrics, Q and T^2, were calculated for each validation day. If a metric exceeded a confidence limit for a day, that day was classified as a stress day.

Results:
Two measures were used to evaluate the performance of the proposed monitoring technique: *sensitivity*, the frequency with which stress days were classified correctly, and *specificity*, the frequency with which normal days were classified correctly. For 14 validation subject days comprising 9 stress days and 5 normal days, the Q statistic was highly sensitive (89%) and also highly specific (100%), while the T^2 statistic was reasonably sensitive (67%) and highly specific (100%). Combining both metrics to make a classification resulted in perfect sensitivity and specificity.

Conclusions:
These experimental results demonstrate that the proposed monitoring technique can accurately detect pharmacologically induced stress states in subjects with T1DM. Such a monitoring technique is crucial to the robustness of an artificial β cell.

Computerized Managing and Tracking Behavior Change in People with Diabetes—AADE7™

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Introduction:
Diabetes self-management training is predicated upon seven self-care behaviors (healthy eating, being active, monitoring, taking medication, problem solving, reducing risks, and healthy coping) that comprise a framework. Building upon this construct, the American Association of Diabetes Educators' (AADE) partnered with the University of Pittsburgh Medical Center to develop the AADE7™ outcomes system, which systematically captures data via Web-based, touch screen and telephonic systems.

Methods:
The AADE7 tracks behavior change in people with diabetes that results from diabetes education. Patients (954) provided data on behavior change goals to the Diabetes Self-Management Assessment Report Tool (D-SMART); mutually identified diabetes educator responses were recorded in Diabetes Educator Tool (D-ET).

Results:
The AADE7 was first used for goal setting with patients. The most commonly patient-identified behavior change goals were healthy eating (74%) and activity (54%). Patient and diabetes educator mutually agreed upon goals showed high concordance. Educators addressed mutual goals in the following percentage of cases: healthy eating (98%), monitoring (94%), activity (90%), risk reduction (80%), medication (75%), problem solving (72%), and coping (48%). We are now using the tool to determine education outcomes and their influence on diabetes control.

Conclusions:
AADE7 tools have the potential to help establish benchmarks and identify best practices for people with diabetes.

Differences between Point-of-Care Blood Glucose Measurements in Simultaneously Sampled Blood from the Radial Artery, Central Venous Catheter, and Fingertip

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Introduction:
Frequent blood glucose (BG) monitoring is required to direct intravenous (IV) insulin delivery. Arterial, venous, and capillary blood sources may yield different results because of physiological differences between sites and/or sampling issues.

Methods:
One hundred fifty-eight blood samples were collected near-simultaneously from a radial artery catheter, central venous catheter, and fingertip of 10 patients undergoing cardiac surgery. Samples were analyzed using an Accu-Chek® glucose meter. Ten venous measurements (6.3%) were considered outliers and were removed from data set #1. In a separate analysis, 31 venous (19.6%), 2 arterial (1.3%), and 2 capillary (1.3%) measurements were considered outliers and were removed from data set #2. Differences among capillary, arterial, and central venous measurements were analyzed in a linear mixed effects model accounting for between-subject and within-subject variability and correlation between measures from the same individual.

Results:
For data set #1, mean capillary BG measurements were 16.8 mg/dl higher [$p < 0.001$; 95% confidence interval (CI): 11.6, 22.0] than arterial measurements and 9.8 mg/dl higher ($p = 0.003$; 95% CI: 3.4, 16.2) than venous measurements. The mean difference between venous and arterial measurements was 7.0 mg/dl ($p = 0.027$; 95% CI: 0.8, 13.2). For data set #2, mean capillary BG measurements were 16.2 mg/dl higher ($p < 0.001$; 95% CI: 10.8, 21.6) than arterial measurements and 13.2 mg/dl higher ($p < 0.001$; 95% CI: 7.4, 18.9) than venous measurements. The difference between venous and arterial measurements was no longer significant.

Conclusions:
Measurement of BG depends on the source and quality of the blood sample. Mean capillary measurements were significantly higher than arterial and venous measurements. Nearly one-fifth of the venous samples yielded outlying results and were likely contaminated with IV solutions. These physiological and sampling-related differences could affect IV insulin titration.

Effects of Atorvastatin and Pioglitazone on Microvascular Function in Nondiabetic Patients at Cardiovascular Risk— The PIOVASC Study

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Background and Aims:
In patients with hypertension and increased cardiovascular risk, microvascular and endothelial function is impaired in association with an increasing degree of insulin resistance. To evaluate the effects of atorvastatin and pioglitazone on microvascular function in this special risk population, we measured microvascular skin blood flow in patients with increased cardiovascular risk.

Patients and Methods:
Eighty-nine nondiabetic patients with increased cardiovascular risk, defined as hypertension and/or previous cardiovascular event (49 males, 40 females; age 61.1 ± 6.8 years; body mass index 29.5 ± 4.5 kg/m^2; mean ± SD) were included in our double-blinded, placebo-controlled parallel study. Patients were randomized to 40 mg atorvastatin and placebo or 40 mg atorvastatin in combination with 45 mg pioglitazone. At baseline and after 6 months, skin microvascular blood flow was measured by laser-Doppler fluxmetry (LDF). Microvascular function was assessed by the microvascular response to the iontopheresis of acetylcholine (LDF_{ach}) and the microvascular response to heat (LDF_{heat}).

Results:
LDF measurements were not significantly different between the two treatment groups at baseline [LDF_{ach}: 36.5 ± 37.5 vs 26.3 ± 23.7 arbitrary units (AU), n.s.; LDF_{heat}: 16.2 ± 9.6 AU vs 14.7 ± 7.3 AU, n.s.; mean ± SD]. During combined treatment with atorvastatin and pioglitazone a significant improvement in the microvascular response to acetylcholine (LDF_{ach}) from 360 ± 315 to 578 ± 921% ($p < 0.05$) could be observed, while the heat response (LDF_{heat}) slightly decreased from 673 ± 371 to 587 ± 314% (n.s.). No significant changes in the LDF response were obtained during single atorvastatin treatment LDF_{ach} from 490 ± 441 to 500 ± 303% (n.s.) and LDF_{heat} from 768 ± 307 to 692 ± 343% (n.s.).

Conclusions:
Pioglitazone in combination with atorvastatin significantly improved microvascular endothelial function as measured by LDF_{ach} in a population of nondiabetic patients with increased cardiovascular risk. No such effect could be observed during single atorvastatin treatment.

Performance of the Bayer CONTOUR™TS Blood Glucose Monitoring System: Capillary, Venous and Alternative Site Blood

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Introduction:
The CONTOUR™TS blood glucose monitoring system requires a small sample (0.6 µl), has a 250 result memory, hematocrit compensation, universal sampling, 8-second test time, and does not require coding by the user. The flavin adenine dinucleotide glucose dehydrogenase-based test strip chemistry eliminates interference by maltose, making the system suitable for patients undergoing peritoneal dialysis. The system is unaffected by galactose.

Methods:
One hundred six persons with diabetes and four health-care professionals evaluated the user guide and performance of the system with capillary and venous blood in a clinical trial. Meter results were compared to Yellow Springs Instruments (YSI) laboratory glucose analyzer results. A second study was conducted with 49 subjects using the system at home for 1 week to determine the system's acceptability for self-testing. In a third study, blood from alternative sites (forearm and palm) was assayed.

Results:
Capillary and venous test results exceeded the International Organization for Standardization 15197 performance guidelines (≥97.9% of results were within ±20% of YSI for samples ≥ 75 mg/dl and within ±15 mg/dl for samples < 75 mg/dl). Clinical accuracy was demonstrated (≥97.1% of results were within zone A of the error grid; the remaining results were in zone B). The average within-run coefficient of variation was ≤6.0 and ≤4.2% for capillary and venous blood, respectively. Subjects successfully learned to use the system from the user guide without training. The system was acceptable for self-testing at home. Clinical accuracy with blood from alternative sites was demonstrated. At least 95.3% of the alternative site test results were within zone A of the error grid; the remaining results were in zone B.

Conclusions:
In summary, the CONTOUR TS system was accurate, precise, and easy to use by people with diabetes and does not require coding by the user.

Performance and Ease of Use of the BREEZE®2 Blood Glucose Monitoring System

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Introduction:
The BREEZE® 2 system was designed for improved performance over its predecessor. The new system requires less blood (1 µl), has a 5-second countdown, and does not require coding by the user. The purpose of these studies was to evaluate its performance and ease of use.

Methods:
A study was completed by 201 subjects and eight health-care professionals (HCP) at two clinical research centers. Subjects and HCPs tested subject fingertip blood using the meter (duplicate tests). Results were compared with Yellow Springs Instruments (YSI) glucose results. Subjects evaluated the meter user guide and completed a questionnaire. A home use study of the BREEZE 2 meter was conducted by one clinical center. In this study, 53 subjects used the BREEZE 2 meter at home for 1 week to determine its acceptability for self-testing.

Results:
There were 394 capillary blood samples with YSI glucose concentrations ranging from 55.9 to 342.0 mg/dl (3.1 to 19.0 mmol/liter). Subject and HCP BREEZE 2 results exceeded International Organization for Standardization 15197 performance guidelines (97.5% of subject and 99.0% of HCP results were within ±15 mg/dl or ±20% of YSI results). Parkes error grid analysis results were 98.2% in zone A for subjects and 98.7% for HCPs; no results were in zones C, D, or E. The average within-run CV was 4.3% for subjects and 3.8% for HCPs. Subjects learned to use the meter from the illustrated user guide and completed a series of tasks, with success rates ranging from 70.3 to 98.2% for individual tasks. Subjects gave positive ratings to the meter features and ease of use.

Conclusions:
The BREEZE 2 system was found to be accurate, precise, and easy to use.

Comparison of Two Microdialysis Continuous Glucose Monitoring Devices

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Introduction:
Microdialysis systems provide highly accurate continious monitoring (CM) data, yet fluid propulsion issues can significantly compromise long-term reliability. In this pilot study we compared two microdialysis systems, the continuous monitoring research tool (CMRT) system featuring inter alia an improved roller pump, a flow rate sensor, and a bubble removal unit, with the former subcutaneous continuous glucose monitor 1 (SCGM1) system.

Methods:
Six persons with type 1 diabetes participated in the study (5 males, 1 female, HbA1c 7.0% (6.2–8.3) [mean (range)]). In each subject, one CMRT and one SCGM1 system (investigational devices, Roche Diagnostics GmbH) were placed in the abdominal subcutaneous tissue for ~5 days. The CMRT and the SCGM1 systems collect 86,400 and 1440 data points per day, respectively. The retrospective calibration model of CM data is based on a run in time of 24 hours and three duplicate blood glucose (BG) measurements per day, while at least 12 daily, duplicate BG values are used for validation.

Results:
The sustainable monitoring time of SCGM1 experiments was found to be 102 hours (78–116) on average. In contrast, all CMRT systems were functional over the total monitoring time of 116 hours. For SCGM1, 236 reference–CM data pairs were available compared to 401 for CMRT with 97.9% of SCGM data and 97.3% of CMRT data in the A+B region of the Clarke error grid.

Conclusions:
Results show that the CMRT system is a reliable microdialysis device for a period of 5 days. Resolved flow propulsion issues lead to high accuracy data for the whole experimental time. In an ongoing trial, the performance of the CMRT system is being investigated, including a larger number of systems to confirm the high analytical performance.

A Unique Method for Accurate Noninvasive Glucose Monitoring

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Introduction:
Generally, noninvasive (NI) devices measure a physiological phenomenon (PP) that is correlated with the blood glucose level rather than measuring it directly. The NI device combines a sensor that measures PP through tissue parameters with suitable resolution for glucose determination and interpretation of these parameters into a glucose value following calibration. Because factors other than glucose alter tissue parameters and introduce "noise" into the measurement, either limited conditions of measurement (patient immobility or large device size) or cumbersome analysis of results is required. Using a unique approach combining three independent NI technologies (ultrasound, conductivity, and heat capacity) can minimize the noise impact.

Methods:
Eighty subjects were tested in clinical trials (282 data pairs): 14 type 1 diabetes mellitus (T1DM) (7 females, 7 males), 56 T2DM (14 females, 42 males), and 10 healthy subjects (7 females, 3 males). The average age was 61.2 ± 24.5 years, and the body mass index was 24.6 ± 10.5 kg/m^2. Calibration was performed individually using basal and postprandial measurements, which were compared to capillary blood determinations using Abbott FreeStyle® and HemoCue Glucose 201 devices. Fifty patients performed at least 1 measurement pair, 21 patients performed 6 measurement pairs in a 1.5-hour period, and 9 patients were evaluated during the full daytime session, where 12 pairs were taken during 8 to 10 hours.

Results:
Clarke error grid analysis of the weighed results showed 92% of the points falling into zones A + B, of which 60% are in zone A. Clinical trials are still taking place in Israel, to be followed in Europe and the United States.

Conclusions:
Although the present version of GlucoTrack™ gives promising results, further improvement of the device's characteristics has been set as a goal (already in process). A key issue for the device's accuracy level is calibration quality for the entire dynamic range of readings.

Online Detection of Therapeutically Wrong Measurements of Continuous Glucose Monitors Using Support Vector Machines

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Introduction:
Current continuous glucose monitors have limited accuracy mainly in low-level glucose measurements, which leads to readings out of the therapeutically safe zones in Clarke's error grid analysis (EGA) (zones A and B). Detection of therapeutically wrong glucose readings is of utmost importance in clinical applications of continuous glucose monitors, such as closed-loop glucose control. The goal of this work was to detect online wrong measurements (zones C, D, and E) taken from a continuous glucose monitor.

Methods:
Twenty-two type 1 diabetic patients were monitored for 3 days (1 day at the hospital and 2 days at home) using the Medtronic MiniMed continuous glucose monitoring system (CGMS) sensor. During the stay at the hospital, blood samples were taken every 15 minutes for 2 hours after meals and every 30 minutes otherwise. A support vector machine (SVM) was implemented and trained using (ISIG monitor glucose prediction-blood glucose) data sets to classify monitor readings in two classes following Clarke's EGA: AB and CDE. Five hundred eighty-three data sets were used for training. Once trained, 300 monitor readings (ISIG monitor glucose prediction) were supplied to the SVM to be classified as AB or CDE for validation.

Results:
For the validation data set, 19 of 21 of the CGMS predictions that fell into the therapeutically unsafe CDE group were detected. Four false positives were also obtained. The resulting sensitivity was 0.9048, and the specificity was 0.9859.

Conclusions:
Most of the erroneous estimations of blood glucose given by real-time monitoring systems can be detected online using support vector machines. This may improve significantly the overall performance of such systems and its use in clinical applications such as closed-loop glucose control.

Using a Glucose-Binding Protein-Based Glucose Assay Combined with Microdialysis to Track the Changes in Glucose Concentration

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Introduction:
Continuous or frequent blood glucose monitoring is a vital first step in preventing the onset of complications in diabetes. Here we describe a glucose monitoring technique developed by combining a glucose-binding protein (GBP)-based glucose assay with a microdialysis sampling system, which was tested in mammalian cell culture as an analogous system to human blood.

Methods:
The glucose biosensor was prepared by introducing a mutation in the plasmid expressing the wild-type GBP through site-directed mutagenesis. The protein was then expressed, released, purified, and labeled with the thiol-reactive probe acrylodan. The dialysis probe immerged in the mammalian cell culture broth was connected to a microsyringe through plastic tubing, and the perfusion speed was controlled by a controller. Two or three samples were taken each day. The fluorescence intensity for all samples was read on a plate reader.

Results:
The glucose assay is highly sensitive and reversible, but some factors can interfere with the measurements. The glucose concentration in the dialysate is affected by the glucose concentration in the medium, the flow rate of the perfusion buffer, and the temperature. When the flow rate and temperature are fixed, the glucose concentration in the medium is the sole factor affecting the glucose concentration in the dialysate.

Conclusions:
The glucose monitoring system can track the changes in glucose concentration in the mammalian cell culture. The high sensitivity of the glucose assay allows the use of a high perfusion rate, which greatly decreases the delay time. This preliminary result shows that the system may find application in blood glucose monitoring in diabetes.

Increased Skin Autofluorescence: A More Pronounced Marker of Mortality in Hemodialysis Patients Than Diabetes Mellitus?

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Introduction:
Accelerated formation and tissue accumulation of advanced glycation end products (AGEs), representing cumulative glycemic and oxidative stress, occur in patients with diabetes mellitus (DM), renal failure, and dialysis. Skin autofluorescence (AF) based on the fluorescence characteristics of certain AGEs measures its tissue accumulation noninvasively. We investigated whether skin AF has an additional predictive value concerning mortality in diabetic hemodialysis versus nondiabetic hemodialysis patients.

Methods:
Patients were recruited from our hemodialysis center. Baseline skin AF was assessed at the lower (nonshunt) arm. After a follow-up period of 3.2 years we assessed mortality in relation to the presence or absence of DM and to the level of baseline skin AF.

Results:
Baseline skin AF was obtained in 106 hemodialysis patients: mean age 65; mean renal replacement therapy duration 3.6 years; 83 nondiabetic patients; and 23 type 2 diabetic patients (mean diabetes duration 16.1 years; mean hemoglobin A1c 6.8%). At the end of follow-up, 38 patients had died: 12 diabetic (52%) and 26 nondiabetic patients (31%), which was borderline nonsignificant [$p = 0.065$ (χ^2)]. The *T* test showed no significance in the diabetes group between mean skin AF of nonsurvivors [3.43 ± 0.89 arbitrary units (AU)] compared to survivors (3.00 ± 0.81 AU). In the nondiabetic group, mean skin AF was significantly higher in deceased (3.56 ± 0.67 AU) compared to survivors (2.94 ± 0.91 AU)($p = 0.002$).

Conclusion:
Our study confirms a higher mortality rate in diabetic hemodialysis patients compared to nondiabetic hemodialysis patients. Mortality was increased in hemodialysis patients with a higher baseline skin AF, independent of the presence or absence of DM. This might implicate skin AF as a better predictor of mortality in hemodialysis patients than the presence or absence of DM.

Electrocardiogram Disturbances to Hypoglycemia in Type 1 Diabetic Children

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Introduction:
It is known that the onset of hypoglycemia activates the sympathetic nervous system to trigger changes within certain physiological parameters. This study examines the degree of change of the electrocardiogram (ECG) in type 1 diabetic adolescents during both daytime and nighttime insulin-induced hypoglycemic clamp studies.

Methods:
Two sets of hyperinsulinemic clamp studies were conducted on a total of 36 type 1 diabetic children (14.4 ± 1.6 years), hemoglobin A1c 7.65% (5.9–12.7), including daytime clamps (n = 25) and overnight sleep clamps (n = 11). The HypoMon® measured the ECG, incorporating the QTc interval, the heart rate (R-R interval), and the T-wave characteristics, while venous blood glucose was collected as reference (Yellow Springs Instruments).

Results:
During the daytime study (n = 25), a total of 84% (21/25) demonstrated a mean change in the heart rate and QTc interval from the euglycemia phase [blood glucose level (BGL) = 97.6 ± 2.6 mg/dl] to hypoglycemia phase (BGL = 49.9 ± 5.9 mg/dl) and measured change of +14.2% ($p < 0.004$) and +8.2 % ($p < 0.001$) respectively. During the overnight sleep study (n = 11), with the same duration in the euglycemia and hypoglycemia phases, a total of 73% (8/11) registered a mean change in the heart rate and QTc interval of +12.1% ($p < 0.005$) and +8.2% ($p < 0.001$), respectively.

Conclusions:
Changes within certain physiological parameters during the onset of hypoglycemia in type 1 diabetics are less prevalent at the nocturnal stage than that of daytime onset. Although less responsive, these physiological parameters can provide markers for the early detection of nocturnal hypoglycemia in type 1 diabetics prior to complications.

Islet Encapsulation in Epoxy-Based Microcontainers

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Introduction:
Present-day islet encapsulation techniques such as polymeric encapsulation and microelectromechanical system (MEMS)-based encapsulation devices have shown promise in insulin replacement therapy, but each have their own limitations (permeability characteristics of existing polymeric capsules cannot be strictly controlled because of tortuosity, and the large size of present-day MEMS biocapsules leads to necrotic regions within the encapsulation volume). Our goal is to devise islet-encapsulating microcontainers to address these challenges. The cubic microcontainers have 300-μm linear dimensions, ensuring adequate encapsulation volume for a single islet while still providing sufficient oxygen to the encapsulated cells.

Methods:
We fabricated 300-μm^3 microcontainers from an epoxy-based polymer, SU-8, with 50-μm-thick walls. The microcontainers were gold coated to render them bioinert. To provide selective permeability, the lid of the microcontainer was devised with recessed islands with 2-μm membrane thickness to enable the creation of pores. Fluorescent human IgG was also loaded on a 2-μm lid without pores to determine whether the SU-8 excluded antibodies effectively. Freshly isolated normal mouse islets were loaded into the microcontainers, islet nuclei were stained with the vital nuclear dye DRAQ5, and confocal imaging of the encapsulated islets was performed in the far red optical channel.

Results:
The SU-8 microcontainers with 50-μm walls maintained mechanical integrity upon islet loading and mechanical manipulation. Despite their thin gold coating, the microcontainers were optically transparent and encapsulated islets were visualized easily with confocal imaging. There was no visible evidence that IgG penetrated the microcontainer lid.

Conclusion:
It is hoped that our novel islet-encapsulation microcontainers provide what is currently elusive in encapsulated cell therapy—small mechanically and chemically stable immunoprotective microcontainers.

21st Century Tools for Multiple Input, Multiple Output Identification and Nonlinear Model Predictive Control of Type 1 Diabetic Patients Using Artificial Neural Networks

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Diabetes mellitus is a metabolic disorder affecting the body's ability to regulate blood glucose concentration that includes blindness, kidney failure, and amputation. Type 1 diabetes mellitus is characterized by the inability of the pancreas to produce and secrete insulin; exogenous insulin must be administered throughout the day. In order to improve glycemia sufficiently to result in a significant reduction in the risk of complications, blood glucose determinations must be done as many as 12 times per day, which is a burdensome task. These glucose determinations are then used by the subject to decide on insulin dosing, but are not enough. Ideally, multiple input, multiple output (MIMO) systems with continuous feedback and other inputs such as carbohydrate intake, frame or state of mind, additional diseases, and overall fitness would be available to optimize insulin administration; in such a scenario, closed-loop control would be the ultimate goal. Advances in insulin pump and glucose sensing technology suggest that a closed-loop artificial pancreatic β cell could soon be achieved with suitable control algorithms. Artificial neural networks modeling and identifying patients through clinical data monitoring therefore are not necessary. Physiological models of insulin absorption, glucose absorption, and glucose–insulin kinetics as the Bergman minimal model (linearized) and similar as the basis for glucose–insulin kinetics, for each patient it is possible to obtain an "ad hoc" insulin model and the control algorithms required for communication between pump and sensor. Data obtained for each patient were collected for a total of 30 days from midnight to midnight (midnight–4 AM, 4 AM–10 AM, 10 AM–6 PM, and 6 PM to midnight). Data were acquired using continuous glucose monitoring devices, insulin pump records, subject-reported estimates of time and carbohydrate content of meals, and software-based carbohydrate calculators. Results were quantified using five independent performance metrics, namely the median relative absolute deviation, the coefficient of determination (R^2), Pearson's product moment correlation coefficient, the Clarke error grid, and the rate Clarke error grid. Identified models were then validated against data from which they were not identified, with prediction horizons of up to 210 minutes. Results highlight the inefficiency of open-loop control. This investigation showed computational advantages of the "Design and Stability MIMO Control Tool" (developed with MATLAB®, The MathWorks, Inc., Natick, MA). Future work will involve applications of the presented techniques to more complex physiological models (adding new inputs), with a view to achieving robust closed-loop control.

Assessment of Eating Detection Algorithm in a Gastric Electrical Stimulation Device to Treat Subjects with Type 2 Diabetes Mellitus

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Introduction:
Gastric electrical stimulation is a novel nonpharmacological approach for the treatment of type 2 diabetes. The following describes an investigational device, the TANTALUS® system, intended for use in subjects with type 2 diabetes who are overweight or obese. The TANTALUS system uses an eating detection algorithm to automatically detect food intake, which triggers a delivery of electrical pulses.

Methods:
The TANTALUS system is composed of a pulse generator and three laparoscopically implanted leads. Qualifying patients are on oral medications for the treatment of type 2 diabetes mellitus (T2DM), have a hemoglobin A1c of 7.5–9.5%, and a body mass index of 28–45 kg/m^2. Data were obtained from studies at six sites across Europe and the United States. Thirty-four patients were provided with an external Holter-style device for recording gastric activity as measured from the TANTALUS system. A total of 77 data files were collected with a mean duration of 11.1 hours (6.0–22.3). Data were analyzed to evaluate the performance of the eating detection algorithm as programmed by the clinician. A retrospective analysis was performed to assess the feasibility of an optimization routine for the automatic setting of the algorithm parameters.

Results:
The algorithm, as programmed by the clinician, had a true positive rate of 65% and a false positive rate of 35%. The optimization routine demonstrated the possibility of an increase in the true positive rate to 76% with a decrease in the false positive rate to 23%.

Conclusions:
The eating detection algorithm provides acceptable performance for the automatic detection of food intake. The optimization routine should be provided to the clinician to further enhance the accurate detection of food intake.

Effects of GLP-1 Technosphere® Powder Administered by Pulmonary Insufflation in Male Obese Zucker Diabetic Fat Rats

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Introduction:
The effect of GLP-1 Technosphere® powder administered by pulmonary insufflation was evaluated in male obese Zucker diabetic fat (ZDF) rats using an intraperitoneal glucose tolerance test (IPGTT).

Methods:
Male obese ZDF rats (n = group) were administered air (control) or 0.3 mg GLP-1 (as GLP-1 Technosphere powder) by pulmonary insufflation once daily for 4 consecutive days. After an overnight fast and immediately following treatment on day 4, an IPGTT was conducted, and glucose, insulin, and active GLP-1 concentrations were measured. In a second, similar study, exocrine and endocrine pancreatic cells were evaluated for apoptosis by TUNEL assay. β-cell proliferation was evaluated by immunohistochemistry for colocalization of insulin and Ki67 in insulin-positive islets and exocrine pancreas. Insulin expression was evaluated by immunostaining and microscopic evaluation.

Results:
Glucose concentrations were significantly lower at all time points in all treatment groups following the IPGTT ($p < 0.05$). At 30 minutes postchallenge, glucose concentrations had increased by 47% in control animals versus 17% in treated animals. The mean C_{max} of GLP-1 was 10.6 nM in the treated group at 15 minutes postdose; C_{max} in the control group remained at 0.2–0.3 nM. Insulin concentrations decreased less in treated animals. No differences in apoptosis labeling index or cell proliferation were observed. Although not statistically significant, there was a dose-related increase in insulin expression in treated animals.

Conclusion:
In an IPGTT, male obese ZDF rats receiving GLP-1 Technosphere powder by pulmonary insufflation exhibited lower blood glucose concentrations and higher serum insulin concentrations than control animals. The responses resulted from an increased insulin expression rather than an alteration of β-cell proliferation or apoptosis.

Near Normalization of Metabolic Control in Type 1 Diabetes Mellitus Using Conventional Insulin Therapy and a 13-Point Method Designed to Enhance Compliance

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Adequate compliance is expected to improve metabolic control in diabetes mellitus (DM). The aim was to determine if adequate compliance improves metabolic control in type 1 DM using conventional insulin therapy (CIT). Twenty-five type 1 DM subjects underwent a stabilization phase (SP) (21 entered at day -114 and 4 at day -28). Demographics: 17 males; 8 females; age 28.6 years (9.0); height 164.8 cm (8.53); weight 62.4 kg (8.68); body mass index 22.9 (1.97); and duration of DM 9.7 (5.1). During SP, all subjects received standard therapy with basal subcutaneous (sc) twice daily (BID) isophane insulin (BID-NPH) and three preprandial sc injections of regular insulin (TID-RI). After SP, subjects entered a two-cohort 99-day comparison phase (CP) with basal BID-NPH and two different modalities of prandial regular insulin administration (0 to +99 days). Fructosamine and glycated hemoglobin were measured every 2 weeks. A 13-point method (13-PM) of clinical measures designed to enhance compliance was applied prospectively. Near normalization of parameters of DM metabolic control was achieved using CIT and a 13-PM designed to enhance compliance. Fructosamine and HbA1c concentrations documented every 2 weeks improved in all subjects regardless of the type of prandial insulin used. The combination of CIT (lower cost than other alternatives) and enhanced compliance and self-control may help control type 1 DM safely, efficiently, and appropriately.

	N	FRUCTOSAMINE (mmol/liter)		% GLYCATED HEMOGLOBIN (HbA1c)	
STABILIZATION PHASE (SP) (-114d to 0d)					
Baseline SP 1 (-114d)	21	414.4	(159.5) P≤0.030	8.2	(2.7) P≤0.061
Baseline SP 2 (-28d)	4	358.0	(47.7) P≤0.503	7.6	(0.8) P≤0.391
End of SP (Day 0)	25	331.9	(53.7)	7.0	(0.8)
COMPARISON PHASE (CP) (0d to +99d) (Data reported elsewhere)					
END OF STUDY FOR ALL SUBJECTS					
Day -114 to Day +99	24	335.4	(55.2) P≤0.443	6.5	(0.8) P<0.001

All tests of significance relative to Day 0

Comparison of Metabolic Control of Preprandial Subcutaneous (sc) Regular Insulin versus Prandial Split Doses of an Oral Insulin in Adult Type 1 Diabetes Mellitus Subjects Receiving Basal sc Twice-Daily Isophane Insulin

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Participating subjects were 25 type 1 diabetes mellitus (DM) subjects (17 males; 8 females); age 28.6 years (9.0); height 164.8 cm (8.53); weight 62.4 kg (8.68); body mass index (BMI) 22.9 (1.97); BMI 23.8 (2.0). The duration of DM was 9.7 (5.1) years. During the stabilization period (SP), all subjects received standard therapy (ST) with basal subcutaneous (sc) twice-daily (BID) isophane insulin (BID-NPH) and three preprandial sc injections of regular insulin (TID-RI). Subsequent to the SP, subjects were allocated to two cohorts: 11 subjects (5 males; 6 females) in the control group (CG) and 14 subjects (14 males; 2 females) in the treated group (TG). Subjects in the CG continued receiving BID-NPH and TID-RI. Subjects in the TG received BID-NPH and TID prandial split doses of oral insulin (Generex Oral-lyn™). The comparison phase (CP) lasted 99 days. Fructosamine and glycated hemoglobin (HbA1c) levels were determined every 14 days. After the SP, 25 adult type 1 DM subjects underwent a 99-day CP, during which 11 CG subjects received BID-NPH + TID-RI and 14 TG subjects received BID-NPH + TID OI. Near normalization of parameters of DM metabolic control was achieved in each and all subjects, as reflected by a continuous improvement in fructosamine and HbA1c concentrations documented every 2 weeks. Direct comparison of HbA1c concentrations during the CP demonstrates a superior effect of Generex Oral-lyn over regular insulin injected subcutaneously.

	N	FRUCTOSAMINE (mmol/liter)		% GLYCATED HEMOGLOBIN (HbA1c)	
COMPARISON PHASE (CP) (99 days)					
Baseline CG (Day 0)	11	355.7	(48.6)	7.3	(0.9)
End of Study CG (+99d)	11	354.6	(57.5) N.S.	6.8	(0.8) P≤0.049
Baseline TG (Day 0)	14	313.2	(51.5)	6.8	(0.6)
End of Study TG (+99d)	13	319.2	(49.7) N.S.	6.1	(0.7) P<0.001
HbA1c (CP): 7.3 (0.9) to 6.8 (0.8) CG versus 6.8 (0.6) to 6.1 (0.7) TG P≤0.035					
FRUCTOSAMINE (CP): CG versus TG NS					

CG = CONTROL GROUP **TG = TREATED GROUP**

Six-Month Study on the Safety and Efficacy of Generex Oral-lyn™ Administered at Lunchtime in Juvenile Type 1 Diabetes Mellitus Subjects Maintained on Basal Glargine Insulin and Prebreakfast and Predinner Regular Insulin

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Adolescence in diabetes mellitus (DM) is associated with hormonal, counterregulatory, and psychological changes that make metabolic control difficult. Because injection at lunchtime is frequently missed, replacement of lunchtime injection with oral insulin (Generex Oral-lyn™) was studied. Research subjects were 24 adolescents (12 males; 12 females) and 5 young adults (2 males; 3 females). Demographics were as follow: age 15.7 years (3.0); bone age 14.9 (2.7); height 155.1 cm (10.2); weight 53 kg (10.8); body mass index 21.9 (3.0); DM duration 6.8 (2.6). The initial 21-day stabilization period with standard therapy (ST) was subcutaneous (sc) twice-daily insulin analogue + 3 preprandial sc regular insulin injections (RI). The comparison phase was 28 days of ST; thereafter, split doses of Generex Oral-lyn replaced the lunchtime injection of RI for 6 months. At the end of the study, six independent evaluators blinded to biochemical results assessed compliance using a nine-parameter method. Twenty-one subjects had good compliance (GC); 8 subjects had very poor compliance (PC). The GC score was 51.86 (14.97) vs the PC score of 14 (10.87) ($p < 0.001$). Twenty-nine juvenile type 1 DM subjects replaced safely and efficiently the lunchtime dose of regular insulin for split doses of Generex Oral-lyn for 6 months. Twenty-one subjects were identified as having GC, and 8 subjects had PC with corresponding DM metabolic control.

	N	FRUCTOSAMINE (mmol/liter)		% GLYCATED HEMOGLOBIN (HbA1c)	
ALL SUBJECTS					
Baseline	27	476.9	(130.2)	9.9	(2.4)
End of Regular Phase	29	371.3	(90.6) P<0.001	8.8	(1.8) P<0.001
End of 6-Month Generex Oral-lyn™ Phase	27	392.8	(110.3) P≤0.002	8.5	(2.0) P≤0.004
GOOD COMPLIANCE (GC) (72.41%)					
Baseline GC	19	443.4	(102.1)	9.1	(1.9)
End of Regular Phase GC	21	340.9	(54.5) P<0.001	8.1	(1.2) P≤0.002
End of 6-Month Generex Oral-lyn™ Phase GC	21	349.7	(54.4) P<0.001	7.7	(1.1) P≤0.002
POOR COMPLIANCE (PC) (27.58%)					
Baseline PC	8	556.5	(160.9)	11.9	(2.4)
End of Regular Phase PC	8	451.3	(119.5) P≤0.002	10.5	(2.1) P≤0.011
End of 6-Month Generex Oral-lyn™ Phase PC	6	543.7	(127.9) P≤0.863	11.3	(1.9) P≤0.508

Free Serum Acrolein Levels in Type 2 Diabetic Patients Correlate with Hemoglobin A1c and Fasting Glycemia

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The literature shows reports on acrolein adducts in renal failure, stroke, and other conditions, but scarce data are available on free acrolein levels in diabetic patients. Acrolein is a highly reactive unsaturated aldehyde that oxidizes cysteine and forms adducts with lysine through the Maillard reaction, with deleterious consequences on protein function. We performed a nested case-control study with 45 type 2 diabetic patients—25 without renal failure (mean HbA1c 10 ± 1.6%) and 20 with end stage renal disease (ESRD) undergoing hemodialysis—and 40 age-matched controls. The research protocol was approved by the institutional review board of Showa University, and investigations were performed in accordance with the principles of the Helsinki declaration. Free serum acrolein levels were threefold higher in ESRD than in control patients ($p < 0.001$). In diabetic patients without renal failure, acrolein increases did not reach significance, but a much wider distribution was apparent. Interestingly, acrolein levels correlated with hemoglobin A1c and fasting glycemia ($r = 41$ and $r = 52$, respectively, $p < 0.05$), suggesting a link that may explain the heterogeneity found in acrolein levels for this population. Our data seem to indicate that free acrolein accumulates preferentially in cases where myeloperoxidase activity is increased or polyamine oxidase activity is enhanced (renal failure). In conditions where lipoperoxidation predominates (diabetes), the levels may be lower and they are buffered by the protein–adduct fraction. Free acrolein levels in diabetes correlate with glycemic control, suggesting a link with hyperglycemia and oxidative stress.

An *in Vivo* Study of Microneedle-Based Insulin Delivery in Human Diabetic Subjects

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Introduction:
Current insulin delivery methods incorporating hypodermic needles and catheters are perceived as invasive, painful, and inconvenient, which often leads to poor patient compliance. Micrometer-scale hollow microneedles can be used as a minimally invasive and less painful alternative to these delivery methods by shallow penetration into dermal tissue deep enough for effective absorption, yet shallow enough to avoid causing pain and apprehension. This research seeks to perform the first study of microneedle-based insulin delivery on human diabetic subjects.

Methods:
Single hollow glass microneedles with tip radii between 30 and 80 μm were used to deliver lispro insulin (U-50 or U-100) to adult type 1 diabetic subjects undergoing insulin pump therapy. Subjects underwent overnight fasting after which their insulin pumps were shut off to allow glucose levels to rise. Upon the onset of blood glucose elevation, sterile hollow microneedles were used to deliver an insulin bolus at a constant flow rate into the abdominal skin at depths ranging from 1 to 5 mm. In some experiments, subjects were asked to consume a standard meal consisting of 75 grams carbohydrates, 20 grams protein, and 10 grams fat immediately after infusion. Serum insulin and serum and capillary blood glucose levels were measured at periodic intervals during the study.

Results:
Bolus delivery of insulin using hollow microneedles markedly reduced serum and capillary glucose values for experiments without meal consumption from hyperglycemic (175–275 mg/dl) to hypoglycemic (<80 mg/dl) levels within a few hours. For experiments incorporating a standard meal, glucose levels either remained steady or were reduced following microneedle-based insulin infusion. Over a corresponding timescale, free serum insulin levels were elevated consistent with respective glucose levels and depicted distinct peaks at 30 minutes to 1 hour after delivery. Comparison to infusion using a conventional infusion catheter (5–9 mm) had similar pharmacokinetics and pharmacodynamics.

Conclusions:
These results indicate that microneedles are capable of delivering insulin transdermally for diabetes management in a minimally invasive manner.

Continuous Progress toward a Personal Noninvasive Blood Glucose Monitor

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Introduction:
VivaScan Corporation is developing a personal handheld noninvasive blood glucose meter. Advanced prototype devices are being validated in preclinical trials. The instrument is easy to use, performs one measurement in 20 seconds, and will be affordable for individual use.

Methods:
The operation of the instrument is based on the proprietary Optical Bridge™ methodology. It is an optical measurement method that uses two tuned near-infrared wavelengths. The first wavelength is glucose sensitive, and the other is insensitive to glucose. It is tuned in the beginning of each measurement to achieve maximum background rejection. This tuning is performed when the sample is squeezed and therefore contains very little glucose. Glucose measurements are made during sample reperfusion. The instrument utilizes backscattered light from the patient's fingertip. Significant improvements have been made in the size and ergonomics of the device, thus making it more user-friendly, requiring less subject practice to achieve successful measurements. The calibration process was also simplified and automated. In addition, we improved the glucose concentration estimation algorithm. These enhancements increased the reliability of our measurements (higher percentage of successful measurements) and reduced the average measurement error.

Results:
During the last year, preclinical testing has produced more than 500 data points from 12 subjects. Tests on the latest prototype instrument (until June, 2007) yielded an average prediction error of 11.6% or 14.2 mg/dl. Eighty-six percent of the points were in the "A" region of the Clarke graph. Subjects were tested once per week in 4-hour sessions at a rate of four measurements per hour. The first testing day was used for familiarization and calibration of the device. Subsequent test days were used for glucose prediction. Data were referenced to the HemoCue-B invasive blood glucose meter (±3.5%).

Conclusions:
VivaScan is maintaining continuous progress toward a personal noninvasive blood glucose monitor. In the past year, a new prototype was launched, and its operation, maintenance, and performance are superior to that of previous prototypes.

This work is supported by NIH SBIR Phase II Grant 2R44DK072654-02.

A Cause-and-Effect-Based Curvilinear Mathematical Model That Predicts the Effects of Self-Monitoring Blood Glucose Frequency on Hemoglobin A1C and Is Suitable for Statistical Correlations

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Introduction:
Do higher self-monitoring blood glucose tests per day (n) cause lower hemoglobin A1c for noninsulin patients? Finding a cause-and-effect mechanism (herein) is half the answer.

Method:
A cause-and-effect-based curvilinear model was developed as follows: Insulin patients employed boluses to achieve corrections (BG-Target); noninsulin patients employed diet/exercise "corrections"; the process is fuzzier, but the mathematics are the same. Proceeding with an insulin patient, suppose n is increased to $n + 1$ on an otherwise identical day, then the $n + 1$ correction boluses are slightly smaller, but their sum is the same, and comparing the 2 days:

$$\text{Sum of } n \text{ values of (BG} - \text{Target)} = \text{sum of } n + 1 \text{ values of (BG} - \text{Target)}$$

The definition of a mean leads to

$$BG_{mean(n)} - BG_{mean(n+1)} = [\text{Target} - BG_{mean(n+1)}]/n$$

Subscripts are the number of BGs in the mean, which leads to a differential equation:

$$d(BG_{mean})/dn = [\text{Target} - BG_{mean}]/n$$

The solution is a model for BG_{mean}:

$$BG_{mean} = \text{Target} + C2/n$$

The model for hemoglobin A1c is similar:

$$A1c = C1 + C2/(n + C3)$$

C3 ensures that hemoglobin A1c does not go to infinity at $t = 0$. Also, practitioners often adjust patient regimens based on mean BGs. Errors in adjustment are proportional to standard errors of the means, which are proportional to $1/n$. Subsequently, patients often treat (or overtreat) their lows, creating highs and making the errors one-sided, which causes hemoglobin A1c to rise proportionally to $1/n$. A model was formed by the inclusion of a proportionality constant (C2), a baseline (C1), and once again (C3). This model is the same as described earlier.

Results:
This model correlated successfully with retrospective data in insulin regimens and noninsulin regimens. Each regimen also showed lower hemoglobin A1c values for its high-n half (all $P < 0.01$, a significant association).

Conclusion:
Understanding cause and effect is half the proof. Experimental confirmation awaits large randomized controlled trials.

Clinical Performance of Microdialysis—Infrared Spectroscopy for Continuous Bedside Monitoring of Subcutaneous Interstitial Glucose

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Introduction:
As part of the European Unit project Closed Loop Insulin Infusion for Critically Ill Patients (CLINICIP), started in January 2004, we have developed an infrared (IR) spectroscopic sensor device to continuously monitor glucose concentrations in the subcutaneous interstitial fluid.

Methods:
The developed system includes microfluidic technology for harvesting submicroliter sample volumes. Monitoring of the subcutaneous interstitial fluid is realized using microdialysis catheter CMA60 from CMA Microdialysis AB as a body interface. Experiments were carried out on several healthy and type 1 diabetic subjects, lasting up to 28 hours with probands starting under fasting condition, but receiving their normal diet later. For reference measurements, dialysate samples were collected. In parallel, blood glucose concentrations in venous blood samples, collected under arterialized conditions with the arm resting in a hot box, were determined. A simultaneous microdialysis recovery rate determination, using acetate in the perfusate (ELO-MEL) as a marker, was implemented. Multivariate calibration was required for glucose quantification using mainly classical least squares calibration models. Cross-sensitivities from various pharmaceuticals at physiological concentration levels are reported.

Results:
Bland–Altman and CEG plots have shown excellent agreement between IR predicted values and reference blood glucose concentration values. Because of the tubing connecting the catheter outflow and sensor, the lag time for sensor readouts was 30 minutes, which needs further reduction. The method also enables determination of metabolites such as urea and lactate.

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

Financial support by the European Commission with the CLINICIP project (Contract No. 506965, 6th Framework Programme) is gratefully acknowledged.

Inhaled Insulin: Safe and Efficacious Administration with a Commercially Available Dry Powder Inhaler

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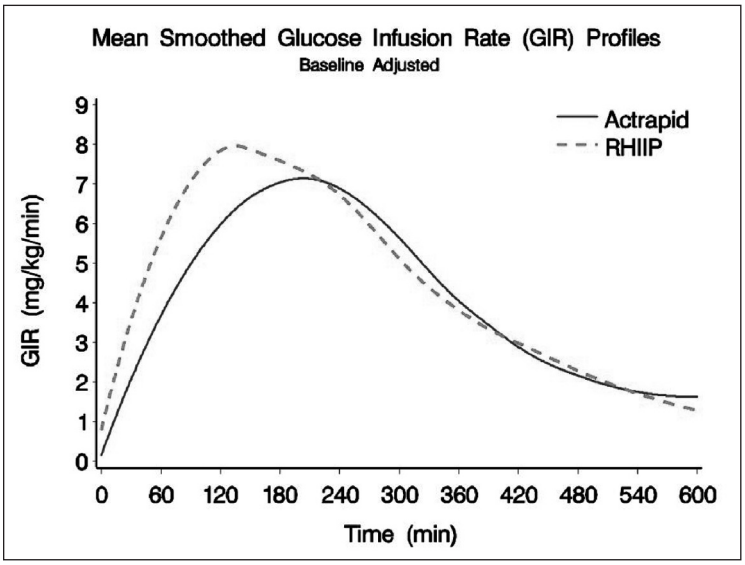
Inhaled insulin is usually delivered with specifically developed inhalers, which are often large and not easy to handle. This study investigated the pharmacokinetics (PK), pharmacodynamics (PD), and safety of recombinant human insulin inhalation power (RHIIP) manufactured using PROMAXX technology, which allows formation of uniform protein microspheres. RHIIP was administered with a small commercially available dry powder inhaler (DPI). Thirty healthy male subjects [30 ± 1.1 years (mean ± SEM), body mass index 24.2 ± 0.3 kg/m^2] in a randomized crossover study received 10 IU human regular insulin subcutaneaously (sc) and 6.5 mg of RHIIP (187 IU) delivered via the Cyclohaler™ under euglycemic glucose clamp conditions. Subjects were trained to inhale RHIIP with an inhalation flow rate of 90 ± 30 liter/min prior to dosing. Inhalation of RHIIP was well tolerated with no episode of cough or shortness of breath. RHIIP showed a faster onset of action than sc [time to reach 10% of total area under the glucose infusion rate (GIR) curves 73 ± 2 vs 95 ± 3 min; GIR–t_{max} 173 ± 13 vs 218 ± 9 min, $p < 0.0001$]. Duration of action (371 ± 11 vs 366 ± 7 min) and total metabolic effect (GIR-AUC0-10h 2734 ± 274 vs 2482 ± 155 mg/kg) were comparable. PK results were in accordance with these PD findings: RHIIP was absorbed faster (time to reach 10% of total area under the insulin curves 44 ± 3 vs 66 ± 3 min, $p < 0.0001$), and maximum insulin levels were reached earlier (86 ± 10 vs 141 ± 12 min, $p = 0.002$). The relative bioavailability (BA) of RHIIP was 12 ± 2%; relative blood pressure was 6 ± 1%. In this study, PROMAXX technology allowed for safe and efficacious administration of human insulin powder to the deep lung with an off-the-shelf DPI designed for upper airway drug delivery. RHIIP showed a fast onset of action and BA comparable to that reported for other inhaled insulin formulations using specifically designed devices. Thus, RHIIP seems to have the potential to achieve even higher BA through further improvements in the insulin delivery technique.



Preclinical Development and Evaluation of a Near-Infrared Whole Blood Glucose Monitor

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Introduction:
Luminous Medical is developing an automated, patient-attached, whole blood glucose monitor that will aid caregivers in achieving tight glycemic control in critical-care patients. Luminous conducted a patient-detached blood study to develop a spectral glucose model and to evaluate preliminary measurement performance.

Methods:
The near-infrared (NIR) spectral glucose model was developed using blood samples obtained from two sources. (1) In blood samples from critical-care patients, Luminous collaborated with central laboratories to acquire residual blood gas specimens following clinical analysis. The samples originated from patients in critical-care settings at Presbyterian and UNM Hospitals. More than 600 leftover blood samples were included in the NIR spectral model. (2) With freshly drawn blood samples, up to 35 serial blood draws were obtained from each of six volunteer subjects cannulated with a peripheral catheter placed in a forearm vein. Samples were transferred to the Luminous instrument for NIR measurement. Some samples were spiked with concentrated glucose to increase the glucose concentration range. The prototype instrument automatically withdrew the blood from a vial into an optical flow cell for NIR spectral measurement, reversed flow to return blood to the cuvette, and then flushed the cuvette thoroughly with saline to ready the system for the next sample. Simultaneous reference glucose measurements were obtained using two Yellow Spring Instrument glucose analyzers. The spectral glucose model was developed by performing multivariate regression on combined data from the two sample sources. A prospective prediction set of samples was then evaluated using the same measurement technique.

Results:
In the overall prediction set (blood gas plus healthy donor samples), the Luminous instrument measured glucose in a prospective sample set with a root mean square (RMS) error of 12.9 mg/dl. Measurements of freshly drawn blood from healthy volunteers yielded an RMS error of 7 mg/dl.

Conclusions:
The Luminous Medical's glucose monitor accurately measures glucose in whole blood samples derived from residual blood gas samples that include representative physiological and chemical variations of the target population for the device.

No Apparent Local Effect of Insulin on Interstitial Glucose Measurements

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Introduction:
It is recommended to perform continuous glucose monitoring (CGM) in the interstitial fluid at a distance from insulin injection sites. However, data investigating the possible disturbing influence of insulin in the vicinity of CGM are lacking. We investigated the hypothesis that high local insulin concentrations would interfere with sensor readings.

Methods:
Two GlucoDay® S microdialysis sensors (A. Menarini Diagnostics, Firenze, Italy) were inserted in the lower periumbilical region of 10 continuous subcutaneous insulin infusion (CSII)-treated type 1 diabetes patients. A test sensor was inserted 0.9 ± 0.2 cm from the insulin catheter, and a control sensor was inserted at the opposite abdominal side. Insulin was infused overnight and after breakfast to induce glucose peak and nadir with frequent blood sampling. Sensor values were retrospectively calibrated against two blood glucose values, at the beginning and at the end of the experiment. Mean absolute differences (MAD) between paired blood and sensor values were calculated per patient and compared using the Wilcoxon signed ranks test. All paired sensor readings were analyzed in a Clarke error grid and Bland–Altman plot.

Results:
Mean MADs were 8.54 ± 2.45% for the test sensor and 9.22 ± 2.27% (SEM) for the control sensor ($P = 0.80$). Accuracy of the test and control sensors was comparable in the Clarke error grid, with 92.3 and 89.9% of the readings in zone A, respectively ($P = 0.32$). Bland–Altman plots showed no evident differences in accuracy in the hypo-, normo-, and hyperglycemic ranges.

Conclusions:
Microdialysis CGM can be performed accurately at a distance <1 cm from a CSII system. This has important consequences for patients with CGMs and for the development of a closed-loop system.

Impact of Postprandial and Preprandial Calibration in the Accuracy of Real-Time Continuous Glucose Monitoring

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Introduction:
The last generation of continuous glucose monitoring (CGM) systems has the advantage of showing glucose data in real time but their accuracy seems to be worse than previous CGM systems with retrospective data download. The aim of this study was to find calibration strategies for improving the agreement of both monitoring systems.

Methods:
Eight patients with type 1 diabetes treated with insulin pumps were requested to use simultaneously the blind CGMS-Gold and the real-time Guardian® RT from MiniMed Medtronic (72 hours) in three different periods. Both needles were placed in the same abdominal side (distance <3 cm), and the time of the monitor was synchronized with the pump and the glucometer. The CGMS-Gold was calibrated preprandially along the study, whereas three strategies were tested for the Guardian RT: three premeal calibrations, calibration at 1-hour postprandial, and, finally, pre- and 1-hour postprandial. The simultaneously measured glucose levels were analyzed with Pearson correlation and their mean absolute differences with the Wilcoxon test.

Results:
Correlation between capillary glucose (used and not used for calibration) and glucose values of the monitor was better for the CGMS-Gold than for the Guardian RT (0.937 vs 0.784). Calibrations including glucose 1 hour after meals achieved a stronger correlation between Guardian RT and capillary glycemia than preprandial calibration (0.950 vs 0.784). The correlation was 0.964 when calibrating both preprandial and 1 hour after meals.

Conclusions:
One-hour postprandial calibration of the Guardian RT achieves a better accuracy than preprandial time. No benefit was shown when adding pre- to postprandial values.

A Glucose Absorption Model Library of Mixed Meals for *in Silico* Evaluation of Artificial β cell Control Algorithms

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Introduction:
Estimating plasma glucose rate of appearance after ingestion of a mixed meal is valuable in diabetes management. Extensive work has been carried out in the areas of modeling hepatic balance, insulin absorption and insulin-independent/dependent utilization. However, less is known about intestinal absorption patterns. Developing a general and accurate mathematical model for glucose rate of appearance for mixed meals remains a challenging task. A practical solution is in the form of a library of glucose absorption profiles representing different types of mixed meals (e.g. fast absorption, slow absorption).

Methods:
The library was constructed using a recently published simulation model of the glucose–insulin system in the postprandial state. Model parameters were based on data from a large database of normal subjects who underwent a triple-tracer meal protocol with a fixed meal composition. Data from published studies on the effect of the meal composition (e.g., carbohydrate type, fat, protein) on the glucose absorption dynamics, and on its corresponding plasma glucose concentration, were used to expand the library. Parameters of the glucose absorption submodel, which are already bounded by physiological domains, were identified to fit the selected meal profiles.

Results:
The library allows *in silico* challenging of a meal-detection algorithm where various mixed-meal combinations have been detected in less than 20 minutes from the onset of the meal and glucose elevation of less than 20 mg/dl.

Conclusions:
This library will enable more thorough testing of proposed artificial β-cell and related algorithms. The realization of a general glucose absorption model remains the final goal, for which the utilization of a more complex model and more specific data will be considered.

The Performance of Subcutaneous Glucose Sensors in Surgical Patients

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Introduction:
Continuous glucose monitoring has the potential to improve glycemic management. Subcutaneous glucose sensors (modified Guardian® RT sensors; Medtronic Diabetes, Northridge, CA) were evaluated in the perioperative period.

Methods:
Six nondiabetic (ND) and four type 2 diabetic (T2DM) patients undergoing major abdominal surgery participated. Six sensors were inserted into each patient prior to surgery. Reference arterial (and venous) glucose concentrations were measured every 20 (and 60) minutes for up to 60 hours. Sensor data were filtered and calibrated using a single one-point calibration with a fixed offset after a 2-hour run-in period. Pearson correlation coefficient (*R*) and mean absolute relative difference (MARD) were calculated from paired reference/sensor values. Individual *R* and MARD were modeled in a linear mixed-effects model and outliers were identified. Statistics were computed from a model based on outlier-free data. Data were reported as mean ± SD unless noted.

Results:
Nine sensors were excluded as outliers. The duration of arterial and venous sampling averaged 36 ± 10 and 48 ± 10 hours. Arterial and venous glucose averaged 155 ± 48 and 143 ± 51 mg/dl in T2DM and 137 ± 24 and 125 ± 24 mg/dl in ND. For arterial concentrations, *R* values were 0.81 [95% confidence interval (CI): 0.65–0.98] and 0.59 (0.45–0.72) in T2DM and DM. For venous concentrations, *R* values were 0.76 (0.60–0.92) and 0.49 (0.36–0.63) in T2DM and ND. MARD was lower for T2DM (-13%, $p = 0.142$) and decreased as the reference glucose range increased ($p = 0.019$). MARD was 21% (95% CI: 9–34) in T2DM and 34% (24–44) in ND.

Conclusions:
T2DM patients had greater glucose variability. *R* increased and MARD decreased as the glucose range increased. However, MARD is also affected in the calibration routine. Further analysis using more sophisticated calibration routines, including the default Guardian RT algorithm, is required.

Acknowledgment:
Research was funded by the Department of the Army and Medtronic Diabetes.

Closing the Loop: Cambridge Ingredients for an Old Recipe

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Introduction:
A concerted effort of the Juvenile Diabetes Research Foundation (JDRF) is leading to development of the first generation of an artificial pancreas (AP). Within this remit, the Artificial Pancreas Project at the University of Cambridge (APPCam) is focusing on the development and testing of an AP prototype for overnight glucose control in children and adolescents with type 1 diabetes (supported by JDRF and the European Foundation for the Study of Diabetes). We report on APPCam components and progress.

Methods and Results:
The APPCam is divided into three areas: technological, clinical, and regulatory. The technological aspects relate to the selection of devices, device integration, development of the control algorithm, and development of a simulation environment. For the first clinical study, we are using the Medtronic Guardian® RT continuous glucose monitor. For subsequent studies we will work with the Abbott FreeStyle Navigator®. Smiths Medical Cozmo® insulin pump is used at present. The latter devices are being modified to allow data transmission and control from a personal computer, which serves as a platform for the control algorithm. The simulation environment is populated by virtual subjects with type 1 diabetes and is used to optimize the glucose controller and to test it prior to clinical use. Our clinical plan includes a series of clinical research center-based studies in children and adolescents with type 1 diabetes, leading to pilot testing of the closed-loop system in home settings. The first clinical study, adopting manual data transfer, is underway and is evaluating the ability of the glucose controller to achieve overnight glucose control compared to gold standard insulin pump therapy. Further studies will evaluate the effect of diet and exercise on overnight closed-loop control together with clinical evaluation of automated data transfer/control. The final study is planned to take the closed loop out of the clinic to home settings in a proof-of-concept multinight study. The UK regulatory agency is supportive and provides guidance on regulatory aspects, which are simplified with the use of CE marked albeit modified devices.

Conclusion:
The APPCam is a multidisciplinary project focusing on overnight glucose control to reduce the frequency of hypoglycemia while achieving near normoglycemia. The biggest challenge is the development and regulatory approval of an AP system suitable for home testing. Given the advanced state of existing components and the European regulatory environment, this appears to be a goal within reach.

Estimating Process Noise of Glucose Excursions in Type 1 Diabetes

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Introduction:
The Kalman filter (KF) is suitable for tracking glucose excursions, providing theoretically coherent and computationally efficient means to predict hypoglycemia in type 1 diabetes. The construction of KF requires the knowledge of statistical properties of unexplained glucose fluctuations, so-called process noise, estimated in the present work (supported by the European Foundation for the Study of Diabetes) following development of an appropriate model of glucose kinetics.

Methods:
We used data from 12 subjects with type 1 diabetes (age 39 ± 11 years; duration of diabetes 24 ± 12 years; body mass index 24.2 ± 2.2 kg/m^2; hemoglobin A1c 7.5 ± 0.7%; mean ± SD) studied over 28 hours on two occasions. Arterialized venous blood was taken every 15 minutes for duplicate measurements of plasma glucose using the Beckman Glucose Analyzer 2 (measurement error with a coefficient of variation of 1.5%). A two compartment model was developed to describe the glucose kinetics. The model included two estimable parameters: time-invariant glucose effectiveness (GE) and time-variant residual glucose balance (RGB) represented by an inverse discrete Fourier transform (DFT). GE and amplitudes of DFT were estimated using the nonlinear regression analysis. Plasma glucose was the model output. The rank of DFT was chosen to provide model misfit comparable to the measurement error. The Q-Q plot was employed to determine the type of distribution of first-order differences in RGB representing process noise (PN). A two-way ANOVA assessed the effect of occasion and subject on GE and the standard deviation of PN (PN-SD).

Results:
Glucose effectiveness was 0.11 ± 0.01/min and was not affected by subject or occasion (P = NS). The rank of DFT ranged from 14 to 41. PN was best described by a Laplace distribution with 0.0000 ± 0.0029 mmol/liter/min per minute. PN-SD was not affected by occasion (P = NS) or subject (P = 0.07).

Conclusion:
In combination with a two-compartment model of glucose kinetics, the variation in unexplained glucose fluctuations follows the heavy-tailed Laplace distribution. The normal distribution is less appropriate. The glucose effectiveness and the standard deviation of the variation in unexplained glucose fluctuations are similar among subjects, simplifying construction of the Kalman filter.

Insulin Replacement Gene Therapy for Type 1 Diabetes

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Introduction:
Recreating appropriately regulated endogenous insulin secretion in surrogate non-β cells in patients with type 1 diabetes is an attractive approach to cure this disease. However, the difficulty with this strategy has been replicating insulin secretion that is tuned to meal intake. We demonstrated that gut K cells can be genetically engineered to synthesize and release insulin in response to glucose consumption in a physiologic manner. Our goal now is to translate this technology to clinical use.

Methods:
We developed a nonviral integrative vector to achieve efficient delivery of a GIP promoter-linked human insulin transgene (GIP/hIns) to duodenal mucosal cells in mice giving systemic production of human insulin. Because the life span of gut epithelial cells is short, the GIP/hIns gene needs to be stably integrated into the genomes of precursor/stem cells located in the crypts to achieve stable insulin production. We incorporated the ΦC31 phage integrase into our vector system, which provides site-specific integration of DNA containing attachment (*att*B) sequences, into mammalian genomes. The CMV promoter-linked ΦC31 and GIP/hIns plasmids were copackaged into nanoparticles with chitosan, a naturally derived mucoadhesive and biocompatible biopolymer. We comparatively studied a panel of chitosan polymers with varying molecular weights and deacetylation degree and identified a class of chitosan that exhibits robust DNA complexing efficiency and provides high levels of *in vivo* gene transfer to intestinal mucosal cells of mice and pigs. A simple, scalable, and consistent process has also been developed to manufacture the chitosan/DNA nanoparticles for commercial use.

Results:
A plasmid containing an expression cassette of a luciferase marker gene and *att*B sequence (pLuc-*att*B) was packaged with the selected chitosan and delivered to the duodenal lumen of mice. When a ΦC31 integrase expression plasmid was copackaged in the nanoparticles, the presence of the marker luciferase gene persisted in the gut mucosa at 14 days postdelivery at a level that was over 100-fold higher than in mice treated with nanoparticles carrying the pLuc-*att*B plasmid alone. This indicates that the ΦC31 integrase successfully integrated the transgene into a long-living duodenal stem cell population. Furthermore, after a single administration of chitosan/DNA nanoparticles carrying GIP/hIns-*att*B and ΦC31 expression plasmids (total DNA dose = 10 mg/animal) to the duodenal cavity of mice, a circulating human C-peptide was detectable in the animals for over 130 days (8.7 ± 2.2 p*M*, mean ± SEM). Following an oral glucose challenge, plasma human C-peptide concentrations in vector-treated mice increased by 5.7-fold over basal and returned to baseline levels by 60 minutes after glucose ingestion.

Conclusion:
We developed a nonviral integrative gene delivery system that can effectively target insulin gene expression to gut K cells *in vivo* giving long-term physiologic production of insulin.

Continuous Transdermal Glucose Monitor for Cardiothoracic Intensive Care and Patients with Diabetes

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Introduction:
Noninvasive continuous transdermal glucose monitors (CTGM) provide many advantages over existing glucose monitoring systems. For instance, optimal management of glucose levels requires frequent self-monitoring of blood glucose (BG) values, which usually requires painful finger stick BG measurements. We have shown that the SonoPrep® skin permeation system can enhance transdermal glucose flux for up to 24 hours. This presentation further demonstrates that glucose levels can be measured using a wireless CTGM system.

Methods:
In two clinical studies, CTGM were applied to patients with diabetes (study I) or patients from a cardiothoracic intensive care unit (ICU) population (study II). Reference BG measurements were taken via the finger stick method or a standard BG analyzer following intravenous blood sampling. At the end of the study, the devices were removed and data were processed for comparison with the reference BG values.

Results:
Data were validated for 10 evaluable subjects (up to 12 hours) in study I and 8 evaluable subjects (up to 24 hours) from the latter phase of study II (after feasibility was established in the initial phase). CTGM required only 1 hour of warm-up on average. Single and triple calibrations were applied to data collected from study I and study II, respectively. Computing predicted glucose versus reference BG values, after pooling all subject results, we found that study I (n = 222) yielded 89.6% in zone A and 9.0% in zone B in the Clarke error grid; study II (n = 147) yielded 86.4% in zone A and 13.6% in zone B.

Conclusions:
Reliable continuous glucose monitoring was demonstrated successfully with our user- friendly CTGM system for a cardiothoracic ICU population and diabetes home care applications.

Sense-A-Touch Auto Puncture

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Introduction:
The design of the Sense-A-Touch Auto Puncture is that of a creative new product that has the unique capability of allowing a person with one-sided paralysis or weakness to monitor their blood sugar independently. This device is cost effective, easy to use, and could be completely appreciated by its users as well as by a manufacturer.

Methods:
The design of the Sense-A-Touch Auto Puncture begins with a basic frame for its specific function and physical support. This is a battery-operated device that allows diabetic patients with hemiplegia (one-sided paralysis) to monitor their own blood sugar independently (glucose testing). This device allows the individual (with only one functional hand) to press their finger onto an oval access area of the unit, which will quickly "pop up" a sharp lancet so as to stick the finger in order to provide a blood sample for testing using the glucose monitor attached. Features included are an easy-to-install and removable carousel that comes from the factory with a cartridge of 12 conventional lancets preinstalled, a control knob located on the side of the nonskid base to calibrate "depth of stick," automatic dulling of the used lancet, automatic protective covering of all lancets, a digital counter that displays the number of lancets for future use, a reset switch, automatic rotation of a new lancet for use when first turned on, automatic rotation of a blank (a nonlancet) area, and an automatic shut off after 5 minutes of nonuse.

Results:
The Sense-A-Touch Auto Puncture device has the ability to provide patients with hemiplegia confidence in blood sugar monitoring, resulting in better control of their diabetes, which can delay or prevent diabetic complications.

Conclusions:
Because of the capability of the Sense-A-Touch Auto Puncture to provide such function in such a different way in the end, the user benefits immensely in ways only initially envisioned by the inventor. (Illustration is available upon request.)

Validation of a Novel Software Program (AutoDecon) for Identification and Characterization of Insulin Secretory Bursts

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Introduction:
Multiparameter deconvolution has been utilized to identify and characterize hormone secretory bursts. Limitations of current deconvolution procedures include the subjective nature of peak selection, lack of rigorous statistical verification of the secretory events, and the user-unfriendly interface. A new method known as AutoDecon addresses these concerns. Here we describe AutoDecon and validate its performance for application to serum insulin concentration-time series. (Software is available free at http://mljohnson.pharm.virginia.edu/downloads.html with a workshop currently open for enrollment, http://mljohnson.pharm.virginia.edu/workshop.html.)

Methods:
We appraised the ability of AutoDecon to identify secretory bursts of insulin within synthetic insulin concentration-time series modeled to mimic insulin concentration-time series from normal fasted healthy women not taking medication affecting carbohydrate metabolism and with no history of diabetes. Samples were collected at 1-minute intervals for 60 minutes. The results from analysis with AutoDecon were compared to those obtained with Cluster, a commonly employed peak detection algorithm.

Results:
The true positive secretory burst detection rate (% of peaks correctly identified) was significantly higher for AutoDecon (89.5%) than for Cluster (64.6%). The false-positive rates (nonexistent peaks identified incorrectly by the program) were higher for AutoDecon (9.2%) than for Cluster (3.4%). In contrast, the false-negative rates (true peaks which the program failed to locate) were much lower for AutoDecon (10.5%) than for Cluster (35.4%). AutoDecon provided secretory burst characteristics (e.g., mass, half-duration, and half-life) that were indistinguishable from those characterizing the synthetic data series; Cluster did not provide these results.

Conclusion:
Multiparameter AutoDecon is a viable alternative to commonly employed pulse detection algorithms and can be successfully applied for analysis of the pulsatile characteristics of insulin secretion.

Analysis of Insulin Secretory Response Using a 2-Hour Continuous Infusion of Glucose with Model Assessment in Type 2 Diabetic Subjects

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Introduction:
β-cell function can be assessed more easily in a near-physiological glucose load by using computer-aided modeling in type 2 diabetic subjects. In order to examine whether continuous infusion of glucose with model assessment (CIGMA) would be a useful method for examining β-cell dysfunction, we compared the prediction of insulin with an estimate derived from CIGMA.

Subjects and Methods:
Thirty-three newly diagnosed type 2 diabetic subjects were studied with age- and body mass index-matched 22 control subjects. The continuous low-dose infusion of glucose was started at time 0 minute, extended to 2 hours, and calculated per body surface area (180 mg/min^{-1}/m^{-2}) with sampling at 110, 115, and 120 minute. Serum glucose was measured by the glucose oxidase method and serum insulin by the chemiluminescence technique. β-cell function was assessed by a 2-hour continuous infusion of glucose with model assessment (2-hour CIGMA) using computer software (HOMA-CIGMA version 2.00).

Results:
Analysis of β-cell secretory capacity of two groups showed that the diabetic group had significantly lower β-cell function estimated by 2-hour CIGMA modeling (55.16 ± 25.6% vs 108.98 ± 32.22%, $p < 0.0001$), as well as a significantly lower insulin:glucose ratio obtained by 2-hour CIGMA (15.26 ± 6.88 vs 25.35 ± 8.31, $p < 0.0001$). In addition, the diabetic group had higher insulin levels after a 2-hour continuous glucose infusion in pmol/liter, but did not differ significantly (220.47 ± 86.62 vs 214 ± 66.34, $p < 0.789$). β-cell function assessed by 2-hour CIGMA significantly correlated with the insulin:glucose ratio after a 2-hour glucose infusion ($r = 0.973$, $p = 0.0001$) in diabetic subjects.

Conclusion:
We conclude that relative insulin secretion rather than absolute insulin secretion reflects 2-hour CIGMA values. Two-hour CIGMA gives comparable results with relative insulin secretion and can be used as a reliable method for the routine measurement of β-cell function in type 2 diabetic patients.

A Computerized Subcutaneous Insulin Protocol to Safely and Effectively Control Blood Glucose and Reduce Insulin Errors in the Hospital

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Introduction:
Insulin leads all other drugs as the source of medication error in hospitals. Only 18% of these insulin-related errors involve the administration of incorrect insulin. The remaining 82% are administration errors, such as drug omission, incorrect timing in relation to meals and omission of prandial coverage for patients who are eating, "naked" sliding scales (without basal coverage), two different rapid-acting insulins (regular and analog) written for the same patient, or prescribing/transcription errors by the physician. We describe an internally developed computerized subcutaneous insulin protocol, the subcutaneous Clarian GlucoStabilizer© (SCGS), designed to safely and effectively control blood glucose (BG) and reduce insulin errors.

Methods:
The SCGS runs on a computer at the patient's bedside. Based on current BG level, carbohydrate intake, weight-based or patient-specific insulin-to-carbohydrate ratios, and insulin sensitivity factor, the SCGS calculates insulin dosing with the goal of maintaining the patient's BG within a selected target range. The SCGS issues reminders for patient BG testing. For BG ≤70 mg/dl, the SCGS recommends hypoglycemia treatment with D50, juice, or glucagon and schedules a follow-up alarm 15 minutes later.

Results:
From April 2006 to May 2007, 1750 patients were treated using the SCGS, with 26,451 BGs recorded. The average BG was 156 ± 71 mg/dl, with 65.2% of BGs in the clinically acceptable range of 80–180 mg/dl, 49.5% in the range of 100–150 mg/dl, and only 0.6% in the hypoglycemic range (BG <50 mg/dl).

Conclusions:
The SCGS is a safe and effective insulin administration program that has the potential to reduce insulin errors in the hospital.

A Passive Miniature Glucose Sensor for Measuring Tear Glucose in the Lacrimal Canaliculi

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Introduction:
The most prevalent method for approximating blood glucose (Glu) concentrations, the finger stick, is limited by patient compliance because of the painful and cumbersome nature of the process. Ideally, people with diabetes need a minimally invasive, passive, glucose sensor that can provide continuous monitoring for trend analysis in order to prevent hypo- and hyperglycemic episodes. Tears produced by the lacrimal ducts have been shown to have glucose concentrations that approximate Glu values in most studies. However, understanding the potential to use human tears for glycemic control is limited by the availability of a tear-based glucose biosensor system.

Method:
We developed a cylindrical microelectrochemical biosensor designed to be placed in the lacrimal canaliculus through the punctum in the eyelid. Glucose in manufactured tears was measured using glucose oxidase (GO/g) with amperometric detection, using a peristaltic pump with controllable flow rates.

Results:
The prototype flow detector responds rapidly and reproducibly to dynamic changes in the levels of Glu, using a simulated tear flow pattern of 0.1 to 4.0 μl/min and submillimolar concentrations.

Conclusions:
We have developed a miniature glucose sensor that has dimensions suitable for insertion into the lacrimal canaliculus, may be manufactured in large quantities, and is capable of measuring glucose in manufactured tears *in vitro*. The sensor works at flow rates that approximate flow rates of tears through the puncta. The next step will involve testing the system in phase I clinical trials.

Disease Management Program

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PDS Health, Inc. is a diabetes disease management company that specializes in the uses of telemonitoring devices and telephonic systems to provide quality care for people with diabetes and people that pay for their care. This poster demonstrates from beginning to end how the patient's blood glucose tests, as well as other markers and indicators, are transferred from the beginning point of the patient to the end point of the health care professional, employer, or third-party payer. The poster also exhibits how the patient, the caregiver, and the managed care company access the system through the complete utilization of the screens, monitors, and reports available. It is important to realize that the disease management program has to be flexible and finalized in partnership with the subscribing party. The program needs to evolve constantly as technological innovations are made and medical and care improvements are discovered. It is intended to serve as a "tool box" with optional tools that a health professional can use to achieve the wellness goals set for each and every patient. This means that any and every tool and technology available today has to be used to reach every patient, regardless of if they have a computer or have no access to the Internet. The parties taking part in the program are the members, the caregivers, and the administrator party. The parties are interconnected through infrastructure utilizing hardware, software, printed materials, Web site, online tools, and so on. This ensures the highest probability of retrieving required data from the patient and an easy and fast analysis, combined with means to intervention by a caregiver. We at PDS Health, Inc. believe that a disease management program will succeed only if data are collected and received from the patient and instantly accessed and interpreted by a health care professional.

Cardiometabolic Health Monitoring Using Dried Blood Spot

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Introduction:
Insulin resistance, obesity, and inflammation are hallmark features of type 2 diabetes and metabolic syndrome. Type 2 diabetes is a major risk factor for developing atheroschlerotic vascular disease. The cluster of all these risk factors is now being termed as cardiometabolic risks. New tools must be made available to patients and their physicians to formulate optimal treatment strategies for the effective management of such cardiometabolic risk conditions. The goal of this study was to develop a minimally invasive dried blood spot technology to screen and monitor patients at risk of developing cardiovascular and metabolic complications.

Methods:
Blood spots obtained from finger sticks on a filter paper were air-dried for 4 hours at room temperature after collection from volunteers. Using an automated dried blood spot puncher, 6.0-mm blood spot disks were obtained and rehydrated in assay buffer/methanol for further testing. New modified methods were developed from commercially available assays to test insulin, hs-C-reactive protein (CRP), triglycerides, and hemoglobin A1c.

Results:
Blood spot and serum insulin levels correlated well in fasting ($R^2 = 0.99$) and nonfasting ($R^2 = 0.93$) samples. A positive correlation was observed for hs-CRP ($R^2 = 0.9776$) and triglycerides ($R^2 = 0.9$) between blood spot and serum values. Hemoglobin A1c levels tested in blood spots (5.41 ± 1.06%; assay range 3.36–12.02%) were comparable to whole blood values (5.44 ± 1.68%; assay range 4.92–12.29%). Intra- and interassay variations in all these assays ranged between 4.39 and 14.39%, respectively.

Conclusion:
Results suggest that the new improved, minimally invasive assay in dried blood provides a reliable and convenient tool for better management and control of patients with cardiometabolic risk conditions. These assays are fully automated, sensitive, and specific and have high throughput potential.

Internet-Based Physical Activity Coaching: Making Healthy Choices Easy Choices: Low-Cost and Effective Lifestyle Coaching

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Introduction:
We describe a 12-week feasibility study using a novel Internet-based coaching approach designed to efficiently increase physical activity in sedentary adults.

Methods:
The user experience is personalized based on individual characteristics and past performance. Weekly, users set attainable physical activity goals and plan physical activities with click-and-drag technology. Daily, subjects track pedometer steps and activities not registered on a pedometer. Weekly, users review prior week's performance, address barriers to achieving goals, and plan and commit to next week's activities. Subjects automatically share progress with others. The application measures if subjects meet their personal goals, calculates number of log-ons, and automatically informs the clinician if the patient is not engaging with the application or meeting personal goals. Twenty-three Internet-recruited subjects (mean age 45.3 years, mean body mass index 30.2 kg/m^2) used the application for 12 weeks.

Results:
The average increase in daily activity points was 61/week. Users logged on 3.7 days/week and planned 11.9 physical activities/week. They met their physical activity goals 35% of the weeks. Of the 20 barriers available, the most commonly addressed were no time, discouraged easily, too tired, no rewards, and no time at work. Sixty-nine percent successfully addressed the barrier chosen the prior week, 79% had a favorable impression of the program, 67% felt confident they could "stick with it," and 74% would recommend it to a friend.

Conclusions:
This feasibility study suggests that an Internet-based personalized behavior-change program designed to increase physical activity might be successful in increasing step counts and mitigating barriers in sedentary and overweight subjects. Internet-based coaching programs may be able to help health-care providers deliver cost-effective diabetes prevention and treatment programs efficiently and effectively with less staff time or administrative burden.

Self-Monitored Blood Glucose in Type 2 Diabetes: The Patient Factor

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Context:
A self-monitored blood glucose (SMBG) diary review to guide type 2 diabetes therapy has been used by physicians in clinical practice. The usefulness of glucose self-monitoring has been debated, especially in patients treated with oral agents alone. Successful management of diabetes relies on patient self-care behaviors, including glucose self-monitoring. The reliability of SMBG diaries and its impact on type 2 diabetes outcomes in day-to-day clinical practice has not been analyzed in detail previously.

Objective:
The purpose of this study was to estimate and explore the reliability of reported SMBG diaries of patients with type 2 diabetes in a clinical practice setting.

Methods:
A retrospective chart review of glucose monitoring was conducted in an urban diabetes clinic. All patients had the same glucose monitoring device and diabetes education and attended the clinic for longer than 6 months. The glucose diary was compared to meter memory readings (if available) and/or hemoglobin A1c test.

Results:
Out of 115 patients, only one-third brought their glucose monitor to the office visit; more than half of the latter patients had discrepancies in their glucose diary ($n = 16$). Patients treated with insulin were threefold ($p = 0.05$) more likely to bring their meter to the office visit compared to noninsulin-treated patients. Those who did or did not bring their meter had similar A1c, point-of-care glucose, and average SMBG. The average SMBG correlated with A1c-predicted glucose (β coefficient 0.38, $p = 0.005$); however, discrepancy between the two grew with an increase in A1c (A1c-predicted glucose was at least 50 mg/dl higher than average SMBG starting with an A1c of 8% and above). The average SMBG of 170 mg/dl corresponded to an A1c of 9% (as compared to a Diabetes Control and Complications Trial-derived A1c of 7%). An average SMBG of 200 mg/dl correlated with an A1c of 13.5%. There was no difference in A1c whether or not patients perceived themselves reporting accurately or inaccurately; however, those patients who perceived themselves reporting their SMBG diary inaccurately had a slightly higher average SMBG for a given A1c value. Having mood impairment or depression did not significantly change the fact whether the patient brought the meter to the appointment. Patients with severe cognitive impairment were 2.5 times less likely to bring the meter ($p < 0.05$).

Conclusions:
We demonstrated that patients with equal glucose monitoring education in an urban diabetes clinic setting provide an incomplete/unreliable report of SMBG to their physicians astoundingly frequently. A glucose monitoring device was not available for the verification of records in two-thirds of cases and was worse in patients not treated with insulin or having severe auditory-learning impairment. In conclusion, "the patient factor" is extremely important in utilizing glucose monitoring to guide therapy in patients with type 2 diabetes in clinical practice.

Improving the Concordance between Multiple Sensors

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Introduction:
Concordance between simultaneously worn glucose sensors could be improved by using all glucose data points during the time trend, a rolling average, and comparing rates of change by selecting the one sensor of two in closest agreement to the reference sensor, the "best of two."

Methods:
In 10 type 1 diabetic pump-treated subjects, three CGMS® Gold sensors were inserted one each in the left and right abdomen and the left arm. The 24-hour spontaneous glucose excursions were observed. All sensors were calibrated near simultaneously by four spaced blood glucose measurements. Only a 20-minute trend analysis was done.

Results:
In all analyses, there was no clinically significant difference between sites. Using a two-point-derived slope (zero time and 20 minutes) the left abdomen agreed (<±1 mg/dl/min) with the reference sensor (right abdomen) 89.3% of all determined trends (*N* = 1927 of 2153) when the reference sensor rate of change was <±1 mg/dl/min. Rolling average trend calculations (using every 5-minute glucose value during the 20 minutes) improved the agreement to 94.3% (*N* = 2362 of 2508). Finally, comparing the rolling average of the "best of two" comparator sensors for each reading, the agreement further improved to 98.2% (*N* = 2455 of 2630). However, at greater rates of change of the reference sensor of ≥±1 but <2 mg/dl/min, the agreement fell to 77.3% (*N* = 157). With further increase in reference rate of change, ≥±2 mg/dl/min, the agreement decreased to 40.0% (*N* = 18).

Conclusion:
Using both rolling average and "best of two" sensor trend data, the agreement improved to nearly 100% but only at minimal rates of glucose change.

A Comparison of Direction and Rate of Change Information Obtained from Simultaneous Use of Three Continuous Glucose Monitoring System Sensors

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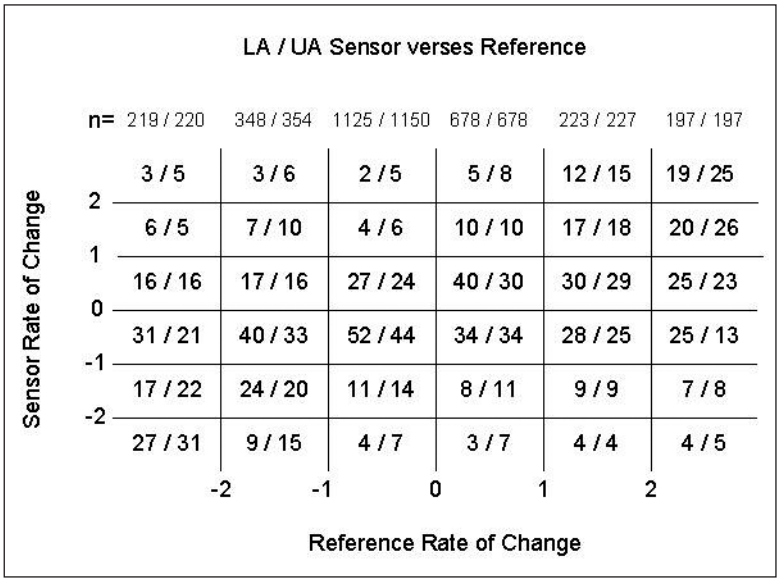
Although capillary blood glucose data are required for insulin dosing, continuous glucose sensors are now being integrated with insulin pumps. Sensor interstitial fluid (ISF) glucose values, as well as direction and rate of ISF glucose change information, are available in real time for patients, allowing lifestyle or insulin modification. The direction and rate of glucose change are being used to adjust insulin dosing amounts or timing, and published algorithms provide guidance to patients and health care professionals. Accordingly, sensors need to report the rate of change information accurately and reproducibly and there should be strong agreement between multiple sensors. In this study of 10 subjects, three continuous glucose monitoring system CGMS® Gold sensors were placed in each subject: one in the right abdomen (REF; selected arbitrarily as reference), one in the left abdomen (LA), and one in an left upper arm (UA). Sensors were calibrated and aligned chronologically. Data were only interpreted and included if there were 24 hours of acceptable data obtained simultaneously from all three sensors. Compared to REF, consensus error grid analysis for LA and UA showed 78 and 79% of values within zone A and 93 and 97% within zones A + B. Mean absolute rank differences of LA and UA were 15.6 and 13.3. When the REF showed a positive/negative direction, 20/21% of readings from the LA and 17/19% of readings from the UA showed readings in the opposite direction. Even when the REF rate of change was >2/≤2 mg/dl/min, the LA and UA directions of change disagreed 27/26% and 36/25% of the time. The chart presented here correlates direction and rate of change among the sensors. In summary, although the sensor glucoses showed reasonable clinical correlation, the direction and rates of change commonly disagree when multiple CGMS Gold sensors are placed in patients; therefore, these parameters should not be used to adjust insulin doses.



Control of Self-Monitoring of Blood Glucose in Community Pharmacies

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Introduction:
Most diabetes patients in Norway obtain their self-monitoring blood glucose (SMBG) equipment at a community pharmacy. The aim of this study was to test the pharmacy as a place to control patients' glucometers and SMBG technique.

Methods:
One employee from each of 16 community pharmacies was responsible for the control procedure. The pharmacies were enrolled in NOKLUS' External Quality Assessment Scheme. A total of 338 diabetes patients were included. Each patient was asked about their self-monitoring of blood glucose and then measured their blood glucose under observation of a pharmacy employee. The pharmacy employee then measured the patient's blood glucose on the HemoCue Glucose 201^{+}. After 3 months, the patient returned to the pharmacy and the procedure was repeated.

Results:
The most frequent reason for choice of current glucometer was that it was recommended by pharmacy personnel (45%). Nearly half of the patients (44%) stated that they were self-educated in SMBG, 27% that they were taught at the pharmacy. Twenty-five percent of the patients sometimes or often doubted the results of their own measurements. Half of the patients said that they felt more certain of the result of the SMBG device after the first pharmacy control. Five percent of the patients' measurements differed from the pharmacies' by more than 20%, whereas 34% differed by more than 10% during the first round of measurements. There was no significant change during the second round.

Conclusions:
Control of glucometers and SMBG technique at the pharmacy improved the patients' confidence in their measurements, but did not improve the accuracy of these measurements significantly, as the patients already performed well during the first consultation.

Fiber-Optic Hybrid Sensor for Continuous Glucose Monitoring in Critically Ill Patients

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Background and Goals:
Most of the sensors used for continuous glucose monitoring are based on the glucose oxidase reaction and electrochemical detection of H_2O_2. Such sensors often suffer from poor selectivity and effects caused by changing pO_2 levels. This is of particular importance in the interstitial fluid (low and varying pO_2 levels) of critically ill patients (high doses of drugs). The objective of this clinical trial was to test an approach for simultaneous measurement of oxygen and glucose with minimized effects of interfering substances in critically ill patients during intensive care.

Materials and Methods:
The hybrid sensor approach consists of two oxygen optodes (each 125 µm in diameter) where one optode acts as a glucose-sensitive probe and the other one as a reference—measuring the surrounding oxygen tension. Both measurements are based on the phase shift method for determination of the luminescence decay time. The final glucose signal is calculated as the difference between oxygen depletion by the enzymatic reaction (glucose oxidase) and local oxygen tension surrounding the probe. A flow-through configuration of the sensor was combined with the microdialysis technique. This approach was tested in four patients at a cardiac surgery intensive care unit with a monitoring period of up to 36 hours. Blood glucose readings were taken at hourly intervals and compared with the sensor signals.

Results and Conclusion:
The results demonstrate the feasibility of a new sensor approach for application in critically ill patients. It turns out that a simultaneous measurement of oxygen and glucose results in stable glucose measurements. Furthermore, the robustness of the approach against interferences was confirmed under *in vivo* conditions in patients during intensive care treatment.

Accurate Measurement of a Small Flow Rate Is the Key to Successful Development of a Micropump

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Introduction:
Accurate measurement of the flow rate is key to developing a micropump for insulin infusion. We developed a micropump for implantable insulin infusion application in 2002 and have been testing it from various aspects. However, one of the difficulties was to verify its delivery performance by measuring the infusion rate with certain accuracy. Because there was no practical way of measuring such a small flow rate (0.1–2.0 μl per minute) available, we developed a compact flow sensor for continuously monitoring the infusion rate of such a small flow.

Methods:
A prototype of the compact flow sensor we developed utilizing the microelectromechanical systems (MEMS) technique detects a time lag of temperature peaks, which propagates in fluid, and then the sensor predicts flow rate as the propagation speeds of temperature differ depending on flow velocity. We used an electronic balance and weighing the cumulative flow amount for verifying the accuracy of our compact flow sensor at our laboratory.

Result:
Some disturbances occurred initially in measuring such a small flow rate with an electronic balance, such as the reduction of cumulative flow amount by evaporation as time passes, the temperature dependency of an electronic balance, the remaining air in the micropump, and so on. However, we solved these problems and found countermeasures against such disturbances. Also, the MEMS compact flow sensor has been able to measure such small flow rates to approximately 1 μl per minute.

Conclusions:
With the success of measuring a small flow rate and development of a MEMS compact flow sensor, the micropump can now be a useful piece for continuous insulin infusion therapy.

A Standardized Evaluation of Continuous Glucose Monitoring Techniques: A New Application of the Diabetes Error Test Model

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Introduction:
The diabetes error test model (DETM) has been developed to characterize the clinical relevance of the large and varying margins of error of parameters affecting postprandial blood glucose (BG) levels, which increase the risk for hypo- or hyperglycemia. Based on this model, a new approach to the clinical evaluation of devices for continuous glucose monitoring (CGM) has been developed and applied to the question whether such devices allow larger measurement errors than accepted for self-monitoring of blood glucose (SMBG).

Methods:
The CGM-DETM is based on a treatment concept aimed at normoglycemia after meals by preprandial injections of rapid-acting insulin in adult people with diabetes. Its parameters include (a) CGM with immediate BG result availability, including information about the rate of BG changes (classified as ↑↑, ↑, =, ↓, ↓↓), (b) patient estimate of carbohydrate amounts (CARB) in food, (c) effect of CARB on maximum BG increase, (d) effect of insulin on maximum BG decrease, and (e) insulin dosage. Within the relevant range of preprandial BG (30–330 mg/dl), the CGM-DETM simulates the maximum effect of these parameters and their margins of error on postprandial BG values according to standard therapeutic guidelines. If the postprandial BG outcome is not within the acceptable BG range (50–200 mg/dl), we define the margin of error as the lowest error within the preprandial BG range that results in BG values outside the postprandial BG acceptance range. For the evaluation of margins of glucose measurement error from SMBG and CGM, all other DETM parameters are kept at 0% error.

Results:
According to the DETM for SMBG, the lowest margin of error at the BG acceptance range limit for hypoglycemia is 16%. For CGM this is also 16% for no BG rate change, but the lowest margin of error for unacceptable postprandial hypoglycemia increases up to 19% for a rate of change of ↑↑, up to 26% for ↓, up to 30% for ↑, and up to 39% for ↓↓. The margins of error for unacceptable postprandial hyperglycemia range between -28 and -51%.

Conclusions:
Because of additional information about the rate of BG change and its trend direction, CGM allows for larger margins of glucose measurement error that result in postprandial hypoglycemia than SMBG (as defined by the International Standards Organization NORM 15197). Combined with results of margins of error for postprandial hyperglycemia, it can be assumed that CGM systems could be used up to the above margins of error also for meal-related treatment decisions.

Implantable Continuous Glucose Monitoring Sensor

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Introduction:
For the last years, researchers have attempted to develop implantable glucose sensors. Many different principles have been tested but no one has succeeded up until now in bringing an implantable sensor to commercial realization. We present a new approach to monitor glucose in the interstitial fluid. The sensor is totally passive (no implanted electronics). This leads to a very small sensor, about 2 mm diameter, with a length of 10 mm. The small size offers the potential for easy, subcutaneous minimally invasive implantation.

Method:
The heart of the sensor is a rotational microviscometer, which measures the rheological properties of a sensitive solution. The rotor is magnetized and can thus be actuated through the skin using a rotating magnetic field generated by external coils. The rotation speed is monitored via Hall sensors. This sensitive solution includes a protein, which has an affinity to glucose. This fluid has the property of changing its viscosity reversibly as a function of the glucose concentration. The sensor is surrounded by a nanoporous membrane, which allows a selective exchange of glucose between the sensor and the interstitial fluid.

Results:
In the relevant physiological glucose range, we can prepare sensitive solutions with relative viscosity change between 200 and 300%. The accuracy of the viscosity measurement is better than 1% under controlled conditions with calibration oils. Using a nanoporous membrane as an interface between the sensor and the surrounding liquid, we obtain a response time of 20 minutes when suddenly changing the glucose concentration (*in vitro*). We are currently investigating how to decrease that lag time and how to avoid any protein leakage from the sensor in order to guarantee long-term stability.

Conclusion:
This electrically passive miniature glucose sensor is an excellent candidate to achieve the goal of continuous glucose monitoring with an implantable device. The chemical binding of the protein to glucose molecules is reversible; as a result of this reversibility, the number of measurement is not limited, and we therefore expect a sensor lifetime of several months to 1 year.

An Automated Blood Sampling and Glucose Monitoring System for Critical Care

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Introduction:
Tight glycemic control (TGC) in the intensive care unit (ICU) has shown substantial improvements in clinical outcomes. However, implementation of TGC in ICU practice is constrained by a lack of automated continuous blood glucose monitoring systems that can facilitate clinically accurate feedback of glycemic data. The aim of this work has been the development of a handheld automated blood sampling system that is integrated with a continuous glucose monitor.

Methods:
In the initial phase, clinical feasibility for glucose monitoring in whole blood samples using a mid-infrared laser spectroscopy-based portable system was established. Then an automated blood sampling system was developed for coupling with the monitoring unit. A programmable microflow pump was used in conjunction with Cascade's customized peripheral venous catheter assembly to continuously sample blood from a human subject.

Results:
Microvolumes of blood samples were obtained in both continuous and intermittent modes at clinically relevant user-defined intervals, namely 2, 5, and 10 minutes. Continuous blood sampling was demonstrated successfully without any venous collapse or thrombosis. The maximum volume consumed was limited to 5 ml per 12-hour period.

Conclusion:
Cascade's automated venous blood sampling system coupled with its mid-infrared-based glucose monitoring system offers numerous advantages over current systems. These include significantly improved workflow in the ICU, minimal discomfort to the patient compared to multiple finger pricks or subcutaneous implants, and the ability to make clinically accurate glucose determinations directly in unprocessed whole blood as opposed to serum or surrogates such as interstitial fluid. Cascade is also integrating its blood sampling system with a novel electrochemistry-based microfluidic subsystem, and preliminary results have shown substantial merit in this approach as well.

Improvement in Closed-Loop Insulin Delivery Algorithm: Effect of Insulin Feedback and Glucose Potentiation

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Introduction:
We previously used a proportion-integral-derivative (PID) model of the β cell to achieve a fully automated closed-loop insulin delivery system using a subcutaneous site for glucose sensing and insulin delivery. Here, the model is expanded to include an insulin feedback (IFB) component analogous to the effect of insulin to inhibit insulin secretion. The PID-IFB model was then evaluated with and without a mechanism to adapt the gain based on past glycemic excursions (analogous to the effect of prior glucose exposure to potentiation insulin secretion).

Methods:
Subjects (N = 2 males and 1 female) with previously diagnosed type 1 diabetes mellitus were admitted to the clinic on the evening prior to beginning closed-loop control. Control was started ~6 AM the next morning and continued for ~36 hours. Four experiments (two with and two without adaptive gain) were performed. Target glucose was set at 90 and 110 mg/dl during the day and night (10:00 PM–6 AM), respectively. Subjects wore two sensors with calibrations performed at 6 AM and 10 PM. IFB was calculated using a two-compartment insulin model to predict plasma insulin based on the past history of insulin delivery.

Results:
Sensor accuracy was 16.7% (mean absolute difference versus Yellow Spring Instrument reference; N = sensors). Pre-, post-, and nighttime (2–4 AM) glucose was 112 ± 35, 134 ± 45, and 89 ± 24 mg/dl, respectively (mean ± SD), and there was one occurrence of glucose below 50 mg/dl.

Conclusion:
While further experiments will need to be completed before testing whether adaptive gain leads to better overall glycemic control than fixed gain, both algorithms resulted in stable control. In both algorithms, IFB resulted in a beneficial reduction in insulin delivery 1–2 hours after meals.

Quality of Description of the Past Glycemic Control by Hemoglobin A1c

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Introduction:
An ideal index of long-term metabolic control should equally weight glycemia from the whole period covered. Yet, the glycated hemoglobin A1c (HbA1c) concentration is commonly used as an index of metabolic control, covering a period of 2 to 4 months, despite the well-known fact that the HbA1c concentration reflects a weighted average of the preceding glycemia. The aim of this study was to quantify changes of HbA1c concentration in response to variable glycemia courses, applying a mathematical model of hemoglobin glycation that was positively verified based on *in vivo* [continuous glucose monitoring (CGM) with a CGM system] and *in vitro* (cultivation of erythrocytes under different glycemic conditions) experiments.

Methods:
Three simulation experiments were conducted addressing problems related to the interpretation of HbA1c tests in case of unstable glycemia courses.

Results:
It was estimated that hyperglycemia [mean blood glucose (MBG) = 250 mg/dl] that directly precedes HbA1c test execution must last 8 days to cause a change of HbA1c concentration by 0.7%, which was considered to be the smallest significant detectable change of two consecutive HbA1c tests. If hyperglycemia is separated from the time of HbA1c test execution by a period of normoglycemia (MBG = 90 mg/dl), then for the same HbA1c change to occur requires a 41-day hyperglycemic period. In the second experiment, it was demonstrated that a serious deterioration of the glycemic control (MBG = 250 mg/dl), lasting for 1 week may pass undetected even if it occurs directly before the HbA1c test execution. It was not possible to detect hyperglycemic spikes based on HbA1c values unless the spikes occurred every day.

Conclusion:
It seems that sparse HbA1c testing, which is recommended by the world's most prominent diabetic associations, has a limited value as an indicator of past glycemic control.

U500 Regular Insulin by Continuous Subcutaneous Insulin Infusion in Patients with Type 2 Diabetes and Severe Insulin Resistance

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Background and Goals:
Patients with type 2 diabetes and severe insulin resistance (insulin requirement >1.4 units/kg/day) present a unique therapeutic challenge to clinicians, which involves finding a method of delivering a large enough volume of insulin to achieve glycemic control defined as a hemoglobin A1c (HbA1c) value of under 6.5%. Multiple daily injection (MDI) regimens often require the use of insulin volumes, which are poorly absorbed and poorly tolerated by this group of patients. Continuous subcutaneous insulin infusion (CSII) in this patient population using U100 regular insulin or insulin analogues still requires the infusion of large insulin volumes for basal infusion and meal boluses, which also are poorly absorbed and require frequent cartridge and battery changes of the insulin pump, leading to sustained hyperglycemia and difficulty using CSII. We examined the efficacy and safety of U500 regular insulin (Eli Lilly, USA) delivered by CSII in 13 patients with type 2 diabetes and severe insulin resistance who were uncontrolled (HbA1c >6.5%) at baseline on either CSII with U100 insulin analogues or basal/bolus MDI regimens with U100 insulins. We compared the primary end point of HbA1c on the previous U100-based insulin regimen (MDI or CSII) and after 1 year of CSII with U500 R while examining the incidence of hypoglycemia and patient satisfaction with each treatment regimen.

Materials and Methods:
The study group consisted of 13 patients with type 2 diabetes and severe insulin resistance with HbA1c values >6.5% (mean HbA1c = 0.55%). All patients had been treated previously with MDI regimens with either glargine or NPH insulin plus insulin lispro, insulin aspart, or U500 R insulin before meals or CSII with insulin lispro or aspart. Treatment was changed to U500 regular insulin by CSII with one of the following insulin pumps: MiniMed 508, Medtronic-MiniMed 511, or Smith Corporation Deltec Cozmo®. HbA1c was determined at baseline and after 12 months of treatment using the Bayer DCA 2000 HbA1c analyzer. Statistical comparison was made using a two-sample *t* test.

Results:
After 12 months, treatment with U500 regular insulin by CSII resulted in a statistically significant mean decrease in HbA1c ($p = 0.0014$) of 1.52% (mean HbA1c = 0.03%). There were no clinically significant (requiring assistance to treat) hypoglycemic episodes in the study population. All study patients preferred the new treatment option of U500 insulin by CSII over their previous treatment regimens.

Conclusion:
U500 regular insulin by CSII is a safe and effective therapeutic intervention for patients with type 2 diabetes who have had treatment failure on MDI insulin regimens or CSII with use of U100 insulin or insulin analogues.

Meal Detection and Magnitude Estimation Based on Glucose Monitoring

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Introduction:
A closed-loop artificial pancreas that uses meal information to deliver an insulin bolus near mealtime may have significantly better performance (reduced peak and mean glucose levels) than a controller operating in purely feedback mode. This requires a method of detecting when a meal has been consumed and automatically delivering a meal bolus without requiring information about the meal from the subject.

Methods:
A meal detection and meal size estimation algorithm is developed based on optimal estimation theory and discrete-time signal processing methods. A set of threshold values for the first and second derivatives of glucose are found to detect a meal within 10–40 minutes of actual meal consumption. When a meal is detected, a finite impulse response filter, based on the estimated second derivative of glucose, is used to estimate the meal magnitude (grams of carbohydrate). Filter training for the meal size estimation is achieved with a clinical data set in which an insulin bolus is withheld for an hour after the meal.

Results and Conclusions:
A test was performed on an *in silico* subject (modified Hovorka model), with time-varying insulin sensitivity, consuming three 50-gram carbohydrate meals (breakfast, lunch, dinner), with a continuous glucose sensor noise SD of 3.32 mg/dl. The resulting meal size estimates were 44.2, 49.9, and 35 grams for each meal, and delays in recognition of the respective meals were 35, 30, and 30 minutes. The resulting insulin boluses based on estimated meals significantly improved the closed-loop performance of a model predictive control strategy, reducing postprandial mean glucose levels from 217 to 145 mg/dl and maximum glucose from 333 to 232 mg/dl.

Time-Varying Insulin Sensitivity in an *in Silico* Model of Subjects with Type 1 Diabetes

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Introduction:
In silico models of type 1 subjects are useful for evaluating changes in insulin therapy and are important for developing and testing algorithms for a closed-loop artificial pancreas. A major limitation of *in silico* models developed to date is that they do not include time-varying insulin sensitivity, such as the well-known dawn phenomenon.

Methods:
The Hovorka *et al.* (2004) model of glucose-insulin dynamics, which includes subcutaneous insulin kinetics, has been extended to incorporate time-varying insulin sensitivity. Clinical data that report time-varying basal rates to maintain constant glucose levels for different age groups are used as a basis for our simulation model. In addition, clinical data from 13 subjects (after basal dose optimization) were used to create a suite of 13 specific subjects with further variations in their basal profiles. Varying meal magnitudes and dynamics, as well as continuous glucose sensor lags and noise, are also included.

Results:
Using the time-varying insulin sensitivity model and meals of equal grams of carbohydrates, 23% more insulin was required for breakfast, as compared to lunch and dinner. This reflects the variation in insulin-to-carbohydrate ratios commonly observed in practice.

Conclusions:
This extended *in silico* model incorporates time-varying insulin sensitivity, variable size glucose meals, and varying meal dynamics and is thus more representative of a typical type 1 subject. The suite of subjects provides further variation, capturing intersubject variability. The simulation model has been used for (i) testing a run-to-run basal insulin dose adjustment algorithm, (ii) testing system identification algorithms (fitting parameters to low-order dynamic models), (iii) testing meal detection and meal size estimation algorithms, and (iv) developing and testing advanced model predictive control algorithms.

Effects of Lispro Intensive Therapy with Insulin Pump on β cell Function and Glycemic Control in Newly Diagnosed Type 2 Diabetes

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Objective:
Effects of lispro intensive therapy with an insulin pump on β-cell function and glycemic control in newly diagnosed type 2 diabetes were studied.

Methods:
Sixty-two patients with newly diagnosed type 2 diabetes were treated for 2 weeks with lispro intensive therapy with an insulin pump. OGTT, IRT, and CPRT were determined before and 6 months after insulin intensive treatment. Fasting insulin/fasting glucose, insulin secretion index, and insulin sensitivity index were calculated.

Results:
The levels of fasting glucose and 2hPG 6 months after insulin intensive treatment were decreased more significantly than those before insulin intensive treatment. The levels of fasting insulin/fasting glucose, insulin secretion index, and insulin sensitivity index 6 months after insulin intensive treatment were increased more significantly than those before insulin intensive treatment. After 6 months, 18 patients were treated with dietotherapy, 19 patients were treated with only one oral antihyperglycemic, 14 patients were treated with two oral antihyperglycemics, and 11 patients were treated with insulin.

Conclusion:
Excellent glycemic control and improvement of β-cell function can be induced by lispro intensive therapy with an insulin pump in newly diagnosed type 2 diabetes.

Effects of Transplantation of Endothelial Progenitor Cells from Autologous Bone Marrow for Hind Limb Ischemia in a Diabetic Rabbit Model

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Objective:
This study explored the effects of transplantation of endothelial progenitor cells (EPC) from autologous bone marrow for hind limb ischemia in a diabetic rabbit model and the difference between diabetes and nondiabetes.

Methods:
Rabbits were allocated randomly into three groups for transplantation therapy: PBS control group (n = 8) (A group), EPC transplantation with diabetes group (n = 14)(B group), and EPC transplantation without diabetes group (n = 8)(C group). The diabetic rabbit model was established by injected alloxan, and hind limb ischemia was induced by complete excision of the femoral artery. Rabbits with hind limb ischemia were therapied by transplanted *ex vivo* expanded EPC, and effects were assessed by capillary density and capillary to muscle fiber ratio. The vascular endothelial growth factor (VEGF) in muscle was also determined.

Results:
Capillary density, capillary to muscle fiber ratio, and VEGF in muscle increased significantly in the EPC transplantation group with or without diabetes after transplanted 14 days ($P < 0.05$).

Conclusions:
Endothelial progenitor cells transplantation was an effective therapeutic method for hind limb ischemia in a diabetic rabbit model, and capillary density, capillary to muscle fiber ratio, and VEGF in muscle were increased significantly.

Development of a Novel Glucose Sensing Fluid with Application to Microelectromechanical Systems-Based Continuous Glucose Monitoring

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Introduction:
We have previously presented a microelectromechanical systems (MEMS) viscometric sensor for continuous glucose monitoring. The sensing fluid used therein was based on the protein concanavalin A, which is known to have significant drawbacks, such as immunotoxicity and instability. To address this issue, a stable, biocompatible polymeric sensing fluid has been developed.

Methods:
In the polymeric sensing system, glucose reversibly forms strong ester bonds with the phenylboronic acid moiety on the poly(acrylamide-*ran*-3-acrylamidophenylboronic acid) (AA-*ran*-AAPBA) backbone, resulting in cross-linking of the copolymers and an increase in the solution viscosity. The copolymers are synthesized via classic free radical copolymerization processes. The viscosity of the AA-*ran*-AAPBA, dissolved in phosphate-buffered saline and in the presence of glucose at physiologically relevant concentrations, was measured.

Results:
Experimental results showed that the viscosity values of the solution became steady within minutes upon changing glucose concentrations, and little changed even after hours, suggesting that the system quickly reached equilibrium. Through adjustment of the composition percentage of the boronic acid monomer in the copolymer, a nearly fivefold viscosity increase was observed when the glucose concentration increased from 0 to 25 m*M*, which was strong enough to be detected by our MEMS device. After dialysis of the mixture against water through a semipermeable membrane, significant decreases of viscosity were observed at different timescales, suggesting that the response of the fluid to glucose concentrations was reversible. Moreover, this sensing fluid has shown a highly specific response to glucose.

Conclusions:
We have successfully developed a stable, biocompatible polymeric system for specific detection of glucose. Its application to MEMS viscometric sensors will potentially enable highly reliable, continuous monitoring of glucose in interstitial fluid in subcutaneous tissue.

Cost-Effectiveness of Self-Monitoring of Blood Glucose in Function of the Testing Frequency in Patients with Type 2 Diabetes

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Cost-effectiveness (CE) studies of self-monitoring of blood glucose (SMBG) in type 2 diabetes patients are rare, even though the acceptance of SMBG as an important tool for metabolic control in diabetes management is increasing. The basis for this cost-effectiveness analysis is a study from Karter and colleagues. We used a diabetes simulation model representing the natural course of the disease with or without SMBG in a predefined cohort and with a German cost-data set. We optimized the resource outcome ratio for the testing frequency (TF) using a derivative function. We focused on the economic aspect (best outcome for invested resources). We considered two testing frequency alternatives (TF1 = 0.5–1.0 times/day and TF2 = 2.5–3.0 times/day) over the simulation time to estimate incremental cost (IC) for SMBG compared to non-SMBG. The incremental cost increased from € 1,524 to € 3,273 for TF1 and TF2, respectively. Similarly, the gain in life expectancy (LE) increased from 0.021 to 0.222 years for TF1 and TF2, respectively. The derived CE ratio ranged from € 70,199 to € 14,710 per life year gained. The estimated optimal resource outcome ratio was in the range of one to two measurements per day. The CE ratio lay by € 33,607 to € 34,211 per life year gained. The model-based analysis showed that SMBG in noninsulin-treated type 2 diabetes patients may elongate LE and reduce complication related costs. This partly compensates for the additional expenditures for SMBG (device, test strips, education). We found an optimal TF of once to twice daily. This TF is by far economically acceptable, also from a third-party payer perspective. A large German multicenter study (ROSSO) confirmed these findings.

Human Islet Longevity Supported by Allogeneic Bone Marrow

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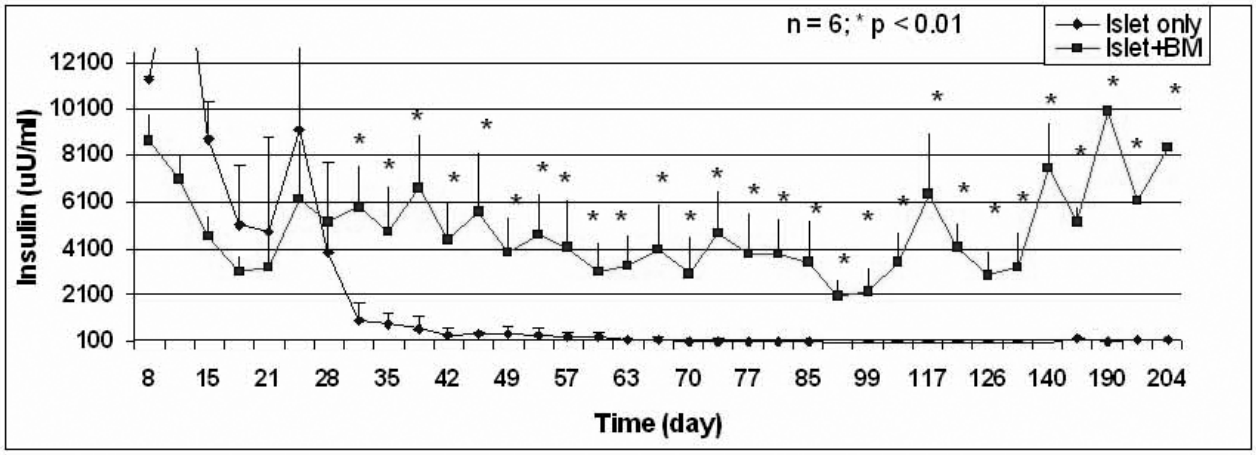
High rates of islet cell death and dysfunction after isolation have impeded the success of islet transplantation in patients with diabetes. The discovery of how to repair islet damage from the isolation process and maintain islets *in vitro* over the long term would represent a significant advance in the field, leading to more widespread use of islet cell transplantation. Given recent evidence that bone marrow and its derived stem cells have demonstrated promise in healing skin, heart, and muscle tissues, we hypothesized that bone marrow cells could provide similar advantages for islet cells. This study explored whether human islets damaged by the isolation process can be repaired by coculture with allogeneic bone marrow. Coculture with bone marrow was shown to increase islet survival and function (evaluated by insulin release and insulin in response to glucose challenge) *in vitro* for more than 200 days (see figure). Bone marrow cells not only improved human islet survival and function, but also stimulated islet growth *in vitro* during long-term culture (evaluated by morphological microscopy in living islets). Allogeneic bone marrow cells demonstrated the ability to heal damage and build up an entire islet by interaction with human islets (observed by time-lapse microscopy technology). Cord blood cells or isolated peripheral blood $CD34^+$ cells resulted in no benefit for islet repair or growth *in vitro*, suggesting that bone marrow cells may offer a unique advantage in the repair of islet injury. In preliminary studies, islet cells cocultured with allogeneic bone marrow (3 weeks) proved to be far superior in recovering hypoglycemia in nonobese diabetic severe combined immunodeficiency disease mice than 3-week cultures of islets only. The mechanism of bone marrow benefit to human islet may result from bone marrow creating an islet-favorable microenvironment. This work was partially funded by a grant from the Juvenile Diabetes Research Foundation.



Comparison of 24-Hour Blood Glucose Variability among Critically Ill Patients, Type 1 Diabetic Patients, and Healthy Individuals

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Introduction:
Blood glucose (BG) variability may contribute to adverse outcomes in type 1 diabetes and poorly controlled critically ill patients. The present analysis [supported by CLINICIP (FP6 IST-506965)] was performed to compare blood glucose variability among different study populations of healthy individuals, type 1 diabetic patients, and critically ill patients after major cardiac surgery or critically ill patients at a medical intensive care unit with standard or tight glucose control, respectively.

Methods:
Blood glucose variability is reported as standard deviation of the mean blood glucose of 24-hourly glucose measurements. Arterialized measurements were performed in healthy subjects (n = 9) and in type 1 diabetic patients (n = 16) with glucose self-management and standardized food intake. Arterial measurements were performed in critically ill patients using either standard glucose control (n = 34) or tight glucose control using a model predictive control (MPC) algorithm (n = 35). Healthy and diabetic subjects received four standardized meals during the 24-hour period, whereas critically ill patients were fed enterally and/or parenterally according to best supportive care.

Results:
Blood glucose variability was highest in type 1 diabetic patients [54.7 ± 16.3 mg/dl (mean ± SD); mean BG: 159.8 mg/dl] and conventionally treated patients at the medical (43.7 ± 25.6 mg/dl; mean BG: 146.7 mg/dl) and the surgical (35.3 ± 37.7 mg/dl; mean BG: 154.4 mg/dl) ICU. In contrast, BG variability both in the medical (30.5 ± 20.7 mg/dl; mean BG: 111.6 mg/dl) and in the surgical (23.9 ± 12.7 mg/dl; mean BG: 113.7 mg/dl) ICU could be reduced using the MPC algorithm and were more comparable to blood glucose variability as seen in healthy controls (28.5 ± 10 mg/dl; mean BG: 114.7 mg/dl).

Conclusions:
Substantial differences in BG variability occur among healthy volunteers, type 1 diabetic patients, and patients at the medical and surgical ICU, respectively. Introduction of an automated algorithm to normalize glucose in critically ill patients improved daily glucose variability in critically ill patient populations.

An Evidence-Based Checklist for Glucose Meter Evaluation Studies

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Introduction:
Evaluations of glucose monitor performance must be designed and executed carefully in order (1) to control protocol-specific bias and specific patient interferences and (2) to isolate monitor bias and imprecision. Although published guidelines and recommendations exist, investigators rarely incorporate consensus standards or quality guidelines into glucose monitor evaluation studies.

Methods:
We performed a literature search for "best practice" quality guidelines for conducting and reporting glucose monitor evaluation studies. These guidelines included Standards for Reporting Diagnostic Accuracy (STARD); Clinical and Laboratory Standards Institute (CLSI) C30-A2 and EP9-A2; United States Food and Drug Administration; International Federation of Clinical Chemistry; Netherlands Organization for Applied Scientific Research; United Kingdom Medicines and Healthcare Products Regulatory Agency; Scandinavian evaluation of laboratory equipment for primary health care; National Standard of the People's Republic of China (China GB/T 19634); and International Standards Organization (ISO 15197).

Results:
We constructed a 14-step checklist that outlines a standardized approach to glucose monitor evaluations, with references from international standards and consensus recommendations. We expect that the checklist could be used as the basis for a protocol that is (1) evidence based, (2) scientifically defensible, and (3) sufficiently descriptive to allow for test and result reproducibility.

Conclusions:
We propose a standardized checklist that facilitates the incorporation of international consensus standards, quality guidelines, and acceptance criteria into the design and reporting of glucose monitor evaluation protocols.

Intelligent Decision Support System for Diabetes Management

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Introduction:
Continuous glucose monitoring in patients with type 1 diabetes provides voluminous patient glucose data; however, these data are not yet maximally used to improve outcomes. A major barrier is the time required to analyze and translate data into clinical solutions that improve blood glucose control. A prototypical intelligent decision support system has been built to automatically analyze both patient glucose and lifestyle data, detect abnormal patterns in blood glucose control, and then recommend solutions to individual problems.

Methods:
Twenty patients with type 1 diabetes on insulin pump therapy participated in a 6-week pilot study. Each patient provided electronic daily logs, including self-glucose monitoring data, insulin dosages, work schedules, sleep patterns, exercise, meals, stress, illness, infusion set changes, pump problems, and hypoglycemic episodes. Each patient also provided Medtronic MiniMed continuous glucose monitoring data for three separate 72-hour intervals. Physicians interpreted data, identifying problems and recommending therapy adjustments to solve them. Knowledge engineers recorded problems, solutions, and physician rationales.

Results:
Fifty problem/solution cases from this pilot study were built into a prototypical case-based reasoning system. Software detected nocturnal hypoglycemia, morning hyper- or hypoglycemia, overcorrection for hyper- or hypoglycemia, pre- or postmeal hyper- or hypoglycemia, over-bolusing at meals, exercise-induced hypoglycemia, and insulin pump malfunction/infusion set problems. Newly detected problems were compared to previously encountered problems to identify potential therapeutic changes. Recommendations were provided for physician review, but might eventually be incorporated into patient devices.

Conclusions:
Integrating glucose and lifestyle data facilitates provider recognition and development of solutions for common problems encountered by patients on insulin pump therapy. Patients accept the concept of an automated advice, and additional research could lead to a practical tool for patients.

Breath Acetone Detection

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Elevated concentration of breath acetone is an excellent marker of metabolic stress and disease states such as diabetes. Southwest Sciences, Inc., has discovered and demonstrated a novel breath acetone measurement method. This method combines a simple gas–solid chemical reaction of acetone with the sensitivity and selectivity of diode laser spectroscopy. We have constructed a prototype, battery-operated, breath acetone sensor based on this method that is a compact stand-alone instrument capable of measuring human breath acetone concentrations ranging from healthy to severely diseased individuals.

A New Basal Regime Calculator

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Introduction:
A good basal insulin regime is essential in establishing good glycemic control. It is, however, difficult to take all the factors into account. Therefore, most regimes are started by using simple calculations only taking patient weight into account. A need exists for an easy-to-use but accurate basal insulin regime calculator.

Methods:
An accurate blood glucose simulation model was used to derive a basal insulin regime calculator. A newly derived energy unit named equivalent teaspoons sugar (ETS) was used to calculate the daily energy requirements of diabetic patients. Furthermore, an accurate blood glucose characterization procedure was used to determine the blood glucose sensitivity to insulin and ETS. A simplified parameter for stress was also introduced to compensate for long- and short-term stress. Regimes were also adjusted to take into account the variance in daily activity profiles of patients.

Results:
Results were verified using retrospective data from clinical trials conducted for Lantus® (n = 2327). The average trial regime corresponded closely to our predictions (average basal regime within 5%). It can also be verified by looking at the typical daily energy intake of a diabetic subject, insulin and ETS sensitivity, and the actual insulin regime used and then by analyzing the current glycemic control.

Conclusions:
An easy-to-use graphical software application can be used effectively to predict the insulin regime of patients that also takes into account various other factors not considered by conventional regime calculation equations, such as stress, activity level, and sensitivity to ETS and insulin. Pharmaceutical companies might improve their clinical trial results and reduce associated costs by utilizing this technology.

Utilizing Blood Glucose Simulation Technology in a Diabetes Educational Simulator

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Introduction:
Blood glucose control is a difficult concept to understand. This is especially the case with newly diagnosed patients and parents of diabetic infants and children. Simulation technology has proved useful in various fields of education. Therefore, it can also be extended to teach diabetic patients about blood glucose control.

Methods:
A graphical software simulator was developed to demonstrate interactively the effect that various inputs (e.g., food, exercise, insulin) have on blood glucose levels. A real-life blood glucose scenario can be created. The diabetic person will then be able to see what the resulting effect of inputs on blood glucose will be and also what type and magnitude of corrective action should be taken to normalize blood glucose levels. Extensive food and exercise databases make it easy to choose inputs. Furthermore, an accurate simulation model using the specific user's blood glucose sensitivity values to food intake and insulin is used to calculate values. All factors are illustrated by arrows of which the direction and magnitude help diabetic subjects understand how exactly a certain input will affect glucose levels. Factors such as blood glucose counterregulation are also demonstrated by the system. Even the effect of factors such as alcohol and exercise while insulin deficient on blood glucose control can be simulated.

Results:
The simulation model and the characterization procedure used by the educational system have been tested extensively. Most diabetic patients who have seen the system indicated that the system allowed them to understand certain aspects of blood glucose control better than before.

Conclusion:
Simulation technology can be used effectively to educate diabetic users in blood glucose control. Pharmaceutical companies might increase their brand awareness by sponsoring distribution of said simulator.

Using Blood Glucose Simulation Technology to Quantify the Effect of Stress on Blood Glucose Levels

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Introduction:
Emotional stress and its glycemic effects contribute to the difficulty in achieving good glycemic control by people with diabetes. These effects are difficult to quantify and therefore also difficult to compensate for in insulin regimes. Simulation technology is a useful tool to investigate the effect of stress on blood glucose levels.

Methods:
The effect of stress was investigated by first measuring blood glucose levels of subjects experiencing little or no stress. An accurate blood glucose simulation model developed previously was then customized for each test subject. The same subjects were measured again and simulated while experiencing either long- and short-term emotional stress. Obviously the measurements during stressful periods were elevated compared to nonstressful periods. The effects of stress were then mimicked by increasing the glycemic energy input to the simulation model until the simulated blood glucose response resembled actual measured data. The additional energy could therefore be attributed directly to the effect of the stress. A newly derived generic energy unit called equivalent teaspoons sugar (ETS), which takes metabolic efficiency into account, was used to measure the energy.

Results:
Simulations showed that for short-term stress (fight/flight), up to 17 ETS/hour is secreted by the blood glucose counter regulation system. Medium term stress (e.g., examinations) results in secretion of up to 8 ETS/hour, whereas long-term stress results in up to 1.7 ETS/hour. This compares well to actual measurements from literature sources used for indirect verification.

Conclusion:
Blood glucose simulation is a useful tool to quantify the glycemic effect of stress and therefore also insulin regime optimization to compensate for these effects. Pharmaceutical companies may be interested in this technology to improve the quality of their clinical trial results.

Blood Glucose Simulator: More Accurate Equations for Metabolized Carbohydrate Energy

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Introduction:
For a blood glucose simulator, energy from carbohydrate (CHO) metabolism must be correct. We always assumed that the 4 kcal/g of CHO, released by full combustion in a bomb calorie meter, will also be released by metabolism. However, as these conversion processes are different, they should release different amounts of energy.

Method 1:
Nine groups of eight rats each were investigated. All received the same kilocalories per body mass based on recommended daily allowance (RDA) guidelines. Each group received different foods high in CHO. If convention is correct, the mass of the rats should not change over 3 weeks as energy supplied to the rats (calculated the conventional way) is their RDA.

Result 1:
However, all the groups lost mass. These losses were not the same for the different groups. Contrary to convention, the full 4 kcal/g of CHO was not extracted. Also, the energy amount extracted differed for different CHOs. A new energy equation was derived using the units of equivalent teaspoon sugar (ETS). A linear relationship ($R^2 = 0.68$) was found between ETS values and percentage mass loss. The new ETS equation is more representative of the metabolized CHO energy than the 4 kcal/g used historically.

Method 2:
It is difficult to conduct a similar experiment (method 1) on humans. An indirect approach was utilized. Insulin secretion is a function of the blood glucose metabolized from CHO. Metabolized energy calculated by the new equation was plotted against measured insulin secretion.

Result 2:
The average R^2 and its standard deviation (S) as a percentage of the average for 15 test subjects were computed using the old (4 kcal/g) and new ETS equations. The new equation resulted in $R^2 = 0.807$; S = 10% and the old one in $R^2 = 0.562$; S = 32%. The ETS equation gives a better approximation of metabolized energy than the historical 4 kcal/g when applied to humans.

Conclusion:
Incorrect estimation of CHO-metabolized energy is one reason why diabetics struggle with blood glucose control. The new ETS equation can help solve this. The equation is also utilized for accurate blood glucose simulators, which predict better basal and bolus dosages than current methods.

A New Blood Glucose Simulator Can Enhance Diabetic Drug and Product Discovery

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Introduction:
Simulating the human energy and control system means that levels of glucose, triglyceride, fatty acid, and so on for any food intake, exercise, stress, drugs, counterregulation control, or a combination thereof can be established. It is then possible to develop better methods, diagnostic tools, and pharmaceutical tools to control these levels, but at a quicker pace and lower cost than before. Simulation is the key to competitiveness. Blood glucose simulation has various applications ranging from blood glucose control to educational purposes. Accurate results are, however, difficult to achieve. A new generic energy unit was derived to produce better results.

Methods:
A blood glucose simulation model was developed utilizing more than 20 years of experience in industrial simulations. Models were developed for all components in the human energy systems. Initial simulations identified the need for improved quality of model inputs such as food intake. Because the carbohydrate counting concept failed the requirements, a new generic energy unit called equivalent teaspoons sugar (ETS) was derived that also takes the metabolic efficiency of specific foods into account. The model is further customized by a detailed blood glucose characterization procedure to determine sensitivities of the patient to ETS and insulin. The model is also able to simulate the effects of exercise, stress, and alcohol on blood glucose levels.

Results:
The simulation model was tested extensively on both diabetic and nondiabetic patients. Accurate results were obtained. Whole day simulations proved the accuracy of the model to include 70.7% of all simulated data points within a range of 1 mmol/liter of the actual measured values while 95.5% of data points were in a range of 2 mmol/liter.

Conclusion:
Accurate blood glucose simulation is made possible by ensuring that (1) the quality of inputs are good, (2) the model is customized for the specific person, and also (3) an integrated simulation approach is used. Accurate simulation models are of special interest to medical hardware manufacturers (e.g., insulin pumps and continuous glucose monitoring equipment).

Diabetic Carbohydrate Energy Requirement Calculator for Endurance Exercise

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Introduction:
If a type 1 diabetic athlete ingests too many carbohydrates during an endurance event, it can lead to hyperglycemia. Too little insulin can also lead to hyperglycemia. However, too few carbohydrates can quickly result in hypoglycemia, as blood glucose release from the liver can be up to four times smaller than in a healthy person. Currently, empirical suggestions for carbohydrate ingestion are published in diabetic books. These suggestions do not, however, take the type of carbohydrate, personal characteristics such as fitness, metabolic efficiency, and blood glucose counterregulation efficiency into account. Therefore, incorrect carbohydrate dosages can easily result.

Methods:
An easy-to-use theoretical procedure with correct links between carbohydrates and all the important elements for a specific individual is being considered. The procedure was derived theoretically using energy balance techniques and was implemented as a software application. The complicating factor of different levels of glucose delivery by the liver in different type 1 diabetic patients can be omitted if the liver store is never utilized. If the diabetic patient ingests the correct amount (grams) and the right type (GI) of carbohydrates, the liver stores will not be used and there will also be a negligible rise in blood glucose. Simulation predictions by the new procedure were verified against measurements. The procedure only holds true if the diabetic person uses the correct amount of insulin. Too little insulin during strenuous exercise can result in high blood glucose, as the glucose cannot be utilized if the insulin levels are too low.

Results:
Typical energy values for different types and intensities of endurance exercises were derived for specific persons. By ingesting the correct type of carbohydrates at the correct rate, optimal blood glucose levels can be maintained, reducing the associated exercise risks of hypo- and hyperglycemia.

Conclusion:
The procedure can be implemented easily on a mobile phone or other electronic device as a software application. An accurate procedure for carbohydrate requirements during exercise reduces the risks associated with endurance exercise for diabetics.

A Cell Phone-Based Multimedia Platform for Improving Diabetes Knowledge and Medication Adherence in Type 2 Diabetic Patients: Design and Technical Aspects

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Introduction:
The effective management of type 2 diabetes requires a multipronged approach with ongoing monitoring, motivation and educational activities. The patient is the key stakeholder in this process, and long-term management of diabetes requires sustained investment of type 2 diabetic patients in their treatment plan. However, successfully engaging and maintaining patient involvement remains a challenging task. New approaches are needed to involve patients in their own care.

Methods:
We describe a diabetes program utilizing a cross-platform software technology developed by Quantia. The software platform is capable of being deployed across a variety of mobile devices including devices running Windows Mobile® and Blackberry®. The software is interactive and enables bidirectional communication between patient and care giver. This enables customization of content to the needs of each patient.

Results:
We created a 6-month structured educational framework on diabetes consisting of video modules that address aspects of diabetes care and management. Video clips are approximately 5 minutes long and are optimized for the cell phone environment. Patients receive two to three video clips every week for the duration of the program. After viewing each video, patients are asked to rate the video and then answer several questions to assess their understanding of the content. Responses are tracked in conjunction with number of views, viewing frequency, and time of viewing.

Conclusion:
Recent advances in multimedia technology and cell phone networks have created channels of information distribution previously unavailable to care providers. Furthermore, the high penetration of cellular networks in the United States opens new opportunities for delivery of care to a patient's home environment. We believe that programs such as this one will provide valuable insight into patient behaviors, as well as help optimize diabetes management strategies. The project is initially being piloted at Massachusetts General Hospital: future plans include bringing the program to scale and integrating clinical data, such as blood glucose readings.

Assessment of Islet Cell Transplant Candidates and Transplant Efficacy Using Continuous Glucose Monitoring to Quantify Glycemic Variability

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Introduction:
Patients choose islet transplantation because of severe hypoglycemia risk and/or marked blood glucose (BG) variability. New measures to assess the risk of glycemic extremes and variability have been developed recently and applied to two islet cell transplant recipients along with conventional glycemia markers (mean, SD).

Methods:
Using 72 hours of continuous glucose monitoring (CGM) data (Medtronic MiniMed CGMS® Gold), mean BG (MBG), SD of BG (SBG), absolute BG rate of change (RATE), and low and high BG indices (LBGI, HBGI) were estimated. Patients had CGM performed prior to and after two (#1) or one (#2) islet transplants. Data were aggregated to reduce data interdependence and the difference pre- vs post-transplant analyzed (ANOVA). The percentage time at euglycemia (EUGL) was also estimated.

Results:
Both patients showed significant post-transplant improvement in MBG, SBG, RATE, LBGI, HBGI, and EUGL. HBGI decreased from moderate to low, and RATE dropped twofold. #1's LBGI decreased from high to moderate, and #2's from moderate to low. EUGL increased from 51 to 79% (#1) and from 59 to 100% (#2). MBG changed from 129 to 114 mg/dl (#1) and from 138 to 114 mg/dl (#2). SBG dropped >twofold (#1) and almost threefold (#2).

Conclusions:
Mean and SD of BG change after islet transplantation. However, quantitative risk of hypoglycemia is better conveyed by LBGI, which is high (#1) or moderate (#2) and decreases risk category in both cases. BG variability reduction (RATE) indicates enhanced stability despite absence of full insulin independence. Dramatic reductions in HBGI and changes in risk category also occur, as well as large increases in percentage time at euglycemia. These measures suggest themselves as useful tools to quantify risks and benefits of islet transplantation.

Correlation of Alternative Site Capillary Blood Glucose Testing Accuracy and Interstitial Fluid Glucose Sampling, as Measured against Venous Glucose Concentration

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Introduction:
Alternative site testing refers to glucose testing from sites other than the fingertip. A lag of approximately 10 minutes has been observed between glucose concentrations at the alternate site and the fingertip. A similar lag between venous and interstitial glucose concentrations has been reported for continuous monitors. In this report, data from a study assessing capillary blood from the forearm against a venous blood reference were compared to data from a study assessing continuous interstitial fluid measurements against a venous blood reference.

Methods:
The study of forearm tests was conducted over 5 years in which patients with type 1 diabetes mellitus (T1DM) and T2DM were tested during routine clinic visits. The tests were performed with the FreeStyle® blood glucose monitoring system and compared to venous samples tested with the Yellow Spring Instrument (YSI) Model 2300 glucose analyzer—1106 patient samples were analyzed in duplicate. In the study of interstitial fluid glucose, 58 subjects with T1DM were tested in a clinic setting. The FreeStyle Navigator® continuous glucose monitoring system was used to measure subcutaneous interstitial fluid at the upper arm and abdomen, and these measurements were paired with venous samples measured with the YSI taken at 15-minute intervals—20,363 paired points were obtained.

Results:
Correlation to and bias from the reference were used as quantitative measures of the difference between methods. Clarke error grid analysis was used to evaluate clinical differences. There was a marked similarity between accuracy of alternative site and interstitial glucose tests.

Conclusion:
If the glucose measurements are sufficiently accurate, differences from the venous reference method are dominated by the physiological differences in glucose concentration of the test samples.

healthcordia™ Technology-Enhanced Diabetes Intervention Social Network Program Improved Hemoglobin A1c in Adults with Type 2 Diabetes

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Introduction:
We hypothesized that equipping patients with a simple mobile diagnostic device, automated transmission to a sophisticated rules engine, and establishment of a support mechanism composed of patient-centric social networks could improve glycemic control in adults with type 2 diabetes without intervention by highly trained diabetes professionals.

Methods:
Twenty-five adults completed this 9-month, nonrandomized, noncontrolled, open-labeled study. Mean age was 49 years. Hemoglobin A1c (HbA1c) averaged 7.4 at program enrollment. A GlucoMON® wireless glucose meter and a highly accurate HomeCheck™ aqueous finger-stick blood sample collection kit were mailed to the patient. Additional kits were sent every 90 days. Samples were screened for hemoglobinopathies and HbA1c.
Data were collected automatically from the GlucoMON and appended to the centralized GlucoDYNAMIX patient record. Interventions were automated based on rules coded into the system. A typical intervention included periodic educational messages sent to the patient and/or a member of the patient's self-selected social network about the importance of blood sugar checking, food choices, or activity in relation to trends identified by the system.

Results:
21/25 (85%) reduced HbA1c an average of 0.9
17/25 (68%) reduced HbA1c >0.3 with an average drop of 1.3
1/25 (4%) increased HbA1c >0.3 with a rise of 1.2
3/3 (100%) enrolled with A1c >9 reduced A1c (-2.2 to -4.5)

Conclusions:
The healthcordia™ program leveraged technology to enhance patient self-care, resulting in a decrease in average blood sugars on par with results obtained in the landmark United Kingdom Prospective Diabetes Study trial without a requirement for labor-intensive interventions by highly skilled diabetes professionals.

Practical Aspects of Field Generation When Using the NLDS™ Electrical Spectroscopic Technique for Noninvasive Determination of Blood Glucose

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Introduction:
In seeking to advance calibration aspects of the NLDS™ technique to a stage where intrasubject variability is minimized, a key variable that needs to be controlled is the impedance of the stratum corneum. This varies considerably between subjects. We sought to determine if a sinusoidal current field could be employed on the basis that the resultant field in the tissue would be less affected by the voltage drop through the stratum corneum, thereby obviating the need for skin preparation.

Methods:
A set of four silver-silver chloride electrodes were applied to the shaven abdomen of five nondiabetic volunteers. The electrodes were connected to a Solartron Model SI 1250 impedance analyzer. A custom front end, which permitted the Solartron to selectively drive a voltage or a current sinusoidal waveform, was connected to the four electrodes. A 100-μA current was applied, and the applied voltage was selected such that the applied current was nominally 100 μA. The reflected field was analyzed for distortion by determining the second (H2) and third (H3) harmonics.

Results:
Mean (SD) H2 and H3 values in dB for the five subjects for cases of voltage and current stimulation were H2, -99.78 (5.79) and H3, -102.52 (5.45) and H2, -117.32 (7.44) and H3, -113.00 (4.47), respectively.

Conclusions:
The case for current stimulation is strong in that the effect of electrode interface nonlinearities can be reduced greatly. From aforementioned data, one can conclude that the nonlinearities seen during voltage stimulation are largely due to electrode effects. Furthermore, it is clear that glucose induced nonlinearities have significantly lower magnitude than previously anticipated. Work is ongoing to produce transducing electronics to better measure such low-level signals.

Diabetes and Disability

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Introduction:
Diabetes mellitus is a leading health care problem and its complications can cause organic, physical, and psychological disabilities. Disability is a social, economic, public health, and political issue that society is confronting today and is also associated with an increased likelihood for hospitalization, institutionalization, and loss of economic self-sufficiency and normal role behaviors. Diabetic patients with disabilities face barriers in their work environment and difficulties in gaining access to public facilities; these constraints influence their meaningful participation in normal activities of everyday life. The aim of this study was to investigate the prevalence of disabilities in diabetic patients.

Methods:
In this study, medical records of 600 diabetic patients were reviewed for the prevalence of disabilities in diabetic patients treated from January 1990 to December 2006 at different hospitals. Data was coded and entered into a computer using SPSS software. The prevalence of disabilities was analyzed by using the number of diabetic patients who developed disability included as the numerator and the total number of diabetic patients as the denominator; prevalence was expressed as a percentage.

Results:
The present study showed that the prevalence of disability, including organic, physical, and psychological disabilities, were coronary artery disease (56.4 %), renal failure (38.6%), impaired vision and blindness (27%), mental illness and retardation (19.6%), hand polyneuropathy (17%), foot polyneuropathy (25.5%), autonomic neuropathy (11.4%), foot ulcers (12.5 %), impotence (5.5%), and balance problem (2.3%).

Conclusion:
It has been observed that diabetes mellitus is a major determinant of disability in which individuals face impairments and limitations that influence their meaningful participation in normal activities of everyday life. Results of the present study suggest that a plan should be developed to decrease the disability rate and burden on the health care system and to help disabled diabetic patients improve their quality of life.

Dose–Response Effect of Duration of Disease on Ventilatory Function in Diabetic Patients

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Introduction:
Diabetes mellitus is a leading cause of illness and death across the world and is responsible for a growing proportion of global health care expenditures. The present study was designed to observe the dose–response effect of diabetes mellitus on lung function in a specific ethnic group of diabetic patients.

Methods:
In this study, a group of 47 apparently healthy volunteer male diabetic patients was randomly selected with age ranging from 20 to 70 years. The diabetic patients were matched with another group of 50, healthy male control subjects in terms of age, height, weight, ethnicity, and socioeconomic status. Both groups met with exclusion criteria as per standard. Spirometry was performed on an electronic spirometer (Schiller AT-2 Plus, Switzerland) and results were compared by a student *t* test.

Results:
Diabetic patients showed a significant reduction in forced vital capacity (FVC) and forced expiratory volume in first second (FEV_1) relative to their matched controls. However, there were no significant differences in the forced expiratory ratio (FEV_1/FVC%) and middle half of the FVC ($FEF_{25-75\%}$) between the groups.

Conclusion:
Lung functions in a specific ethnic group of diabetic patients are impaired by a decrease in FVC and FEV_1 as compared to their matched controls. Stratification of results by years of disease shows a dose–response effect on lung function.

GlucoMen® Day, a New Generation Subcutaneous Glucose Measuring Device

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A new generation subcutaneous glucose measuring device (GlucoMen®Day), based on the microdialysis principle, has been developed by A. Menarini Diagnostic S.r.l. (Florence, Italy). The GlucoMen Day is a relatively light (170 g) and small (10 x 8 x 2 cm) wearable device controlled by a Palm via a wireless connection (Bluetooth®). A microdialytic probe (0.2 mm diameter) is inserted subcutaneously into the abdominal region of the patient by a cannula needle in a one-way mode, rending the system minimally invasive. A constant flow of a buffered saline solution allows recovering of subcutaneous glucose, which is then delivered to an external disposable planar glucose oxidase-based sensor. Glucose is measured every second, and the average is recorded every minute. The GlucoMen Day is intended for 100 hours of continuous monitoring in humans. Data can be visualized in both real time and retrospectively. The GlucoMen Day system has been tested *in vitro* extensively in order to verify its performances in terms of linearity, operational stability, reliability, and so on. Results show that the sensor responds linearly in the interval of concentration between 5 and 600 mg/dl, covering the physiological range. During 120 hours of monitoring, the biosensor evidenced a limited drift (less than 10%). The effects of dissolved oxygen in the working solution and temperature dependence have also been tested. Preclinical studies have been done both *in vitro* and *in vivo* on animals in order to verify the performance and the safety of the GlucoMen Day system. A test on a minipig confirmed that the recovery percentage of the microdialitic probe remained constant over the entire period of monitoring (5 days). Necroscopy observation has also evidenced that the probes are well tolerated over a 100-hour period. Another test conducted on dogs monitored the performance and the reliability of the system for a period of 100 hours. Results have shown how the system is capable of reliably following glucose variations *in vivo*. All the components of the GlucoMen Day system have been tested for biocompatibility, according to the international standard ISO 10993. Results have shown that the materials used are not cytoxic, not genotoxic, do not result in sensitization, irritation, or acute toxicity, and that use of the GlucoMen Day system is safe. A study on human subjects (six type 1 diabetic patients) is ongoing at the Health Site Medical Research in Graz (Austria) in order to verify the performance, safety, tolerability, and usability of the GlucoMen Day system in humans. A multicentric study is ongoing in seven European centers employing 70 diabetic patients (35 type 1 and 35 type 2) to evaluate the performance and safety of the GlucoMen Day. In conclusion, the new GlucoMen Day system is capable of measuring subcutaneous glucose levels continuously up to 100 hours. The system is easily wearable by the patient with low discomfort, without affecting daily activities. The Bluetooth wireless connection makes the system easy to handle, giving the health-care professional the opportunity to manage the results in both real time and retrospectively.

Cost-Effectiveness of Pioglitazone Plus Glimepiride Compared with Rosiglitazone Plus Glimepiride: An Economic Evaluation Projecting Results from a Clinical Study into the Future Using a Valid and Reliable Economic Model from a Third-Party Payer Perspective in the United States

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Background:
Oral antidiabetic drug combination therapies are becoming used more frequently in type 2 diabetes mellitus (T2DM). Combining a sulfonylurea and a thiazolidinedione is an example of such a therapy.

Objectives:
We estimated the cost-effectiveness of using pioglitazone plus glimepiride (P+G) compared with rosiglitazone plus glimepiride (R+G) in treating T2DM.

Methods:
Clinical efficacy and baseline parameters were taken from Derosa *et al.* (2004) and entered into a previously validated, Markov-based economic model for T2DM. The model was used to project long-term improvements in clinical and economic outcomes comparing P+G with R+G. A series of Markov constructs simulated the progression of diabetes-related complications (cardiovascular, neuropathy, renal, and eye disease). Transition probabilities and hemoglobin A1c (HbA1c)-dependent adjustments were derived from published epidemiological studies. Costs of T2DM complications were taken from published sources. Drug acquisition costs for P+G and R+G were assumed to be $5.21 and $4.11/day, respectively (WAC prices – 1/2007), and remained constant. A time horizon of 35 years was used, with costs and clinical outcomes discounted at 3% per annum. Univariate sensitivity analyses were conducted to test robustness of the base case incremental cost-effectiveness ratio (ICER) scenarios.

Results:
Incremental life years (LY) and quality-adjusted life years (QALYs) gained for P+G vs R+G increased by 0.305 and 0.217 years, respectively, at an overall increased cost of $4959 per patient over the simulation period. The ICERs were $16,239/LY and $22,822/QALY gained, respectively, in our base case analysis. One-way sensitivity analyses demonstrated that with variation in key input parameters (discount rates, HbA1c, lipid effects, etc.), cost-effectiveness findings were most sensitive to changes in HbA1c and systolic blood pressure.

Conclusions:
Our economic modeling analysis suggests that P+G is more costly and more effective when compared to R+G with ICERs well within the threshold cost-effectiveness level of $50,000/LY or QALY gained in the United States.

Cost-Effectiveness of Pioglitazone Plus Metformin Compared with Rosiglitazone Plus Metformin: An Economic Evaluation Using a Previously Validated Economic Model from a Third-Party Payer Perspective in the United States

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Background:
Oral antidiabetic drug combination therapies including metformin are frequently used in type 2 diabetes mellitus (T2DM).

Objectives:
We estimated the cost-effectiveness of using pioglitazone plus metformin (P+M) compared with rosiglitazone plus metformin (R+M) in treating T2DM from a third-party payer perspective in a United States setting.

Methods:
Clinical efficacy and baseline parameters were extracted and entered into a previously validated, Markov-based economic model for T2DM. This model was used to project long-term improvements in clinical and economic outcomes comparing P+M with R+M. A series of Markov constructs simulated the progression of diabetes-related complications (cardiovascular, neuropathy, renal, and eye disease). Transition probabilities and hemoglobin A1c (HbA1c)-dependent adjustments were derived from published epidemiological studies. Costs of T2DM complications were taken from published sources. Drug acquisition costs for P+M and R+M were assumed to be $4.35 and $4.39/day, respectively (WAC prices, 2007), and remained constant. A time horizon of 35 years was used, with costs and clinical outcomes discounted at 3% per annum. Univariate sensitivity analyses were conducted to test robustness of the base case cost-effectiveness ratio scenarios.

Results:
The incremental life years and quality adjusted life years gained for P+M versus R+M were 0.221 and 0.161 years, respectively, achieved at an overall lower cost for P+M. Therefore, P+M was considered dominant over R+M. Sensitivity analyses demonstrated that these findings were robust to variation in discount rates, HbA1c, lipid effects, etc. HbA1c changes for both treatments were nearly equivalent, but an improved lipid profile for P+M was a key driver for the estimated difference in long-term outcomes.

Conclusions:
Our study suggested that P+M delivers superior economic value compared to R+M due to enhanced clinical outcomes achieved at an overall lower cost.

Indian Diabetes Risk Score Helps Detect Diabetic Subjects at High Risk for Macrovascular Complications and Peripheral Neuropathy

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Introduction:
We have previously reported on the utility of a simplified Indian diabetic risk score (IDRS) that is a cost-effective method to screen for undiagnosed diabetes in India, as well as to identify metabolic syndrome.

Methods:
IDRS is based on three questions, age, family history of diabetes, and physical activity, and on a simple waist measurement. A score ≥60 has the optimum sensitivity (72.5%) and specificity (60.1%) for determining undiagnosed diabetes. In the present study, we look at whether IDRS is also useful to detect diabetic complications.

Results:
Diabetic individuals with a higher IDRS score had significantly higher prevalence rates of coronary artery disease [IDRS ≥60: 8.6% vs IDRS <60: 4.3%, $p = 0.015$]. Peripheral neuropathy was also observed to be higher in subjects with higher IDRS score [IDRS ≥60: 13.6% vs IDRS <60: 3.4%, $p < 0.001$] compared to those with low IDRS, whereas the prevalence of peripheral vascular disease, diabetic retinopathy, and microalbuminuria did not differ between the two groups.

Conclusions:
The prevalence of coronary artery disease and peripheral neuropathy is higher in those with a high IDRS score. The identification of diabetic individuals at greater risk for these complications could be an additional use of the Indian diabetes risk score.

Development of a Low-Cost Diabetes Risk Score Kit to Identify Subjects with Diabetes and Cardiovascular Risk

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Introduction:
India has the largest number of people with diabetes in the world, but unfortunately over 50% remain undiagnosed. This underscores the need for inexpensive screening programs to identify and overcome the burden due to diabetes. We have previously reported and validated the use of a simplified Indian diabetes risk score (IDRS) as being cost-effective to screen for undiagnosed diabetes in India.

Methods:
IDRS uses three simple questions involving age, family history of diabetes, and physical activity and a waist measurement and was derived from a large population-based study, the Chennai Urban Rural Epidemiology Study. The aim of the present project was to develop a low-cost kit to enable widespread use of IDRS in a field or clinic setting.

Results:
A cut off ≥60 had the optimum sensitivity (72.5%) and specificity (60.1%) for determining undiagnosed diabetes. Moreover, even among subjects with normal glucose tolerance, those who had IDRS ≥60 had higher prevalence rates of cardiovascular risk factors and metabolic syndrome. In order to make application of the risk score more widely used by physicians and epidemiologists, we have developed a simple low-cost IDRS kit. This kit (length: 10 cm, width: 7 cm, height: 2.5 cm), which is smaller than a pocket dictionary, has a plastic card (similar to a credit card) with detailed instructions for calculating the IDRS score printed on it. It also has information regarding interpretation of the risk score derived. An inch tape is placed inside the box, which can be used to measure waist circumference.

Conclusions:
This IDRS kit has already been issued to hundreds of primary health workers in India for opportunistic screening for diabetes. It is expected that thousands of people with undetected diabetes can be diagnosed cost effectively (about 50% of the cost of regular screening) using this simple low tech device, which costs only $1.50.

The Use of Continuous Glucose Monitoring for Assessing the Relative and Absolute Contributions of Postprandial Glucose to Overall Hyperglycemia in Type 2 Diabetes: How? And Why?

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Introduction:
From a mathematical point of view, the overall hyperglycemia as depicted by hemoglobin A1c (HbA1c) measurements at 3-month intervals is the sum of two components, i.e., of two integrals.

$$\left[HbA_1c\right]_0^{3months} = {}_0\int^{3months} FPG(t)\,dt + {}_0\int^{3months} PPG(t)\,dt$$

Methods:
Using 140 patients with type 2 diabetes, we calculated several areas under curves from continuous glycemic profiles using a continuous glucose monitoring system. (i) AUCpp = incremental area above postprandial values over the 4-hour period following the beginning of each meal; (ii) AUCt = total incremental areas above 6 mmol/liter glucose baseline level (the upper limit of normal); and (iii) AUC_0 = incremental area above a glucose level equal to 0 that reflects the overall exposure to glucose. The relative contribution of postprandial glucose (PPG) to overall hyperglycemia was calculated as follows: [AUCpp/AUCt] x 100. The absolute impact of PPG on HbA1c (percentage points) was calculated using the following equation: [AUCpp/AUC_0] x HbA1c.

Results:
The relative contribution of PPG to overall hyperglycemia depended on HbA1c levels, with the relationship between the two parameters being described by a decreasing exponential curve. The contribution of PPG was higher than 50% for those patients who had HbA1c levels <7% while the contribution dropped to less than 50% with worsening diabetic control (HbA1c >7%). The absolute impact of PPG was constant and approximately equal to 1% (percentage points) whatever the HbA1c levels above 6.5%.

Conclusions:
These results indicate that treatment in patients with HbA1c levels ranging from 6.5 to 7% should be initiated or completed with drugs aimed at reducing PPG excursions in order to achieve HbA1c targets <6.5%. In addition, these data explain why the efficacy of such drugs as gliptins and GLP1 analogs on HbA1c levels never exceeds 1% in most interventional trials. Such observations raise the question of their usefulness in patients exhibiting HbA1c levels above 8%.

$$\left[HbA_1c\right]_0^{3months} = {}_0\int^{3months} FPG(t)\,dt + {}_0\int^{3months} PPG(t)\,dt$$

A Personalized Insulin Infusion Advisory System for Type 1 Diabetes Patients for Closing the Loop between Continuous Glucose Monitors and Insulin Pumps

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Introduction:
Closing the loop between continuous glucose monitors (CGM) and insulin pumps through accurate computational algorithms for the adjustment of insulin infusion rates will make an "artificial electromechanical pancreas" feasible. To this end, a personalized insulin infusion advisory system (IIAS) for type 1 diabetes (T1D) patients using CGM and insulin pumps is presented. The goals of the system are to automate real-time calculation and to deliver the appropriate insulin infusion rate.

Methods:
The IIAS is based on a nonlinear model predictive controller (NMPC), which uses a hybrid model. The model comprises a compartmental model, which simulates absorption of the glucose to the blood due to meal intakes, and a real-time neural network, which simulates the glucose–insulin kinetics. The output of the model consists of short-term glucose predictions and provides input to the NMPC in order for the latter to estimate optimum insulin infusion rates. For development and evaluation of the hybrid model, data from seven pediatric patients with T1D were used, while the whole IIAS was evaluated using data generated from an *in silico* T1D patient at multiple meal disturbances, various noise levels, and additional time delays.

Results:
The predicted hybrid model glucose concentrations follow the measured glucose levels accurately. Furthermore, results of IIAS show that the resulting glucose levels are mostly in the normoglycemic range, while both hypoglycemic and hyperglycemic states are not in critical values.

Conclusions:
Although a small number of patients has been used for assessment of the proposed hybrid model and the evaluation of the IIAS is based on *in silico* data, results are encouraging for an "artificial electromechanical pancreas."

Preoperative Hyperglycemia is an Independent Risk Factor for Pulmonary Embolism after Major Orthopedic Surgery

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Background:
The incidence of pulmonary embolism (PE) after major orthopedic surgery still remains between 0.6 and 4%. The recognized risk factors do not include diabetes mellitus (DM), even though DM and/or hyperglycemia might induce a hypercoagulable state. We investigated if preoperative blood glucose (BG) levels ≥200 mg/dl increase the risk of PE independently of known risk factors for PE.

Methods:
After obtaining Institutional Review Board approval, we retrospectively reviewed the medical records of patients undergoing total hip or total knee replacement from January 2001 to April 2006. Data were analyzed using logistic regression, with odds ratios and 95% confidence intervals (CIs).

Results:
A total of 7282 patients who underwent total joint replacements were included in the study. The incidence of PE was 1.47% (107 patients). Multivariate analysis showed that preoperative BG ≥200 mg/ml increased risk by 2.8, CI (1.1–7.2, $P = 0.028$) when compared with patients with BG ≤110 mg/dl, age from 64 to 73 years old increased risk by OR 1.9 (0.9–3.7) and >73 years old by 2.7 (CI 1.4–5.6), $P = 0.005$, body mass index (BMI) of 30 to 40 kg/m^2 by 1.9 (1.2–2.9) and BMI >40 kg/m^2 by 2.4 (1.2–5.0), $P = 0.015$. Cardiac comorbidities were divided into coronary artery disease, h/o arrhythmias, valve disease, and congestive heart failure (CHF). Only CHF increased a risk for PE by 2.5 (1.1–5.7, $P = 0.028$). DM was not found to be a risk factor, as well as sex, American Society of Anesthesialogists status, surgery/OR time, h/o malignancy, pulmonary disease, hypertension, increased lipids, sleep apnea, and stroke. Total knee has 2.3 (1.4–3.8, $P < 0.001$) more risk than total hip arthroplasty. Bilateral procedure increased a risk by 2.0 (1.1–3.6, $P = 0.025$). Revision surgeries did not increase risks for PE compared with primary arthroplasty.

Conclusion:
Data suggest that preoperative hyperglycemia is an independent risk factor for developing PE after major orthopedic surgery, but that DM is not. It appears that preoperative BG is as important as other major risk factors for PE and should be controlled below 200 mg/dl before major orthopedic arthroplasty. A prospective, randomized, controlled trial would determine whether control of preoperative glucose leads to a decreased incidence of PE in this clinical setting.

Mobimons: Agents of Transformation in Diabetes

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Introduction:
Mobimons (patent #6769915) is an invention for promoting a desirable user's behavioral pattern in daily life suggested for children at increased risk for type 2 diabetes. More deeply engaging user interactions leverage the evolution of personal handheld wireless devices and embedded network appliances in computer-aided life management applications.

Methods:
A user-interactive behavioral modification system for modifying undesired behavioral patterns includes a base module with an input means for inputting a first set of personal data by a user into the base module. A feedback interface provides feedback or operatively controls other modules or devices in response to the first set of personal data. The appearance of the character—downloaded to a handheld wireless devices/network appliances/personal computer—is controlled to encourage the user to perform desired behavioral responses according to the behavioral pattern rules. Each figure has a unique "personality" driven by adaptive algorithms that collects and analyzes the user's daily life patterns; the algorithm will determine an effective way to deeply interact, learn, and evolve with the user so that the user will form desirable life patterns, such as sustaining desirable exercise pattern, to achieve personal goals. The character interacts with the user whenever the user initiates interaction and also when the algorithm determines crucial timings for prevention or encouragement of the user's behaviors.

Results:
Mobimons has not been tested formally. The authors welcome clinician or academic collaboration.

Conclusions:
One in three people born in this millennium will likely be diagnosed with diabetes. Today a child spends an average of 5.5 hours a day using media. Managing behaviors that decrease the likelihood of adolescent diabetes requires embracing specialized media as a tool.

Sliver Sensor for Minimally Invasive Optical Monitoring of Glucose and Electrolytes in the Dermis

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Introduction:
We have developed a microminiature optical sensor array that we refer to as the "sliver sensor" for continuous monitoring of glucose and electrolytes in the interstitial fluid (ISF) in the dermis. The sliver sensor combines optode technology and color recognition in a microminiature sensing bar with multiple sensing sites. The bar is implanted in the top layer of the skin and is interrogated noninvasively from outside the skin with a charge-coupled device (CCD) camera.

Methods:
Glucose levels are encoded in color by mixing immobilized glucose oxidase (GOX) containing beads and pH sensing optode beads in a ~300 -μm- diameter well contained in the sliver. GOX catalyzes oxidation of glucose to gluconic acid; thus, increasing glucose concentration translates into lower pH within the glucose sensing well. The coimmobilized pH sensing optode beads change color in response to the changing pH, which is detected by a CCD camera. The sliver sensor also includes a pH sensing site that can be used to correct for background pH changes in the ISF and a white spot as optical reference. Further sensing sites can be included for other electrolytes.

Results:
Results of *in vitro* experimentation indicate that the sensor is responsive to glucose concentration changes in phosphate-buffered saline in the range of 0 to 500 mg/dl with a response time of ~5 minutes. It was possible to achieve sensing that is essentially independent of buffer capacity variations typical of ISF using a suitable additive molecule in the glucose sensing well. The sliver sensor was found to be biocompatible for at least 28 days in rats.

Conclusions:
In vitro results indicate that optode technology and a pH-based sensing scheme may be suitable for continuous glucose monitoring in the ISF, despite physiological variations in buffer capacity. Experiments are currently performed to characterize functionality *in vivo* using a noninvasive optical *ex vivo* detection scheme.

Bio-Rad VARIANT™ II TURBO Link System for On-Demand Hemoglobin A1c Testing on the Sysmex HST-N Hematology Automation Line Correlates with the Bio-Rad VARIANT™ II TURBO Hemoglobin Testing System

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Introduction:
The Bio-Rad VARIANT™ II TURBO Link (Link) integrates the VARIANT™ II TURBO (TURBO) hemoglobin A1C (HbA1c) testing system with the Sysmex HST-N hematology automated line and MOLIS WAM software. The Link system uses proven TURBO chemistry and enhanced CDM software to offer improved workflow. Sysmex HST-N with Bio-Rad HbA1c and MOLIS WAM software provide hematology and HbA1c testing with automated data decisions, consolidating workstations and improving sample management and turn-around times.

Methods:
In this application on the HST-N conveyor line, samples arrive randomly and continuously. The Link software control is modified to increase instrument readiness while minimizing reagent consumption. Linear regression correlation of TURBO results was performed versus the Link using 180 samples from ACL Laboratories. Precision was evaluated by performing 40 runs on one instrument over 20 days. In each run, aliquots of normal (mean = 0% HbA1c) and diabetic (mean = 4% HbA1c) specimens were analyzed in duplicate. Normal and diabetic samples were spiked with ~3% labile HbA1c and 3% carbamylated hemoglobin (CHb) to determine if there is interference from labile HbA1c or CHb.

Results:
Correlation: y (Link) = 0.983 x (TURBO) + 0.225 (n = 0, R^2 = 998). Total precision for normal and diabetic samples is 1.27 and 0.92% CV, respectively. Labile HbA1c up to 4.7% in normal and 6.4% in diabetic patients shows no interference. CHb up to 3.1% in normal and 4.9% in diabetic patients shows no interference.

Conclusions:
The VARIANT II TURBO Link offers accurate and precise HbA1c results without interference from labile HbA1c and CHb on a fully automated hematology HST-N line.

Direct Supervision and GlucoMON® Improve Glycemic Control in Children with Poorly Controlled Type 1 Diabetes Mellitus

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Introduction:
Good glycemic control prevents and/or delays the onset of long-term complications of type 1 diabetes mellitus (T1DM). Glycemic control in children with T1DM continues to be challenging because of nonadherence to treatment regimen and barrier to collecting an accurate and timely blood glucose (BG) record, which permits appropriate insulin dose adjustment. This study hypothesized that supervised insulin injections and BG monitoring with GlucoMON®, an automated and wireless device, at lunchtime in school improve glycemic control in children with poorly controlled T1DM.

Method:
Thirty-four children completed this 3-month, randomized, controlled, open-labeled study. Subjects aged 13.6 ± 1.8 years had T1DM for 5.8 ± 3.7 years, hemoglobin A1c (HbA1c) 11.0 ± 1.5%, and attended a school with a school nurse. The control group (N = 16; 9 females/7 males) monitored glucose and followed either mixed split or intensive insulin management as prescribed by their health-care providers. The intervention group (N = 18; 8 females/10 males) monitored their BG and took their lunchtime insulins under supervision of school nurses. We adjusted the insulin dose as indicated by the BG record. We measured HbA1c at the beginning and at the end of the 3-month study period for both groups.

Results:
At the beginning, HbA1c was comparable in the control and the intervention group (11.2 ± 1.3% vs 10.8 ± 1.6%, $p = 0.56$). HbA1c in the control group was unchanged (11.2 ± 1.3% vs 11.5 ± 1.7%, $p = 0.40$), whereas HbA1c went from 10.8 ± 1.6 to 9.2 ± 1.1% ($p < 0.0001$) in the intervention group in 3 months.

Conclusions:
Direct supervision and GlucoMON improve HbA1c in children with poorly controlled T1DM.

Instrument and Method for Analyzing Metabolic Turnover Condition in the Body

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We provide an instrument and a method for analyzing the metabolic condition of a living body that can measure the metabolic condition of a living body correctly and easily. It is the approach of analyzing the metabolic turnover condition of the living body characterized by computing based on the fat free mass multiplier showing the rate of a basic fat-free mass, by analyzing a living body's energy metabolism condition. By analyzing a living body's energy metabolism condition, the method of analyzing the metabolic turnover condition is characterized by computing the formula delta DFT = DFT - aW; however, a multiplier a, based on the fat-free mass DFT and the basic fat-free mass. Here, a basic fat-free mass is a fat-free mass at the time of rest and fast (which is expressed by the numeric value which multiplied weight W by the fat-free mass multiplier a showing the rate of the basic fat-free mass to weight W). The fat-free mass multiplier a is or more 0.3 0.72 or less range, and is 0.7 or less (0.5 or more) preferably. It is the approach of analyzing a living body's metabolic turnover condition by analyzing a living body's energy metabolism condition. Two sets of fat-free masses DFTA which set the time of A and the back to B for the time of start at the different two times, and were measured at said different two times. It is based on DFTB, amount of body fat FTA and FTB or amount of body water H2OA, and H2OB. Variation detlaDFTAB of a fat-free mass, variation deltaFTAB of amount of body fat, and variation deltaH2OAB of amount of body water how to analyze the metabolic turnover condition of the living body characterized by computing based on the formula deltaDFTAB = DFTB - DFTA, deltaFTAB = FTA - FTB, deltaH2OAB = H2OB - H2OA. How to analyze the metabolic turnover condition of the living body characterized by computing the amount of energy production from fat tissue based on the variation of said amount of body fat. For formula EAB = (FTA - FTB) x b, however a multiplier b, the procedure that computes the amount EAB of energy production from said adipose tissues is the approach of analyzing the metabolic turnover condition of the living body characterized by what is expressed with the energy coefficient showing the amount of energy production from adipose tissues when 1 g of fats burns. How to analyze the metabolic turnover condition of the living body characterized by computing the oxygen demand when, as for formula oxygen consumption VO2AB in said adipose tissues expresses an oxygen consumption when, as for formula VO2AB = (FTA-FTB) x c/FTA/TAB, however c, 1 g of fats burns, and TAB be characterized by what is expressed with the time difference of between the two times. It can lead with b = 1.436 and c = 39.63 from formula 1 g fat + 2.023L-VO2 = 1.436L-CO2 + 1.07g-H2O + 39.63KJ-E showing the amount of water and energy. What was computed based on what was computed based on data which a fat-free mass, amount of body fat, or the amount of body water may be computed with what kind of calculation means, for example, were acquired by MRI, CT, height, and weight, and the measured value of bioelectrical impedance is measured (Japanese patent number: 3848818, application number: JP2000-225767).

Using Information Technologies for Diabetes Treatment in Siberia

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Introduction:
The Krasnoyarsk region has the largest Arctic territory in the Russian Federation. A problem of diabetes care in Siberia includes the giant size of the region and large distances from diabetes centers. Often the diabetic patient lives in far northern villages, without diabetes help. As a result, poor metabolic control, early development of vascular complications, and high mortality from acute and chronic diabetes complications occur. With the rapid development of computer technologies and telecommunication infrastructure, information and communication technologies for diabetes treatment have attracted considerable attention as a promising medical system. An ordinary Internet connection and telemedicine can provide benefits for patients, physicians, and medical professionals in distant Siberian areas.

Methods:
We assessed the feasibility of developing a virtual diabetes clinic for diabetic children and adolescents using the Internet. Our test case was a 3-year-old girl with type 1 diabetes living in the polar town of Svetlogorsk (about 2000 km from Krasnoyarsk). Type 1 diabetes was diagnosed in coma at the age of 2 years in the city Norilsk. The girl had clinic visits every 6 months and transmitted blood glucose information electronically to our clinic approximately every 2 weeks during the 6-month period. We used ordinary modem technology, connecting between an endocrinologist in Krasnoyarsk and a Svetlogorsk hospital. Hemoglobin A1c values were measured at 0 and 6 months.

Results:
Mean baseline GHbA1c values were 8.2 and 7.5% after 6 months.

Conclusion:
The use of modem technology for biweekly communication of blood glucose results and other diabetes-related information to a diabetologist was shown to be a viable alternative to clinic visits every 3 months.

Study to Compare the Injection Force Required for the Following Insulin Pen Devices: Lilly Disposable Pen, Novo FlexPen®, and SoloStar®

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Introduction:
This study (supported by Sanofi-Aventis) compared the injection force of three prefilled insulin devices: Lilly disposable pen (Eli Lilly, Indianapolis, IN), Novo FlexPen® (Novo Nordisk, Bagsvaerd, Denmark), and SoloStar® (sanofi-aventis, Paris, France), a new prefilled insulin pen for injecting insulin glargine and insulin glulisine.

Methods:
Injection force testing (the force required to dispense 40 units of insulin within 4 seconds) was performed in 210 pens: 60 Lilly disposable pens (30 NPH and 30 lispro), 90 Novo FlexPens (30 detemir, 30 NPH, and 30 aspart) and 60 SoloStar (30 glargine and 30 glulisine). All pens were fitted with Becton Dickinson Micro-Fine™ needles [0.25 mm (31 gauge) x 8 mm].

Results:
The injection force required to dispense 40 units in 4 seconds was 23.5 Newtons (N) for the Lilly disposable pen, 15.5 N for the Novo FlexPen, and 10.7 N for the SoloStar pen. Therefore, the mean injection force with SoloStar was 54.5% lower than the Lilly disposable pen and 31.0% lower than that measured for the Novo FlexPen. The peak dose force was 30.9, 22.9, and 14.4 N with the Lilly disposable pen, Novo FlexPen, and SoloStar, respectively. The SoloStar also exhibited a lower peak priming force (15.6 N), mean plateau force (12.2 N), and mean peak plateau force (12.6 N) compared with the Lilly disposable pen (26.1, 26.3, and 26.7 N, respectively) and Novo FlexPen (21.8, 16.9, and 20.0 N, respectively).

Conclusions:
The SoloStar has improved force characteristics, particularly a lower mean injection force and peak injection force, compared with the Lilly disposable pen and Novo FlexPen. This lower injection force can facilitate the injecting of insulin and may provide clinical benefits for people with diabetes with limited ability to inject insulin themselves.

User Acceptance of a Laptop-Based Algorithm to Establish Tight Glycemic Control in Medical Intensive Care Unit Patients

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Introduction:
Establishment of tight glycemic control (TGC) makes great demands on intensive care unit (ICU) nursing staff. Frequent blood glucose (BG) measurements are needed, and the majority of insulin titration protocols require intuitive decisions from the operating nurse. The aim of the present study was to evaluate user acceptance of a computer algorithm (eMPC) as a decision support system.

Methods:
An open randomized controlled study [supported by CLINICIP (FP6 IST-506965)] of 50 critically ill, mechanically ventilated medical patients was included for a study period of 72 hours. Patients were randomized either to a control group (n%) treated by a paper protocol implemented in the ICU or to an eMPC group (n%) using a laptop-based automated algorithm. The target range for BG was 4.4–6.1 m*M*. Efficacy was assessed by mean BG concentrations and BG sampling intervals, with safety by the number of hypoglycemic BG measurements <2.2 m*M*. At the end of the trial, each participating nurse was asked to fill in a standardized questionnaire.

Results:
Applying a shorter sampling interval (eMPC: 117 min (±34) mean (±SD) vs control: 174 min (±27), $p < 0.001$), the eMPC improved median BG significantly (eMPC: 6.0 mM (±0.7) vs control: 7.8 mM (±1.6), $p < 0.001$). One single BG measurement <2.2 m*M* was detected in the MPC group vs 0 in the control group. Thirty-four of 36 participating nurses filled in the standardized questionnaire. Thirty nurses positively answered the question whether BG control of their patient was more efficient using the eMPC algorithm. Twenty-eight voted that mistakes can be avoided using the eMPC algorithm. Thirty nurses thought that the present version can be used in the daily routine of an ICU.

Conclusion:
The use of the eMPC was well accepted. TGC applying the eMPC algorithm was improved significantly compared to standard care.

Variability of Nocturnal Glycemia Related to Severity of Sleep Apnea in Type 2 Diabetic Patients: Results of Continuous Glucose Monitoring

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Introduction:
Severe sleep-disordered breathing (SDB) with airflow obstructions and hypoxemias is suggested to affect diabetes control adversely. We assessed nocturnal glucose variability in diabetic patients with various degrees of SDB using continuous glucose monitoring (CGM, Medtronic MiniMed).

Methods:
Twenty-nine type 2 diabetic patients on diet/oral hypoglycemic therapy (19 males; aged 55.41 ± 7.5 years, body mass index 35.64 ± 8.46, diabetes duration 3.14 ± 1.48 years, hemoglobin A1c (HbA1c)/Diabetes Control and Complications Trial 6.85 ± 0.98%) were tested for SDB and divided into three groups: A, normal [apnea/hypopnea index (AHI) <10/h]; B, mild to moderate sleep apnea (AHI 10–25/h); and C, severe sleep apnea (AHI >25/h). Overnight glucose standard deviation (SD) and mean of nocturnal glucose differences (MOND) were calculated to assess the degree of nocturnal glucose variability.

Results:
Continuous glucose monitoring (r = 0.89 ± 0.15; MAD = 11.96 ± 6.0%) showed the most stable overnight glucose control in A (n = 15/46 profiles; MOND 1.7 ± 0.57 mmol/liter, SD 0.41 ± 0.13), less stable control in B (n = 6/19 profiles; AHI 12.73 ± 3.56/h; MOND 2.52 ± 0.77 mmol/liter, SD 0.63 ± 0.22), and most labile control in C (n = 8/21 profiles; AHI 42.08 ± 21.65/h; MOND 4.07 ± 2.12 mmol/liter, SD 1.05 ± 0.53). ANOVA showed significant differences ($p < 0.005$) in SD and MOND between A and B, and A vs C. Mean nocturnal glucose values were significantly higher in C than in A (9.01 ± 1.74 mmol/liter vs 5.84 ± 1.03 mmol/liter; $p < 0.0001$) and in B than in A (8.51 ± 2.42 mmol/liter vs 5.84 ± 1.03 mmol/liter; $p < 0.0001$). Significant differences in MOND and SD between B and C (both $p < 0.0001$), despite no significant difference neither in mean nocturnal glycemia nor in HbA1c, indicate that these parameters do not provide information about glycemic peaks or fluctuations.

Conclusions:
Although glucose variability is usually less pronounced in type 2 diabetics with endogenous insulin secretion, CGM results indicate that SDB in these patients may enhance nocturnal glucose variability, which increases with increasing severity of SDB, as compared to a type 2 diabetic state without sleep apnea.

Screening for Sleep Apnea in a Slovak Diabetic Population Using Simultaneous Recording of Ventilation, Respiratory Effort, Heart Rate, and Oxygen Saturation

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Introduction:
It has been shown previously that sleep-disordered breathing (SDB) is often associated with impaired glucose metabolism. Cardiovascular, neurocognitive, metabolic, and endocrine sequelae of untreated sleep apnea make early diagnosis and treatment of this disease important. Our aim was to perform screening for SDB in people with diabetes/prediabetes using a simultaneous recording of ventilation, respiratory effort, heart rate, and oxygen saturation.

Methods:
Twenty-eight consecutive adults (15 men, 13 women; 9 type 1 diabetics, 15 type 2 diabetics, 4 with prediabetes; aged 49.25 ± 14.89 years; body mass index (BMI) 30.81 ± 10.56; hemoglobin A1c/Diabetes Control and Complications Trial 7.15 ± 1.07%) underwent overnight home recording of respiration, oximetry, and pulse using ApneaLink oxi™ (ResMed Europe). The device automatically analyzes apnea/hypopnea index (AHI), flow limitation, and snoring based on recording time. A simple nasal cannula was used for sensing patient's breathing. Oximetry and pulse were detected using a reusable or single-use sensor. ApneaLink oxi software automatically generated patient reports with pulse and oximetry signals and detailed SpO_2 information and waveform data for the clinician to review.

Results:
Mild to moderate sleep apnea with an AHI 5–25/h was found in 13 investigated subjects (BMI 31.2 ± 11.36; AHI 11.46 ± 3.45/h; oxygen desaturation index/ODI 12.15 ± 5.4/h; Avg$SatO_2$ 93.08 ± 2.47%; Min$SatO_2$ 82.08 ± 5.22%). Moreover, more than 21% of the patients had severe sleep apnea with an AHI >25/h (n = 6; BMI 35.13 ± 7.05; AHI 49.83 ± 19.85/h; ODI 29 ± 13.21/h; Avg$SatO_2$ 91.33 ± 3.08%; Min$SatO_2$ 74.83 ± 5.04%). Only 32.2% of the samples had an AHI <5/h (n = 9; AHI 2.11 ± 1.17/h).

Conclusions:
Preliminary results demonstrated the clinical utility of ApneaLink oxi as a screening device for sleep apnea in diabetic and prediabetic subjects. Given the increased prevalence of SDB in the population with impaired glucose metabolism, a role for the screening for sleep apnea in this setting is warranted.

Changes in Nocturnal Glycemic Variability in Type 2 Diabetic Patients with Severe Sleep Apnea—Effects of Ventilation Therapy

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Introduction:
Previous studies have demonstrated that continuous positive airway pressure (CPAP) may improve insulin responsiveness in diabetic patients with severe sleep apnea/hypopnea syndrome (SAHS). Using the continuous glucose monitoring system (CGMS, Medtronic MiniMed), we sought to evaluate changes in nocturnal glycemic variability in diabetic patients before and under CPAP treatment of severe SAHS.

Methods:
Seven type 2 diabetic males (on diet/oral hypoglycemic therapy, aged 52.71 ± 6.34 years; diabetes duration 3.14 ± 1.07 years, hemoglobin A1c/Diabetes Control and Complications Trial 7.5 ± 0.87%, body mass index 39.09 ± 7.05) with severe SAHS underwent two overnight sleep studies with parallel CGMS, including a diagnostic night and CPAP night. Overnight glucose standard deviation (SD), coefficient of variation (CV), and mean of nocturnal glucose differences (MOND) were calculated to assess nocturnal glucose variability.

Results:
Continuous positive airway pressure decreased the apnea/hypopnea index significantly from 55.36 ± 18.66 to 5.84 ± 2.82/h ($p = 0.0008$). Thirty-six nocturnal CGMS profiles ($r = 0.89 \pm 0.11$; MAD = 10.79 ± 4.79%) showed significant changes in glucose variability between nights before and under CPAP as indicated by changes in SD (1.13 ± 0.43 vs 0.63 ± 0.2; $p = 0.0013$), CV (14.91 ± 5.01% vs 7.84 ± 3.66%; $p = 0.0083$), and MOND (4.28 ± 1.65 mmol/liter vs 2.48 ± 0.85 mmol/liter; $p = 0.0023$). Mean nocturnal glucose values and nocturnal $AUC_{>7,8(0-480\ min)}$ were significantly higher for diagnostic nights as compared to CPAP titration nights in the sleep laboratory. Despite significant decreases in glucose variability during all CPAP nights, no significant differences either in average glycemia or in $AUC_{>7,8(0-480\ min)}$ were observed during the CPAP nights at home because of frequent episodes of overeating, indicating that a balanced diet remains a crucial part of diabetes management.

Conclusion:
Continuous glucose monitoring system results in type 2 diabetics with untreated severe sleep apnea showed enhanced variability of nocturnal glycemia, which could potentially increase the risk for diabetic and microvascular complications. Findings suggested that CPAP might prevent apnea-related nocturnal hyperglycemic fluctuations, thus helping maintain a more stable glucose control.

Adaptive Meal Detection Algorithm for Enhancing Closed-Loop Control in Type 1 Diabetes

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Introduction:
An important prerequisite to optimal closed-loop control is accurate detection of glucose elevation following meals. In addition to patient-initiated meal announcement, two approaches are possible: retroactive—detecting glucose appearance in blood/interstitial fluid—and predictive—using prognosis based on analysis of biobehavioral patterns. While the former brings delays that make control difficult, the precision of the latter is limited by uncertainties inherent to any prediction.

Methods:
The proposed meal detector was developed and tested *in silico* using a computer simulator equipped with 30-day glucose "traces" of 100 virtual diabetic "patients." The algorithm was validated in a large data set containing 40-day continuous glucose monitoring traces: 120 type 1 diabetes mellitus (T1DM) and insulin-requiring T2DM patients collected in a clinical trial of the FreeStyle Navigator® (Abbott Diabetes Care, Alameda, CA).

Results:
We found that the optimal detector required two components interacting via the Bayesian probability rule: (i) a self-learning module analyzing glucose patterns and creating 24-hour personalized profiles of meal times updated daily and (ii) a prediction module based on autoregression analyzing sliding 45-minute data blocks and predicting glucose 30 minutes ahead. *In silico*, the combined algorithm achieved nearly 100% meal detection. *In vivo* experiments showed that in some subjects the algorithm identified other periods of increasing glucose, such as pronounced dawn phenomenon.

Conclusions:
Self-learning pattern recognition combined with real-time autoregressive meal detection is superior to autoregression alone. It is therefore important for closed-loop control to utilize adaptive methods that take advantage of accumulated information about patient behavior.

A New Blood Glucose Characterization Device Improves Glycemic Control

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Introduction:
It is difficult to prescribe an insulin regime if it is uncertain how an individual's blood glucose levels respond to the various inputs. Therefore, establishing good insulin regimes usually involves lengthy trial-and-error work. It is almost impossible to take all the factors into account without using some form of extensive data analysis.

Methods:
A software application was developed that analyzes continuous glucose data in response to various inputs, such as food intake, insulin administration, and exercise. A newly derived energy quantification unit called equivalent teaspoons sugar (ETS) was used as an improved predictor of postprandial glycemic response. Extensive databases make it easy to enter inputs such as food ingested during a test period. An accurate blood glucose simulation model is used to predict blood glucose profiles in response to the inputs. The model is then iteratively adjusted to reduce the error (difference) to a minimum by manipulating the parameters, such as insulin and ETS sensitivity. Furthermore, a newly defined rating called blood glucose control performance (BGCP), which takes into account the frequency of hypo- and hyperglycemia, average glucose levels, and tightness of control, is also measured by the device.

Results:
The device was retrospectively tested on 19 patients. Eight patients with poor BGCP were shown to have an average error (difference between simulated and actual dosage) in basal insulin regimes of 47%, whereas patients with good BGCP had regimes closer to our suggestions with an average error of 22%. Thus the calculated regimes are closer to the actual regimes of patients with good glycemic control.

Conclusions:
The blood glucose characterization device has a lot of potential in simplifying the task of achieving good glycemic control by the doctor. The said device uses the latest continuous glucose monitoring (CGM) technology. Therefore, it will stimulate CGM acceptance into the market and improve the service doctors offer their patients. Patent applications have been registered.

A New Insulin Bolus Calculator Improves Glycemic Control

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Introduction:
Insulin dosage calculation devices hold great potential. They have, however, so far proven to be expensive and lack user-friendliness and accuracy. They are not adequately suited to the demands of a typical diabetic patient's lifestyle. Outdated simple algorithms also contribute to the problem.

Methods:
A cellular phone-based bolus calculator was developed that utilizes extensive food and exercise databases. Furthermore, accurate patient blood glucose characterization is used to customize this product. A new accurate blood glucose simulation model is used that relies on more accurate inputs than merely grams of macronutrients. In fact, an accurate clinically tested generic energy unit that proved to be a more accurate measure of glycemic energy was derived and used. This unit, called equivalent teaspoons sugar, takes metabolic efficiency and true energy content into account. The new bolus calculator effectively addresses all the major concerns.

Results:
A clinical trial on type 1 diabetic subjects was conducted where an average reduction in glycated hemoglobin of 0.53% was recorded over 3 months. The reduction in HbA1c levels indicated that the patients' HbA1c levels were brought 32% on average closer to the American Diabetes Association's guideline for acceptable glycemic control. Furthermore, hypoglycemic and hyperglycemic frequencies were reduced by 1.92 and 1.50, respectively, for 11 trial subjects. All patients responded positively to the assistance of the device and its ability to calculate insulin boluses.

Conclusions:
A combination of accurate blood glucose simulation, accurate inputs, and aspects relating to the user-friendliness and perceptions of diabetic patients has shown that glycemic control can be improved using a mobile phone software application. Pharmaceutical companies might increase their brand awareness by sponsoring distribution of said basal regime calculator. It may also improve the quality of clinical trial results.

Closed-Loop Control and Advisory Mode Evaluation of an Artificial β cell: Use of Proportional-Integral-Derivative Equivalent Model-Based Controllers

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Introduction:
Diverse architectures for closed-loop control algorithms in type 1 diabetes management have been presented in the literature. Under certain conditions, several of these structures are equivalent, namely proportional-integral-derivative control, model predictive control (MPC), and internal model control. The subject of this study is the performance of such equivalent structures on an *in silico* subject and evaluation on clinical data in retrospective advisory mode.

Methods:
A glucose–insulin kinetic model was combined with an intravenous insulin delivery model. The inverse of this model was combined with a second–order exponential filter to form the controller. Model mismatches (structural and parametric) were introduced to the simulated subject. The system response to inputs of step changes of insulin infusion and unannounced meals was then analyzed. Advisory control was implemented using data obtained from glucose sensor and insulin pump records.

Results:
In the nominal case (no plant/model mismatch), filtered set point changes were perfectly tracked and meal disturbances were rejected while maintaining normoglycemia. Introducing mismatch of three parameters by 100% and increasing the order of the plant model, the set point was tracked best with a less aggressive controller, while the disturbance was best rejected by a more aggressive controller. Oscillatory controller action was observed with aggressive control. Advisory control made qualitatively sound recommendations and was sensitive to historical insulin delivery.

Conclusions:
Distinct controller settings are required for different simulation problems, thus motivating the use of a two degree-of-freedom controller, with one degree of freedom assigned to each task. Use of an MPC framework would be beneficial, as explicit penalties for oscillatory control action could be implemented. This study has also shown that MPC can be successful in advisory mode with simple models.

Realistic Finger Phantom for Noninvasive Monitoring of Glucose

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Introduction:
A noninvasive method for glucose monitoring will greatly improve the treatment and health of diabetic patients. For this purpose, OrSense Ltd. has developed the NBM, a fully noninvasive device for glucose monitoring, based on occlusion spectroscopy technology. In this study, the OrSense finger phantom was used to show the NBM optical device's capability of sensing glucose under strong physiological interferences. The phantom represents a realistic model of the finger that was validated via comparison to *in vivo* results.

Methods:
The finger phantom was designed to mimic the scattering and absorption properties of the finger in the red near-infrared spectral region using a mixture of Intralipid™ and red blood cells. Concentrations of glucose ranging from 0 to 1000 mg/dl were checked in parallel to changes in hematocrit and saturation. Transmission data were then analyzed by applying the *in vivo* NBM multiwavelength algorithm.

Results:
Analysis of data showed an increase of transmitted light concurrently with the increase in glucose concentration. This effect is attributed to changes of the refractive index induced by glucose. Applying our *in vivo* algorithm to the *in vitro* finger phantom, we showed that changes in glucose levels are monitored accurately with a correlation of 95%. Simultaneous changes in hematocrit and saturation levels do not interfere with our glucose prediction. Furthermore, the correlation between calculated levels of hematocrit and their reference values is above 99%.

Conclusions:
We developed a finger phantom that enables monitoring of realistic physiological processes. Using OrSense's NBM noninvasive glucose monitoring device, we demonstrated the capability of detecting glucose variations in addition to measuring other blood analytes.

Reduction of Hemoglobin A1c Resulting from 1 Month of Continuous Glucose Monitoring in Persons with Type 1 Diabetes on Paradigm® 722

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Introduction:
The insulin pump Paradigm® 722 (Medtronic MiniMed, Northridge, CA) enables daily reading of 288 glucose concentrations determined by a subcutaneously inserted sensor. Sensor signals are transmitted wirelessly into the pump, enabling one to see the glucose concentration on the display and adapting treatment. This study assessed the changes in hemoglobin A1c (HbA1c) concentrations in the course of a 12-week period with a nearly continuous use of glucose sensors in persons with type 1 diabetes on Paradigm 722.

Methods:
Ten previously educated type 1 diabetics 23 to 69 years old, diabetes duration 21.5 ± 3.5 years (mean ± SE), and insulin pump therapy 3.88 ± 1.19 years, underwent real-time continuous glucose monitoring (RT-CGM) over the 12-week period using the Paradigm 722 (insulin aspart) and enough consecutive continuous glucose sensors. All subjects performed intensive self-management according to their actual real-time glycemic trends and self-monitored glucose values. No special Bolus Wizard training was provided. HbA1c was determined at baseline and at 4-, 8-, and 12-weeks follow-up.

Results:
All patients actively used real-time values and alerts to control their glycemic fluctuations. HbA1c (IFCC, normal range 2.4–4.0%) decreased from 7.5 ± 0.75% at baseline to 6.3 ± 1.81% at the end of the 4th week ($p = 0.034$) and remained stable at 8-week (6.03 ± 0.52%) and 12-week (6.08 ± 0.52%) follow-up. Differences in HbA1c among the 4th, 8th, and 12th weeks were not significant. Thanks to early detection of developing hypoglycemia in real time with immediate appropriate treatment, we did not observe any serious hypoglycemia.

Conclusions:
Paradigm 722 with RT-CGM used over the 12-week period resulted in a significant improvement of HbA1c occurring as early as within the first month. However, these benefits remain limited by constant care for sensors and the transmitter.

Design and Validation of a Tool for Collection and Analysis of Episodic, Intensive Blood Glucose Monitoring Data in Primary Care Practice

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Introduction:
Episodic, intensive blood glucose (BG) monitoring by patients with type 2 diabetes (T2D) is recommended by the American Association of Family Physicians in situations of symptomatic hypoglycemia/hyperglycemia, addition or adjustment of medications, acute illness, stress, changes in nutrition and/or physical activity, and worsening hemoglobin A1c values. Because electronic download and analysis of BG data are often not practiced in the primary care setting, a paper-based tool was developed to facilitate collection and analysis of episodic, intensive BG data.

Methods:
A human factors study was conducted with 30 T2D subjects to determine if they could use the tool to collect episodic, intensive BG data. A subsequent study with 61 primary care physicians (PCPs) was conducted to determine if they could accurately identify glycemic abnormalities in data collected with the tool and if such data would influence their therapeutic choices.

Results:
Written BG data obtained from study subjects matched meter downloads >90% of the time. Survey results indicated that 90% of subjects were willing to complete the tool on a quarterly basis if asked to do so by their PCP. PCPs correctly identified glycemic abnormalities in BG data displayed on the tool 82% of the time. PCPs selected different therapies 82% of the time for cases with BG data compared to their selections for the same cases without BG data. PCPs (88.5%) found BG data to be of equal or greater value than hemoglobin A1c.

Conclusions:
These findings suggest that patients and PCPs can effectively utilize a paper-based tool for collection and analysis of episodic, intensive BG data in a primary care setting where electronic management of self-monitoring of BG data is usually not utilized.

Intermittent Hyperglycemia in Continuous Subcutaneous Insulin Infusion Use

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Objective:
Intermittent hyperglycemia in continuous subcutaneous insulin infusion (CSII) patients can result in diabetic ketoacidosis (DKA) and long-term control challenges. The goals of this study were to determine and categorize common causes of intermittent hyperglycemia and to suggest potential measures to prevent and treat the identified causes. When selected and trained properly, patients using CSII can see improvements in insulin dosage requirements, fasting and postprandial blood glucose levels, hemoglobin A1c levels, nocturnal hypoglycemia, insulin resistance, and quality of life.

Methods:
Endocrinologists, certified diabetes educators, and pump manufacturing company trainers were interviewed for their clinical observations. Manufacturers of CSII systems were contacted to determine incidence of reported hyperglycemia and relationships to pump failures, programming/patient error, and infusion set/catheter disruption. A literature review was conducted to obtain relevant information on hyperglycemia and CSII. Medical departments from Novo/Nordisk, Eli Lilly and Company, and sanofi-aventis were contacted requesting information on their insulin temperature stability, the compatibility of insulin with insulin/pump reservoirs, and tubing sets/catheters.

Results:
This study found that causes of intermittent hyperglycemia in CSII patients included problems with mechanical evaluation of the pump, basal/bolus review, reservoir/tubing, catheter site selection/placement, and insulin compatibility/stability.

Conclusions:
As more patients and health care providers strive to improve the control of diabetes, the use of insulin pump therapy will continue to increase. Unexplained hyperglycemia will continue to occur, which can lead to increased health care costs as a consequence of complications such as DKA. Evaluation of patient techniques and pump programming can uncover many potential causes, and the health care provider can assist in patient education to prevent further episodes.

Integrating Web-Based Video Conferencing, Distance Learning, and Electronic Medical Records in a Telemedicine Solution for Diabetes Management

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Introduction:
Telemedicine holds significant promise for the ability to manage patients with chronic problems, such as diabetes. Patients utilizing telemedicine may benefit from remote, Web-based video and audio conferencing with their physician. Additionally, the physician may leverage the same solution for patient education and share critical data with an electronic health record (EHR) system.

Methods:
In order to have patients participate from the comfort of their homes or offices, we had to use a Web-based video conferencing system. Anyone, anywhere can access this Web-based system anytime. Access is only contingent upon the patient meeting the minimum requirements of high-speed bandwidth and a webcam. Additionally, the physician has access to a Web-based EHR for clinical documentation and reference.

Results:
This strategy results in broader access to patients by eliminating geographic and mobility barriers. The integrated EHR solution provides a more efficient means of delivering remote care, while maintaining high-quality interaction. Patient education can be easily tailored to the specific patient, while allowing an opportunity to address questions and record the fact that the information was shared.

Conclusions:
Most of the telemedicine patients expressed the desire to continue with telemedicine visits, and many patients treated with traditional methods requested to be included in the telemedicine group. The system seems to be reliable, simple to use, and friendly for the patients. A Web-based telemedicine system can incorporate features that make it suitable for implementing a remote diabetes management program. Integration with an EHR directly improves the practice's efficiency and eliminates fragmented records.

Closed-Loop Control of Glucose Concentration in Subjects with Type 1 Diabetes: An *in Silico* Trial

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Introduction:
The artificial pancreas has been the subject of extensive research since the 1970s. However, the first devices, e.g., Biostator™, have been cumbersome, using intravenous insulin and glucose infusion. Nowadays, the availability of short-acting insulin permits avoiding excessive delays in subcutaneous insulin delivery and, together with new minimally invasive subcutaneous glucose sensors, has paved the way for successful implementation of an extracorporeal artificial pancreas. The major control problems remaining are time delays, constraints, meal disturbances, and nonlinear dynamics.

Methods:
Most of the control schemes proposed in the literature are based on either proportional-integral-derivative (PID) or model predictive control (MPC) laws. This work considered PID, MPC, and nonlinear MPC (NMPC) designed to maintain normoglycemia in subjects with type 1 diabetes. Performances were compared via an *in silico* experiment based on a model of the human glucose–insulin system during mixed meals. One hundred synthetic type I diabetic subjects were "followed" for 4 days, receiving breakfast, lunch, and dinner each day. Closed-loop control started after the first day dinner.

Results:
Simulation experiments show the advantages of MPC over PID due to the ability of MPC to account for constraints and meal announcement. State-feedback NMPC further improves glucose regulation due to the explicit consideration of the nonlinear dynamics.

Conclusions:
NMPC appears a very promising technique to maintain normoglycemia in subjects with type 1 diabetes. Nevertheless, most of the virtual patients considered are also well regulated by a linear input–output MPC scheme.

Integrating Web-Based Video Conferencing, Hemoglobin A1c, and Electronic Medical Records in a Telemedicine Solution for Diabetes Management

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Introduction:
Are forgotten or omitted insulin injections a major contributing factor to poor glycemic control in people with type 1 diabetes? The purpose of this study was to examine how much hemoglobin A1c (HbA1c) can be improved by remembering otherwise forgotten insulin injections.

Introduction:
Telemedicine holds significant promise for the ability to manage patients with chronic problems, such as diabetes. Patients utilizing telemedicine may benefit from remote, Web-based video and audio conferencing with their physician. Additionally, the physician may leverage the same solution for patient education and share critical data with an electronic health record (EHR) system.

Methods:
In order to have patients participate from the comfort of their homes or offices, we had to use a Web-based video conferencing system. Anyone, anywhere can access this Web-based system anytime. Access is only contingent upon the patient meeting the minimum requirements of high-speed bandwidth and a webcam. Additionally, the physician has access to a Web-based EHR for clinical documentation and reference.

Results:
This strategy results in broader access to patients by eliminating geographic and mobility barriers. The integrated EHR solution provides a more efficient means of delivering remote care, while maintaining high-quality interaction. Patient education can be easily tailored to the specific patient, while allowing an opportunity to address questions and record the fact that the information was shared.

Conclusions:
Most of the telemedicine patients expressed the desire to continue with telemedicine visits, and many patients treated with traditional methods requested to be included in the telemedicine group. The system seems to be reliable, simple to use, and friendly for the patients. A Web-based telemedicine system can incorporate features that make it suitable for implementing a remote diabetes management program. Integration with an EHR directly improves the practice's efficiency and eliminates fragmented records.

Methods:
Five sets of blood glucose profiles with and without a forgotten injection were obtained. The difference in HbA1c was calculated using an HbA1c estimator and was multiplied by the frequency of forgotten events. A frequency of 2.1 forgotten injections per week for pump users was found in the literature. Another study showed 58–65% of insulin taken as prescribed for adults in insulin therapy.

Results:
Calculations showed that a decrease in HbA1c of 0.26–0.38% points is possible by remembering 2.1 meal-related injections per week that would otherwise have been forgotten, and similar 0.33–0.55% points for long-acting insulin injections. In the unsatisfactory end of the adherence spectrum (using Cramer's numbers), there is a possible improvement of HbA1c of 2.3% points by remembering all injections.

Conclusion:
The magnitudes of the possible decrease in HbA1c agrees well with other studies in the relationship between adherence and HbA1c levels. Numbers suggest that missing injections are a major source for suboptimal treatment. HbA1c could possibly be improved by an intelligent insulin dosing device that reminds people with diabetes when an expected injection is forgotten.

Conclusions:
Most of the telemedicine patients expressed the desire to continue with telemedicine visits, and many patients treated with traditional methods requested to be included in the telemedicine group. The system seems to be reliable, simple to use, and friendly for the patients. A Web-based telemedicine system can incorporate features that make it suitable for implementing a remote diabetes management program. Integration with an EHR directly improves the practice's efficiency and eliminates fragmented records.

Acceleration of the Pharmacodynamic Profile of Insulin Delivered by Continuous Subcutaneous Infusion Pumps by Application of Local Heat

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Introduction:
A limiting factor in the prevention of postprandial glycemic excursions is the slow pharmacokinetic (PK)/pharmacodynamic (PD) profile of even rapid acting insulin analogs delivered subcutaneously. This is partly due to delays in insulin absorption from the subcutaneous space. The aim of this study was to test whether increasing local perfusion in the vicinity of a continuous insulin infusion catheter will accelerate the PK/PD profile of insulin analogs.

Methods:
Patients with type 1 diabetes were recruited to receive a standard 0.15 unit per kilogram insulin bolus using their own insulin pumps and insulin analog regimens. The bolus was given while performing a euglycemic clamp in order to evaluate its pharmacodynamic profile, with and without local heating of the vicinity of the catheter insertion site. Sixteen studies were performed with local heating and 14 were performed in control conditions.

Results:
The mean time to peak action (T_{max}) with local heating was 51.2 ± 13.2 vs 81.6 ± 23.7 minutes in control conditions ($p < 0.001$). The time to return to baseline infusion rates tended to be shorter when heating was applied. Local heating of the catheter insertion site caused a significant reduction of ~30 minutes in the T_{max} of in insulin action.

Conclusion:
Thus, applying this technique has the potential to reduce postprandial hyperglycemic excursions.

Predictive Monitoring for Improved Management of Glucose Levels

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Introduction:
Recent developments and expected near-future improvements in continuous glucose monitoring (CGM) devices provide opportunities to couple them with mathematical forecasting models to produce predictive monitoring systems for early, proactive glycemia management of diabetes mellitus patients before glucose levels drift to undesirable levels. This work assessed the feasibility of data-driven models to serve as a forecasting engine of predictive monitoring systems.

Methods:
We investigated the capabilities of data-driven autoregressive (AR) models to (1) capture correlations in glucose time-series data, (2) make accurate predictions as a function of prediction horizon, and (3) be made portable from individual to individual without any need for model tuning. The investigation was performed by employing CGM data from nine type 1 diabetic subjects collected over a continuous 5-day period.

Results:
With CGM data serving as the gold standard, autoregressive model-based predictions of glucose levels assessed over nine subjects with Clarke error grid analysis indicated that, for a 30-minute prediction horizon, individually tuned models yielded 97.6 to 100.0% of data in the clinically acceptable zones A and B, whereas cross-subject, portable models yielded 95.8 to 99.7% of data in zones A and B.

Conclusions:
This study showed that, for a 30-minute prediction horizon, data-driven AR models provide sufficiently accurate and clinically acceptable estimates of glucose levels for timely, proactive therapy and should be considered as the modeling engine for predictive monitoring of patients with type 1 diabetes mellitus. It also suggested that AR models can be made portable from individual to individual with minor performance penalties, while greatly reducing the burden associated with model tuning and data collection for model development.

Disclaimer:
The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Army or of the U.S. Department of Defense.

Health-Care Professional-Reported Usability of SoloStar® in a 3-Month Observational Survey in Everyday Clinical Practice

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Introduction:
SoloStar® (sanofi-aventis, Paris, France) is a new prefilled insulin pen device for the injection of insulin glargine and insulin glulisine. This study reported on the usability of SoloStar, as reported by health-care professionals (HCPs), in clinical practice.

Methods:
Individuals with type 1 diabetes (T1DM) or type 2 diabetes (T2DM) were eligible for this 3-month observational survey (supported by sanofi-aventis) conducted in Australia (November 2006–January 2007). Participants were supplied SoloStar pens containing insulin glargine, the instruction leaflet, and a toll-free help line number. Training was offered to all participants. Health-care practitioners [diabetes educators (DEs) and doctors] were invited to participate in one-on-one interviews during weeks 6–10 to examine their views on SoloStar.

Results:
Overall, 150 HCPs across 93 sites supported this survey. Of these, 65 HCPs (14 doctors; 51 DEs) provided feedback on ease of use and training in 1669 patients, with the remaining 85 HCPs unable to participate. All HCPs rated participant training as either "very easy" or "easy" [doctors: 12 (86%) and 2 (14%); DEs: 43 (84%) and 8 (16%), respectively], and most [doctors: 12 (86%); DEs: 47 (92%)] reported that SoloStar made training easier and quicker. Most HCPs spent <10 minutes training their participants [doctors: 14 (100%); DEs: 38 (75%)]. Similarly, all HCPs rated ease of use as either "excellent" or "good" [doctors: 11 (79%) and 3 (21%); DEs: 40 (78%) and 11 (22%), respectively]. The most frequently cited contributing factor to the "excellent"/"good" ease of use rating was that SoloStar was "better than others."

Conclusions:
In this survey of everyday clinical practice, HCPs considered SoloStar to be both easy to train and easy to use for people with diabetes.

Extensive Noninvasive Exogenous Wiener Simulation Modeling of Glucose for Type 2 Diabetic Patients under Free-Living Conditions

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Introduction:
This work took on the challenge of simulation modeling (i.e., prediction without the use of measured glucose) of the dynamic response of blood glucose in type 2 diabetic (TTD) subjects from an extensive set of noninvasive exogenous (i.e., input) variables under free-living conditions.

Methods:
The full model included three nutrients and 20 activity input variables. All data were sampled at 5-minute intervals for 25 consecutive days for one TTD subject. The first 20 days were used to build a Wiener model, and the next 5 days were used for cross validation. The strengths of the Wiener structure include a dynamic model for each input with phenomenological interpretation, the separation of dynamic and static model forms, and the modeling of nonlinear dynamic and nonlinear static behavior. The dynamic function for each input was second order, plus dead time, plus lead with four parameters each. The nonlinear static function was a second-order multiple linear regression function, including interaction terms, bringing the parameter total to 421 for the full Wiener model.

Results:
The final reduced model had only 11 variables and 115 parameters. Its training and testing fitted correlation coefficients equaled 0.80 and 0.65, respectively, strongly supporting its efficacy. Quantitative dynamic results and input spectra match periodic glucose responses quite well. In addition, this presents quantitative results for the residence time of all inputs, e.g., residence time.

Conclusions:
Consequently, this work represents a new paradigm of information to aid in the diagnosis, treatment, and glucose control of TTD people.

Role of Glycated Albumin as a Monthly Glycemic Index of Choice

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Introduction:
Recent studies suggest the importance of glycated albumin (GA) as a more dynamic (intermediate in time—20-day half-life) indicator of diabetes control than glycated hemoglobin (A1c) tested every 3-6 months. This is especially true in gestational diabetes (GD) and in the growing population of type 2 diabetic patients, where oscillations in blood glucose may be of significance. Because of its dependence on renal tubular absorption, the short-term indicator, 1,5-anhydroglucitol, is probably not useful in monitoring GD. Another intermediate indicator, the fructosamine assay, has proven unreliable due to the influence of intercurrent disease factors, biochemical interference, and baseline standardization problems. For many patients, a monthly report of overall glycemic control offered by GA measurement could be vital to effectively limit and manage hyperglycemia. Epinex has developed a system capable of rapid measurement of GA for POC and OTC testing.

Methods and Results:
The system is composed of a dual channel test strip capable of measuring GA and total albumin simultaneously from a 40-µl blood sample using immunochromatography. A hand-held monitor is being designed that calculates the GA percentage as a ratio of the measured values, stores information, and performs trend analysis. Signal strength analysis and frequency produced by antibody complexes formed by GA and total albumin are presented as relevant to serum values obtained by affinity chromatography and ELISA.

Conclusions:
In conclusion, GA has been directly implicated in atherosclerosis (macroangiopathy) and microangiopathy and in nephropathy independent of hyperglycemia due to GA interacting with renal mesangial cells. Thus, unlike blood glucose measurement, GA may represent a direct measure of organ damage and complications from diabetes. This technology in the hands of diabetic patients can foster self-empowerment and enhance the ability to control glycemia.

Prevalence and Predictors of Metabolic Syndrome in Saudi Women with Polycystic Ovary Syndrome: A Prospective Study

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Design:
A prospective case control study.

Setting:
Tertiary Referral University Hospital.

Subjects:
Six hundred Saudi women living in the Jeddah area were classified as follows: 300 with polycystic ovary syndrome (PCOS) and 300 age-matched women without PCOS.

Interventions:
Blood samples were collected from all women with or without PCOS between 8:00 and 11:00, after an overnight fast.

Main Outcome Measures:
Measures included abdominal obesity, blood pressure, and serum levels of lutenizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, free thyroxine, 17-hydroxyprogesterone, androstenedione, dehydroepiandrosterones, total and free testosterone (T), sex hormone-binding globulin, insulin, high-density lipoprotein cholesterol (HDL-c), triglycerides, and plasma levels of glucose. Measures of insulin resistance (IR) included fasting serum insulin, glucose infusion rate, and homeostatic model assessment.

Results:
The age-adjusted prevalence of metabolic syndrome (MBS) was higher in women with PCOS (53.5%, 95% CI: 37.6–61.2%) as compared with women without PCOS (14.7%, 95% CI: 10.2–18.6%) ($P < 0.000$). In the same age group, the risk of MBS in women with PCOS was greater than that for women without PCOS ($P < 0.001$). Markers of IR were significantly abnormal in women with both PCOS and MBS in comparison to those without MBS ($P < 0.001$). The most common abnormal components of MBS in women with both PCOS and MBS (after adjustment for age) were decreased HDL-c (83.1 ± 10.5%), increased triglycerides (53.4 ± 7.7%), and increased body mass index (38.2 ± 4.6%), respectively. The prevalence of MBS from lowest to highest tertile of free T level was 20.1, 33.7, and 54.2%, respectively, in women with both PCOS and MBS. In women with PCOS, 9% exhibited all five components of MBS, 14.1% had four components, and 40.5% had three components.

Conclusions:
Women with PCOS exhibited a significantly higher prevalence of MBS (3.6-fold) as compared with age-matched controls without PCOS. IR is a possible common pathogenetic factor for both MBS and PCOS. It is suggested that more intensive screening and/or therapy monitoring of MBS among women with PCOS should be part of the therapeutic modalities of the condition.

Innovations in Continuous Glucose Monitoring

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The GlucoDay®S (A. Menarini Diagnostics, Florence, Italy) is a portable device that measures the glucose concentration in subcutaneous tissues continuously by means of a microdialysis technique. It has been already shown to be accurate for 48 hours in diabetic patients (types 1 and 2). Since its first appearance in the European market (2002), several clinical studies have been performed on the GlucoDay system to investigate potential new applications of the system. The most important clinical trial sponsored by A. Menarini on the GlucoDay S was performed on 80 pregnant woman (20 type 1; 20 GDM; 40 normal). The study was conducted in three centers in Italy to investigate the correlation between glycemic profiles and fetal outcomes. Results showed a strong correlation between postprandial glucose areas and fetal fat body mass measurements during the third trimester of pregnancy. The GlucoDay S offers the possibility of maternal glucose control, essential for normalization of fetal growth during pregnancies complicated by glucose intolerance such as gestational diabetes. Other studies have been conducted to investigate potential applications of the GlucoDay S in different settings, such as in the intensive care unit. New prediction algorithms for the GlucoDay S are currently under development at the University of Padua (Italy). Data obtained from 20 diabetic patients (types and 2) are currently under investigation to create a prediction algorithm and hypo- and hyperglycemia alarms in order to prevent negative events 30 minutes before their appearance. A new generation subcutaneous glucose measuring device (GlucoMen® Day), based on the microdialysis principle, has been developed by A. Menarini Diagnostic S.r.l. The GlucoMen Day is a relatively light (170 g) and small (10 x 8 x 2 cm) wearable device controlled by a Palm via a wireless connection (Bluetooth). It has been tested extensively *in vitro* and *in vitro*. A multicenter study is ongoing in seven European centers, employing 70 diabetic patients (types 1 and 2). A. Menarini Diagnostics is also looking for new noninvasive technologies in continuous glucose monitoring. Extensive bench studies have been performed on Raman scattering. The idea is to develop a new noninvasive glucose monitoring system based on the unique behavior of glucose when it is beat by a laser beam. The response of glucose is a fingerprint able to distinguish it from all other analytes, eliminating the effect of interference.

Automated Discontinuous Venous Blood Sampling System for Glucose Determination of Intensive Care Unit Patients

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Introduction:
Intensive insulin therapy to establish normoglycemia reduces mortality and morbidity in critically ill patients. Frequent or continuous glucose monitoring is restricted in this population group because of the high workload that has to be performed by staff. Hence usage of an automated discontinuous venous blood sampling system might be an alternative to improve the adjustment of insulin therapy. The primary aim of this study was to investigate whether the glucose concentration of automatically withdrawn blood samples correlates with manually withdrawn blood samples.

Methods:
In a 30-hour trial, six volunteers were investigated (male/female: 6/0; age 28.2 ± 2.04 years, body mass index 23.0 ± 2.04 kg/cm^2, nondiabetic subjects). Two venous cannulae were inserted into the dorsal hand for reference measurement and for connection to the automated blood sampling system. To enable a better dynamic range of the glucose signal, four meal ingestions were given to the subjects. Pressure, air bubble sensor, and flushing fluid monitoring were integrated into the system as safety features. Blood samples were obtained frequently in 15/30/60-minute intervals. After centrifugation, plasma glucose readings were determined using a Beckman Coulter glucose analyzer.

Results:
The study was finished successfully in all six volunteers. The mean blood volume per automatically withdrawn blood sample was 302.75 ± 42.74 ml. The median Pearson coefficient of correlation between uncalibrated manually and automatically withdrawn blood samples was 0.976 [0.953–0.996]. Implementing a "keep vein open rate" into the automated blood sampling system reduced blood withdrawal failures through occluded catheters from 2.11 to 0.56%. A total of 420 data pairs were analyzed via the recently published "Insulin Titration Error Grid Analysis," and 100% of data suggest an "acceptable treatment." Results of traditional "error grid analysis" showed that 98.6% (414) and 1.4% (6) of data were in zone A and zone B, respectively.

Conclusions:
(1) The automated discontinuous blood withdrawal system provides stable and reproducible blood samples from a peripheral vein. (2) Implementing a "keep vein open rate" reduces catheter block. (3) This system is a promising alternative to frequent manual blood sampling at an intensive care unit. (4) In combination with a glucose sensor and an algorithm it might be used in the future as a closed-loop system for insulin and glucose infusion.

An Approach to Solving the Basic Hurdles to Develop an Artificial Pancreas

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It is well established that intensive control of glucose in type I diabetes requires a monitoring schedule that many find difficult to maintain. A solution is the "artificial pancreas," a combination of an infusion pump, an implanted glucose monitor, and a controller/power supply. Ideally the pump would be implanted and capable of pumping at a speed to match the signals from a glucose monitor during periods of activity and rest, sleep and awake, and during and after meals, as well as providing baseline insulin delivery. A pump design that could provide the required performance is based on a thin film NiTi shape memory alloy acting as a diaphragm element with appropriate check valves. An implanted pump would require a means for recharging the associated controller/power supply. Recent developments involving remote power, such as multiturn printed loop antennas, could be used for telemetry for performance monitoring, as well as providing a means for charging a lithium ion battery. The most difficult aspect of any concept for an artificial pancreas is the stability of the glucose monitor. When implanted the typical electrochemical monitor based on bovine enzyme has a very limited life, suffering from tissue reaction at the implantation site. Past studies of the problem showed that depositing slow-release microspheres containing an anti-inflammatory agent such as dexamethasone at the monitor site provided protection for the monitor of up to 1 month. An alternative for drug delivery would be to add a second thin film pump that, like the insulin pump, would be refilled by a percutaneous hypodermic syringe. The implanted controller would control both pumps. These concepts are discussed in this presentation.

Impact of Insulin Infusion Pump Accuracy

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Introduction:
Today's insulin infusion pumps are based on the syringe drive principle. Debiotech developed the insulin Nanopump™, a membrane pump fabricated using microelectromechanical system (MEMS) technologies with a microscopic stroke volume of 200 nl. We demonstrated the superior infusion accuracy of this pump and investigated theoretically its impact on the insulin concentration in blood plasma.

Methods:
We measured the infusion accuracy (trumpet curve) of different insulin infusion pumps according to the IEC 60601-2-24 standard. We adapted a simple theoretical pump model to obtain similar trumpet curves. Using a mathematical model for rapid-acting insulin analogue pharmacokinetics, we simulated flow rate variations impact on the plasma insulin concentration.

Results:
Flow variation measurements showed considerable short-term deviations from the set flow rate for syringe drive pumps. Deviations larger than 10% are the rule for 2 U/h. For 0.5 U/h, deviations exceed 15% on a 15-minute average. The insulin Nanopump showed deviations smaller than 5% for large and small flow rates. A pure random noise model does not reproduce the observed syringe drive trumpet curves well. Their flow rate deviations show a correlation over more than 30 minutes. Introducing such a correlation in the noise source, the trumpet curves can be modeled well. The long-term correlations have a significant impact on the simulated plasma insulin concentrations. Resulting deviations from the equilibrium concentration are larger than 5%.

Conclusions:
The MEMS pumping mechanism in the insulin Nanopump offers extremely small flow rate deviations in comparison to conventional syringe drive pumps. Flow rate deviations of syringe drive pumps are not completely random but are correlated over longer periods, which have a considerable impact on the insulin concentration in the blood plasma.

Validation of the SoloStar® Pen

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Introduction:
Insulin pens offer greater convenience, portability, discretion, and ease of use over vials/syringes. The objective of this study (supported by sanofi-aventis U.S. Group) was to validate SoloStar®, a new disposable insulin pen developed for use with insulin glargine.

Methods:
This single-center, open-label, single-arm, sequential trial enrolled subjects aged 21–78 years with type 1 or type 2 diabetes. After face-to-face training (part 1) or self-training (part 2), subjects performed three dose-delivery repetitions into an injection pad using separate pens; pens were weighed before and after each dose delivery. The primary end point was the proportion of subjects delivering successful doses with all three repetitions. For each part, validation was achieved provided the 95% lower confidence bound (LCB) on the chance for successful dose delivery on all three repetitions exceeded 90%. Secondary end points included accuracy and precision of the subject delivered dose.

Results:
In part 1, all 50 subjects in the validation population delivered each dose successfully (100% success rate; 95% LCB, 94.2%). In part 2, 53 of the 54 validation subjects completed dose deliveries successfully (98% success rate; 95% LCB, 91.5%). The mean dose delivered was 40.2 units [95% confidence interval (CI), 40.1–40.3 units] for 86 subjects in part 1 and 38.0 units (95% CI, 36.7–39.3 units) for 95 subjects in part 2 (study populations); 99 and 88% of dose repetitions in parts 1 and 2, respectively, were within 38–42 units.

Conclusions:
This study successfully validated the SoloStar pen device for use by subjects with type 1 and type 2 diabetes mellitus, with or without face-to-face training. Subjects using the SoloStar pen device accurately delivered the dose that was dialed. There were no adverse events or pen malfunctions.

Using a Computerized Student–Patient Encounter Log System to Diagnose Septic Arthritis of the Lower Extremity: A Case-Control Study

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Introduction:
In 2001–2002, the California School of Podiatric Medicine (CSPM) introduced a computerized student–patient encounter log (CSPEL) system to replace the handwritten sheets that students used to describe their patient contacts. The CSPEL allows for the diversity and frequency of student–patient interactions to be monitored and allows for gaps in students knowledge to be easily identified and remedial measures taken. Septic arthritis is a serious rheumatological condition that is generally considered to be more common in diabetic patients than in the nondiabetic population. Little is known about how podiatric medical students diagnose septic arthritis.

Methods:
A case-control study design was employed. Sixty-two patients with a primary diagnosis of septic arthritis of the lower extremity were compared to sixty-two control patients. Data from the CSPEL were extracted and analyzed to compare the diagnosis of septic arthritis of the lower extremity with control patients.

Results:
Students made sixty-two primary diagnoses of septic arthritis of the lower extremity between 2001 and 2004. Most of the patients diagnosed with septic arthritis of the lower extremity were from CSPM training sites in California (31). Septic arthritis patients were more likely than control patients to have a secondary diagnosis of an infection-related disease. The most frequently diagnosed secondary diagnoses were limb pain, walking difficulty, and diabetes mellitus, with neuropathy.

Conclusion:
Use of the CSPEL indicates that podiatric medical students made only sixty-two primary diagnoses of septic arthritis of the lower extremity, suggesting that they may be familiar with the septic joint from their didactic courses but that exposure to this condition during clinical rotations is limited.

Blood vs Interstitial Glucose Dynamic Fluctuations: The Nyquist Frequency of Continuous Glucose Monitors

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Introduction:
It is commonly accepted that interstitial glucose (IG) levels are related to blood glucose (BG) concentration through a diffusion process. We hypothesized that fast variations in BG will be absent from IG and used signal processing to investigate the consequences of BG/IG interplay. Characterization of the BG/IG process is crucial to any application using IG levels to estimate BG, e.g., continuous glucose monitors (CGM).

Methods:
Minutely data were collected from 26 subjects wearing two Navigator® CGMs for 21 ± 3 hours in addition to very frequent finger stick measures (15 ± 5/day). Raw sensor output was treated by signal processing followed by Fourier analysis. Physiological and noise processes were differentiated using noise spectral characteristics and low-band vs high-band power-variance comparison.

Results:
As reported previously, the Nyquist sampling period (NSP) for BG is ~10 minutes. In contrast, the highest detectable frequency in IG has a period of 30 minutes, which corresponds to a NSP of 15 minutes. IG variation is represented primarily by fluctuations (waves) with 2- to 24-hour periods. From peak power at 8–14 hours, the signal strength declines until it is indistinguishable from additive white noise for periods less than 33 ± 4 minutes.

Conclusions:
Diffusion between BG and IG acts as a low-pass filter: high-frequency BG variations are dampened by the BG/IG process. Using Nyquist methodology, IG levels can be fully reconstructed with a sensor that produces readings every 15 minutes.

Pharmacokinetics and Pharmacodynamics of VIAject™ and Insulin Lispro When Injected Subcutaneously Immediately before a Meal in Patients with Type 1 Diabetes

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Introduction:
The aim of this study was to investigate the effect of VIAject™ (a very rapid acting formulation of regular human insulin) and insulin lispro on postprandial blood glucose (BG) excursions after a standardized meal in patients with type 1 diabetes who routinely use rapid-acting insulin analogues for prandial insulin coverage.

Methods:
The BG of 10 patients with type 1 diabetes (4 males and 6 females; age 37 ± 12 years, body mass index 24.0 ± 2.6 kg/m^2, HbA1c 7.7 ± 1.3%) in this cross-over study was stabilized by means of a glucose clamp (target BG 120 mg/dl) prior to meal ingestion. Glucose infusion was turned off prior to insulin injection, followed by a standardized meal. The insulin dose was individually based on patient's experience, and the same dose was administered for both VIAject and lispro on two study days. Postprandial glucose excursions were monitored for 8 hours. Glucose infusion was reinitiated if BG <60 mg/dl. Plasma insulin levels were determined throughout the study.

Results:
Mean insulin T_{max} was reached faster with VIAject (29 ± 23 minutes) than with lispro (58 ± 28 minutes; $p < 0.05$). BG excursions in the first 3 hours following the meal were higher with lispro (peak BG 176 ± 47 mg/dl at 54 ± 22 minutes) than with VIAject (159 ± 29 mg/dl at 42 ± 27 minutes). The difference between maximal and minimal BG was less for VIAject (73 ± 18 mg/dl) than with lispro (96 ± 20 mg/dl; $p < 0.05$). More glucose was infused to prevent hypoglycemia with lispro (mean 1303 mg) than with VIAject (394 mg). The total BG AUC(0–480 min)>140 and <80 mg/dl was 90,257 mg/dl*min for lispro and 57,115 mg/dl*min with VIAject.

Conclusions:
The rise in BG following a standardized meal was reduced more by injection of VIAject compared to lispro and was confirmed by VIAject's statistically significant faster insulin T_{max}. The risk of late postprandial hypoglycemic events was lower with VIAject, demonstrating better postprandial glycemic control than lispro in these patients.

Search for Complementary Biomarkers for Metabolic Control in Type 2 Diabetic Patients

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Introduction:
Ischemia-modified albumin (IMA) is a new biochemical marker of ischemia, which may be useful in characterizing acute coronary syndrome patients (ACS), but there is concern that IMA concentrations may be affected by ischemia occurring in tissues other than the myocardium. Advanced oxidation protein products (AOPP) are new markers of oxidative stress and inflammation discovered in plasma of dialysis patients. Because diabetic patients have increased inflammation in parallel with oxidative and carbonyl stress, we hypothesized that IMA and AOPP levels should also be higher than in control patients. We correlated AOPP with IMA, advanced glycated end products (AGEs), and glycemic control (supported by Touro and Showa Universities).

Methods:
Ischemia-modified albumin was measured by a test based on an ischemia-induced decrease in cobalt 2+ binding to an N-terminal octapeptide in the albumin molecule. Determination of AOPP is based on spectrophotometric detection according to Witko-Sarsat and colleagues. Determination of AGEs is based on spectrofluorimetric detection.

Results:
Ischemia-modified albumin levels are higher in type 2 diabetic patients (24% higher, $p < 0.001$) than in their matched controls, even in the absence of ongoing myocardial ischemia. AOPP were significantly elevated in this population, even in the absence of renal failure (44 % higher, $p < 0.01$) in diabetic patients. A low, but significant, correlation was found between IMA or AOPP and glycemia in diabetic patients. If IMA is used for the diagnosis of ischemia in diabetic patients, our work suggests that special reference ranges should be derived for this population.

Conclusions:
Data suggest that AOPP and IMA changes in diabetic patients reflect two different altered pathways and could be complementary biomarkers of oxidative and hypoxic stress in these patients.

Development of GLP-1 Technosphere® Powder: An Inhaled GLP-1 Product

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Introduction:
Technosphere® technology is a platform for the pulmonary delivery of therapeutics that are usually dosed parenterally. GLP-1 Technosphere, an inhalable, dry powder formulation of GLP-1, was developed to control postprandial hyperglycemia in patients with diabetes. The pharmacokinetic profile of GLP-1 administered as GLP-1 Technosphere powder was evaluated in Sprague–Dawley rats.

Methods:
GLP-1 was adsorbed onto Technosphere particles using a proprietary process to prepare inhalation powders containing 5, 10, or 15% GLP-1 (w/w). GLP-1 content was assayed using high-performance liquid chromatography, and aerodynamic powder performance was evaluated using Andersen cascade impaction. Female Sprague–Dawley rats (n = group) were administered 0.12 mg GLP-1 in solution (pulmonary instillation) or GLP-1 Technosphere powder containing 0.12, 0.19, or 0.37 mg GLP-1 (pulmonary insufflation). Plasma-active GLP-1 concentrations were evaluated.

Results:
The drug content of each powder was within 10% of target, and at least 30% of the particles exhibited an aerodynamic diameter less than 5.8 μm. Following insufflation of 0.12, 0.19, or 0.37 mg GLP-1, maximum plasma GLP-1 concentrations (C_{max}) were 2.3, 4.9, and 10.2 nM. Exposure also increased with increasing GLP-1 dose: 57.1 nM/min (0.12 mg), 92.6 nM/min (0.19 mg), and 227.9 nM/min (0.37 mg). Time to maximum GLP-1 concentration was approximately 10 minutes, and the half-life of GLP-1 was approximately 10 minutes. GLP-1 Technosphere produced higher GLP-1 C_{max} and exposure than GLP-1 alone.

Conclusions:
GLP-1 Technosphere powders with suitable aerodynamic performance produced dose-related increases in plasma GLP-1 concentrations after single-dose administration by pulmonary insufflation in Sprague–Dawley rats. GLP-1 C_{max} was achieved at approximately 10 minutes postdose with detectable levels at 40 minutes postdose.

Patient History Predicts Pregnancy Outcome in Diabetic Patients

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Purpose:
This study identified risk factors at first diabetes counseling session to aid in triaging the patient to the appropriate level of obstetric and neonatal care.

Materials and Methods:
Diabetic patients were referred in 2006 to the California Diabetes and Pregnancy Program for consultation. Multifetal pregnancies and congenital anomalies were excluded. Pregravid body mass index (BMI) was calculated per Institute of Medicine BMI guidelines. Macrosomia was defined as birth weight >4000 g. The fetal demise (IUFD) rate was calculated per 1000 births. Data were analyzed by ANOVA, regression analysis, and discriminant analysis. A p value of <0.05 was considered significant.

Results:
Of 8641 patients, 54.3% were Hispanic, 20.7% Caucasian, 12.0% Asian, and 3.1% Black. Of these patients, 50.1% had Medi-Cal and 45.7% had other insurance coverage. Only 1.1% delivered before 32 weeks. Blacks had the highest rate of obesity (63.0%) and Asians had the lowest (13.6%)($p < 0.001$). The rate of macrosomia increased with BMI from 2.5 to 14.9% ($p < 0.001$) and was similar between diabetic groups, as well as between insulin and oral agent groups. Among ethnicities, the rate of primary cesarean delivery (CD) was higher in Blacks (34.7%) and Caucasians (28.1%) than others ($p < 0.005$). The rate of neonatal intensive care unit (NICU) admission increased with BMI from 4.4 to 10.4% ($p < 0.001$). In discriminant analysis, type 1 (T1) and T2 diabetes predicted the risk for IUFD and NICU admission, whereas high maternal BMI predicted the rate of macrosomia and CD.

Maternal and Fetal Complications by Type of Diabetes

	T1-DM	T2-DM	GDM	IGT	
n (%)	175 (2.1)	662 (7.8)	7425 (87.3)	246 (2.9)	*p* value
Obesity (%)	29.3	72.7	44.4	31.1	<0.001
Macrosomia (%)	22.3	17.8	10.6	11.2	NS
IUFD/1000 births	21	27	3	0	<0.001
Primary CD	41.4	32.7	21.9	15.6	<0.001
NICU admission	24.8	20.8	8.2	7.1	<0.001

Conclusion:
T1 and T2 diabetic subjects had the highest risk of IUFD and NICU admission. Rates of fetal macrosomia and CD increase with maternal BMI. These findings can aid in triaging diabetic patients to the appropriate level of care for optimum delivery and neonatal care.

Maternal Glucose Excursions Detected by Continuous Glucose Monitoring Predict Large Birth Weight

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Introduction:
This study tested the hypothesis that maternal blood glucose (BG) excursions correlate with newborn birth weight (BW).

Methods:
Patients were recruited at the Stanford University obstetric clinic for 3-day continuous glucose monitoring (CGM) at around 27 weeks and a glucola screen at 28 weeks gestation. Data were collected prospectively. Patients and caregivers were blinded to CGM results. A "hyperglycemia index" was calculated by measuring the magnitude and duration of BG above 110–140 mg/dl. A BW centile was calculated.

Results:
Twenty-three patients consented, 21 completed the study, 1 with elevated glucola, 1 type 2 diabetes mellitus (T2DM), and 3 T1DM. The duration of CGM was 3.0 (±0.3) days. Among 17 nondiabetic patients, 10 had several BG excursions above 130 or 140 mg/dl (range, 2–338 episodes). Gestational age at delivery was 38.4 (±1.5) weeks, mean BW was 3393 (±543) g, with 12 newborns (57%) having a BW centile >50 and 4 >90. A positive correlation was observed between BW centile and hyperglycemia index above 130 and 140 mg/dl, $p < 0.03$ and < 0.05, respectively. A similar pattern existed among the diabetic subjects. No significant correlation was noted between BW centile and glucola, fasting BG, or average 3-day BG values.

Conclusions:
Ten of 17 nondiabetic pregnancies had several BG excursions above 130 and 140 mg/dl. The hyperglycemia index is a better predictor of above average BW than glucola, fasting BG, and average BG values in a mixed diabetic and nondiabetic population. Fetal exposure to maternal glucose excursions may play a role in large BW, even in nondiabetic patients with apparently normal glucose tolerance.

Effect of a Slow Release Formula (Glucerna SR) on the Risk of Hypoglycemia and Blood Glucose Profile

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Introduction:
Diabetes mellitus type 1 is frequently characterized by instability of the glucose values, both fasting and in the postprandial period. A remarkable cause of this is the frequent occurrence of hypoglycemic episodes. In the first years of the disease the phenomenon of counterregulation causes unpredictable swings. Later on in the course of the disease, when hypoglycemia unawareness supervenes, the fear of hypoglycemia tends to limit an effective antihyperglycemic therapy and frequent overreaction to the episodes aggravates the waning of the insulin levels.

Methods:
In an effort to eliminate glucose instability, we used a slow release formula of carbohydrates (CHO) during continuous glucose monitoring (CGM). We used the S gold device (Medtronic) with the Medtronic Sof glucose sensor for 4 consecutive days and 4 nights on 12 type 1 diabetic subjects with a disease duration of 8–18 years (M+DS), CGM was started at 12 AM of the 1st day and was interrupted at 12 AM of the 4th day. During the first 2 days the subjects followed their usual diet and lifestyle. On the 4th day, 100 cc of a slow release formula (Glucerna SR) was started after dining and in the interprandial period. The CHO content of the diet was reduced an equivalent amount. We focused our attention on five topics: number of hypoglycemic episodes (Hypos), conventionally set at a value <70 mg/dl; lowest BG recorded during the episodes (lowest BG, mg/dl); time spent at <70 mg/dl (time down, hours); time spent at >180 mg/dl (time up, hours); and maximum BG level reached during time spent at >180 mg/dl (highest BG, mg/dl).

Results:
Results are found in the following table:

	No. Hypos	Lowest BG	Time down	Time up	Highest BG
Before Glucerna SR	**3**	**32**	**7.21 ± 5.4**	**10 ± 3**	**350**
With Glucerna SR	**0.83**	**68**	**0.79 ± 0.59**	**1.41 ± 1.3**	**275**
P	**0.001**		**0.034**	**0.001**	**NS**

Conclusion:
Addition of a formula of slow release CHO, with fibers and many nutrients at bedtime, before physical activity, and in the interprandial period, reduced the number of hypoglycemic episodes, time spent in hypo- and hyperglycemia, and the highest and lowest glucose levels during the period of observation.

Toward DNA Molecular Devices for Insulin Release

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We used DNA-based functional elements, such as DNA recognition elements (aptamers) and DNA enzymes (deoxyribozymes), to construct molecular devices for insulin release from the surface of microscopic beads. The first type of device is based on DNA aptamers that recognize small molecules and release insulin in the form of an active oligonucleotide–PEG conjugate. We demonstrate that beads coated with such a device can release several pulses of insulin when triggered by a small molecule drug. The second type of device is based on polycatalytic–DNA enzyme assemblies with phosphodiesterase activity, which releases such conjugates through a cleavage reaction. We also discuss progress in the construction of glucose-sensitive recognition regions that could potentially be incorporated into DNA molecular devices to achieve a closed-loop insulin release system capable of physiological response to changes in glucose concentrations.

Glucometrics: One System's Journey to Measure Success with a Diabetes Initiative

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Although glycemic target ranges have been recommended for hospitalized acute care and intensive care unit (ICU) patients, no consensus exists on how a single hospital or hospital system can gauge its success over time or measure its improvement compared to others. We detailed the 5-year evolution of glucometrics at our four acute-care hospital system, as well as where to go next. Our diabetes measurement journey began in 2002 when we launched our system-wide diabetes initiative. We analyzed all available blood glucose (BG) results in our electronic documentation systems. Using this rich data set we created rules, such as grouping closely timed BGs, to increase the validity of the analyses. We defined and analyzed the glucometrics, including "control days," "extreme days (high and low)," average BG, and variation. We discovered limitations of the measures and created additional metrics, including "adequately monitored," "well managed day," and ICU BG distributions. Our metrics currently range from system and hospital levels to service line, medical group, and unit-based reports, which are regularly distributed electronically across the system. Examples of our substantial improvements include a reduction of "out-of-control" days by 60% ($p < 0.001$), a mean surgical intensive care unit BG reduction of 15 mg/dl ($p < 0.001$), and a system reduction of average BG by 17 mg/dl overall ($p < 0.001$), without increased hypoglycemia. The development, implementation, and distribution of these metrics have been instrumental in the successes achieved in glycemic control across our system. We present additional helpful metric definitions and suggestions for implementation.

Effect of Fenofibrate and Pioglitazone on Expressions of Inflammatory Factors in Pancreatic Islets of High-Fat Diet Rat Models

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Objective:
This study explored the expressions of peroxisome proliferator-activated receptor (PPAR)-α/PPAR-γ and inflammatory mediators in pancreatic islets of obese rat models induced by high-fat diets and investigated the effects of the PPAR-α agonist fenofibrate and PPAR-γ agonist pioglitazone on the function of islets.

Methods:
S-D obese rat models were established with a high-fat diet, including a high-fat diet (HF group) and a high-fat diet with fenofibrate (FF group) or pioglitazone (FP group) treatment; control rats were fed a normal diet (control group). After 8–10 weeks of intervention, immunohistochemistry was performed to evaluate the expressions of insulin, glucagons, somatostatin, PPAR-α, PPAR-γ, NF-κB, I-κB, p38, and ERK1 proteins in islets; islets mass were scored in tissue slides at the same time.

Results:
Islet mass was enlarged in the HF group. The compositions of islet cells were the same as the control. The expression of insulin was lower in the HF group than the control, but after using pioglitazone, less islet mass and more insulin expression were found in the FP group. Compared to the control group, expression levels of PPAR-α and PPAR-γ protein were reduced in the HF group, the expression of PPAR-α protein was increased in the FF group, and the expression of PPAR-γ protein was elevated in the FP group. Levels of NF-κB, p38, and ERK1 proteins were increased significantly in the HF group, expressions of NF-κB and p38 were decreased in the FF and FP groups, and the level of ERK1 was only decreased in the FP group. The protein level of I-κB was no different among control, HF group, and FF group.

Conclusion:
Fenofibrate and pioglitazone protected β-cell function and survival by corrected inflammatory factors.

In Search of a Better "Glucose" Sensor

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Introduction:
Continuous or frequent metabolic monitoring is a vital first step in preventing the onset of complications such as heart or kidney disease in chronic illness type 1 and type 2 diabetes. Although it may be sufficient in some instances to monitor a single metabolite such as glucose, there is arguably more that can be gleaned when the levels of several interacting metabolites are known.

Methods:
In this context, we are developing a device for continuous glucose, lactate, fatty acid, and glutamine monitoring attached to a microdialysis membrane that can be implanted under the skin. The biosensing elements of this device are a series of binding proteins specific for each analyte. The sensing scheme involves a change in fluorescence of a dye attached to a site on the protein that is structurally responsive to ligand binding. A second dye with a longer decay rate (but nonresponsive) attached to the N-terminal serves as a reference. This dual label allows for a robust method of sensing we call lifetime-assisted ratiometric sensing. Additionally, the high selectivity and sensitivity of the protein sensors allow real-time measurements using fast, low-efficiency microdialysis.

Results:
Preliminary data will be presented on the components of the metabolite monitor including the engineered proteins, optoelectronics, microfluidics design, and microdialysis.

Conclusion:
To realize a workable, user-friendly and low-cost device requires the multidisciplinary effort of a team with expertise in molecular biology, analytical chemistry, microfluidics, electrical engineering, fluorescence spectroscopy, and sensor development. Here, we describe our work on the various aspects of assembling a better "glucose" sensor.

Evaluation of an Automated Blood Glucose Monitor in Critically Ill Intensive Care Unit Patients

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Introduction:
In critically ill patients, normalization of blood glucose (BG) with intensive insulin therapy (IIT) can improve patient outcomes but is labor intensive, requiring multiple BG measurements. There is currently no in-hospital automated BG monitor to provide frequent BG measurements in hospitalized patients. The Glucon OPTImus™ under development enables frequent automated glucose monitoring for the purpose of implementing IIT. This study evaluated the operational aspects of the OPTImus system in intensive care unit (ICU) patients.

Methods:
Four ICU subjects on IIT were recruited for this institutional review board-approved study. OPTImus was connected to the subject's central access catheter proximal port and normal saline was infused for line flushing. Blood draws were performed according to the IIT protocol for up to 96 hours. BG was referenced against a Yellow Springs Instruments (YSI) 2300 BG analyzer and the hospital Accu-Chek® BG meter. Recorded variables included catheter type, BG concentrations, BG meter errors, blood draw failures, and autosampler failures. BG data were analyzed using the Bland and Altman technique, median relative absolute difference (MRAD), and correlation analysis. ANOVA was used to examine measurement differences between instruments. Data are reported as means ± SD with $p < 0.05$ considered statistically significant.

Results:
Four critically ill ICU diabetic subjects (mean age 49 ± 12, body mass index 42 ± 13) had 305 BG measurements. BG ranged from 60 to 192 mg/dl based on a duplicate YSI reference. Approximately 9.0% of the draws were attributable to BG meter errors, 3.0% to autosampler technical problems, and 3.0% to catheter-related difficulties. OPTImus mean bias versus YSI was 5.6 ± 19.5 mg/dl, and MRAD was 12.6%. Accu-Chek mean bias was 11.7 ± 7.3 mg/dl and MRAD was 9.6%. Both OPTImus and Accu-Chek showed a positive bias that was significantly higher for Accu-Chek ($p = 0.001$); however, precision was lower for OPTImus.

Discussion:
OPTImus was able to safely and effectively draw and reinfuse blood from central access catheters in these critically ill ICU patients on IIT. Difficult draws requiring operator intervention were infrequent, with an occurrence rate generally ≤3%. OPTImus showed 3% lower accuracy compared to Accu-Chek and a higher BG measurement variability reflected by a higher precision value. Development of such technologies will facilitate the practice of tight BG control for patients requiring IIT and may positively impact patient care.

Locally Smoothed Median Absolute Difference Curves for Pattern Recognition of the Accuracy of Bedside Glucose Testing: A New Recommended Standard

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Introduction:
We introduced locally smoothed (LS) median absolute difference (MAD) curves and International Standards Organization (ISO) 15197-integrated modified Bland–Altman plots to evaluate the accuracy of hospital point-of-care (POC) glucose meter systems (GMS). LS MAD curve pattern recognition facilitates clinical understanding of accuracy for decision making in tight glucose control (TGC).

Methods:
We analyzed paired observations ($N = 1702$) from 35 U.S. sites using a GMS that compensates for hematocrit and oxidizing substances. Plasma glucose values were obtained using the clinical laboratory instrument available at each site. Randomly selected paired observations helped identify the sensitivity of LS MAD curves to sample size.

Results:
Locally smoothed MAD curves were relatively flat (≤5 mg/dl), from 35 to 186 mg/dl. Above 180 mg/dl, the curves trended upward. The 95% confidence intervals were ±1 mg/dl, from the MAD for reference values 35 to 133 mg/dl, and then splayed in higher ranges. Sensitivity analysis revealed a relative consistency of break-through points from $N = 300$ to 1702. ISO 15197 Bland–Altman plots visualized bias, scatter, heteroscedasticity, and potentially erroneous results well. All but 6 observations fell within ISO 15197 error tolerances. Linear regression analysis produced an r^2 of 0.995. Clarke error grid analysis placed 100% of observations in zone A.

Conclusions:
Locally smoothed MAD curves documented acceptable GMS performance from 35 to 186 mg/dl and simultaneously identified performance in the hypo-, TGC, and hyperglycemic domains. This new method is nonparametric, unforgiving, and unbiased. We recommend an accuracy envelope of 5 mg/dl as the new standard for hospital bedside glucose testing devices. LS MAD curves allow immediate pattern recognition relevant to decision making, monitoring, and treatment and can be extended to other types of POCT.

Investigation of Various Amperometric Modes for Implantable Glucose Sensors

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Introduction:
Major problems associated with the development of totally implantable, enzymatic glucose sensors are the lack of linearity in the hyperglycemic region and the lack of sensitivity in the hypoglycemic region. These are consequences of the large imbalance between glucose and oxygen levels in the blood and plasma, which causes the sensor enzymatic reaction to be oxygen limited. We have successfully overcome these limitations through the development of alternative amperometric methods, which enable the use of these sensors over the complete range from hypo- and hyperglycemia with adequate sensitivity and linearity.

Methods:
Sensors were fabricated by immobilization of the glucose oxidase (GO_X) enzyme on 50-µm platinum wire, followed by sequential adsorption of various ionic species via a layer-by-layer (LBL) process to grow semipermeable membrane. Alternative amperometric methods were developed and systematically investigated over a range of bias and time intervals as well as various LBL-grown outer sensor membranes.

Results:
Under certain conditions, these glucose sensors exhibited linearity extending into the hyperglycemic regions compared to the traditional control enzymatic sensor, which only functioned in a linear fashion up to 10 m*M*. In addition, our newly developed amperometric method enabled a twofold increase in the magnitude of the measured current at the hypoglycemic range.

Conclusions:
A variety of amperometric measuring techniques were investigated for implantable glucose sensors to improve sensor functionality. Under optimized conditions, the newly developed method achieved the desired sensitivity and linearity along with a significantly improved signal-to-noise ratio. Through this advance in sensor functionality, a totally implantable glucose sensor for long-term continuous glucose monitoring can be achieved.

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Statistical Approach of Assessing the Reliability of Glycemia Sensors: The GLYCENSIT™ Procedure

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Introduction:
Blood glucose meters and glucose monitoring systems are used to control glycemia, but some may lack reliability. This work proposes a statistical assessment tool for testing the significant difference of paired glucose measurements (the *reference gold standard* sensor versus a *test* sensor device): the GLYCENSIT™ procedure.

Methods:
The developed GLYCENSIT procedure consists of three phases: (1) testing possible consistent measurement behavior as a function of the glycemic range, (2) testing the number of measurement errors with respect to a standard criterion for binary assessment of glycemia sensors, and (3) computing the tolerance intervals that indicate possible test sensor deviations for new observations. The method can be tuned according to the clinician's preferences regarding significance level, tolerance level, and glycemic range cutoff values.

Results:
The main result is embodied in the proposed assessment technique. GLYCENSIT analyses for three real-life clinical examples from the intensive care unit are discussed extensively: GlucoDay® (A. Menarini Diagnostics, Italy), Accu-Chek® Inform™ (Roche Diagnostics, Switzerland), and HemoCue® Glucose 201 (HemoCue, UK) versus ABL 700® series blood gas analyzer (Radiometer, Denmark). Further, advantages of the GLYCENSIT procedure with respect to currently existing evaluation methods (e.g., Bland–Altman analysis, error grid analysis) are indicated. Finally, this procedure is implemented as a Web-based assessment tool, freely available at www.esat.kuleuven.be/GLYCENSIT. The analysis runs on the host server after uploading sets of paired glucose measurements.

Conclusions:
The GLYCENSIT analysis, which relies on tunable design parameters, aims to guide clinicians in the assessment of the reliability of blood glucose meters and glucose monitoring systems.

Model-Based Predictive Control for Glycemia Normalization in Critically Ill Patients

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Introduction:
Intensive insulin therapy to maintain blood glucose between 80 and 110 mg/dl reduces morbidity and mortality in critically ill patients. Introduction of a predictive control system to normalize glycemia may reduce the workload for medical staff. This work presents a model-based predictive controller (MPC) that can be used to control glycemia in critically ill patients.

Methods:
A model, particularly developed for describing glucose and insulin dynamics of critically ill patients, was estimated individually for 19 patients based on the first 24 hours of data. The model was reestimated as new measurements were obtained during the second 24 hours. The developed MPC simulated insulin flow sequences for the second day. The first analysis was characterized by a comparison between MPC insulin infusion sequences and insulin flows (determined by the nurse) that were effectively administered to the patient. In the second analysis the robustness of the MPC was tested by adding (to the MPC unknown) 15% measurement noise and a disturbance (medication) factor. Finally, a glycemic penalty index (GPI) was proposed as a new tool to evaluate the performance of glycemia control systems.

Results:
When comparing MPC insulin schemes to nurse-driven insulin rates that were effectively administered to the patient, some hyperglycemic and hypoglycemic events could have been avoided. The obtained GPIs illustrate the robustness of the developed MPC.

Conclusions:
Results of the developed MPC are satisfactory in terms of both control behavior (reference tracking and suppression of unknown disturbance factors) and clinical acceptability. The GPI is a new method for quantitatively evaluating glycemia control systems.

Interactive Diary for Diabetes: A New Telemedicine System to Support the Decision-Making Process in Type 1 Diabetes

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Background and Goals:
The interactive diary for diabetes (IDD) is a bolus calculator and a telemedicine system based on communication between a patient and a specialist by short messages (SMS) through mobile phones. Good glycemic control can be achieved not only by self-monitoring of blood glucose testing and hemoglobin A1c monitoring, but also by a correct nutritional regimen. Carbohydrate (CHO) counting is effective in promoting dietary freedom, quality of life, and glycemic control, without worsening severe hypoglycemia or cardiovascular risk. However, the widespread use of carbohydrate counting is limited by its complex patient educational approach. IDD can represent an important tool for easy communication between patients and physicians and can help patients adjust the insulin bolus according to the amount of CHO ingested in a meal, while avoiding the use of complex calculations. A pilot study has been made to evaluate the applicability and acceptability of the interactive diary.

Materials and Methods:
The IDD is set up in patients' mobile phones and allows (1) recording blood glucose values; (2) quantifying the total CHO assumed during a meal by choosing from a list of pictures the specific food and the amount ingested; (3) suggesting the most appropriate bolus insulin in relation to the patient's CHO/insulin ratio, the factor of insulin sensitivity, and the blood glucose goal; and (4) sending data filed in the mobile phone as SMS to the physician. Four Italian diabetes outpatient clinics enrolled 50 patients with type 1 diabetes, aged between 18 and 65 years, familiar with the use of mobile phones. Sociodemographic and clinical information was collected, and questionnaires investigating the quality of life (SF-36 Health Survey Instrument and WHO-DTSQ) and satisfaction with the IDD were filled in at baseline and after 12 weeks.

Results:
At the end of the study, 67 and 27% of the patients found the system good and excellent, respectively; 65% stated that the system was very or extremely helpful; and 90% judged it easy to use. CHO counting and insulin bolus calculation were considered by the patients as the most useful functions of the IDD. No significant changes were documented in clinical parameters and in DTSQ-WHO and SF-36 scores after 12 weeks. No serious hypoglycemic episodes requiring medical intervention were reported during the study, although patients could choose the food they wished, modifying their premeal insulin doses as suggested by the IDD.

Conclusion:
This pilot study showed that the IDD was safe, easy to use, and well accepted by all of the patients. A new large-scale, randomized trial is planned to compare the efficacy of this system with the usual practice in teaching CHO counting to patients by structured training.

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

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Introduction:
Measuring blood glucose levels accurately is one of the key components for treating diabetes and preventing further complications. We demonstrated the ability of a heart rate-enabled version of BodyMedia's SenseWear Pro2 wearable armband to estimate blood glucose values in a noninvasive manner in free-living conditions.

Methods:
The study was performed on 11 individuals diagnosed with either type 1 (8 subjects) or type 2 (3 subjects) diabetes during both a standard 75-gram oral glucose tolerance test (OGTT) and a 24-hour free-living period. For each subject, comparison data were obtained with finger sticks during the OGTT every 30 minutes and during the free-living period every 4 hours. All subjects wore the BodyMedia heart rate-enabled SenseWear Pro2 armband on the back of the upper left arm during the trial. This armband measured movement, heat flow, skin temperature, galvanic skin response, and heart rate and estimated energy expenditure. An equation for estimating blood glucose values was developed from these data and evaluated using by-subject cross validation.

Results:
The mean glucose sample of the participants during treatment was 160.29 ml/dl by finger-stick measurements. The equation developed by BodyMedia Inc. estimated mean glucose values at 150.95 ml/dl with a correlation of 0.70 to finger-stick glucose values.

Conclusion:
This study indicates that the wearable armband may provide reasonable estimates of blood glucose levels during normal daily living conditions. Further studies are needed to determine whether the armband can estimate more accurately if food composition information was added to the glucose estimation equation.

Real-World Use of Advanced Features in Insulin Pump Therapy

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Introduction:
Today's insulin pumps offer significant advantages to patients. However, there are little published data that provide the level of specific detail required to understand how current insulin pumps are actually used in the field.

Methods:
Anonymous data from 541 insulin pumps with associated glucose data from diabetes patients (primarily type 1) were uploaded and analyzed with MatLab® software to determine patterns of insulin use.

Results:
Of 201,538 boluses, 64.8% were given within 4.5 hours of a previous bolus, demonstrating the need for a proper setting of duration of insulin action. Carbohydrate boluses averaged 3.4 per day (range: 0 to 17), and correction boluses averaged 2.0 per day (range: 0 to 8.1). More than a third of pump users averaged 5 or more carbohydrate boluses a day. The average maximum number of boluses per pump per day was 6.9 (range: 0 to 40). For carbohydrate boluses, 55.5% were given within 4.5 hours. In 14.0% of boluses, both a blood glucose value and carbohydrate intake were entered at the time. Results of more detailed analyses are presented.

Conclusions:
Current insulin pumps are highly customizable and have multiple useful tools that have the potential to improve diabetes care. Data suggest that a correct parameter setting and implementation of advanced pump features are important for people with diabetes.

Use of the FreeStyle Navigator® Continuous Glucose Monitoring System in Children on Glargine-Based Multiple Daily Injection Therapy

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Introduction:
Real-time continuous glucose monitoring (CGM) can potentially revolutionize the treatment of type 1 diabetes (T1D) in children. The Diabetes Research in Children Network showed previously that pump-treated youth with T1D using the FreeStyle Navigator® lowered hemoglobin A1c (HbA1c) and increased time spent in the target range. We hypothesized that the use of multiple daily injection (MDI) regimens, which offer less flexibility than pumps, may limit the effectiveness of CGM to improve glycemic control. Our objective was to determine whether youth utilizing glargine-based MDI would benefit from daily use of the Navigator.

Methods:
Following use of a masked Navigator for 4–7 days to characterize baseline glycemic control, 27 subjects (mean age 11.0 ± 3.9 years, mean diabetes duration 4.0 ± 3.1 years) with T1D using basal-bolus MDI therapy with glargine were asked to use the Navigator daily for 26 weeks.

Results:
Twenty-three subjects completed both the 13- and the 26-week visits. Sensor use decreased slightly from median 121 hours per week at weeks 1–4 to 101 at weeks 9–13 ($p = 0.07$) and continued to decline to 48 by weeks 22–26 ($p < 0.001$ c/w weeks 1–4). Median HbA1c decreased from 7.9% at baseline to 7.2% at 13 weeks ($p = 0.001$), but rose again by 26 weeks (7.6%, $p = 0.10$ from baseline). Subjects and parents reported overall high levels of satisfaction with the Navigator, and subjects showed improved quality of life with the Navigator.

Conclusions:
Real-time CGM with the Navigator is feasible and tolerable in pediatric patients using basal-bolus MDI and is associated with reduced HbA1c and improved quality of life over a 3-month period. Future pediatric trials of CGM should include both MDI- and pump-treated patients and should concentrate on obstacles to continued sensor use.

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Time-Based Postmarket Surveillance for Blood Glucose Test Strips

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Introduction:
Current point-of-care glucose testing performance is considered inferior to standard reference laboratory methods. Prior studies have sought to evaluate variability as a consequence of lotto-lot variability and operator errors. We examined the accuracy of a new technology looking specifically at possible additional effects of aging of the strips and clinical site variability.

Methods:
Four lots of test strips manufactured by AgaMatrix, Inc. (Salem, NH) for use with WaveSense™ powered blood glucose meters were monitored over time (aged 7–16 months) over a period of up to 13 months at five different clinical sites ($N = 50$ for each lot at each clinical site). For each subject, fresh whole capillary finger stick blood was obtained and sampled by two strips from each lot. Additional blood from the same finger stick puncture site was collected and centrifuged to obtain plasma and analyzed (YSI 2300 STAT Plus).

Results:
Of the 2219 data points collected, 2194 (98.9%) of all data met the International Standards Organization 15197 acceptance limits (where 95% of all data must be within ±15 mg/dl for concentration below 75 mg/dl and within ±20% for concentrations above 75 mg/dl). In addition, 2218/2219 points fell in zone A of the Parkes–Ginsberg consensus error grid, with the remaining 1 point falling in zone B.

Conclusions:
The strips tested (AgaMatrix) demonstrated consistent performance for up to 16 months, regardless of locale studied. Such robust performance may increase confidence in point-of-care testing. This study may serve as a model for an enhanced method to conduct postmarket clinical surveillance to test the aging effects of test strips even across varied clinical sites.

Role of Simulation Environment in the Development of Artificial Pancreas for Overnight Glucose Control in Children and Adolescents with Type 1 Diabetes

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Introduction:
An *in silico* simulation environment can facilitate the development of closed-loop glucose control systems by supporting debugging, assessing the improvements of and comparison among glucose controllers, carrying out technical evaluation, and predicting the outcome of clinical trials. The simulation environment created to support the development of an artificial pancreas (AP) for overnight closed-loop glucose control in children and adolescents with type 1 diabetes (T1D) in the Juvenile Diabetes Research Foundation-funded AP project at the University of Cambridge plays a vital role in technical evaluation of the glucose control algorithm.

Methods:
The simulator was implemented in Matlab®. The simulation environment reflects the environment of a real-life clinical trial with protocol, synthetic subject (model of glucose regulation with parameters), glucose sensor, insulin pump, glucose controller, and outcome measures as its main components. Parameter sets representing a virtual population of 18 subjects with T1D were obtained from validated studies and informed probability distributions.

Results:
The simulator was used routinely to evaluate modifications and assess the impact of various physiological and operating conditions on the safety and efficacy of the glucose controller. The virtual population was employed to simulate clinical trials with the glucose control algorithm using varying treatment protocols and experimental designs. The experimental design was modified to assess the effect of glucose sensor measurement error (2, 3, and 6% of coefficient of variation), glucose sampling rate (15-, 10-, and 1-min sampling), sensor failure (loss of sensor signal distributed randomly in time and duration), insulin pump occlusion (150-min duration at the beginning and in the middle of the experiment), and size of meal (range of 20 to 80 g of carbohydrates) on the safety and efficacy of the controller.

Conclusions:
The simulation environment proved essential to fast and efficient development of the AP system.

Internet-Based Pilot Study Comparing Low-Fat with High-Fat Evening Snacks in Children and Adolescents with Type 1 Diabetes Using Continuous Glucose Monitoring

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Introduction:
Bedtime snacks are frequently employed in the treatment of children with type 1 diabetes to prevent nocturnal hypoglycemia, and the inclusion of protein and/or fat is commonly recommended.

Methods:
Ten subjects with type 1 diabetes mellitus (T1DM) (age 6–18 years, hemoglobin A1c 6.9 ± 0.5%) enrolled in a pilot trial evaluating the FreeStyle Navigator® glucose sensor completed a study comparing the effect of bedtime snack fat content on nocturnal hypoglycemia. On ≥12 separate nights, each subject received either a low-fat [30 g carbohydrate (CHO), 3 g protein, 1 g fat; 138 kcal] or a high-fat (30 g CHO, 2 g protein, 20 g fat; 320 kcal) snack in random order. Subjects checked their glucose and, via a Web site, were assigned to a high- or low-fat snack. Subjects used their usual evening snack algorithm to determine the size (in 15-g carbohydrate increments). Data were from nights with at least 5 h (average of 8.1 ± 1.3 h) of sensor data after the snack.

Results:
Average blood glucose (mg/dl) on 128 valid study nights before a snack was similar in both groups (163 ± 55, high fat; 164 ± 53, low fat). The proportion of nights with hypoglycemia (sensor glucose ≤70) was similar in both groups (23% high fat vs 21% low fat). Also, the proportion of nights with hyperglycemia (sensor glucose ≥200) was similar in both groups (68% high fat vs 61% low fat).

Conclusion:
Even very well controlled children and adolescents with T1DM have a very high frequency of high and low glucose levels. However, altering the amount of fat in a bedtime snack had no impact on the frequency of hyperglycemia or hypoglycemia. This study also highlighted the feasibility of Web-based research in patients' home environments.

Telemedicine Process Used to Implement an Effective and Functional Screening Program for Diabetic Retinopathy

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Introduction:
There are 20.8 million people in the United States, or 7% of the population, who have diabetes. Complications of diabetes result in 12,000 to 24,000 new cases of blindness each year. In the 20- to 74-year age group, it is the leading cause of blindness. Laser therapy can help prevent blindness from diabetic retinopathy, but early detection is essential. The American Diabetes Association recommends annual eye examinations for patients with diabetes. The purpose of this study was to develop a modular, mobile image capture and transfer system with an efficient workflow process for screening for diabetic retinopathy.

Methods:
We developed a telemedicine process for capturing digital images of the retina with no dilation required using single-field nonmydriatic digital fundus photography. Patients were screened in clinics and community settings. Portable equipment enabled screenings for people in areas with poor access to eye care. Medical information and retinal images were captured, "packaged," and transferred to a designated server. Specialists used software on-site or remotely to grade images and make recommendations for follow-up eye care. Subsequently, a follow-up telephone call was made to each subject to determine compliance.

Results:
We created customized registration, imaging, grading, and reporting software and screened 706 patients with diabetes for retinopathy. Of these patients, 81% had gradable images. Fifty-one percent reported that their last eye examination was "greater than 12 months" or "never." Out of our traceable sample, 55% were compliant with follow-up recommendations, 10% were not compliant, and 35% had incomplete data.

Conclusion:
We showed that eyes do not need to be dilated to produce a gradable retinal image. This may become an effective means to alert people with diabetes of early retinopathy detection and the need for eye care.

Continuous Monitoring of Blood Glucose Using a Thin-Film Optical Sensor

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Introduction:
We recently described a novel holographic optical sensor with improved selectivity for glucose over fructose based on a thin-film polymer hydrogel containing phenylboronic acid receptors. These Lewis acids can bind the *cis*-1,2- or 1,3-diols of glucose covalently to form five- or six-membered rings. We present here the measurement of glucose in human blood plasma as opposed to simple buffers and track changes in concentration at a rate mimicking glucose changes *in vivo*.

Methods:
Holographic sensors containing acrylamide, *N,N'*-methylenebisacrylamide, 3-acrylamidophenylboronic acid, and (3-acrylamidopropyl)trimethylammonium chloride were used to measure seven different human blood plasmas at different glucose concentrations (60–600 mg/dl) in static mode. Using a flow cell separately, the glucose concentration was varied at approximately 3–5 mg/dl/min and the ability of the sensor to monitor glucose continuously was investigated over an extended period.

Results:
Results of *ex vivo* static measurements were subjected to error grid analysis. Forty-two out of 46 (91.3 %) measurements fell in zone A of a Clarke error grid with the remainder (8.7%) falling in zone B. *Ex vivo* flow experiments showed that the sensor was able to accurately track changes in concentrations occurring in real time without lag or evidence of hysteresis.

Conclusions:
The ability of a phenylboronic acid-based sensor to measure glucose in human blood plasma is demonstrated for the first time *in vitro*. Holographic glucose sensors can be used without recourse to recalibration. Their robust nature, coupled with their format flexibility, means that they are an attractive alternative to conventional electrochemical enzyme-based methods of glucose monitoring for people with diabetes mellitus.

Clinical Insights from Preliminary Testing of an Artificial β cell Algorithm—Modeling and Tuning

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Introduction:
We present results from a pilot clinical study of basal closed-loop glucose regulation using model predictive control using subject-specific empirical models. Using clinical insights, we have modified the original controller structure to improve performance and safety. Further testing of the controller is done using advisory-mode simulations on the retrospective data.

Methods:
The DexCom™ STS® glucose sensor (DexCom Inc., San Diego, CA) and the OmniPod® insulin management system (Insulet Corp., Bedford, MA) were used for controller implementation. Blood glucose, insulin delivery, and meal information was collected during the 5 days prior to the closed loop. Data were divided for model development and validation. Empirical models were fitted to capture insulin–glucose dynamics. Controller development focused on recovery from hyperglycemia under fasting conditions. We switched to closed-loop control during the fasting state, when the subject's glucose was 150 mg/dl.

Results:
It was obvious that the controller had a very aggressive insulin output that was quickly overridden by the physician. Insight from the closed-loop session resulted in multiple modifications to the controller. These controller constraints involved a retuning of the prediction horizon, and the development of basal insulin-on-board used in combination with the subjects nominal basal insulin rates. Advisory mode simulations using the retrospective data show the viability of such a strategy.

Conclusions:
The experience from this pilot test has been translated into clinically driven controller development and testing. As clinical trials progress for the testing of the artificial β cell control algorithms, further clinical insights will most likely be incorporated, thereby increasing the safety and reliability of the system.