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Performance of the Guardian® REAL-Time Continuous Glucose Monitor in Critically Ill Children

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Introduction:

The Guardian® REAL-Time continuous glucose monitoring (CGM) system performance is well described in ambulatory diabetics, but its usefulness in critically ill patients remains unproven. Accurate CGM in the intensive care unit (ICU) could significantly decrease hypoglycemia risk, particularly in centers attempting tight glycemic control (TGC). We describe Guardian REAL-Time performance in a prospective, randomized pediatric trial of TGC.

Methods:

Fifty-seven patients aged below 3 years received postsurgical TGC [80–110 mg/dl blood glucose (BG) target range] in the cardiac ICU. CGM sensors were inserted preoperatively and used for hypoglycemia detection during TGC. Glucose meters, used for insulin dosing and CGM calibration, were checked every 0.5–4 hours according to a computerized algorithm.

Results:

The mean absolute relative difference of 1162 sensor versus glucose meter comparisons was 16.8%. Consensus error grid analysis assigned 87% of comparisons to zone A, 13% to zone B, and 0.2% to zone C. Regression analysis of comparisons revealed a biased slope (slope = 0.68 ± 0.02 , intercept = 34 ± 2). CGM detected 2 of 4 hypoglycemic episodes (BG <40 mg/dl) in advance with the alarm set at 70 mg/dl. Subsequent regression analysis of sensor current versus reference BG revealed a median intercept (offset) of 4.9 nA (range: -14–12). Because the Guardian REAL-Time calibration algorithm assumes a 0-nA offset, higher offsets compress glucose estimations toward BGs used for calibration, causing an overestimation of hypoglycemic BGs. Retrospective recalibration of sensors, factoring in offset, detected all four hypoglycemic events.

Conclusions:

In this study of critically ill children, Guardian REAL-Time CGM sensors overestimated glucose at low glucose levels, leading to poor hypoglycemic detection. This was attributed to an assumed offset of 0 nA that was consistently greater in practice. Better hypoglycemia detection in the ICU could be achieved by prospectively factoring offset into sensor calibration or actively calculating it at regular intervals.

Continuous Glucose Monitoring Demonstrates Less Glycemic Variability with a Diabetes-Specific Nutritional Formula Compared to a Standard Formula in Patients with Type 2 Diabetes

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Objective:

The objective of this pilot study was to use continuous glucose monitoring (CGM) to compare (1) mean amplitude of glycemic excursions (MAGE), (2) mean glucose, and (3) percentage of glucose readings <70, 70–139, 140–179, 180–200, and >200 mg/dl between a diabetes-specific formula (DSF) and standard formula (STF) in patients with type 2 diabetes in a bolus tube-feeding simulation.

Method:

Ten subjects [body mass index (BMI) range: 27.0–39.7 kg/m², 47–75 years) were enrolled from one site into a randomized, double-masked, parallel study. Daily energy needs were estimated for each subject. They were instructed to consume either DSF or STF every 3 hours over a 12-hour feeding cycle, avoid calorie-containing foods and beverages and vigorous exercise for 4 days, and continue all medications. Glucose measurements were collected every 10 minutes using CGM.

Result:

MAGE (mean ± SEM) was significantly higher in the STF group (83.9 ± 12.6 mg/dl) than the DSF group (45.3 ± 5.7 mg/dl, $p < 0.05$). The DSF group tended toward a lower mean glucose (139.7 ± 11.0 mg/dl vs 162.5 ± 13.5 mg/dl, $p > 0.05$). In addition, subjects consuming DSF tended to spend more time in glucose levels 70–139 mg/dl (50.0 ± 19.5% vs 37.9 ± 10.3%) and 140–179 mg/dl (41.1 ± 16.1% vs 29.4 ± 6.4%) and less time in hyperglycemia (180–200 mg/dl: 7.3 ± 5.2% vs 9.5 ± 2.7%, and >200 mg/dl: 1.4 ± 1.4% vs 23.0 ± 11.4%, all $p > 0.05$).

Conclusion:

Using CGM as a tool to assess glucose variability, we demonstrated that DSF improved glycemic stability and tended to lower mean glucose levels compared to STF without increasing significant hypoglycemia in patients with type 2 diabetes.

Impact of Dietary Knowledge, Attitude, and Behavior on Metabolic Risk Factors among Adults Visiting the Kuwait Heart Association Screening Unit

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Objectives:

The objectives of this study were to assess dietary knowledge, attitude, and habits among adults visiting the Kuwait Heart Association screening unit and to evaluate the impact of the aforementioned on the following metabolic risk factors: random blood glucose, random cholesterol level, body mass index, and blood pressure.

Methodology:

A cross-sectional survey was done of 294 adults who visited the Kuwait Heart Association screening unit. Data were collected by self-administered questionnaires, as well as measurement of blood pressure, glucose, cholesterol levels, and weight and height.

Results:

Two-thirds of the study population were at least overweight. Among the participants, a fifth had high blood pressure, a quarter had high cholesterol values, and a few had elevated random blood sugar values. An interesting finding was that the ratio of having more than two risk factors to having nil risk factors was 6:1 in adults, while in the teenager group it was the reverse and approximately 1:5. Although the association among gender, age, and the number of metabolic risk factors was not statistically different, nevertheless, about half of the teenagers, three-quarters of the young adults, and the vast majority of the adults had at least one metabolic risk factor. After stratifying for age, there was no significant association between the eating behavior inventory and metabolic risk factors.

Conclusion:

Although the prevalence of overweight and obesity, hypertension, diabetes, and increased total cholesterol observed in this study suggests that it is a significant health problem even in our relatively younger population in Kuwait, the use of standardized eating behavior inventory was not useful in our population. A more culturally sensitive tool might be more appropriate.

Artificial Pancreas Project at Cambridge: Year 2 Status and Toward Home Testing

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Introduction:

The Artificial Pancreas Project at the University of Cambridge (APCam) focuses on closed-loop (CL) overnight insulin delivery in young people with type 1 diabetes (T1D), combining a purpose-made model-predictive control algorithm with off-the-shelf continuous glucose monitor and insulin pump. APCam is in the second year of clinical evaluations. To date, two clinical studies have been completed and a third study is ongoing.

Methods and Results:

The first clinical study (APCam01) compared the continuous subcutaneous insulin infusion against CL in 12 children and adolescents with T1D. Results showed improved glucose control with CL while reducing the risk of hypoglycemia. The second study (APCam02) evaluated the performance of the CL system following the ingestion of a rapidly and slowly absorbed large meal. A subset of six subjects from APCam01 participated. The results demonstrated that CL is safe and efficacious in controlling overnight glucose following the ingestion of a large meal irrespective of its composition. In the third ongoing study (APCam03) we are testing CL in post-exercise conditions.

Conclusions:

The clinical plan of the APCam project has been constructed to lead to early home testing. Based on results of clinical studies demonstrating safety and efficacy of CL, utilizing fruitful collaboration with the medical-devices industry, and benefiting from the Juvenile Diabetes Research Foundation infrastructure support, pilot home testing of overnight CL glucose control appears to be an achievable goal in year 3 of the APCam project.

A New Team Approach to Manage Diabetes: Pharmacists, Podiatrists, Optometrists, and Dental Professionals

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Pharmacist, podiatrist, optometrist, and dental care (PPOD) professionals are often a primary point of care for people with type 2 diabetes. These professionals play an important role in ensuring that diabetes care is continuous and patient centered. PPOD professionals can educate people with diabetes about the disease, encourage them to practice self-management, and refer those who require the care of other health professionals. The purpose of this abstract is to reinforce consistent diabetes messages and promote a team approach to comprehensive diabetes care that encourages collaboration among all diabetes care providers. Furthermore, many people with diabetes and those who are at risk do not regularly visit a primary care provider but may seek the services of a PPOD provider. PPOD providers are well positioned to deliver prevention messages, communicate the need for metabolic control, and encourage multidisciplinary team diabetes care. When PPOD providers understand the diabetes care issues of other PPOD disciplines, they can recognize symptomatic concerns warranting timely referrals, reinforce annual screening recommendations, and contribute to a proactive approach to diabetes care beyond the scope of their particular discipline.

An Advanced Fluorescence Affinity Sensor for Short-Term Continuous Glucose Monitoring in Small and Large Animal Models

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Objective:

This study designed and tested the performance of an advanced fiber-coupled fluorescence affinity sensor (FAS) *in vivo* in small and large animal models in order to assess its feasibility and safety for short-term glucose monitoring in humans.

Design:

The glucose-monitoring concept is based on optical interrogation of a small hollow fiber (regenerated cellulose), which is coupled to a 200- μm multimode optical fiber. To allow connection between the sensor and the light source, a new magnet-based optical coupler was implemented. The glucose-dependent fluorescence change is based on fluorescence resonance energy transfer (FRET) between near-infrared-compatible donor and quencher dyes, which are linked chemically to dextran and concanavalin A, respectively. The design and performance of the fluorescence sensor have been shown successfully *in vitro* and *in vivo* applications for subcutaneous glucose monitoring.

Methods:

The performance of a freeze-dried formulation of the FAS was investigated in *in vitro* experiments. Determination of interstitial glucose concentrations in skin tissue of hairless rats and small pigs was facilitated by measuring the fluorescence response of the implanted FAS over several hours and multiple days. Blood sugar changes in animals were induced by injections of insulin and dextrose. Blood samples were withdrawn and analyzed with a FreeStyle glucometer. The MiniMed/Medtronic CGMS[®] was used for comparison.

Results:

The *in vitro* glucose response of the freeze-dried FAS formulation after rehydration in saline buffer was stable within 1–2 hours. The acute *in vivo* performance study of the fiber-coupled FAS showed that more than 96% of the paired FAS/venous blood glucose readings were in the clinically acceptable A and B regions of the Clarke error grid. Mean absolute relative differences (MARD) and root mean squared error (RMSE) for small and large animal models were 18.5% and 19.8 mg/dl and 15.9% and 16.3 mg/dl, respectively. In comparison, MARD and RMSE for MiniMed/Medtronic CGMS in small and large animal models were similar (in rats 25.4% and 19.8 mg/dl; in pig 18.4% and 16.2 mg/dl, respectively). No instance of irritation or infection was observed visually at any implantation site. The *in vivo* performance of FAS over 3 days was demonstrated successfully in both animal models.

Conclusions:

The newly developed formulation of the freeze-dried FAS would allow for sterilization by irradiation, for dry packaging and storage, and for achieving full operational *in vivo* functionality within 1 hour. Overall, the fiber-coupled FAS was safe, and its performance during 4-hour and 3-day testing compared extremely favorably to the commercially available MiniMed/Medtronic CGMS, indicating its potential value for diabetes therapy.

Toward an Integrated Feedback Control System in a Pancreatic Cell Culture Comprising Sensors for Glucose and Insulin

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Objective:

Recent scientific advances in islet transplants research in bioreactors have opened new avenues for the implementation of innovative sensing technology. Monitoring of insulin secretion, as well as glucose consumption in islet cell cultures, will be crucial to reproducibly generate islet cells with high intrinsic viability for achieving high survival rates when transplanted into humans. Our goal was therefore to implement the BioTex fluorescence affinity sensor (FAS) for glucose sensing and an innovative fluorescence affinity-based sensor for insulin by developing an insulin-specific aptamer ligand for their integration in a rotary cell culture system (RCCS) made by Synthecon, Inc.

Design:

The BioTex FAS was inserted into the flow loop of the RCCS and was instrumented with a miniature universal serial bus spectrophotometer for signal output. Similarly, the insulin sensor was implemented by containing a fluorescence resonance energy transfer (FRET) assay comprising a molecular beacon-type insulin-specific ligand (aptamer) developed by SELEX (Systematic Evolution of Ligands by EXponential enrichment) inside a membrane housing, which was then positioned in the flow loop.

Methods:

To determine response time and stability over time, we tested the response of the BioTex FAS to glucose in the flow loop of the RCCS in the absence and presence of a cell culture over several days. We also developed and tested a prototype FRET assay—comprising quantum dots (emission 655 nm) and QSY21 (absorbance 670 nm) used as donor and quencher dye, respectively—for the detection of insulin, which was based on an insulin-specific aptamer obtained after 10 rounds of the SELEX protocol.

Results:

The BioTex FAS was studied successfully for monitoring glucose in the RCCS over several days. However, its response to changes of glucose inside the bioreactor was initially quite slow (several hours) due to the small surface area of the membrane (tubular membrane) separating the bioreactor from the flow loop. To increase the diffusion rate, preliminary studies with a hollow fiber bundle having a much larger surface area (by several orders of magnitude) have been performed. The time delay for detecting changes in glucose levels inside the bioreactor was reduced to about 60 minutes. In further preliminary *in vitro* experiments, the aptamer-based FRET assay for insulin showed reversibility and a detection level in the submicromolar range.

Conclusions:

Overall, results indicate feasibility of combining Synthecon's superior three-dimensional cell culture with BioTex's optical sensing technology toward a sensor-based feedback control system that may significantly advance the quality of islet cell production for diabetes therapy. Future work will include packaging of the glucose and insulin sensor into a format for online use in the bioreactor setting.

Comparison of Two Laboratory Methods in the Course of a Study According to EN International Standards Organization 15197 Assessing Accuracy of Blood Glucose Monitoring Systems for Self-Testing

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Objective:

In intensified diabetes therapy, therapeutic decisions are made based on blood glucose concentrations. Since 2003 EN International Standards Organization (ISO) 15197 specifies requirements for *in vitro* glucose monitoring systems measuring glucose concentrations in capillary blood samples and defines procedures to verify and validate the performance. Accuracy of the systems was evaluated versus defined reference methods, which therefore play a pivotal role and must have traceable accuracy. Here, we provide data on finger prick plasma glucose measurements with two different reference methods.

Method:

Two capillary blood samples of 200 µl from finger pricks were collected from each of 100 different patients with plasma glucose concentrations distributed according to EN ISO 15197. Plasma was separated immediately, and double measurements for all samples were performed with COBAS c111 (Roche Diagnostics GmbH, Germany) and YSI 2300G STAT Plus (YSI Incorporated, USA), respectively. For quality assurance, reference standard samples were analyzed and control measurements were performed according to the manufacturer's instructions.

Result:

COBAS c111 and YSI 2300G STAT Plus were in proper quality control throughout the evaluation period. Evaluated glucose concentrations (mean values from double measurements) were between 28.8 and 608 mg/dl and between 29.59 and 605.66 mg/dl with YSI and COBAS, respectively. Both methods showed good agreement and a linear relationship (Bland-Altman analysis: difference: -0.2%; Bablok-Passing regression: $y = 0.99x + 0.5$).

Conclusion:

Finger prick plasma glucose measurements with COBAS c111 and YSI 2300G STAT Plus showed good accuracy and provided nearly identical results. Both devices provided suitable performance for the application in studies according to EN ISO 15197.

Performance of the TRUE2go™ Blood Glucose System: A Novel Integrated System for Meter and Strips

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Introduction:

The TRUE2go™ blood glucose monitoring system uses a very small, unique meter. The meter attaches to a vial of 50 biosensor test strips and is transferable to new vials of strips. This novel combination provides the user with 50 test strips providing three to five times more strips in a smaller package than other integrated blood glucose test systems. Performance is state of the art with results in as little as 4 seconds using only 0.5 µl blood without user coding.

Methods:

TRUE2go performance was evaluated at four clinical sites with diabetic subjects according to the protocol established by the International Standards Organization (ISO). Health care professionals (HCP) tested diabetic subjects' blood after the subjects performed a self-test on finger tips and forearm. Results from the subjects and HCP were compared to each other and the reference method.

Results:

All subjects and health care professionals obtained accurate results with the TRUE2go system. Of the results, 99.8% were within zone A of the standard error grid when compared to the YSI result. Only 1 result of 664 results was in zone B. The accuracy of the HCP results also met the requirements of ISO 15197. Of the 339 HCP results, 99.1% (336) were within ISO 15197 requirements. The system also provided excellent results for alternate site testing using the forearm. Of the 660 results obtained by the HCP and diabetic subjects, 99% were in zone A and 1% in zone B.

Conclusions:

The TRUE2go system provides a small meter-and-strip package that makes self-blood glucose monitoring easier and more convenient than conventional systems. The system exhibits excellent accuracy and precision. Users found the system very easy to use.

Impact of a Video Cell Phone Reminder System on Glycemic Control in Patients with Diabetes Mellitus: Preliminary Results

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Objective:

The goal of this study was to determine if a video-enabled cell phone reminder system improves glycemic control in patients with diabetes mellitus (DM).

Methods:

Subjects with DM type 1 or 2 with a hemoglobin A1c >8% were recruited for a 1-year, prospective, randomized, controlled trial with a projected enrollment of 170 subjects. Patients randomized to the video group received a daily, 15-second video from their diabetes care manager reminding them to test their blood glucose, take their diabetes medications, and provided an “educational tip of the day.” Those in the control group received a comparable cell phone but no video reminders. The primary outcome was change in hemoglobin A1c (HbA1c).

Results:

Thirty-three subjects have completed 3 months of the study. Fifteen subjects were randomized to the video group; 18 were randomized to the control group. Baseline HbA1c in the video group was 9.57% (± 1.16) and decreased significantly at 3 months to 8.87% (± 1.24) ($p = 0.03$). Baseline HbA1c in the control group was 8.67% (± 0.54) and at 3 months was 8.37% (± 1.43) ($p = 0.39$). Subjects in the video group that watched >50% of the daily videos ($n = 10$) had a significant decrease in HbA1c of 0.92% ($p = 0.05$) at 3 months. Subjects in the reminder group that watched <50% of the videos ($n = 5$) did not have a significant change in HbA1c (-0.24% , $p = 0.38$).

Conclusions:

A video cell phone reminder system is effective in lowering hemoglobin A1c in patients with DM. This effect was most pronounced in patients who viewed the videos greater than 50% of the time.

Requirements for Calibration in Noninvasive Glucose Monitoring by Raman Spectroscopy

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Objective:

We derived guidelines for the minimum quantity of data sufficient to derive a valid universal calibration, based on empirical observations of the quality of the calibration. We also defined an exit criterion for establishing when data are approaching sufficiency.

Method:

Over a 13-month period, data were taken from 30 type I diabetic patients in glucose clamp studies and uncorrelated snapshot measurements. The target clamp profiles were varied according to a criterion based on the subject's glucose level on arrival. Sufficiency of scale was determined by adding new data into an existing calibration algorithm with the requirement that the prediction error should be preserved or improved, without significant reoptimization. Using this criterion, we established guidelines for the number of subjects, sites, and independent glucose measurements.

Result:

The number of independent parameters required to model data rises more slowly than the set size. We found that the minimum sufficient scale was an increasing function of the rate of change in glucose values that was permitted in the clamps. This sensitivity was attributed to variance in the delay between skin glucose and blood glucose and was mitigated with a model that calculates delay parameters from spectra. We also found that elimination of extraneous variance from thermal, mechanical, and optical sources was a prerequisite for achieving acceptable calibration.

Conclusion:

It was necessary to measure >15 subjects with at least 200 independent sites. We obtained a preliminary calibration wherein >94% of validation data is in the A or B zones of the Clarke error grid. The model provides a sufficient framework for the design of a wearable apparatus.

Long-Term Monitoring of Plantar Temperature during Activity of Daily Living: A Proof of Concept Trial

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Objective:

The purpose of this investigation was to determine thermal changes at the plantar foot during activity of daily living (ADL). Additionally, it is envisaged to incorporate resulting knowledge into the diabetic foot care and prevention initiatives involving thermometry and physical activity monitoring using smart sensors and telemedicine.

Methods:

Our investigation involved body-worn sensors based on microelectromechanical systems technology, Physiolog[®] data acquisition system, and FLIR[®] thermal imager to visualize thermal changes. After 20 minutes of acclimatization with ambient temperature (consistently maintained at 24°C) for baseline measurement, all subjects had four walking episodes over a walkway distance of 500 meters. Thermal images were acquired after each walking episode. Two image data sets were recorded to assess the reliability of thermal images.

Results:

After a slight drop in temperature ($p = 0.15$) with the first 400 steps we observed a linear increase in temperature as a function of number of steps during gait ($1.6 \times 10^{-3} \text{°C/step}$, $p < 0.0001$) up to the first 2000 steps. After 1500 steps, the average increase in temperature with standard error was $1.8 \pm 0.22 \text{°C}$ (6.3%). Retest recordings suggest good reliability and accuracy of thermal data.

Conclusions:

This preliminary investigation sheds light on how plantar temperature varies as a function of number of steps during ADL. Such a weight bearing and ambulatory assessment holds key for neuropathic evaluation of the diabetic foot. From a physiological standpoint, our results suggest an initial drop, which may be because of multiple factors (metabolic factors, normal perfusion status, physical state of tissue) and association between them, followed by a linear increase in temperature. This increase is due primarily to raised perfusion levels as a result of sustained repetitive stress, resulting in higher metabolic demand.

Smart Thermometry Insoles for Ambulatory Assessment of Plantar Temperatures for Prevention of Diabetic Foot Ulcers

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Objective:

This investigation considered real-time contact thermometry to measure plantar temperatures in weight bearing during ambulation to detect inflammatory changes at the plantar foot and identify reliable clinical outcomes such as reduction in foot ulceration, risk stratification, dosing physical activity, and off-loading measures.

Methods:

First we did bench characterization of the smart sensors to assess their accuracy, linearity, reliability, and temporal response using a controlled temperature chamber. Each insole contained eight thin film thermistor sensors, factory calibrated for a robust performance. In the second set of tests, we gathered dynamic data sets to capture typical trends/episodes during activity of daily living (ADL).

Results:

The insoles consistently tracked temperature changes over long-term physical activity. Foot temperatures typically increased as a function of number of gait steps and replicated local hemodynamic changes. Results suggested a temperature accuracy of $\pm 0.4^{\circ}\text{C}$, linearity $>98\%$, and temporal response of the order of 5 minutes within the physiologically relevant range of temperatures ($20\text{--}50^{\circ}\text{C}$). Thermometry insole showed good reliability for tests conducted over 5 days at 10 hours per day.

Conclusions:

Preliminary results suggest that dynamic behavior of plantar temperature, as a function of number of continuous gait steps, is a reliable parameter for delivering robust clinical outcomes. This parameter may be used to identify diabetic patients with poorly organized physical activity and abnormal thermal profile during ADL. These insoles provide whole foot measurements unlike point measurements for handheld thermometers and are lightweight, portable, and ergonomically designed to encourage patient compliance. This investigation is part of the research initiatives at authors' units targeted at limb salvage.

Nip and Tuck for the Feet: A Novel Way to Reduce Callus, Inflammation, and Ulceration

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Objective:

The aim of this investigation was to present a case study regarding tissue volumizing (or tissue augmentation) agents for redistributing plantar pressures in patients with diabetic neuropathy.

Methods:

We considered three different modalities to assess the benefits of tissue augmentation therapy using silicone injections at bony prominences for a diabetic patient with neuropathy. We used plantar pressures using force platform, tissue thickness using weight bearing ultrasound, and foot temperature using infrared imaging pre/postinjection therapy. We used the repetitive stress model to identify sites of local inflammation and in most need of silicone therapy.

Results:

Thermal imaging of the plantar feet sensitively detected the preulcerative callus under metatarsal heads, and these sites appeared as local hot spots on the plantar foot surface following 15 minutes of treadmill walking at 3.3 mph. Tissue thickness increased by 1.3 mm, and both peak plantar pressure and pressure time integral reduced post-therapy.

Conclusions:

Results from this case study are consistent with published literature and suggest that tissue augmentation therapy may be an alternative to prescription footwear, for which poor patient compliance has been reported. Recent technological advances in thermal imaging have afforded the ability to monitor the therapy in a serial imaging fashion to assess benefits to the patient. The use of such agents acts as fat pad replacement or dermal filler for patients with diabetic neuropathy and creates an internal orthotic effect that has the potential to reduce the risk for ulceration.

Causal System Modeling: A Novel Method for Identifying Molecular Mechanisms of Caloric Restriction and Its Application for Diabetes Diagnosis and Treatment

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Introduction:

Understanding the cellular and molecular networks impacted by caloric restriction (CR) is crucial for the development of novel therapeutic strategies that mimic CR health benefits. CR consistently slows many physiological and pathological changes that occur with advancing age such as adiposity, insulin resistance, reduced body temperature, and changes in serum lipids, thereby maintaining health and vitality. However, the molecular targets and downstream networks that regulate the CR response remain largely unknown and identification of those targets is crucial for pharmaceutical research and development. Identification of these molecular targets will also enable screening for small molecules with the potential to mimic the effects of CR and possibly treat diabetes.

Method:

Systems biology methods permit comprehensive modeling of biological systems by elucidating the integrated molecular network affected by a perturbation. High-throughput omic technologies produce large data sets, but the challenge lies in elucidating the molecular mechanisms that underlie these data. Here we describe causal network modeling, a computable framework for modeling biological networks, using omic data to infer from existing scientific knowledge the causal networks evident in those data. We used this approach to characterize the caloric restriction causal network model.

Results:

Using publicly available RNA expression microarray data, we described the identification of the molecular signature of caloric restriction. This molecular signature includes well-established CR-related physiological processes (decreased food intake, decreased oxidative stress, decreased serum insulin and glucose) and molecular processes such as increased peroxisome proliferator-activated receptor activity and decreased Toll-like receptors 3 and 4 activity. In addition, novel CR molecular effectors were discovered and will be presented.

Conclusion:

Elucidation of this causal network provides novel targets for drug discovery, which could prove effective for aging-related diseases, including diabetes.

Efforts Related to Interfacing a Noninvasive Blood Glucose Device to Tissue

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Objective:

A noninvasive method for the analysis of blood glucose is sought to offer an alternative to the finger stick method. The noninvasive method should offer the potential of additional bloodless measurements at minimal additional expense.

Method:

The use of near-infrared spectroscopy to measure glucose in human tissue provides high signal to noise and measurement precision. The challenge is to develop a model capable of robust measurement under varying optical conditions. The spectroscopic measurement—established under highly controlled conditions in the research laboratory—is based on minimum energy contact between the probe and the skin.

Results:

Regression vectors developed under these minimal energy conditions yield a stronger analyte signal based on the signals relation to the inverse of the second norm of the regression vector. The use of topological mapping of the arm surface, the effects of arm curvature on the wetting/lubrication of the measurement site, and the adjustment of the device probe to be proximally tangent to the tissue contact site are discussed. Results from low energy near-infrared measurements are illustrated and supported with simulations.

Conclusions:

The use of an arm guide in controlling probe placement increased the reliability in the past. The initial result of removing the arm guide was not encouraging, but recent testing indicates that further limiting energy transfer between the sensing head and the skin has led to an improvement in the accessible glucose signal, or the net analyte signal. The control of tissue consistency and optical volume will be critical to the development of a self-monitoring blood glucose device.

Implementation of Standards of Medical Care in Diabetes Is Associated with Reduction of Random Serum Glucose in Hospitalized Diabetic Patients

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Objectives:

The present study was designed to evaluate the impact of an intensive glucose management protocol on glucose levels measured by an automated glucometer and on the number of hyper- and hypoglycemic events among adults hospitalized from July through December 2007.

Methods:

Starting gradually in July 2007, all diabetic patients hospitalized at the E. Wolfson Medical Center, Holon, Israel, were monitored and treated according to the American Diabetes Association Standards of Medical Care in Diabetes 2007. Glucose was monitored using the Accu-Chek Inform (Roche) automated glucometer. Mean hospital serum glucose levels were calculated and compared over time and by department.

Results:

A total of 85,377 glucometer readings were performed in approximately 4879 patients during the follow-up period. Mean serum glucose levels decreased from 282.3 ± 149.2 mg/dl in July 2007 to 206.2 ± 106.6 mg/dl in January 2008 ($p < 0.0001$). The proportion of diabetic patients with mean random glucose levels 60–180 mg/dl increased from 31.7% in July 2007 to 49.5% in January 2008 ($p = 0.002$). This is driven by the decline in the proportion of patients with random glucose values >300 mg/dl, which declined from 43.6% in July 2007 to 17.4% in January 2008 ($p < 0.0001$). The proportion of patients with events of serum glucose <60 mg/dl did not change significantly over time and remained at approximately 1.1% of the population throughout. During follow-up, patients hospitalized in internal medicine units had significantly greater random glucose levels than surgical patients even after controlling for follow-up time (206.9 ± 102.1 mg/dl vs 192.9 ± 87.4 , $p < 0.0001$).

Conclusions:

Implementation of the recommendations for standards of care in diabetes resulted in significant reductions in random serum glucose levels, particularly in internal medicine units.

A Dynamic Basal/Bolus Advisor: Changing the Paradigm

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Objective:

Basal and bolus insulin determinations in intensive insulin therapy for type 1 diabetes mellitus are currently considered independently of each other. A new strategy that dynamically changes both basal and bolus insulin infusions to cope with postprandial glycemia in pump therapy is proposed. Superior performance of this new strategy is demonstrated through a formal analysis of attainable performances in an *in silico* population.

Method:

The Set Inversion Via Interval Analysis (SIVIA) algorithm has been applied to a well-established glucoregulatory model to obtain the feasible set of basal and bolus doses that, for a given meal, mathematically guarantee a postprandial response fulfilling International Diabetes Federation (IDF) guidelines (nonhypoglycemia and 2-hour postprandial glucose below 140 mg/dl) in a 5-hour time horizon. The approach was evaluated on meals in the range of 30 to 80 grams of carbohydrates.

Result:

The computed feasible sets demonstrate that fixing basal insulin limits the attainable performance dramatically. For a nominal basal of 0.8 IU/h, leading to a basal glucose of approximately 100 mg/dl, IDF guidelines cannot be fulfilled for meals greater than 50 grams, independent of the bolus insulin computed. However, coordinating basal and bolus insulin can achieve this. A decrement of basal insulin during the postprandial state is required together with an increase in bolus insulin, in appropriate percentages, which is meal dependent. After 3 hours, basal insulin can be restored to its nominal value.

Conclusion:

The new strategy meets IDF guidelines in a typical day, contrary to the standard fixed basal/bolus strategy. The application of interval analysis for the computation of feasible sets demonstrates to be a powerful tool for the analysis of attainable performance in glucose control.

A Pilot Study with GlucoPront: A Continuous Glucose Monitoring Device

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Objective:

Tight glycemic control in patients admitted to the intensive care unit (ICU) resulted in significant reduction of mortality and morbidity. Therefore, Sensile Medical has developed the continuous glucose monitoring device GlucoPront for this particular use. This study evaluated the performance of the GlucoPront device in diabetic patients with fast, provoked, postprandial glucose excursions.

Method:

Sixteen patients with type 1 diabetes mellitus were enrolled. Two GlucoPront devices were inserted in the subcutaneous tissue of each patient. In groups of four, the patients carried the devices for 48, 72, and 96 hours, respectively. In order to provoke glucose excursions, patients had breakfast with fast-acting carbohydrates and delayed their insulin bolus up to 30 minutes. To induce hypoglycemia, patients increased their correction bolus. Twenty-nine capillary blood glucose measurements were performed daily to verify glucose signals and for prospective as well as retrospective calibration.

Result:

Continuous glucose monitoring with GlucoPront devices provided reliable results for up to 96 hours in diabetic patients. The glucose signals correlated with the capillary blood measurements. Further test with a running time of 120 hours are planned. The signal drift was minimal and the overall performance of the system was good. The system was able to follow very fast changing glucose signals up to 5 mg/dl/min in a range from 2.5 to 25 mmol/liter.

Conclusion:

GlucoPront provides reliable results, and with this system and the already established and validated production environment, Sensile Medical plans to aim CE certification in the last quarter of 2008. Further studies in critically ill patient are in progress and will document the capabilities of this continuous glucose monitoring device in the ICU setting.

Investigation of Inflammatory Potential of Biomaterials Intended for Cell Encapsulation or Device Coating

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Objective:

Alginate and hyaluronic acid (HA) are two biomaterials commonly used for tissue engineering constructs (e.g., islet encapsulation) and coating biosensors (e.g., mitigating biofouling). The inherent biomaterial immunogenicity is a necessary consideration for adequate device function and longevity. The objective of this study was to investigate the inflammatory potential of alginate and HA under physiologically relevant conditions. The effect of biomaterial purity and/or molecular weight (MW) on device immunogenicity was examined.

Method:

A murine macrophage cell line, RAW264.7, was cultured for various lengths of time in the presence of alginate microspheres or HA of defined MW in the absence or presence of murine interferon γ (IFN- γ) and/or endotoxin. At defined time points, the supernatant assayed for nitrite concentration [formed as a result of nitric oxide (NO) production] using a spectrophotometric assay. The amount of nitrite formed served as an indicator of the inflammatory response.

Results:

For alginate, the no observable effect level (NOEL) for endotoxin after 20 hours was determined to be 10 EU/ml and the lowest observable effect level (LOEL) was 15 EU/ml. However, in the presence of IFN- γ (high inflammatory state) the NOEL was 0.1 EU/ml and the LOEL was 0.25 EU/ml. HA with an endotoxin content lower than 0.01 EU/mg exhibited a low or no inflammatory response. However, in the presence of a higher endotoxin amount and IFN- γ the HA modulated macrophage inflammatory function, correlating with MW.

Conclusion:

The inflammatory potential of implantable biomaterials may be tested on RAW264.7 cells as a model system for macrophage-mediated inflammation. This assay has the potential to be used as a high-throughput screening test for biomaterials. NO production and other end points may signal inflammatory reactions that can compromise the safety and efficacy of the implanted device.

In Silico Preclinical Trials: From Mathematical Models to Food and Drug Administration Approval

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Objectives:

Advancements in continuous glucose monitoring (CGM) and insulin delivery (subcutaneous and implanted pumps) enable increasingly sophisticated insulin treatments, and ultimately closed loop glucose control. Such treatments require thorough testing in clinical trials, preceded by an arduous validation process, potentially involving numerous animal studies. We proposed an *in silico* environment based on established mathematical models of human physiology and extensive data, providing *in silico* assessment of insulin treatment strategies.

Methods:

Using mathematical models of the glucose/insulin system, insulin pumps, and continuous glucose sensors, we developed a Simulink® model capable of reproducing *in vivo* reactions to glucose and insulin. We added a set of outcome measures quantifying the performance and risks of treatment, as well as a graphical user interface enabling hardware, outcome, scenario, and subject selection.

Results:

The *in silico* simulation environment was equipped with 300 subjects in three age groups covering the distribution of key metabolic parameters observed *in vivo*. It is capable of simulating insulin treatment protocols, including (i) a screening visit (e.g., biometrics), (ii) initial admission (e.g., oral glucose tolerance test), (iii) tuning of a subject-specific treatment, and (iv) treatment execution. The system was approved by the Food and Drug Administration (FDA) for preclinical testing in January 2008. We used the *in silico* environment to design a closed loop control study and test its control algorithm. Based solely on *in silico* testing, the study received FDA investigational device exemption in April 2008.

Conclusion:

A comprehensive *in silico* platform capable of simulating complex clinical protocols has the potential to greatly accelerate the path from development of novel insulin treatment strategies, through regulatory approval, to human clinical trials.

Glucose Trend Management: Continuous Glucose Monitor Device versus Frequent Real-Time Blood Glucose Measurements

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Objective:

Preprandial glucose trends were shown to affect postprandial glucose, suggesting the importance of glucose trend in diabetes management. A real-time glucose trend can be obtained from continuous glucose monitoring (CGM) systems or frequent blood glucose (BG) measurements. The two real-time methods were compared against the true BG trend.

Method:

Data from 58 type 1 diabetes mellitus subjects were used. Each of the 115 FreeStyle Navigator® CGM system wears had 50 hours of Yellow Springs Instrument (YSI) data at 15-minute intervals. The real-time CGM trend was displayed in the FreeStyle Navigator CGM system. The real-time BG trend was computed from YSI pairs spaced 15, 30, 45, and 60 minutes apart. The true BG trend was represented by a retrospective three-point rate using YSI data. Both prebinned and binned trend comparisons were performed. The binned trend comparison used the trend arrow bin convention used by the FreeStyle Navigator CGM system. The bins were (in mg/dl/min units): decreasing faster than -2, decreasing between -2 and -1, between -1 and 1, increasing between 1 and 2, and increasing faster than 2.

Result:

Both prebinned and binned comparisons suggest that the glucose trend of the FreeStyle Navigator CGM system lies between real-time BG trends computed every 30 and 45 minutes.

Conclusion:

The point-wise accuracy of the FreeStyle Navigator CGM trend was equivalent to real-time BG trend calculation using YSI data taken every 30 to 45 minutes. Practically, SMBG meter data are less reliable than YSI glucose data. Hence, modifying treatment using the real-time trend from the FreeStyle Navigator CGM system may be more accurate than the real-time trend from an SMBG meter every 30 to 45 minutes.

Has the Accessibility of Insulin Pumps for People with Vision Loss Changed Since 2004?

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Background:

In 2004, Uslan and colleagues determined that insulin pumps on the market were inaccessible to blind and visually impaired persons. The objective of this study was to determine if the accessibility status had changed since 2004.

Methods:

Five insulin pumps on the market in 2008 were acquired and analyzed for key accessibility traits, such as speech and other audio output, tactual nature of control buttons, and quality of visual displays. It was also determined whether a blind or visually impaired person could independently complete tasks such as programming the pump for insulin delivery, replacing batteries, refilling insulin, reading manuals and other documentation, and working with infusion sets.

Results:

It was found that insulin pumps have not improved in accessibility since 2003. None have speech output and most have eliminated the audio bolus feature that can assist a blind patient. With the exception of the Animas 2020, no improved visual display characteristics were found. Although documentation is still not completely accessible, improvements were found, allowing a person to at least learn about the pump to help in directing a sighted person to assist with controlling the insulin pump.

Conclusion:

Insulin pumps are relatively complex devices, with serious health consequences resulting from improper use. For insulin pumps to be used safely and independently by blind and visually impaired patients, they must include voice output to communicate all the information presented on their display screens. Enhancing display contrast and the size of the displayed information would also improve accessibility for visually impaired users. The pumps must also come with accessible user documentation in alternate formats.

Noninvasive Glucose Monitoring in Patients with Type 1 Diabetes: Repeatability in the Same Subjects

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Introduction:

A noninvasive multisensor device for continuous glucose monitoring, based on dielectric spectroscopy, combined with additional sensors for optical, sweat/moisture, and temperature measurement, has been developed. Motivation for the multisensory device is based on the understanding that various temporal fluctuations of the properties of skin can introduce significant perturbations to the actual glucose related measurement. The aim of this study was to measure glucose excursions on different study days in the same subjects using an identical set of calibration parameters.

Methods:

The device was worn on the upper right arm by 10 patients with type 1 diabetes (age 45 ± 13 years, body mass index 25.5 ± 2.2 kg/m², duration of diabetes 22.5 ± 10.5 years, hemoglobin A1c $7.0 \pm 0.5\%$). Glucose was administered orally to induce two consecutive hyperglycemic excursions (maximum 12–15 mmol/liter) within 8 hours. Euglycemia was reestablished by intravenous insulin administration. Based on the sensor signals registered after the first study day, a global calibration model was derived, and the respective coefficients of the individual sensor signals were determined. The model included one coefficient specific to each run. On the second study day, 5 of these patients were again administered glucose orally to induce a glucose profile with one hyperglycemic excursion. Coefficients from the first study day were reapplied to the five test runs of the second study day in order to study the prediction power of the model.

Results:

Application of the calibration model from day 1 to 2 two yielded an $R^2 = 0.68$ and a mean absolute relative difference of 27.3%.

Conclusions:

These data indicate that a global model can be derived using training runs and applied successfully to a set of test runs with a different glucose profile.

Testing a Multisensor Concept under Simulated Home Use Conditions for Noninvasive Glucose Monitoring

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Introduction:

Numerous techniques for noninvasive glucose monitoring (NIGM) are under development. Dielectric spectroscopy (DS) is a promising approach. However, a number of extrinsic and intrinsic factors can affect the measurements. In order to be able to compensate for such factors, a novel multisensor concept, including sensors for broadband DS, optical, sweat/moisture, acceleration and temperature measurements, has been developed.

Methods:

Eight patients with type 1 diabetes mellitus (4 T1DM, age 43 ± 9 years; body mass index 26.1 ± 2.9 kg/m², duration of diabetes 22 ± 14 years; hemoglobin A1c $7.4 \pm 0.9\%$ and 4 T2DM patients, 66 ± 2 years; 30.6 ± 1.8 kg/m²; 10 ± 8 years; $6.9 \pm 0.3\%$) performed up to 4 study days. Glucose was administered orally to induce a hyperglycemic excursion (15 mmol/liter). Euglycemia was reestablished by subcutaneous insulin administration. In 2 of the 4 study days, movements/perturbations were introduced within 10-minute movement blocks (cycling, walking, regular deskwork) distributed randomly throughout the day. In the other 2 study days, in addition to the movement blocks and oral glucose administration, patients drank 3 liters of water.

Results:

For data evaluation, a multiple regression analysis was performed to establish a global model, including all subjects and a personal model for the individual patient including all study days. They allowed for investigating the effect of perturbations induced on the dielectric characteristics. With the personal model, glucose excursions could be tracked with an $R^2 = 0.71$ and a mean absolute relative difference (MARD) of 17.9%, the global model yielded an $R^2 = 0.6$ and an MARD of 21.5%, respectively.

Conclusions:

These results indicate that under less controlled conditions, NIGM can be achieved by a multisensor approach. A parameterization strategy for the individual patient performs better than a global approach. No detectable effect was found for water administration on the statistical outcome.

Toward Eliminating Faulty Measurements in Blood Glucose Calibration

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Introduction:

We extended real-time blood glucose (BG) estimation from finger stick blood glucose (FBG) and interstitial glucose (IG) measurements to additionally provide accuracy estimates and the likelihoods of measurements. These features can potentially detect faulty measurements and thereby provide better BG information for diabetes treatment decisions.

Methods:

We used an extended Kalman filter (EKF) with a detailed sensor model and rudimentary diabetes model. Including physiologic and sensor lags in the sensor model allows the use of FBG measurements regardless of the actual BG rate of change. We calculated both the standard deviation of the current BG estimate and the likelihood of current FBG and IG measurements. We tested 13 inpatient days with 1-minute IG (FreeStyle Navigator®) and 3–4 FBG values per day. Additional FBG values (49 per day) were used to assess performance. Three percent of the IG and FBG measurements were physiologically inconsistent, as characterized by sudden changes in the BG rate of change followed immediately by equally sudden reversals.

Results:

Our EKF method performed similarly to a published Navigator calibration when both used the same 3–4 FBG measurements for calibration. The root mean-squared errors (RMSE) were 37.4 and 36.6 mg/dl with continuous glucose error grid analysis zone C, D, and E clinically relevant error rates (CRER) of 2.6 and 2.2%, respectively. The EKF calculated in real time that physiologically inconsistent data were unlikely. Ignoring these data for performance and calibration improved the EKF results to an RMSE of 26.3 mg/dl and a CRER of 1.3%.

Conclusion:

This work demonstrated the potential to significantly improve calibration accuracy by removing faulty FBG and IG measurements using real-time BG magnitude and accuracy estimates and measurement likelihoods from an extended Kalman filter.

Locally Weighted Learning for Blood Glucose Reliability Estimation

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Objective:

This work estimated situation-dependent blood glucose (BG) prediction reliability. Standard predictors inaccurately assume constant reliability for all predictions regardless of time of day, recent BG, or any other factors. They do not understand increased predictive power at night and decreased predictive power right after meals. Locally weighted learning (LWL) uses past, similar situations to estimate prediction reliability in real time. This generates more precise confidence levels (CL) for insulin injection decisions.

Method:

Locally weighted learning collects past relevant BG predictions and measurements to determine the prediction reliability as expressed by a standard deviation (SD). The relevance of past points is determined by similarity in the states: recent calibrated BG, time since meal, time of day, and calculated insulin on board. These SDs also provide CLs that the calibrated BG will be within a symmetric interval around the prediction. We used DirecNet data from 26 similar, 1-day clinical visits. One-minute interstitial (FreeStyle Navigator®) and finger stick (52/day) glucose measurements, food, and insulin events were recorded.

Results:

The LWL was trained on 13 visits and evaluated on another 13 visits. We compared calculated CLs against actual rates of occurrence of calibrated BG in the same interval. The LWL method generated CLs with 20, 19, and 23% maximum relative errors for prediction horizons of 30, 45, and 60 minutes, respectively. Comparisons assuming a constant SD produced errors of 27, 35, and 34%. With only 378, 230, and 168 training values, respectively, LWL improved estimates by 26, 46, and 32%.

Conclusion:

Here, with only a few training points, LWL captured local effects and generated more precise state-dependent estimates of prediction reliability. This gives higher confidence for insulin therapy based on BG predictions.

Dual Insulin Therapy— Application of Run-to-Run Control: A Simulation Study

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Introduction:

Multiple-daily injections (MDI) therapy is still the dominant protocol for most type 1 diabetes mellitus patients (T1DM), especially in developing nations and in medium- to low-income households. Immerging technology, such as an artificial β cell, is not likely to be affordable to these patients in the next 20–30 years. However, MDI therapy can be improved using advanced control algorithms designed for continuous glucose monitoring and continuous insulin infusion pumps.

Methods:

An extension of the run-to-run framework to MDI therapy employing lispro and glargine insulins is suggested. Two protocols were evaluated with both pre- and postprandial glucose measurements (60 minutes postprandial): (A) prandial lispro at 7 am, 2 pm, and 9 pm (breakfast, lunch, and dinner, respectively) with a glargine injection at breakfast and dinner and (B) lispro boluses at 8 am, 2 pm, and 8 pm (breakfast, lunch, and dinner, respectively) with glargine at 8 am and 11 pm and a bedtime glucose measurement. Regulation performance was then evaluated using the preprandial glucose concentration and postprandial glucose peak. The run-to-run control was evaluated in simulation using a glucose–insulin model developed by Chiara and colleagues and a subcutaneous insulin absorption model by Tarin and colleagues.

Results:

Results show that both protocols are successful in achieving a tight glucose concentration (80–130 mg/dl) despite variable meals (10% variation in carbohydrate content and timing). No hypoglycemic (<60 mg/dl) or hyperglycemic (>180 mg/dl) events were observed during the evaluation.

Conclusions:

This work showed that the run-to-run framework for insulin update can be extended successfully to a MDI protocol. These results motivate the practical implementation of this scheme in portable units such as personal digital assistants or cell phones.

An Advanced Telemedicine Architecture for Managing Diabetes and Related Complications

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Objective:

Diabetic patients, in addition to managing their illness state, are frequently asked to front several complications that also require a strict monitoring activity. This study proposed a generic architecture for implementing telemedicine services deployed on mobiles aimed at supporting continuous monitoring for glycemia and for other critical parameters concerning the assessment/treatment of complications.

Method:

We designed a multitier architecture supporting self-medication and follow-up for chronic patients also improving interaction with the health care center. The lower tier is implemented by a mobile able to acquire data and provide first-level advice to the patient. The mobile automatically uploads data to the health care center, representing the higher tier, and receives any therapeutic plan or measure reminder schedules supplied by the physician. On the patient's side the mobile phone also exploits the Bluetooth technology acting as a hub for a wireless network, including glucometers, scales, and blood pressure monitors.

Result:

This architecture is being used for implementing two prototypes currently undergoing evaluation. The first one is used by pediatric diabetic patients for keeping in close touch with their physician and enabling parents to become aware of their kids' conditions at school. The second prototype monitors diabetic adults with nephropathies self-administering peritoneal dialysis at home. The mobile proactively reminds the patient of measuring his weight and blood pressure and then acquires data directly from the peripheral device without any manual intervention exploiting the Bluetooth connection.

Conclusion:

Our architecture will enhance patient-physician interaction, improving management of complications and patients' life quality, thus reducing overall health care costs. A subsequent effort will be undertaken to exploit the prototypes within a pilot study involving patients cared at a major hospital located in northern Italy.

Basal + Bolus versus Bolus-Only Insulin Delivery: Is There a Difference?

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Objective:

The objective of this study was to establish an optimal insulin delivery pattern that minimizes the frequency of insulin pump actuation while preserving glucose levels. We compared the effects of basal + bolus versus bolus-only insulin delivery on glucose levels and determined an optimal bolus frequency.

Method:

We first simulated *in silico* the effect of bolus-only delivery of insulin lispro using a computer simulation environment equipped with 300 *in silico* type 1 diabetes mellitus (T1DM) “subjects.” The simulation tested bolus periods from 1 to 60 minutes and random pump errors with fixed and relative variance. The statistical significance of the induced glucose oscillations was assessed and the optimal bolus frequency was determined. Then, the results were tested *in vivo* on T1DM patients subjected to bolus-only insulin delivery and monitored continuously by Navigator™ CGM (Abbott D.C., Alameda, CA) during an overnight hospitalization.

Results:

In silico, there were no significant glucose oscillations resulting from insulin boluses spaced up to one every 15 minutes. Boluses are smoothed out by insulin transport and do not translate into glucose level oscillations. The lack of effect of boluses on glucose levels has been confirmed *in vivo*: T1DM patients using 15-minute insulin boluses instead of continuous basal rate overnight did not exhibit significant glucose oscillations as verified by a Fourier analysis.

Conclusion:

We demonstrated that insulin boluses with frequency 1/15 minutes produce smooth glucose levels similar to those obtained by basal rate alone. This is important because bolus-only insulin delivery has the potential to facilitate the implementation of closed-loop control algorithms. In addition, less frequent injections could have implications on insulin pump battery life and optimal performance.

An Innovative Interactive Computer Program to Assess Diabetes Risk Factors in Youth

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Objective:

In parallel with the epidemic of pediatric obesity, type 2 diabetes has emerged as a significant clinical condition among youth. Although childhood is a critical opportunity for delivering prevention education, very few pediatricians appropriately assess for obesity and diabetes risk factors. Therefore, the objective of this study was to implement an innovative interactive technology to assist with the identification of risk factors for type 2 diabetes in youth.

Methods:

HeartSmartKids™ is a Web-linked program that facilitates measurements of adiposity, physical activity patterns, and dietary habits through an interactive computer kiosk. The software compares obesity, activity, and nutrition measures to recommendations published by the American Academy of Pediatrics and provides a printout for patients and providers. The program was installed in a community-based diabetes prevention clinic that sees a large number of overweight high-risk youth. Children were asked to complete the 12 item questionnaire prior to their enrollment.

Results:

Sixty-eight children (12.4 ± 2.8 years) entered information into the HeartSmartKids program. The majority of the children were able to complete the questionnaire in less than 5 minutes. Of the sample, 95.6% were overweight or obese with a body mass index ≥ 85 th percentile (sample mean = 28.1 ± 5.0 kg/m²), 36.8% did not meet physical activity guidelines of at least 1 hour/day, and 92.6% did not meet nutrition recommendations related to fruit and vegetable consumption.

Conclusions:

These results suggest that an interactive computer program is a feasible way to assess for diabetes risk factors in the pediatric setting. As a whole, children were able to navigate the system with very little instruction, which suggests that this form of technology is well accepted by youth.

Model-Based Insulin Sensitivity and Pharmacodynamic Surfaces

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Objective:

The minimal model (MM) is widely used for model-based insulin sensitivity testing. A pharmacodynamic (PD) surface analysis shows how the MM can underpredict insulin sensitivity and its changes over time, particularly in high(er) insulin dose tests.

Methods:

PD surfaces at steady state are fitted to $N = 77$ clinical results for (1) the MM, (2) a receptor model for type 1 diabetes (RM), and (3) an MM-derived nonlinear metabolic control model (CM). The MM has no insulin effect saturation. The CM has insulin effect saturation and glucose removal saturation can be added. The RM model saturates the combined insulin and glucose removal effect. Errors are reported as (1) RMS, (2) mode of the absolute error (AME) distribution; and (3) frequency of errors near zero (FNZ)—over all 77 reported results.

Results:

Results for the MM were as follow: RMS = 4.77; AME = -0.05 , FNZ = 3 (of 77). For the RM, RMS = 0.04; AME = -0.01 , FNZ = 32. For the CM, RMS = 0.07; AME = -0.01 , FNZ = 36. Adding glucose saturation effects to the CM yields: RMS = 0.06; AME = -0.01 , FNZ = 39. CM and RM have small and tight error distributions.

Conclusions:

The MM consistently underpredicted insulin saturation, resulting in large errors due to the shape of its PD surface. The ability to fit a single or small group of data sets can yield large error for others, illustrating the value of using a large set of clinical results to test these models. Results showed that insulin and/or glucose saturation dynamics are necessary to yield consistent model-based insulin sensitivity values.

Modeling the Effect of Hypoglycemia on Serum Potassium Levels

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Objective:

Diabetes and hypoglycemia affect the serum potassium level. It has been proposed that hypoglycemia triggers cardiac arrhythmia by causing low serum potassium levels (hypokalemia) through elevated insulin and adrenalin levels. Studies so far have focused on the level of serum potassium in a series of independent situations. Mathematical models, however, have the ability to combine knowledge from different studies and enable simulations of a range of situations. A mathematical model could provide a better basis for assessing of the risk of hypokalemia in diabetes.

Method:

We developed a mathematical model describing the serum potassium level using several studies published in the literature. The model consists of a release of potassium described as a linear function depending on the fall in potassium ($R^2 = 0.95$, $p < 0.001$), a fall in potassium described as an exponential function depending on the insulin concentration ($R^2 > 0.99$, $p < 0.001$), and a linear function depending on the adrenalin concentration ($R^2 = 0.41$, $p < 0.05$).

Result:

The model was tested on data from a study where hypoglycemia was induced by an intravenous bolus of insulin with and without administration of the β -blocking agent propranolol. Without propranolol the model produced a root mean square (RMS) error of 0.09 mmol/liter and a correlation to measured potassium of $R^2 = 0.84$ ($p < 0.001$). With propranolol the result was an RMS error of 0.16 mmol/liter and a correlation of $R^2 = 0.44$ ($p < 0.01$).

Conclusion:

The test showed that the model is able to predict the level of serum potassium during hypoglycemia. The model is thus a step toward being able to assess the risk of hypokalemia in diabetes. Further studies are needed to test the model and to link it to cardiac arrhythmia.

Spontaneous Hypoglycemia Causes Significant Changes in Cardiac Repolarization in Type 1 Diabetes: 72 Hours of Continuous Glucose Monitoring and Mobile Electrocardiogram Monitoring

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Objective:

Unexplained sudden death is more frequent in young people with type 1 diabetes. A theory is that hypoglycemia affects the repolarization of the heart, resulting in cardiac arrhythmia. This study investigated the effect of spontaneous hypoglycemia on changes in cardiac repolarization using continuous glucose monitoring (CGM) and Holter monitoring.

Methods:

Nineteen subjects with type 1 diabetes prone to hypoglycemia had CGM and electrocardiograms (ECG) monitored continuously for 72 hours. The 72 hours consisted of 12 hours of admission to a hospital ward and 60 hours of monitoring at home. CGM measurements were blinded to the subjects. Glucose strip measurements were taken by the subjects 7 ± 2.6 times per day. Hypoglycemic episodes were defined as any measurement (CGM or strip) < 3.5 mmol/liter. Episodes were excluded if an antecedent episode within 2 hours had occurred. Single lead ECG (lead II) was measured using a digital Holter monitor. QT interval measurements were made using a computer algorithm. Heart rate-corrected QT intervals, QTc, were calculated according to Fridericia's formula.

Results:

In total, 39 episodes of spontaneous hypoglycemia occurred, of which 13 were detected by CGM, 22 were detected by strip measurements, and 4 were detected by both. The mean change in QTc from baseline to hypoglycemia was 7 ± 8 ms ($p < 0.001$). Hypoglycemia detected by strip measurements had a more pronounced change (10 ± 8 ms, $p < 0.001$) than those detected by CGM (3.5 ± 8 ms, $p < 0.05$).

Conclusion:

Results from this trial showed that there is a significant QT interval prolongation during spontaneous episodes of hypoglycemia. It remains to be shown, however, that this QT interval prolongation causes cardiac arrhythmia.

A New Method for Assessing Sample Volume Requirements for Blood Glucose Monitoring Systems

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Objective:

Published methods for evaluating sample volume effects on blood glucose monitoring systems (BGMS) involve repeated pipetting of fixed microvolumes. The validity of this approach rests on the assumption that all samples are measured and applied to test strips accurately and precisely. We proposed a new method for delivering submicroliter blood volumes as well as analyzing BGMS results to characterize performance.

Method:

Venous blood samples adjusted to 70 or 400 mg/dl glucose were tested on three test strip lots of a currently marketed BGMS. Data were generated across a range of sample volumes (0.8–1.6 μ l). Samples were dispensed by a programmable pump, and a gravimetric method (based on blood sample density) was used to determine the sample volume applied to each test strip. Logistic regression and empirical methods were used to develop probability estimates that the BGMS would yield numerical results and accurate results across the range of sample volumes tested.

Result:

Using the programmable pump to dispense samples increased the speed and efficiency of testing. The gravimetric method of determining sample volume demonstrated a high degree of precision (SD = 0.012 μ l). Robustness of the logistic regression model was demonstrated in a Monte Carlo simulation.

Conclusion:

The proposed method is useful for evaluating the relationship between sample volume and BGMS performance and thus is suitable for verifying a BGMS sample volume claim. The new method has sufficient flexibility to be generally applicable to any BGMS.

Transdermal Glucose Monitoring Enabled by Prelude™ SkinPrep System

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Objective:

The Prelude™ SkinPrep system is a novel, convenient, low-cost, and effective device for skin permeation. We demonstrated that glucose can be measured continuously and reliably for 24 hours in patients with diabetes using a needle-free approach: Symphony™ transdermal continuous glucose monitoring (tCGM) system applied to skin sites pretreated with Prelude SkinPrep.

Method:

The study was performed in a clinical site mimicking homecare setting for patients with type I or type II diabetes. After Prelude skin permeation, two tCGM devices were applied to each of the patients. Venous reference blood samples of minimum volume were taken from intravenous lines at 15-minute intervals for 24 hours. The reference blood glucose (BG) values were measured with both Yellow Springs Instrument glucose analyzers and handheld glucometers. At the conclusion of the study, test skin sites were inspected for redness or any other undesirable effects. Accuracy of tCGM data relative to reference BG values was determined using Clarke error grid analysis, mean absolute relative difference, modified Bland–Altman analysis, and the International Organization for Standardization 15197:2003 standard.

Result:

Ten subjects were enrolled in the study. A total of 20 tCGM data sets and more than 900 reference BG samples were analyzed. The effect of lag time and calibration protocol on accuracy will be discussed, and both point and trending analysis will be performed in detail.

Conclusion:

A combination of our new skin permeation and transdermal sensing technologies provides a low-cost, convenient, safe, and effective solution for continuous glucose monitoring in patients with diabetes.

Use of CareLink Therapy Management Software to Assess Patterns of Use, Performance, and Utility of Continuous Glucose Monitoring Systems

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Introduction:

The CareLink™ therapy management systems software allows users of the Paradigm™ and Guardian™ REAL-Time to upload their continuous glucose and insulin information. The information is stored in the CareLink database and is available for the user and their physician to review on demand. The CareLink database was “mined” to determine (1) patterns of use, (2) sensor performance, and (3) utility of continuous glucose monitoring (CGM) systems. A query of the CareLink system showed that the database contains over 1.2 million sensor days across 21,000 patients.

Method:

Registered users of the CareLink database, who self-reported as having type 1 or type 2 diabetes, currently using a Paradigm 522/722 and/or a Guardian REAL-Time monitor were included in the analysis.

Results:

Results from a subset of these CareLink users indicated that continuous use (>80% over 1 year) of CGM systems on average showed a 7.0% reduction in blood glucose (159.1 to 149.4 mg/dl) levels, which is approximately equivalent to reducing hemoglobin A1c (HbA1c) values from 7.3 to 6.9%. Furthermore, sensor accuracy, as measured by mean absolute percent difference, was calculated at 14.3%, which is consistent, if not better, than recent Medtronic sensor studies. An additional sample of the database revealed that, on average, 8.1% of users upload their HbA1c value voluntarily. Of these users, 42%, on average, have HbA1c values less than 7.0%.

Conclusion:

Based on these data, it is suggested that continuous use of the Paradigm or Guardian REAL-Time systems, in conjunction with the use of the CareLink therapy management software, may result in an overall reduction in mean blood glucose levels, and a reduction in the number of blood glucose measurements taken, while maintaining consistent sensor accuracy.

Stakeholder Perspectives on Devices Used for Risk Monitoring in Type II Diabetes

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Background:

Type II diabetic patients use various devices to monitor aspects of their condition, including blood sugar, blood pressure, and heart rate. Research has shown that these devices can effectively improve glycemic control and long-term cardiovascular outcomes of diabetes, but the factors that affect device acceptance and adherence to protocols need further study. The goal of this research was to identify gaps in the published literature and develop improved methods for developing and evaluating monitoring technology from the point of view of key stakeholders.

Methods:

In order to probe the need and feasibility for new technologies to assist in the prevention and treatment of the cardiovascular complications of type II diabetes, six focus groups ($n = 6-12$ per group) held in London, Ontario, Canada, identified issues relevant to access, delivery, and impact of new technologies and devices on the user. Focus groups included patients with type II diabetes who use medical technology devices, caregivers, health professionals, and physicians and explored the effectiveness of these technologies and factors associated with their acceptance.

Results:

Findings suggested a conceptual framework that provides a rationale for the expected outcomes from using monitoring devices. The model addressed user perspectives of health technologies used for monitoring type II diabetes and related cardiovascular complications.

Conclusions:

Information on the effectiveness and usability of devices used to monitor cardiovascular health is critical for research teams to refine technology and create new devices to help monitor type II diabetes and cardiovascular complications. The framework may contribute to developing a research agenda for diabetes monitoring technologies by highlighting measures that need to be developed and by identifying testable hypotheses concerned, for example, with the manner and duration of device usage.

Acknowledgment:

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Validation and Performance Testing of the AlphaTRAK Handheld Blood Glucose Monitoring Device for Use in Mice and Rats

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Introduction:

Metabolic disease research commonly employs mice and rats in animal models of diabetes. Handheld glucose meters offer the convenience of rapid result turnaround and small sample size; however, their use may be limited by the range of the device (upper end of range for most devices is 500 mg/dl) and unknown or poor accuracy in rodents. The AlphaTRAK is a handheld glucose monitoring device specifically calibrated to measure glucose in animal blood. The device has been modified to support a range of 20–750 mg/dl. The AlphaTRAK was calibrated using whole blood samples of mice and rats with glucose levels throughout the range of the device.

Methods:

Samples were taken by exsanguination and manipulated in order to achieve concentrations in the hypoglycemic, euglycemic, and hyperglycemic ranges. Each sample was tested on six different meters in quadruplicate and compared to plasma testing results on the Aerosep instrument. In a clinical performance study, whole blood samples from 40 mice (C57, db-db, and db-lb) and 35 rats (CD and Zucker diabetic fatty) were taken by exsanguination and tested on the calibrated AlphaTRAK device, Accu-Chek, and plasma testing on Aerosep. Hypoglycemia and hyperglycemia were induced in groups of 10 animals each by the administration of insulin and dextrose, respectively.

Results:

The extended range of the AlphaTRAK device provided results up to 750 mg/dl, whereas the highest sample readout for Accu-Chek was 599 mg/dl. The average bias for mice and rats was 8 and 5%, respectively, and for Accu-Chek was 29 and 24%, respectively.

Conclusions:

The AlphaTRAK device had an extended range compared to the human meter, Accu-Chek, and provided more accurate results in rodent whole blood samples.

A New Cuffless Optical Device for Assessing Peripheral Arterial Disease

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Objective:

Peripheral arterial disease (PAD) is a significant comorbidity in people with diabetes, in which current ankle brachial index (ABPI) PAD assessment is unreliable due to arterial calcification. A new spectrophotometer system (PoDX) assesses peripheral arterial perfusion without pressure cuffs. We evaluated PoDX on people with diabetes in a feasibility study.

Methods:

Twenty-nine people with type 2 diabetes (mean age 71.2 years, SD 7.8 years) were recruited from a vascular clinic, and 10 controls without diabetes, believed free from PAD (mean age 69.9 years, SD 11.6 years), were recruited from orthopedics clinics. All participants underwent resting ABPI, PoDX, and color duplex ultrasound (CDU) as the gold standard, determined by a vascular technologist. For PoDX, two optical sensors were placed on the foot to assess pulse strength and skin color redness changes during a 1-minute, 12-inch leg raise functional test, producing a perfusion index.

Results:

Twenty legs were free from PAD (15 control, 5 diabetic) via CDU, leaving 57 legs with PAD (5 control, 52 diabetic). Agreement with CDU for disease discrimination was assessed using k statistics. ABPI had a maximum k of 0.68 (SE 0.092) with a disease cutoff of 1.17. PoDX had a maximum k of 0.71 (SE 0.090) with a 0.96 cutoff. The PAD discrimination at maximum k for ABPI was sensitivity = 86%, specificity = 85%. The k -derived optimum performance of PoDX was sensitivity = 90%, specificity = 85%.

Conclusion:

Although an expert operator performed ABPI, a relatively high optimal ABPI cutoff was observed, attributed to arterial stiffening producing falsely elevated ankle pressures. PoDX may be superior to resting ABPI for the detection of early stage PAD in people with diabetes.

Risk Evaluation of the Artificial β Cell: Assessment of Hypoglycemia Incidence

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Objective:

The future artificial β cell will automatically regulate insulin delivery through a computer algorithm; however, there is a potential risk that the rate of hypoglycemia will be increased compared to current intensive insulin therapy (IIT). It has been reported previously that IIT can lead to a higher rate of hypoglycemic episodes. We proposed a formal rating system to define the risk of hypoglycemia in closed-loop studies to determine if closed-loop automation increases the risk over IIT.

Method:

A formal system-level risk analysis was performed on an artificial β -cell algorithm that utilizes subcutaneous glucose measurements from either the FreeStyle Navigator[®] (ADC, Alameda, CA) or the STS7[®] (DexCom, San Diego, CA) continuous glucose monitor and the OmniPod[®] (Insulet, Bedford, MA) continuous subcutaneous insulin infusion pump. The system uses interface software developed for the Juvenile Diabetes Research Foundation artificial pancreas project. The risk analysis is based on formal hazard and operability study and fault tree analysis. Risk in clinical practice is based on DirecNet published data.

Result:

Risk is the combination of the likelihood of an abnormal event and its severity as defined where A, B, and D denote no risk, as seen in clinical practice, and unacceptable risk, respectively. The proposed system with its safety algorithms exhibits a risk level of either A or B for a top event of hypoglycemia.

Conclusion:

The future artificial β cell not only can provide “tight” glycemic control that will minimize long-term complications associated with diabetes, but also can provide the means to minimize hypoglycemia through intelligent insulin delivery. Frequent glucose measurements and the automated insulin infusion control within such a system can lower the likelihood of excessive delivery of insulin, hence improving patient safety.

		Severity of the hazard				
		Negligible ^a	Low ^b	Moderate ^c	High ^d	Very high ^e
Likelihood	Improbable	A	A	A	B	D
	Remote	A	A	B	B	D
	Occasional	A	B	B	D	D
	Probable	A	B	D	D	D
	Frequent	B	D	D	D	D

^aGlucose measurement of 55–70 mg/dl, asymptomatic and duration <15 minutes.

^bGlucose measurement of 55–70 mg/dl, asymptomatic and duration <30 minutes.

^cGlucose measurement of <55 mg/dl, symptomatic.

^dSeizure, loss of consciousness.

^eDeath.

Minimization of Hematocrit Effect Using Novel Time-Resolved Amperometry

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Background:

Electrochemical biosensors are used extensively for point-of-care medical diagnostics, in particular for blood glucose monitoring systems (BGMS). One of the key issues facing biosensor systems is the effect of sample matrix on system accuracy. For example, biosensor-based BGMS show a negative dependence on the hematocrit level of the blood sample. Many BGMS compensate for the hematocrit effect based on a secondary measurement on sample hematocrit level.

Objective:

We presented a novel approach for reducing hematocrit effect without the need for a secondary measurement. It was discovered that current decay curves for blood samples of different hematocrit levels converge when they are at the same analyte concentration. The convergence time is a function of the analyte concentration, i.e., a shorter convergence time is observed at a lower analyte concentration. Based on this convergence phenomenon, we developed a novel measurement algorithm that is based entirely on amperometric measurement. The algorithm employs multiple time segments for different analyte concentration ranges. In addition, the algorithm projects the current decay based on measured currents.

Conclusions:

Compared to the fixed time amperometric method, time-resolved amperometry offers several significant benefits. (1) Bias due to blood sample hematocrit is reduced significantly without any hematocrit correction from a secondary measurement. (2) Coding accuracy can be improved, as each segment of calibration curve covers a much smaller range of analyte concentration. In fact, this method has shown excellent accuracy and precision at the lower range of detectable analyte concentration. (3) This method improves measurement precision, as no secondary measurement is used for hematocrit correction. Experimental results will be presented to demonstrate a possible mechanism for the convergence of current decay curves and improvements of hematocrit performance using time-resolved amperometry algorithm.

Performance and Ease of Use of the TRUEresult™ and TRUE2go™ Companion Blood Glucose Monitoring Systems

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The TRUEresult™ and TRUE2go™ companion blood glucose monitoring systems are to be used with TRUEtest™ strips, which contain proprietary on-strip coding. This removes a source for potential incorrect results due to miscoding. The TRUEresult meter has extensive features and capabilities, including a 500 result memory, ketone alarms, and clock alarms to remind the user when test needs to be performed. The TRUE2go meter is a portable meter that can be attached directly to a strip vial. The resulting combination provides the smallest meter- and strip-integrated system that makes self-blood glucose monitoring easier and more convenient than previous systems. Performance of both systems is state of the art with a test time as short as 4 seconds using only 0.5 µl blood from either finger tip or forearm.

The performance of TRUEresult and TRUE2go companion blood glucose monitoring systems were evaluated according to guidelines from International Organization for Standardization 15197 and Food and Drug Administration draft guidance for portable invasive blood glucose monitoring systems. Laboratory studies were conducted to demonstrate equivalence of performance between the two systems. Performance evaluations included system range and linearity, system precision, hematocrit performance, environmental study, and interference study. Test results will be presented to demonstrate system robustness against potential misuses, such as incorrect sample dosing method and strip flexing during the test. In addition, ease-of-use features and key system performance will be compared to leading blood glucose monitoring systems on the market.

Influence of Modern Insulin Injection Devices on Treatment Adherence and Health Economics

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Introduction:

The prevalence of type 2 diabetes is increasing considerably worldwide, and the associated morbidity and mortality of the disease represent a major health care burden. Several studies have demonstrated that tight glycemic control is important in order to reduce microvascular complications. Glycemic control may be influenced by a number of factors, e.g., type of medication and patient self-management. A part of the self-management is adherence to the treatment regimen, and adherence has been reported as low as 38% in patients with diabetes on oral antidiabetic treatment. Adherence to insulin therapy, from direct measurements, has not been reported previously. Thus, the purpose of the present study was to investigate a possible correlation between adherence and glycemic control using direct measurements of insulin injections.

Methods:

This was an exploratory, open, noninterventional, multicenter study investigating adherence to basal-bolus insulin therapy. Seventy subjects with type 1 or 2 diabetes (28–77 years old) were included in the study. The subjects' insulin injections were registered by an insulin delivery device. Neither patients nor investigators had access to injection data.

Results:

Results from this 22-week study showed a positive correlation between hemoglobin A1c and the number of missed insulin injections in patients with type 1 and 2 diabetes.

Conclusion:

Results from the present study showed that glycemic control is influenced negatively by reduced adherence in patients with type 1 and 2 diabetes. Interestingly, Lee and colleagues reported that modern insulin injection devices can increase patient adherence and reduce health care cost. Taken together, studies imply that devices and technologies that can improve patient treatment adherence are needed in clinical practice and that devices and technology that can improve patient adherence potentially can improve treatment efficacy and reduce health care cost.

Potentially Therapeutic Glycemic Actions of Glucagon-like Peptide-1 Agonist Are Similar in Type 1 and Type 2 Diabetes during Intensive Insulin Therapy

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Objective:

To evaluate actions of glucagon-like peptide-1 (GLP-1) agonists in diabetes, we compared effects of exendin-4 (E4) in type 1 diabetes (T1D) [$n = 7$, stimulated C-peptide (CP) <0.2 mmol, fasting plasma glucose (fpg) 6.1 ± 0.5 mmol, hemoglobin A1c (HbA1c) $7.1 \pm .52$, age 41 ± 6 years, body mass index (BMI) 25 ± 1.3] with corresponding measures in type 2 diabetes (T2D) ($n = 6$, stimulated CP ≥ 0.5 mmol, fpg 6.3 ± 0.6 mmol, HbA1c 7.5 ± 0.42 , age 45 ± 6 years, BMI 29 ± 2.6) during unmodified intensive insulin therapy (IIT).

Method:

E4 was administered subcutaneously with insulin before standardized breakfasts (0, 0.01, 0.02, 0.04, 0.06, or 0.08 $\mu\text{g}/\text{kg}$, with each subject receiving vehicle or two to five doses on separate occasions). Threshold and ED50 doses for blood glucose, glucagon, and pancreatic polypeptide (HPP) reduction were similar (approximately 0.01 and 0.03 $\mu\text{g}/\text{kg}$, respectively). The area under the curve (AUC) fasting insulin resistance index did not vary with E4 dosage. The maximum side effect-free dose was ≤ 0.06 $\mu\text{g}/\text{kg}$.

Results:

Without E4, AUC glucose and HPP, and their reductions with E4, were similar in T1D and T2D. However, reduction of AUC glucagon in T1D was approximately double that in T2D. E4 reduced mean incremental plasma glucose in T1D and T2D comparably through 240 minutes, by more than 50% in both.

Conclusion:

Thus actions of the GLP-1 agonist cannot be attributed to effects on secretion or clearance of insulin. They may be because of suppression of glucagon, and/or delayed absorption of nutrient, and/or other actions. GLP-1 agonist(s) administered with insulin during IIT can enhance glycemic control in insulin-requiring diabetes with or without residual insulin secretion, with apparent improvement of insulin sensitivity according to classical definition in both types of diabetes, calling for assessment under clinical conditions.

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 does not require blood draws or patient fasting and provides an immediate test result. An 18-site clinical study has been completed involving over 2200 subjects and 22 premarket devices.

Methods:

Study sites were selected to provide geographic and ethnic diversity to the study population. Consented subjects were tested by SCOUT in both fasting and random-fasting states on two separate visits. Subjects also received fasting plasma glucose (FPG), hemoglobin A1c, and oral glucose tolerance (OGTT) tests. Participants were either aged 45 years or older or between 18–44 years with two or more risk factors for type 2 diabetes.

Results:

Subjects with 2-hour OGTT values equal to or exceeding 140 mg/dl defined the positive screening class. The performances of SCOUT, 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 over both blood tests with no increase in false positives. Subcohort analysis indicates that SCOUT performance is unaffected by fasting status or skin color. In addition, the Hoorn coefficient of variation for the SCOUT measurement was less than 5%.

Conclusions:

This noninvasive technology shows clinical performance advantages over both FPG and hemoglobin A1c. The combination of higher sensitivity, good reproducibility, and rapid results with no fasting or blood draws make the SCOUT well-suited for point of service diabetes screening. The poster provides an overview of the technology and recent clinical results.

Thermographic Assessment of Cold Stimulation on Autonomic Vascular Reactions

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Objectives:

The objectives of this study were to determine the potential usefulness of thermal imaging technology as a tool to evaluate autonomic vascular reactions and to establish whether noninvasive thermal imagery can be used to effectively detect preclinical stages of diabetes and identify other circulatory problems.

Materials and Methods:

To test the hypothesis a double blind cold stimulation test was performed on 60 participants using a radiometric thermal imager. The participants included diabetic patients, smokers, and a normal/control group. Participants submerged their left hand in $62 \pm 2^\circ\text{F}$ water for 20 minutes while keeping the right hand on a wood surface. A thermal image was recorded of the right hand every 5 minutes starting with a preliminary test image.

Results:

Three groups of people were clearly defined by the thermal imager. The diabetic patient group had no visible thermographic finger tip change while the overall average temperature did decline slightly by an average of 2°F . The smoker group had an extremely mottled and uneven thermographic appearance of all fingers and hand with a slight decline initially in temperature while rising 2°F and holding constant until the end of the 20-minute test period. Thermographic assessment of the circulatory system of the normal/control group showed that the right hand was significantly affected, with a steady decline in surface temperature of $8 \pm 2^\circ\text{F}$.

Conclusions/Discussions:

Using a radiometric thermal imager test, results were immediate and visual, clearly identifying differences in vascular reactions of the three groups. Two undiagnosed participants with family history of diabetes had thermal images identified as diabetic. Using this thermal imaging technique may prove to be the most cost-effective solution for third world countries, as only a low-cost, midperformance imager is needed. Data from the test support the hypothesis in regards to thermal imaging being a useful tool for examining circulation.

Summary:

This research proved that thermal imaging can be used effectively to detect preclinical stages of circulatory problems and would be an excellent tool to use to quickly access compromised or damaged autonomic vascular reactions.

Bihormonal Closed-Loop Control of Blood Glucose Using Dual Subcutaneous Infusion of Insulin and Glucagon in Type 1 Diabetes

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Objective:

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

Methods:

The control algorithm developed (i) has no run-in period and requires only the subject's weight for initialization; (ii) requires only regularly sampled BG for online operation; (iii) requires no feed-forward information regarding carbohydrate consumption or physical activity; (iv) keeps track of and adjusts dosing relative to SC accumulation of insulin and, as a result, exercises restraint from administering excessive insulin; (v) employs SC dual infusion of insulin and glucagon, thereby offering counterregulatory control; and (vi) scales its response with subject weight. The algorithm was tested successfully in ambulatory diabetic pigs and is now being tested in an inpatient clinical trial in healthy adult volunteers with type 1 diabetes in the Mallinckrodt General Clinical Research Center, Massachusetts General Hospital.

Results:

Closed-loop results in ambulatory insulin-deficient diabetic pigs, in which the control response was based on either frequent plasma glucose testing or continuous interstitial fluid glucose monitoring, established the efficacy of our closed-loop control system. BG was regulated successfully after numerous meals with no episodes of hypoglycemia in 12- and 24-hour experiments. In 24-hour experiments, the controller achieved a mean BG between 140 and 155 mg/dl. Results also demonstrated the effectiveness of SC glucagon to stave off hypoglycemia. Preliminary results from our clinical trial in patients with type 1 diabetes will also be presented.

Conclusions:

Results demonstrated the efficacy and efficiency of a bihormonal closed-loop control system in virtually normalizing blood glucose in type 1 diabetes without episodes of hypoglycemia.

Parental Attitudes Toward the Artificial Pancreas for Overnight Glucose Control in Type 1 Diabetes

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Objective:

The objective of this study was to examine parental attitudes toward overnight closed-loop (CL) glucose control in children with type 1 diabetes (T1D).

Method:

Fifteen families recruited by the INsulin PUmp Therapy group (INPUT), a UK patient/carer-led support group for people with T1D, attended an INPUT-organized focus meeting on CL. The parents were explained the concept of CL utilizing a subcutaneous continuous glucose monitor (CGM), a control algorithm, and an insulin pump. Clinical results and plans regarding the Artificial Pancreas Project at Cambridge were presented. Then the parents completed a questionnaire to evaluate parental feelings about T1D management and attitudes toward overnight CL insulin delivery.

Results:

Nineteen parents (14 mothers and 5 fathers) completed the questionnaire anonymously. Main worries about diabetes were related to long-term complications (84.2%) and hypoglycemia (15.8%). Achieving good glucose control represented a major challenge for most carers (83.3%) with nighttime being the most difficult period to manage (55.6%), worrying most parents (70.6%) partially because of fear of hypoglycemia (33.3%). Of the parents, 44.4% struggled to achieve good glucose control in the morning, 100% welcomed the development of CL to manage diabetes, 84.2% expressed trust in CL to deliver the correct insulin dose, 89.5% were not worried about their child's insulin delivery being controlled by a computer overnight, 94.7% of parents were happy for their child to wear CGM together with an insulin pump, and 100% were ready to respond to additional alarms at night.

Conclusions:

Parents of children with T1D have a positive attitude toward CL. They expressed trust in technology for overnight CL insulin delivery. As nighttime glucose control presents the major challenge while worrying most parents, development of a commercially available overnight CL system is an important goal.

Safety Constraints in an Artificial β Cell: An Implementation of Model Predictive Control with Insulin on Board

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Objective:

An artificial β -cell controller should regulate both basal insulin delivery and overcome disturbances such as meals without excessive delivery of insulin that can cause severe hypoglycemia. The nature of the problem is that there can be a substantial mismatch between the controller model and the actual patient's dynamic behavior that can result in an overdose of insulin. A novel way to address this potential risk is the use of adaptive insulin on board (IOB) together with clinical parameters such as the insulin-to-carbohydrate ratio (I:C) and the correction factor (CF) to constrain the insulin delivery.

Method:

A simulation study of type 1 diabetes mellitus subjects based on the model by Dalla Man and colleagues was performed in MATLAB® and Simulink® (The MathWorks, Inc., Natick, MA). The controller was developed using the MATLAB® MPC toolbox with IOB to update the maximum insulin delivery at each time step. Ten *in silico* subjects were used to evaluate the algorithm, and the controller for a given patient was evaluated against all 10 patient models to evaluate the robustness of the approach.

Result:

Following 100 simulation scenarios, we observed that the proposed methodology decreased the incidence of hypoglycemia from 48% (without IOB constraint) to 10% (IOB constraint implemented). It should be noted that 90% of the observed hypoglycemic incidents were related to the same *in silico* patient, suggesting incorrect I:C and/or CF values in the original publication.

Conclusion:

Constrained insulin delivery by IOB calculations provides a safe and robust insulin delivery and generalizes, in an intuitive manner, the current practice implemented on most pumps. This is an essential component of any future artificial β -cell for a safe and effective therapy.

Blood Glucose Regulation for Patients with Type 1 Diabetes with an Augmented Self-Tuning Controller

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Objective:

Current insulin therapy often results in high variability in blood glucose concentrations and may cause prolonged hyperglycemic/hypoglycemic episodes for insulin-dependent patients. Closing the glucose regulation loop with a fully automated mechanical pump will improve the quality of life for patients with diabetes. The objective of this work was to develop self-tuning controllers that account for the time lag between subcutaneous and blood glucose concentrations, and delays in absorption of insulin to provide blood glucose regulation within the normoglycemic range.

Method:

An implicit self-tuning tracker was developed to keep blood glucose concentrations close to a time-varying reference glucose trajectory. Adaptation of the controller to intra/intersubject variability was assured with recursive identification of patient-specific time-series models derived from patient's own continuous glucose monitoring (CGM) device data. The recursive identification strategy was integrated with a change detection method to provide faster converge of model parameters. Insulin (manipulated variable) absorption into the bloodstream and the time lag between subcutaneous glucose (measured variable) and blood glucose (controlled variable) concentrations introduce large delays to the closed-loop system. The self-tuning regulator is augmented to include time-delay compensators.

Result:

The self-tuning tracker is able to keep blood glucose concentrations within desired limits (postprandial maximum glucose values below 160 mg/dl, normalization of glucose levels to 120–70 mg/dl within 2–3.5 hours after meals) with subcutaneous insulin infusion (route with largest delay).

Conclusion:

A self-tuning tracker for the regulation of blood glucose concentrations has been developed. Including a change detection method to the recursive algorithm and integrating a time-delay compensator to the controller structure improve blood glucose control.

FoodFit: A Web Application to Illustrate Healthier Food and Physical Activity Choices

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Objective:

The incidence of type 2 diabetes and obesity could be reduced by educating the population to change their lifestyles to include healthier food choices and more frequent physical activities. Lack of motivation is a major obstacle to achievement of a healthier lifestyle. The objective of this study was to introduce a newly developed Web application, FoodFit, which balances energy intake from food and energy consumption by physical activity to motivate people to live a healthier life.

Method:

FoodFit is a Web application used to illustrate food and activity choices in an interactive environment that helps users develop healthier choices. Depending on the gender and age, default food and activity plans (in an interactive calendar view) are provided for first-time users to make it easier for personal adjustments. FoodFit uses the U.S. Department of Agriculture food database and the Compendium of Physical Activities list. Users are taught calorie counting and the effects of the glycemic index on blood sugar levels. What makes FoodFit distinct is its interactive blood glucose plots for user-defined daily food–activity plans. Conventional nutrition value analysis is also provided in an engaging way.

Result:

FoodFit makes planning a food–activity journal fun, such as playing a game that teaches a healthier lifestyle. Instead of tedious calorie counting, users can see visually how healthier food choices and activities affect their blood glucose concentrations in a more motivating way.

Conclusion:

The interactive platform of FoodFit encourages users to learn more effectively about healthier choices and motivates them to live a healthier life.

Effects of Lifestyle Modification in Type 2 Diabetes: The Diabetes-MOBIL Study

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Objective:

The Diabetes-MOBIL study evaluated to which degree patients with manifested type 2 diabetes benefit from lifestyle modifications when they received intensive coaching by a diabetes nurse for 6 months.

Method:

During weekly group meetings with a duration of approximately 2 hours, the 3–12 patients in each group were motivated to implement exercise in their daily life and to change their nutrition habits. By means of a systematic risk analysis before and after the study, the individual risk profile to develop diabetes-related late complications was evaluated. Changes in behavior and well-being were evaluated by means of validated questionnaires.

Results:

Of the 104 patients (mean diabetes duration 10.4 years) participating in the weekly meetings, 72 (69%) remained active for 6 months (on average they participated in 13 meetings). With respect to starting values, this led to an average reduction in hemoglobin A1c by 0.5% (from 7.5 to 6.9%; $p < 0.0005$), in weight by 1.8 kg (from 93.2 to 91.8 kg; $p = 0.0054$), in waist circumference by 2.6 cm (from 111.2 to 108.9 cm; $p = 0.0001$), in total cholesterol by 9 mg/dl (from 213 to 204 mg/dl; $p < 0.0183$), in systolic risk ratio (RR) by 4.3 mm Hg (from 139.0 to 134.3 mm Hg; $p < 0.0288$), and in diastolic RR by 3.7 mm Hg (from 83.8 to 79.8 mm Hg; $p < 0.0007$). The risk to develop diabetes-related late complications was reduced by 11.6%. The intervention led to changes in nutrition behaving ($p < 0.0001$), reduced the level of depression ($p < 0.033$), increased patients satisfaction ($p < 0.005$), and reduced diabetes-related stress ($p < 0.010$).

Conclusion:

The Diabetes-MOBIL study demonstrated that appropriate coaching in patients with type 2 diabetes can be implemented successfully and led to an improvement in metabolic control and other relevant parameters.

Effect of Lemon Juice and Peanuts on the Glycemic Index

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Objective:

Because some authors suggest that the ingestion of complementary foods, such as organic acids and peanuts, may favor a reduction in postprandial glycemia, this study evaluated the effect of the ingestion of lemon juice or peanuts in the glycemic index (GI) of two test foods.

Methods:

This study involved the participation of six healthy, normal weight women, 25.5 ± 1.3 years of age, with a mean body mass index of 20.3 ± 0.7 kg/m². Test meals [boiled potatoes + 60 ml of lemon juice solution (test) or protein supplement + 25 grams of peanuts + 200 ml of water (test) or 200 ml of water (control)] containing 25 grams of available carbohydrate were consumed after a 10- to 12-hour overnight fasting. While test foods and control food were consumed once, reference food (glucose) was consumed three times by each subject. There was a 2-day minimum interval between each test day. Capillary finger-stick blood samples were taken in the fasting state (0 minute) and 15, 30, 45, 60, 90, and 120 minutes after the start of the test meal. The positive area under the curve changes in blood glucose for each food was computed by the trapezoidal method and then expressed as a percentage of the mean response to glucose consumed by the same subject. Statistical analyses were conducted by repeated-measures analysis of variance. The criterion for statistical significance was $p < 0.05$.

Results:

There were no differences in the mean GI values obtained for the two test treatments.

Conclusion:

Other studies should be conducted to investigate the effects of the acute and chronic ingestion of higher amounts of the tested complementary foods in the postprandial glycemic response and in the GI.

Effect of Glycemic Index on Body Weight, Body Fat of Type 2 Diabetic Patients

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Objective:

The goal of this study was to verify the effect of daily consumption of two meals differing in glycemic index (GI) during 30 consecutive days on food intake, body weight, and body composition.

Method:

A total of 16 type 2 diabetic patients, aged 50.1 ± 6 years, with a body mass index of 29.2 ± 5 kg/m² were allocated randomly in the high glycemic index or low glycemic index (LGI) group. Both test meals were ingested in the laboratory and presented similar calories, energy density, macronutrient composition, and fiber content. The GI, glycemic load (GL), ingestion of calories, macronutrients, and fiber at baseline and after the intervention were evaluated through diet records.

Result:

There were no changes in GI, GL, calorie intake, protein, fat, and fiber after the intervention in both experimental groups. However, there was an increase ($p = 0.028$) in carbohydrate consumption for the AIG group in the postintervention period compared to baseline. Body weight and body composition were not affected in either group. The women of both groups presented a higher ($p = 0.036$) body fat (BF) percentage at the beginning of the study than men. After the study intervention, the percentage of BF of the women did not differ from the one presented by men of the LGI group. Although there was no significant reduction in BF percentage in both experimental groups, this parameter started to decrease in the LGI women.

Conclusion:

These results also suggest that the reduction in BF level could have been more evident if the study had been conducted for more than 30 days or if more than two LGI meals had been offered under laboratory conditions.

Effect of Glycemic Index on Metabolic Control of Type 2 Diabetic Patients

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Objective:

The present study was conducted to verify the effect of the consumption of two meals daily, during 30 consecutive days, in some biochemical parameters related to glycemic control and insulin resistance (IR).

Method:

A total of 16 type 2 diabetics, with a mean age of 50.1 ± 6 years and a body mass index 29.2 ± 5 kg/m², were allocated randomly into a high glycemic index (HGI) or low glycemic index (LGI) group. The test meals were ingested in the laboratory and did not differ in terms of caloric density, macronutrients, and fiber content. The other meals were consumed in free-living conditions, and the participants were instructed to consume preferentially foods that had a glycemic index (GI) similar to the GI group they were allocated. The concentrations of glucose, insulin, total cholesterol, and high-density lipoprotein cholesterol, free fatty acids, triglycerides, fructosamine, and uric acid concentrations, and IR (homeostasis model assessment of insulin resistance) were evaluated before and after the study intervention.

Result:

There was no change ($p > 0.05$) in GI, GL, biochemical data, and IR level after the study intervention in any of the experimental groups. However, there was an increase ($p = 0.048$) in the fructosamine concentration in the HGI group after the study was completed compared to the concentration observed in the beginning of the study. The consumption of LGI diets was not able to reduce significantly ($p = 0.06$) the fructosamine levels.

Conclusion:

Results indicate the need to conduct studies to evaluate the effect of GI in the biochemical parameters that reflect glycemic control and in the IR when two or more daily meals are consumed for a period of time greater than 30 days.

Real Time Adaptive Kalman Filtering for Continuous Glucose Monitoring Noise Removal

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Objective:

Noise attenuation in continuous glucose monitoring (CGM) data is complicated by the apparent inter- and intrasubject variabilities of the signal-to-noise ratio (SNR). The aim here was to develop a method able to automatically estimate, and adapt, filter parameters during online functioning in a subject.

Method:

A new Bayesian estimation method, exploiting a versatile prior model of “signal regularity” and resorting to Kalman filtering implementation, was designed. Simulated problems were used to test the method ability to adapt its parameters to different noise levels, as well as to changes occurring during the same monitoring (e.g., due to deterioration of the sensor performance). Real data obtained with three different commercial devices, i.e., Menarini GlucoDay (25 subjects), Medtronic MiniMed (10 subjects), and Abbott FreeStyle Navigator (6 subjects), were also considered. Method performance was assessed by measuring the delay introduced by the filter and by the smoothness of its outcome. Results obtained by standard moving average (MA) filtering approaches were also used for comparison.

Result:

The simulation study demonstrated that the new algorithm is able to adapt filter parameters to different SNR and to correctly, and accurately, track possible changes of noise variance during the monitoring. Real data analysis shows that the amount of smoothing is always adequate to the sensor/individual/local SNR. Signal distortion is minimal and the average filtering delay is more than 50% less than that with MA filtering.

Conclusion:

The new filtering method allows one to deal with inter- and intrasubject variabilities of the SNR of CGM data. Moreover, the filtered glucose level is returned together with a confidence interval, which could be important, e.g., in hypo/hyperalert generation. A patent request for the algorithm has been deposited (MI2008A000837).

A New Online Method for Improving Calibration of Continuous Glucose Monitoring Sensors

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Objective:

In continuous glucose monitoring (CGM) sensors, calibration allows one to transform the raw current level, obtained from the glucose-oxidase reaction process, into an estimate of interstitial glucose (IG) by exploiting the reference offered by a small number of capillary blood glucose (BG) values per day. This study presented a new calibration method to enhance the accuracy of CGM data in real time applications.

Method:

Blood glucose and IG *in silico* time series lasting 7 days were performed by exploiting BG literature data and a two compartmental model of BG-to-IG dynamics. A time-varying multiplicative error (up to 50% of nominal value), subject to a smoothness constraint, was generated to simulate calibration error on 1 minute of sampled IG data. In order to restore the correct IG using a state-space model and extended Kalman filter (EKF), BG samples at equally spaced 5-hour intervals were considered to be available. All samples were corrupted by artificially generated Gaussian additive noise.

Result:

Ten simulations were performed. After exclusion of the burn-in interval necessary for EKF tuning, results were compared with those provided by a recently proposed retrospective (noncausal) calibration method. The new method not only has the advantage of being able to work in real time, but it also seems much more effective. In particular, in the last 4 days of simulation, root mean square error was 3.7 ± 2.3 and 21.8 ± 15.2 mg/dl with the two methods, respectively.

Conclusion:

Results on simulated data are encouraging. Before investigating the performance of the new calibration method on real data, further simulations are, however, needed in order to find the optimal sampling schedule of BG reference points.

Effectiveness of Self-Management Education Intervention Elements: A Meta-Analysis

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Background:

Previous meta-analytic studies demonstrated the effectiveness of diabetes self-management education (DSME) intervention in improving self-management. However, they did not evaluate the elements of interventions associated with the achievement of intended outcomes.

Objectives:

This meta-analysis aimed to examine differences in knowledge, self-management behaviors, and metabolic control in relation to the DSME intervention elements.

Methods: Fifty randomized controlled trials evaluating DSME interventions in adults with type 2 diabetes published in English between 1990 and 2006 were included in the study. Data related to including types of intervention, teaching method, mode of delivery, and dose were extracted.

Results:

Results showed that the overall weighted mean effect size (ES) was +0.56, which signals moderate but significant improvements on all outcomes. Knowledge gain was most affected (ES = 1.29), followed by metabolic control outcomes (ES = 0.51) and self-care behaviors (ES = 0.36). In terms of DSME intervention elements, (1) a mixed intervention type that combines education, behavioral, or psychological components, (2) incorporating a didactic and interactive teaching method, face-to-face strategy for delivering the intervention, and (3) mixed one-on-one and group delivery formats are the most effective in achieving knowledge, self-care behaviors, and metabolic control in this study. Interventions with an increased number of session, duration of intervention, and incorporated booster sessions yielded large effect sizes on knowledge, behaviors, and metabolic control outcomes.

Conclusions:

Results provide researchers and practitioners with evidence to develop specific guidelines for designing DSME interventions that are most effective in improving knowledge, behavior, and metabolic outcomes among patients with type 2 diabetes.

Effectiveness of an Intensive Foot Self-Care Education in the Prevention of Foot Complications in Patients with Diabetes

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Background:

Patients with diabetes are at risk for developing foot problems, which can contribute to significant physical, emotional, and financial losses. Instructing patients about foot care is necessary to prevent foot complications.

Objectives:

The study aimed to evaluate the effectiveness of an intensive foot self-care education intervention in preventing foot complications in adult Chinese patients with diabetes.

Methods:

A randomized controlled trial was used. Eligible participants were assigned randomly to an intensive foot self-care educational (experimental $n = 110$, withdraw 24) group and to a usual educational (comparison $n = 110$, withdraw 18) group. The completed sample consisted of 178 adult patients with diabetes; the average age was 61.6 ± 11.9 years old and the average duration of diabetes was 7.9 ± 6.2 years. Data were collected at pretest and 9-months follow-up. The experimental intervention included individual intensive instructions on foot care, including a 4- to 5-hour training section, and three booster sections at 1, 3, and 6 months after the training section given by nurse educators, in addition to usual diabetes education.

Results:

Results indicated (1) improvement in patients' recognition of signs of foot problems and increased knowledge and skills of daily foot self-care strategies; (2) reduction in occurrence of foot problems, including presence of dryness and cracked skin, fungal infection, callus, occurrence of foot lesions, numbness in legs and foot, and abnormal foot pulse, and (3) improved fasting blood glucose level, postprandial blood glucose level, hemoglobin A1c, and blood pressure control in the experimental group than in the comparison group ($P < 0.05$ vs $P < 0.001$).

Conclusions:

The intensive foot self-care educational intervention was effective in enhancing patients' foot self-care skills and in preventing complications. This intervention should be incorporated as an additional component in an intensive and comprehensive educational program to assist patients' diabetes self-management.

Glucagon Counterregulation Enhancement by Switch Off of α -Cell-Suppressing Signals

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Objective:

Glucagon counterregulation (GCR) is a key protection against hypoglycemia, which is compromised in diabetes. We have shown that, in insulin-deficient rats, intrapancreatic infusion and switch off of insulin and somatostatin amplify the pulsatile GCR. Data suggest that the two signals improve GCR via different mechanisms, as insulin switch off caused a higher response than somatostatin switch off, but the preswitch-off levels trended lower in the somatostatin group. The objective of this study was to use advanced mathematical modeling to explain these differences and to probe *in silico* whether the GCR can be further augmented by *simultaneous* switch off of insulin and somatostatin.

Method:

Nonlinear differential equations approximated the glucagon control network assuming an α/δ -cell feedback interaction under glucose control. The model was used for the analysis of the differences in the responses to insulin and somatostatin switch off.

Result:

Model-based simulations demonstrated that suppression by insulin of basal and pulsatile and of only pulsatile glucagon release by somatostatin was consistent with data, explained GCR amplification, and explained differences in the responses to the two signals. The simulations predicted that simultaneous switch off of insulin and somatostatin will further improve the GCR amplification achieved by each of the individual signals.

Conclusion:

Results support the hypothesis that defective GCR can be amplified by α -cell suppression followed by switch off. The model predicts that insulin and somatostatin may act through different (but complementary) switch-off mechanisms, thereby suggesting ways to maximally enhance GCR in β -cell-deficient diabetes using dual feedback inhibition. Results are clinically relevant as they could have application to artificial pancreas design by providing strategies to augment GCR in a way that would not require glucagon infusion.

Evaluation of a New Diagnostic Device (PM-25) for the Measurement of Vibration Perception Threshold for the Detection of Early Diabetic Neuropathy in Patients with Diabetes Mellitus

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Background:

Measurement of vibration perception thresholds (VPT) is an essential tool for the screening of diabetic polyneuropathy. This investigation was performed to evaluate the newly developed pallaesthesiometer PM-25.

Methods:

Sixty diabetic patients (36 males; 5 type 1; age 66.3 ± 8.1 years; duration of diabetes 15.8 ± 9.5 years; mean \pm SD) suffering from diabetic polyneuropathy were evaluated according to the Neuropathy Disability Score (NDS) and received vibration perception measurements by the use of different technologies for the measurement of VPT. VPT was measured twice at the finger ball of digit 3, distal joint of digit 3, malleolus lateralis, and the distal joint of digit 1 on both body sites using the new device (PM-25, IBE-Engineering, Feilbingert, Germany) and a 125-Hz Rydell-Seiffert tuning fork (TF). In addition, VPT was measured at the finger ball of digit 3 and the distal joint of digit 1 at both feet using a commercially available pallaesthesiometer (VSA 300; Medoc Ltd., Israel).

Results:

A good correlation could be observed between the PM-25 and the other diagnostic tools for the toe of the lower limb (NDS $r = 0.36$; TF $r = 0.48$; VSA $r = 0.52$; $p < 0.0001$, respectively) and the malleolus lateralis (NDS $r = 0.36$, $p = 0.005$; TF $r = 0.39$, $p = 0.0001$). A much weaker correlation was observed for the distal joint of Dig III at the upper extremity (NDS $r = 0.10$, not significant; TF $r = 0.37$, $p < 0.0001$), while no association could be observed at the fingertip.

Conclusions:

VPT measurement using the PM-25 device was shown to provide reasonable results compared with established technologies for the detection of sensory deficits in patients with distal diabetic polyneuropathy.

Continuous Subcutaneous Glucose Monitoring in Type 2 Diabetic Patients: A 72-Hour Comparison during Diet Alone with Add-On Metformin Treatment

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Background and Aims:

This study aimed to compare 72 hours of continuous glucose monitoring (CM) glucose curves in type 2 patients during diet and during add-on treatment with metformin.

Materials and Methods:

Nineteen type 2 diabetic patients [5 females, 14 males; age 58.9 ± 11.0 years; body mass index 30.0 ± 5.0 kg/m²; hemoglobin HbA1c (HbA1c) 7.6 ± 1.9 % (mean \pm SD)] were included. The two in-house visits were identical in terms of meals and exercise. During the first visit patients were on diet alone. Metformin intake (2×850 mg) started after the first visit in order to ensure a steady state for the second visit 4–6 weeks later. The study made use of microdialysis subcutaneous continuous glucose monitoring devices (Roche Diagnostics, Mannheim, Germany). Two devices were applied to each patient for ~84 hours. Up to 32 capillary blood glucose (BG) measurements were performed and used for calibration. The two CM data sets from each patient were merged into one curve. Areas under the curves (AUC) were calculated for both BG and CM values.

Results:

HbA1c decreased significantly from 7.6 ± 1.7 to 6.7 ± 1.0 % between the two visits. In 18 of 19 patients, BG and CM data could be compared. During diet, mean 72-hour BG and CM glucose concentrations were 182 ± 47 and 166 ± 45 mg/dl, respectively, and 72-hour AUCs were $728,199 \pm 190,178$ mg/dl*min (BG) and $716,004 \pm 195,065$ mg/dl*min (CM). After 34.2 ± 2.7 days of metformin therapy the mean 72-hour glucose concentrations (BG 143 ± 22 mg/dl, CM 132 ± 21 mg/dl) and the mean 72-hour AUCs (BG $567,940 \pm 89,481$ mg/dl*min, CM $569,273 \pm 88,517$ mg/dl*min) were decreased significantly.

Conclusion:

Compared to BG measurements, CM data provided detailed information about postprandial glucose excursions. These results suggest that CM is a valuable tool for the adaptation and control of oral antidiabetic therapy.

Bariatric Surgeries' Effect on Weight Loss and Resolution of Type II Diabetes in Hispanics and Non-Hispanic Whites

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Introduction:

Morbid obesity surgery (MOS) has shown to be an effective procedure for aiding weight loss for severe obesity and helping type II diabetes mellitus (DM). This study was designed to not only look at bariatric surgery efficiency in treating obesity, type II DM, and ameliorating related comorbidities, but also compared the efficacy of these procedures between Hispanics and non-Hispanics and surgery type.

Method:

Morbidly obese, type II DM patients who had undergone laparoscopic gastric bypass (LRYGB), laparoscopic sleeve gastrectomy (LSG), laparoscopic adjustable gastric band (LAGB), and combinations of gastric banding and partial gastrectomy (GBSR) were evaluated retrospectively. Patients (194) were divided into matching cohorts—45 LAGB, 72 LRYGB, 39 GBSR, and 38 LSG—and evaluated for a decrease in body mass index (BMI) and glucose. Then, within each cohort the results were compared between Hispanic and non-Hispanic White patients. Gaussian regression evaluated relations of surgery type, BMI, gender, and ethnicity to excess weight loss.

Result:

The BMI went from 39.2 to 29 (kg/m²) for LRYGB, 43.4 to 32 for LAGB, 40.5 to 32 for GBSR, and 45.6 to 30 for LSG, respectively, before surgery and at 18 months. Glucose levels measuring milligrams per deciliter with LRYGB were 115, 117, and 118 at 3, 12, and 18 months, respectively; 120, 151, and 152 with LAGB; 128, 126, and 125 with GBSR; and 105, 116, and 118 with LSG.

Conclusion:

MOS surgery is highly effective for aiding weight loss, type II DM resolution in both Hispanic and non-Hispanic White patients. Furthermore, LAGB showed to be the least effective surgery for controlling type II DM.

Sleeve and Partial Gastrectomy Effect on Weight Loss and Diabetic Control

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Objective:

Laparoscopic sleeve gastrectomy (LSG) has shown to successfully produce excess weight loss (EWL) and amelioration of associated comorbidities in obese patients. This study seeks to review differences, if there are any, in weight loss and diabetic control using different restriction degrees.

Method:

In an institutional review board-approved retrospective patient review, we evaluated LSG and gastric banding with partial gastrectomy (GBSR) performed between 2004 and 2008. Patients were divided into three groups according to type of LSG performed: LSG with a 29 French endoscope (31 patients), LSG with a 38 French bougie (11 patients), and LSG with GBSR (21 patients). The last measurement at follow-up after surgery was taken at 18 months. We collected the amount of weight loss and glucose level for each patient every 3 months postsurgery. Additionally, postsurgery patient interviews were held. Collected results were compared.

Result:

EWL were 20, 50, and 55% at 3, 12, and 18 months using a 38 bougie and 21, 53, and 59.8% using a 29 endoscope with LSG; with GBSR %EWL were 22, 52, and 54, respectively. Glucose levels for LSG with a 38 bougie were 115, 117, and 120 at 3, 12, and 18 months respectively; 105, 116, and 118 with LSG with a 29 endoscope; and 128, 116, and 130 with GBSR.

Conclusion:

Greater stomach restriction levels yielded larger amounts of weight loss and better long-term glucose stabilization.

Analysis of Interfering Factors in Noninvasive Glucose Measurement: Mathematical Modeling Approach

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Objective:

Conducting noninvasive glucose measurements using glucose-correlated physiological phenomena is inherently complex. Using a combination approach of three independent measurement channels (ultrasonic, thermal, and electromagnetic) can minimize the impact of disturbances on the measurement. Although this approach has justified itself in clinical trials, it needs to be extended and improved in order to increase the accuracy of the measurements. There is a need for an adequate mathematical model for each measurement channel to allow a multidimensional analysis of the relationship between the channels' output signals and glucose concentration plus accompanying disturbances.

Method:

The model of the electromagnetic channel represents a tissue (earlobe) located between two electrodes and links earlobe skin and underlying tissue electrical parameters relating to the blood glucose variations and the output signal of the channel. The model of the thermal channel simulates heat transfer processes that occur in a multilayer sensor-tissue mechanical structure, linking glucose concentration with the thermal properties of the tissue.

Result:

The output vector of each channel allows distinction between the impacts of different sets of parameters involved in the measurement. The most substantial interferences for the electromagnetic and thermal channels were found in the various properties of the skin, which in part are dependent on the earlobe compressing force (caused by the ear clip) and the earlobe skin condition.

Conclusion:

Based on model analysis, the ear clip has been mechanically redesigned to allow more consistent pressure on the earlobe. In addition, structural changes are implemented in the sensors. These modifications will improve the measurement process and data gathering, allowing sophisticated and adequate analysis, resulting in an increased signal-to-noise ratio.

Comparison of Postprandial Plasma Glucose Control of Single-Dose Subcutaneous Hepatic-Directed Vesicle-Neutral Protamine Hagedorn (NPH) versus Control NPH Treatment in Patients with Type 1 Diabetes Mellitus

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Objective:

Hepatic-directed vesicles (HDV) insulin is a liposomal insulin delivery system that contains a proprietary hepatocyte targeting molecule that directs the delivery of the encapsulated insulin to the liver. Postprandial glucose (PPG) control of single-dose subcutaneous (SC) HDV-neutral protamine Hagedorn (NPH) was compared to SC NPH in a two-meal model in type 1 diabetes patients.

Method:

The study was an inpatient, randomized, single-blind, single-dose, two-meal model, two-way crossover design in patients ($n = 5$) aged 46 ± 12 years, with a hemoglobin HbA1c of $8.9 \pm 1.2\%$ and a body mass index of 28.7 ± 2.0 kg/m². Following an overnight intravenous insulin drip to control morning fasting blood glucose to 100 mg/dl, randomized single-dose treatments were as follow: day 1, NPH 30 minutes before breakfast; and day 2, HDV-NPH 30 minutes before breakfast. Doses were equivalent to the morning dose of NPH on the day before admission. At breakfast and lunch, 60-gram carbohydrate meals were given. Venous blood was sampled for measurement of plasma glucose, insulin, glucagon, cortisol, β -hydroxybutyrate, and clinical laboratory tests. Humalog was allowed when blood glucose levels exceeded 350 mg/dl. Safety was monitored by adverse events.

Results:

HDV-NPH induced a greater significant lowering of mean incremental PPG area under the curve (AUC) (44337 ± 22514 vs 78195 ± 8977 ; $p = 0.004$) and blood glucose AUC (115617 ± 20667 vs 156105 ± 21305 ; $p = 0.020$) compared to NPH over the two-meal test period. Also, mean β -hydroxybutyrate levels were consistently lower with HDV-NPH treatment. Three subjects required Humalog treatment during NPH treatment compared to none for HDV-NPH. HDV-NPH treatment was associated with hypoglycemia in one subject.

Conclusion:

Single-dose HDV-NPH induced a significant 43% additional PPG lowering compared to the same dose of NPH over a two-meal period in type 1 diabetes patients. The lower β -hydroxybutyrate levels associated with HDV-NPH treatment indicate a hepatically mediated effect. Both treatments were generally safe and well tolerated.

Factors Influencing Electrocardiogram Changes Associated with Hypoglycemia in Adolescents with Type 1 Diabetes Mellitus

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Objective:

The onset of hypoglycemia is regularly associated with changes in electrocardiogram (ECG) activity. This study examined differences among ECG changes in three groups of subjects: daytime hyperinsulinemic hypoglycemic clamps, nighttime hyperinsulinemic hypoglycemic clamps, and nighttime free-fall studies (normal subcutaneous insulin regimen).

Method:

Two sets of hyperinsulinemic clamp studies (day $n = 25$ and night $n = 11$) were conducted on adolescents (14.4 ± 1.6 years) with type 1 diabetes mellitus; mean hemoglobin A1c (HbA1c) of 7.65% (5.9 to 12.7). Nighttime free-fall studies were conducted on a total of 54 volunteers aged 17.1 ± 2.3 years; mean HbA1c of 8.38% (6.8 to 9.96). AiMedics HypoMon® systems were used to monitor ECG while venous blood samples were collected and analyzed (Yellow Springs Instruments) at specified intervals to provide blood glucose profiles.

Result:

Hypoglycemia induced changes in raw and normalized average heart rate and corrected QT were subdued at night and further diminished in the free-fall group. ECG trend features were less affected, maintaining distinctive hypoglycemia characteristics across all three groups.

Conclusion:

Basic ECG changes such as heart rate induced by hypoglycemia onset are influenced by sleep state and probably glucose/insulin rates during clamp studies. ECG trend features appear to retain value in detecting natural nighttime hypoglycemia.

Development of a Novel Questionnaire to Assess Quality of Life Differences between Continuous Subcutaneous Insulin Infusion and Multiple Dose Insulin in Type 1 Diabetes

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Background:

Measures of quality of life (QOL) correlate with treatment compliance in diabetes. QOL in continuous subcutaneous insulin infusion (CSII) therapy may be improved when compared to multiple dose injection (MDI) treatment, but this difference has not been shown consistently, partly due to the methodology of QOL assessment.

Objectives:

The objectives of this study were to develop a novel tool assessing QOL differences CSII and MDI treatment and to test the novel tool for reliability, concurrent validity, and clinical validity.

Methods:

This novel tool was developed from existing literature and group discussion. Subjects on both CSII (15) and MDI (14) treatment regimes completed the novel tool and the Diabetes Quality of Life (DQoL) questionnaire.

Results:

The novel tool consists of 26 questions organized into frequency and satisfaction subsections. QOL assessed by the DQoL and novel tool was not significantly different between CSII and MDI groups, although QOL was higher using the novel tool. The frequency subsection score of the novel tool was nonsignificantly higher in CSII patients compared with the MDI group ($p = 0.72$). The satisfaction subsection scores of the novel tool were significantly higher in the CSII group ($p = 0.03$). Cronbach's α ranged from 0.75 to 0.90 in the novel tool, indicating acceptable reliability. A significant correlation was seen between the novel tool and DQoL scores for all subjects, showing concurrent validity.

Conclusion:

The novel satisfaction subsection is sensitive to quality of life differences between CSII and MDI. The questionnaire showed reliability, acceptability, and concurrent validity, assessing QOL to a similar level as the DQoL. The novel tool requires further development but has potential to better assess QOL in insulin-treated patients, thus assessing compliance and the effects of new technologies on QOL.

Use of Perfluorocarbons in Encapsulated Cell Systems: Their Effect on Cell Viability and Function and Their Use in Monitoring the Cellular Microenvironment Noninvasively

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Introduction:

Implantation of insulin-secreting β cells offers significant promise in providing more physiologic and less invasive regulation of blood glucose levels than insulin injections. To partially alleviate the immune rejection of allogeneic or xenogeneic grafts, cells are encapsulated in hydrogels surrounded by semipermeable membranes. The membranes allow the passage of nutrients and metabolites, including insulin, but exclude antibodies and cytotoxic cells of the host, thus protecting the implant. A major concern in designing encapsulated cell systems is ensuring sufficient oxygenation of the cells within, as oxygen is an important parameter affecting cell viability and function. Additionally, poorly known factors that influence construct oxygenation *in vivo* often lead to implant failure and can be detected only based on end physiologic effects. To improve oxygenation, investigators have incorporated perfluorocarbons (PFCs), which have a high solubility of oxygen and can act as temporary oxygen reservoirs. Results, however, have been mixed. The research presented here aims at providing a definitive answer to the question of whether PFCs improve the viability and function of encapsulated β cells. Furthermore, we investigated the use of PFCs in monitoring the dissolved oxygen (DO) concentration within an encapsulated cell system through ^{19}F nuclear magnetic resonance spectroscopy.

Methods:

A perfluorotributylamine (PFTBA) emulsion at a concentration of up to 10 vol% was coencapsulated with $\beta\text{TC-tet}$ insulinoma cells in calcium alginate beads. Cell viability, metabolic activity, and insulin secretory function were evaluated in PFC-containing beads and compared against PFC-free controls under constant normoxia and constant and transient anoxia. A dual PFC system, where a PFTBA emulsion was incorporated in the experimental, cell-containing beads and perfluoro-15-crown-5-ether emulsion in control, cell-free beads, was developed and tested for feasibility *in vitro*. The control beads were used to monitor the surrounding DO environment while studying the DO level within the experimental beads.

Results:

There was no significant difference in cell viability, metabolic activity, or insulin secretory function between the PFTBA-containing beads and the PFC-free control group cultured under both normoxic and anoxic conditions. These results are in agreement with a previously developed mathematical model of the encapsulated cell system. The dual PFC system was capable of simultaneously measuring the DO concentration in the cell-containing and cell-free beads, thus allowing for an assessment of the cellular metabolic activity in the former.

Conclusion:

The incorporation of PFTBA does not have an effect on cell viability and function. The dual PFC system can be used as a method of monitoring the cellular microenvironment *in vitro* and could potentially be used to monitor the physiologic status of encapsulated cells *in vivo*.

Advances in Robust Control Applied to Artificial Neural Network Controllers Based in an Artificial Pancreas Project

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Introduction:

Type 1 diabetes mellitus is characterized by the inability of the pancreas to produce and secrete insulin; exogenous insulin must be administered throughout the day. In order to improve glycemia 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 systems with other inputs such as carbohydrate intake, frame or state of mind, diseases, and fitness make continuous feedback would be available to optimize insulin administration; in such a scenario, closed-loop control would be the ultimate goal. Robust stability and performance are the two most basic features of feedback control systems. The harmonic balance analysis technique enables one to analyze the stability of limit cycles arising from a neural network control-based system operating over nonlinear plants such as the artificial pancreas.

Methods:

Recent advances in insulin pump and glucose sensing technology suggest that a closed-loop artificial pancreatic β cell could soon be achieved with suitable control algorithms. Using artificial neural network modeling and identifying patients through clinical data monitoring for each patient, it is possible 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 (6-hour periods). 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. A robust stability analysis based on the harmonic balance is presented and applied to a complete system with unstructured uncertainty. We analyzed the robustness of neural-based multivariable control systems with uncertainty, provided that both the neural controller and the plant are represented by its sinusoidal input describing function (SIDF) approximation and linearized model, respectively. For this purpose, we make use of the generalized Nyquist stability criterion applied to analyze nominal stability. The artificial pancreas consisted of a minimally invasive subcutaneous glucose system, a personal portable meal calculator, a computer control system, and an insulin pump delivering subcutaneously insulin lispro /neutral protamine Hagedorn.

Results:

Results were quantified using graph methods, the $inv(\bar{\sigma}(M))$ for controlling sensitivity function has been plotted together with the $\bar{\sigma}(\Delta N)$ controller uncertainty, and an upper bound for plant uncertainties for the absence of limit cycle oscillations is calculated.

Conclusions:

We have analyzed the robustness of neural-based multivariable control systems with uncertainty, provided that both the neural controller and the plant are represented by its SIDF approximation and linearized model, respectively. Future works are directed toward the development of a design method for training the neural controller in order to satisfy not only performance requirements but robustness conditions.

Free Software Tools for Diabetes Education Program

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Introduction:

This project is about a Web educational platform for course management system (CMS) Moodle© based to help diabetes educators and health care professionals in order to create effective online learning communities. Current scientific evidence demonstrates that much of the morbidity and mortality of diabetes can be prevented or delayed by aggressive treatment with diet, physical activity, and new pharmacology approaches to normalize blood glucose levels, blood pressure, and lipids. Unfortunately, differences still exist between current and desired diabetes care and practices. Public awareness about the seriousness of diabetes and its treatment is low, despite the fact that the disease is one of the leading causes of death and disability in the world.

Methods:

A demonstration for deploy software tools is done with next free components. A) SME (A free Distribution Linux Based), XAMPP (is a compilation of free software (comparable to a Linux distribution), it is free of charge, and it is free to copy under the terms of the GNU Public License), and Moodle (a free, Open Source software package designed using sound pedagogical principles) is designed to help educators create online courses with opportunities for rich interaction. Its open source license and modular design means that people can develop additional functionality.

Results:

A Web site for trial and research purposes is created with some features: it is suitable for 100% online classes, as well as supplementing face-to-face learning; has a simple, lightweight, efficient, compatible, low-tech browser interface; course listing shows descriptions for every course on the server, including accessibility to guests; courses can be categorized and searched; and emphasis is on strong security throughout. Forms are all checked, data are validated, cookies are encrypted, and so on; goals are to reduce administrative involvement to a minimum, while retaining high security. It supports a range of authentication mechanisms through plug-in authentication modules, allowing easy integration with existing systems. The site uses the standard email method: patients can create their own log-in accounts. Email addresses are verified by confirmation. An external database is used: any database containing at least two fields can be used as an external authentication source. Each person requires only one account for the whole server—each account can have different access. An admin account controls the creation of courses and creates educators by assigning users to courses. For security, educators can add an “enrollment key” to their courses to keep out nonpatients. They can give out this key face to face or via personal email etc. Educators can enroll and unenroll patients manually if desired even after a certain period of inactivity. Patients are encouraged to build an online profile. Personal data can be protected from display if required. Every user can specify their own time zone, and every date in the server is translated to that time zone. Every user can choose the language used for the interface (English, French, German, Spanish, etc.). Modules are Chat, Choice, Forum, Quiz, Resource, Survey, and Workshop.

Conclusions:

We have demonstrated the free software tools used for fighting diabetes and presented useful resources for clinics, hospitals, and research centers.

Do We Need Different Predictive Models for Different Individuals?

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We explored the possibility of developing “universal,” data-driven predictive models for short-term predictions of subcutaneous glucose concentration in humans. The data-driven modeling approach adopted for this study consisted of two steps: data smoothing and predictive modeling. To eliminate unphysiologic, high-frequency noise, subcutaneous glucose concentration data were first smoothed using constraints imposed on the glucose rate of change. Then, a data-driven autoregressive (AR) model of order 30, with coefficients obtained through constrained least squares, employed smoothed data to make short-term (30-minute ahead) predictions.

To test the model’s performance across different subjects, continuous glucose monitoring (CGM) devices, and diabetes types, we used data from three separate studies. Each study employed a different CGM device and different subjects. Two out of three studies involved type 1 diabetes patients and the other involved type 2 diabetes patients. The number of subjects in each study varied from 7 to 18, and the collection time varied from 5 to 56 days. The age of the subjects varied from 3 to 70 years old.

For each subject, an AR model was developed using a portion of the subject’s data and was subsequently tested on the subject’s remaining data, as well as on all other subjects. The same-subject predictions served as a reference for comparison against cross-subject and cross-study predictions. The model’s predictive capabilities were evaluated using the root mean squared error (RMSE), which was averaged over all testing subjects.

We found that average cross-subject and cross-study RMSEs are similar to same-subject RMSEs. The predictive capabilities of the models are not affected by diabetes type or measuring device. We conclude that the underlying mechanisms of glucose regulation are similar for different diabetes patients and that such similarity can be exploited by data-driven techniques to develop universal predictive models.

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. This abstract has been approved for public release with unlimited distribution.

Use of Continuous Glucose Monitoring in Subcutaneous Fat to Govern Laptop-Based Enhanced Model Predictive Control Algorithm for Tight Glucose Control in Cardiosurgical Intensive Care Unit: A Pilot Study

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Objective:

The objective of this study was to assess the feasibility and performance of a system combining continuous glucose monitoring (CGM) with the enhanced model predictive control (eMPC) algorithm for intensive insulin therapy in postcardiac surgery patients.

Methods:

Six patients undergoing elective cardiosurgical operation were enrolled. Intensive insulin therapy was governed using the eMPC algorithm. Glucose measured with a real-time continuous glucose monitoring system (Guardian RT CGMS) served as an input for the eMPC every 15 minutes. The accuracy of continuous monitoring was evaluated every 1 hour using reference arterial glucose and Clarke error-grid analysis (C-EGA) and, when clinically unacceptable, reference glucose was used instead for the eMPC and to recalibrate the CGMS. The monitoring was scheduled to run 24 hours in each patient.

Results:

Of the total number of 135 paired glycemic values obtained, 127 (94.1%) were found in clinically acceptable zones of C-EGA and only 8 (5.9%) were in the unacceptable D zone. Overall, reference glycemia had to be used to govern eMPC nine times (one time in three patients, two times in one patient, three times in one patient, respectively). In one patient, continuous monitoring was finished 3 hours before the scheduled time due to the inability to further recalibrate the sensor. Mean blood glucose was 6.3 ± 2.1 mmol/liter, and the percentage of time spent within the target range (4.4–6.1 mmol/liter) was 36.7 %. No severe hypoglycemia was observed during the study.

Conclusion:

In this feasibility trial the combination of the eMPC algorithm with CGM was reliable enough to test this approach in a larger study population. This combination might be a promising step toward a fully automated closed-loop system for insulin delivery.

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Glycemic Control with Computer Software

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Objective:

This report reviewed glycemic control outcomes in a single hospital experience using computer software. The objective was to evaluate use of an insulin dosing computer software protocol for glycemic control.

Method:

Glycemic control with intravenous insulin is a complex dosing challenge that is best solved with software-based dosing using control mathematics. The EndoTool® software uses control math applied to a physiologic insulin dosing relationship to yield an individualized dosing equation for each patient based on responses to insulin. The computer/caregiver interface is easy to use, providing a uniform, consistent, and math-free work environment. The blood glucose (BG) level outcomes were evaluated over 14 months of the software use and compared to relevant historical controls and medical literature.

Results:

During this time period, 582 patients received 19,156 insulin dose calculations. Data were collected from these units for analysis of glycemic control: mean glucose levels, time to control, incidence of hypoglycemia, and analysis of hypoglycemic episodes. The average BG after 4 hours of control was 116 ± 29 mg/dl. The hypoglycemia (BG < 40 mg/dl) incidence for all readings was 0.024% (0.9% of patients). The hypoglycemia (BG < 50 mg/dl) incidence for all readings was 0.12% (4.1% of patients). These data compare very well with the literature-reported incidences of hypoglycemia (<40) of 9 to 20% of patients. A detailed analysis of the hypoglycemic events and glycemic control outcomes compared to historical controls and referenced literature is provided.

Conclusion:

The EndoTool glucose management system provided better, safer, and easier BG control for hyperglycemic patients in these critical care units compared to previous paper-driven protocols.

Diabetes Information Management: e-Diabetes

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Objective:

We have leveraged our integrated electronic medical record system in developing a suite of support tools for the full range of diabetes management activities integrating public health and clinical practice. The system will allow providers, especially primary care providers, to make expert level decisions both at the point of care and across the entire diabetic population and empower patients to participate actively in those decisions. The software is anticipated to improve processes of care, preventing development of complications and generate cost of care savings.

Methods:

Implementation of the protocol of 6-month duration will occur in a single primary care site. We plan to include all patients in the study who have an identifiable International Classification of Diseases, ninth revision code for diabetes and have an identifiable drug to lower the blood glucose. The control group would be usual care, as well as a comparable group managed by endocrinologists. During the encounter, patients will make choices on how to manage their diabetes and cardiovascular risk. In the process, patients will be informed of the benefits of each choice and the associated relative value in risk reduction. A risk engine will calculate the patient's risk for micro- and macrovascular complications of their disease. During the encounter, the physician will be informed of patient choice, future risk, and expert recommendations given future risks. It is anticipated that the normal clinic flow will not be altered by this intervention. Finally, we expect to also have software for evaluating home glucose monitoring data in combination with health risk as part of decision support to enable the provider and the patient to share decision making more effectively.

We anticipate recruitment to begin in late fall, 2008.

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

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Objective:

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 the medical personnel. This work presents a nonlinear model predictive control strategy that can be used to tackle nonlinear control problems with changing model parameters, unknown disturbance factors, and specifications on the rates of change of the inputs.

Method:

A nonlinear patient model, which is particularly developed for describing the glucose and insulin dynamics of critically ill patients, is used for online state/disturbance estimation and control under a realistic disturbance realization (process noise, unknown model disturbance, sensor noise, and unknown initial states/parameters). Unknown states (e.g., insulin concentration) are estimated using a moving and fixed-size window of data (moving horizon estimation, MHE). The insulin input that yields the blood glucose output at the set point is formulated as an optimization problem (target calculation).

Result:

The computed glycemic penalty index for the simulated glucose behavior equals 10 (≤ 23), indicating that the observed blood glucose range was clinically acceptable. The MHE is able to recover quickly from a wrong initial guess of the state vector. The target calculation leads to the removal of the effect of disturbances and changing parameters.

Conclusion:

The results are satisfactory in terms of both control behavior (set point tracking and the suppression of unknown disturbance factors) and clinical acceptability. The proposed control system is potentially suitable to control glycemia in the intensive care unit and will be soon tested in real life.

New Opportunities of Diabetes Research Using Different Fish Species

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According to the International Diabetes Federation, current tendencies will almost double the number of diabetics from the present 194 million to 333 million by 2025. Scientific investigations have to become more effective and simpler to fight this disease successfully. An increase in the number of people suffering from diabetes requires the development of techniques and methods that allow fast and accurate diagnosis on a daily basis.

Glucose metabolism (hypoglycemia, hyperglycemia) of diabetics was tested using serum/plasma fructosamine (SeFa) and glycated hemoglobin (GHb), as glycated proteins permit the calculation of blood plasma glucose concentrations for several weeks. The objective of this study was to develop a measurement method for SeFa in the zebra fish (*Danio rerio*). Currently, the zebra fish is used in most medical and biotechnology laboratories instead of mice and rats. Their advantages are small size, easy maintenance, fast growth, transparency, and a genome that is very similar to humans.

Before the investigations, the modified Johnson's macro method was used and tested on larger fish (common carp, grass carp, catfish, silver crucian carp) in order to standardize SeFa concentrations. Because of the small size of zebra fish and thus the minute quantity of blood that can be sampled, the modified method had to be remodified. The new method is also based on a colorimetry method that uses the nitroblue tetrasolium reagent, automated and easily performed.

Several years of research in our laboratory have revealed that the concentration of SeFa can be measured in fish, its value is somewhat lower than that of humans, and its concentration is negatively correlated ($R^2 = 0.6-0.85$) with water temperature. Determination of SeFa levels in the zebra fish opens new possibilities in diabetes research.

Noninvasive Monitoring of Glucose Using Near-Infrared Reflection Spectroscopy of Skin: Constraints for Effective Strategies in Multivariate Data Analysis

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Introduction:

Noninvasive blood glucose assays have been promised for many years, and near-infrared reflection (NIR) spectroscopy of the skin in combination with diffuse reflection techniques has come forward as a candidate for a successful assay. The measurement physics, anatomy of the tissue and spectral data behind the assay including the tiny spectral signatures of the glucose hidden among the other spectral variance sources has to be discussed to ensure the applicability for self-monitoring of blood glucose.

Methods:

The traditional approach using statistical partial least-square (PLS) calibrations, even with sophisticated data pretreatment is rather limited. The most useful spectral range, containing important fingerprint signatures of the analyte, includes the so-called combination and overtone NIR-regions. A strategy called science-based calibration (SBC), has been developed that relies on a priori information such as the spectral absorptivities of the analyte ("response spectrum") with statistical estimates of the variance of a sample population with negligible glucose dynamics.

Results:

For the SBC-method, the situation with transcutaneous reflection skin spectra is more difficult than for simple cell transmission spectra because of the wavelength-dependent photon penetration depths, which require a scaling of the response spectrum. The latter can be obtained by simulating the photon migration based on estimates of optical tissue constants and optics configuration. The validity of the multivariate data analysis approach for glucose concentration estimates can be demonstrated for NIR-spectra of plasma samples measured in a quartz cuvette.

Conclusions:

The special tissue optics conditions, tissue inhomogeneity and physiological aspects dealing with glucose in different tissue compartments require more calibration effort. First results from the SBC method are promising, providing also tools for estimating the uncertainty budgets in concentration prediction.

Model-Based Fault Detection in the Artificial β -Cell Framework

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Objective:

The main requirement for the practical realization of an artificial β cell is safety. In this proof-of-concept study, a consolidated industrial fault detection technique was translated to the artificial β -cell field to detect faults both in the insulin infusion and in the sensor measurements.

Method:

The technique used in this study to detect faults is analytical redundancy, which compares the behavior of a real system to that of a model. An important drawback of this technique is deciding whether the mismatch is due to a fault or to uncertainty, leading to false or missed alarms. This problem can be tackled using numerical intervals to represent the uncertainty. The result of the corresponding simulation is an envelope containing all possible nonfaulty behaviors. When the measurement is not consistent with the predicted manifold of behaviors, a fault is considered to exist. Two scenarios were tested: (a) *in silico* tests, using the Cobelli's model as *in silico* patient and the Bergmans' model as simulation model. Insulin infusion and sensor faults were simulated for this purpose. (b) Real retrospective data from an artificial β -cell clinical trial were carried out at the Hospital de la Santa Creu i Sant Pau.

Result:

(a) The sensitivity of *in silico* tests was acceptable from a clinical point of view. (b) For retrospective clinical data, an obstruction in the insulin infusion system was detected by the algorithm 60 minutes before the expert physicians realized the problem.

Conclusions:

Interval model-based fault detection has been proven to be suitable for its application to the artificial β -cell framework. More clinical tests are still required to test the robustness of the method.

Validation of a Complex Glucose Metabolism Model

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Introduction:

The mathematical description of the processes that regulate the production and uptake of glucose increases understanding of the complex balance between metabolites and hormones. Such a description can ultimately aid in the development of tools to manage glycemia in diabetes and stress-induced hyperglycemia.

Methods:

The ability of a glucose metabolism model to simulate published experimental data was assessed. Data consisted of pancreatic clamp experiments where glucose was infused for 90 minutes at a rate of 6.5 mg/kg min⁻¹ into a peripheral vein of five male nondiabetic subjects. The rates of hepatic glucose output, splanchnic glucose uptake, and peripheral (all nonsplanchnic) uptake were measured every 15 minutes using a labeled glucose technique. We compared experimental data to model estimates of these rates. Then we refined specific model parameter values and reran the simulations.

Results:

Using the original model parameter values published by Sorensen in his 1985 doctoral thesis, the model accurately estimated the time course of hepatic glucose output and peripheral glucose uptake. However, there was considerable difference in the model's estimation of splanchnic (hepatic and gut) glucose uptake; the estimated steady-state values were twofold greater than experimental values. Once we modified the parameters governing the rate hepatic glucose uptake, the model simulated experimental data accurately.

Conclusions:

The original relationship between glucose and its uptake by the liver as developed by Sorensen used data from both clamp studies and oral glucose tolerance tests. Hepatic glucose uptake estimates from oral glucose tolerance tests were distinctly larger than estimates derived from experiments using intravenous glucose. The magnitude of this difference supports the need to model the glucose absorption from the gut differently than intravenous infusion of glucose.

Evaluation of a Laser Doppler Device O2C for the Measurement of Microvascular Skin Blood Flow and Hemoglobin Oxygenation in Diabetic and Nondiabetic Subjects

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Objective:

Skin microvascular assessment has progressed to an important evaluation in patients with diabetes mellitus. This study was done to evaluate a new device using microlight guide spectrophotometry (O2C; LEA Medizintechnik, Giessen, Germany) in the assessment of skin microvascular function.

Method:

Twenty nondiabetic subjects (age 46.6 ± 14.8 years; mean \pm SD) and 20 diabetic patients (age 59.4 ± 8.4 years) participated in repeated microvascular measurements using microlight guide spectrophotometry. This technique allows simultaneous, noninvasive measurement of microvascular blood flow and hemoglobin oxygenation (SO₂) at the same anatomical area in different tissue layers. A skin probe was placed on nonhairy skin at the thenar eminence of the left hand for the measurement of SO₂ and the postischemic reactive hyperemia response (PRH) in skin and underlying muscle tissue.

Results:

Repeated measurements in PRH revealed a good correlation at the superficial skin layer ($r = 0.97, p < 0.0001$) with a coefficient of variation at $9.2 \pm 1.7\%$ and at the superficial muscle layer ($r = 0.80, p < 0.0002$) with a coefficient of variation at $9.7 \pm 1.5\%$. A slightly weaker correlation was observed for the SO₂ measurement at the skin layer ($r = 0.69, p < 0.0001$) with a coefficient of variation at $17.5 \pm 3.8\%$ and at the muscle layer ($r = 0.48, p = 0.0016$) with a coefficient of variation at $18.1 \pm 10.5\%$.

Conclusion:

Light guide spectrophotometry is an easy, noninvasive, and reliable method for the measurement of superficial microvascular blood flow and skin oxygenation. Further studies are required to clarify the validity of these measures in special patient populations such as diabetes mellitus with specified microvascular complications.

Clinical Evaluation of Bionime Self-Monitoring Blood Glucose Rightest GM100

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Objective:

The main prevention of chronic diabetic complications is maintaining near-normoglycemia. Meters for self-monitoring of blood glucose (SMBG) meter are indispensable home use devices for the effective control of glycemia levels by diabetics. In this study, clinical evaluation of the Bionime self-monitoring of blood glucose Rightest GM100 applying injection-molding test strips was carried out.

Methods:

During the sensor fabrication process, barrel-plated Au electrodes were inserted into an injection mold base to fabricate test strips. Technical measurements, including imprecision and linearity tests, were analyzed. In clinical trials, capillary blood glucose concentrations measured using Rightest GM100 and the plasma glucose values obtained from Olympus AU640 (hexokinase method) were performed in the Chung Shan Medical University Hospital, Taichung City, Taiwan. Three alternative sites, the fingertip, palm, and arm, were tested by experienced technicians. Results were evaluated according to International Standards Organization 15197 (ISO 15197:2003) criteria and Clarke error grid analysis.

Results:

The measurement range of glucose was 0.6–30.5 mmol/liter ($y = 0.96x - 0.34$, $r^2 = 0.9969$). The *coefficient* of variations (CVs) in the within-run imprecision test was 1.1–2.8%, and overall CV was 2.0%, indicating good reproducibility. In clinical trials, the agreement of the Rightest GM100 meter with a laboratory method complied with ISO 15197:2003 criteria. In error grid analysis, values within the acceptable zone (A+B) were 100%, and values within zone A exceeded 95% for all alternative site tests.

Conclusions:

The Bionime Rightest GM100 meters applied a simplified process for biosensor fabrication and displayed high precision and clinically superior performance for monitoring glycemia concentrations in alternative site testing.

A Microelectromechanical System Continuous Glucose Monitoring Device Based on a Biocompatible Affinity Sensing System

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Objective:

We present a microelectromechanical system (MEMS) affinity glucose sensor that is aimed at long-term, stable continuous monitoring of glucose in interstitial fluid (ISF) with a biocompatible affinity sensing system.

Method:

The device features a magnetically driven vibrational element (a polymeric microcantilever or diaphragm) situated in a microchamber (volume: 30 μ l) sealed by a cellulose acetate semipermeable membrane (molecular weight cutoff: 3000). A poly(acrylamide-*ran*-3-acrylamidophenylboronic acid) (PAA-*ran*-PAAPBA) copolymer solution, developed as a novel biocompatible sensing fluid, fills the chamber and surrounds the vibrational element. Glucose permeating through the semipermeable membrane reversibly cross links the copolymer via affinity binding, resulting in an increase in viscosity and vibrational damping, which is measured to determine the glucose concentration.

Result:

We have designed, fabricated, and characterized the MEMS affinity sensor. In a 1.9% PAA-*ran*-PAAPBA solution, the vibration response of a microcantilever was measured as the glucose permeated through the semipermeable membrane. The time constant for the sensor response to glucose concentration changes was approximately 3 minutes. Steady-state and transient responses were measured at physiologically relevant glucose concentrations. It was observed that as the glucose concentration increased from 27 to 324 mg/dl, the vibration amplitude of the microcantilever consistently decreased by about 50%. This was accompanied by a shift of vibration resonance frequency from 25.25 to 24 Hz and a drop of Q-factor from 25 to 5, indicating a significant increase in vibrational damping and solution viscosity. The device has also shown a highly specific response to glucose.

Conclusion:

The MEMS affinity sensor exploits viscometric measurements using a biocompatible copolymer solution to specifically detect glucose and has the potential for long-term, stable, continuous monitoring of ISF glucose.

The Nursing Impact of Starting a Tight Glycemic Control Protocol Using Continuous Glucose Monitoring

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Objective:

Tight glycemic control (TGC) improves outcomes in critically ill patients but increases the risk of hypoglycemia. Safe maintenance of normoglycemia is labor-intensive, requiring close blood glucose (BG) monitoring and precise insulin titration. We report our clinical experiences using continuous glucose monitoring (CGM) and a computer-assisted titration algorithm in an ongoing pediatric trial of TGC.

Methods:

Fifty-seven patients aged below 3 years received postsurgical TGC (80–110 mg/dl BG target range) in the cardiac intensive care unit. The protocol was nurse managed, generally with one nurse per patient. Nurses could override suggested dosages. BGs were monitored by a CGM (Medtronic Guardian® REAL-Time) with hypoglycemia alarms. Blood glucose was checked every 0.5–4 hours according to the computer. Repeat checks were required when sensor and glucose meter values differed by 30%. Repeatability of the BG measurement was compared before and after introduction of a blood-sparing catheter sampling device (VAMP Jr.).

Results:

Sensor glucose was read 25.5 times daily and arterial BG values were checked 17.5 times daily. Repeat glucose meter checks were required 1.9 times daily. The sensor was calibrated 5.4 times daily. Subjects were treated with insulin 14.8 hours daily with infusion rates changing 10.2 times daily; 4.4% of insulin and 9.4% of glucose dose recommendations were overridden. The blood sampling device improved the precision of measured BG values by decreasing the 95% confidence interval of repeated glucose meter checks from ± 26.9 to ± 17.9 mg/dl.

Conclusions:

Despite the use of computerized insulin dosing and CGM, nurse workload remained high. To ensure sustainability of the protocol, future efforts will focus on decreasing BG check frequency by improving sensor performance and encouraging the use of a blood-sparing sampling device to minimize the need for repeat BG checks.

Risk Index of Postprandial Hypo- and Hyperglycemia in Type 1 Diabetes Mellitus with Consideration of Inpatient Variability and Other Sources of Uncertainty

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Objective:

A methodology to quantify the risk of suffering different grades of hypo- and hyperglycemia episodes has been derived. This methodology is based on predictive models considering inpatient variability, uncertain initial state, and food intake.

Method:

A nonlinear physiological model of the patient is considered. Interval simulations of the model are performed for a 5-hour period after a meal. A degree of uncertainty in the patient's sensitivities and in the carbohydrate (CH) contents of the planned meal has been considered. As a result, upper and lower envelopes of all the possible glucose excursions suffered by the patient are predicted. A normalized area-under-the curve of the worst-case predicted glucose excursion for severe and mild hypo- and hyperglycemia glucose ranges is obtained and weighted accordingly. For the case of hyperglycemia, a weight of the time of occurrences is also introduced. As result, a single measure of the risk is obtained.

Result:

The risk index has been evaluated in 25 different scenarios, varying preprandial glucose and uncertainty in food intake and insulin sensitivities. For the considered scenarios, the risk measure varied in the range of 3.02 to 50.31, performing well in all cases, according to clinical judgment. In the scenarios, 67.9% presented risk of severe hyperglycemia, 18.9% mild hyperglycemia, and 13.2% mild hypoglycemia. The variation in the uncertainties permits determining their influence in the risk index.

Conclusions:

By considering inpatient variability and uncertainty in the CH, a safer prediction of possible hyper- and hypoglycemia episodes induced by the tested insulin therapy can be calculated. This tool may be integrated in a decision-aid system to help the patients calculate the insulin doses more safely.

Toward an Injectable Continuous Glucose Sensor

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Objective:

We present the development of a new injectable osmotic sensor for automated continuous measurements of glucose in patients with diabetes mellitus. The sensor implements micro- and nanofabrication technologies for reduced size and incorporation of molecular features. The concept represents a unique platform technology for the development of a long-term *in vivo* glucose sensor that will replace current conventional measurement techniques, which can be inserted under the skin without the need of surgery.

Method:

The osmotic principle of nature is implemented as the basis of the sensor technology where a reversible competitive affinity assay performs the glucose specific recognition. The absolute change in particle concentration generates a pressure that is proportional to the glucose concentration. This pressure change is measured by an integrated pressure transducer and corresponding components that are all developed from the silicon micro- and nanofabrication industry.

Results:

The sensor has been realized in a ceramic package that measures $3 \times 7 \text{ mm}^2$ in extent. The integrated $2 \times 2\text{-mm}^2$ large pressure transducer and semipermeable membrane enclose a sensor lumen of $0.5 \mu\text{l}$ housing the osmotic reference solution and affinity assay components. The transducer is controlled by a $1 \times 1\text{-mm}^2$ large integrated circuit operating in weak inversion allowing powering from a 1-volt direct current supply source. The consumption of $1.7 \mu\text{W}$ of power is supplied from an externally coupled inductive link, through which continuous wireless transmission of glucose data is relayed and recorded on an external receiver.

Conclusion:

The miniaturized implant has been developed on the basis of a feasibility study on a larger prototype. Current investigations will determine the reactions from the immune system on capsule materials and the semipermeable membrane.

Acknowledgments:

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Calibration of a Continuous Glucose Monitor: Effect of Glucose Rate of Change

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Objective:

Continuous glucose monitors (CGMs) sample from interstitial fluid, but are calibrated with blood glucose. During glycemic fluctuations, glucose concentrations in the blood and interstitial fluid are not in equilibrium. Does this mean that CGM calibration must occur only when glucose is stable? This analysis shows the effect of rate of change at calibration on CGM accuracy, based on clinical trial data of the DexCom Seven.

Method:

CGM data were collected from 117 adult subjects with insulin-dependent diabetes (75% type 1) across eight U.S. centers. Each subject was asked to wear the CGM for 7 days, calibrate twice per day with a blood glucose meter, and collect an additional six to eight meter values per day for accuracy comparison. At each calibration, glucose rate of change was estimated using the previous 20 minutes of CGM trend data (provided data did not exceed criteria of the CGM for noise and/or physiologic feasibility). Paired CGM meter values collected after that calibration and until the next calibration were placed into a corresponding rate-of-change bin: ≤ -2 , -2 to -1 , ..., ≥ 2 mg/dl/min. For each bin, accuracy vs meter was evaluated with median absolute relative difference (ARD); this result was compared across bins.

Result:

The median ARD of the 4264 paired values was 11.7%. The range was within $\pm 3\%$, across all rates of change.

Rate of change at calibration (mg/dl/min)	≤ -2	-2 to -1	-1 to 0	0 to 1	1 to 2	≥ 2
Median ARD	8.6	13.5	11.7	11.2	12.5	10.1
<i>N</i> (%) pairs	116 (2.7)	579 (13.6)	1482 (34.8)	1505 (35.3)	407 (9.5)	175 (4.1)

Conclusion:

For this CGM, calibration need not occur only when glucose is stable.

Dried Blood Spot Study Shows Improvement of Cardiometabolic Risk with Higher Testosterone Levels in Men

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Purpose:

“Cardiometabolic risk” defines a number of conditions that contribute significantly to the development of cardiovascular disease and type 2 diabetes. An inverse relationship has been observed between testosterone levels and some known cardiometabolic risk factors in men, including visceral adiposity, insulin resistance, and blood levels of triglycerides, C-reactive protein (CRP), and fasting insulin. One-third of men with type 2 diabetes have been found to be testosterone deficient. Studies of testosterone replacement therapy have shown improvement in some of these indicators of developing cardiometabolic risk. This study investigated the relationship between testosterone levels and markers of cardiometabolic risk using dried blood spot analysis.

Method:

A group of 124 male patient samples from the ZRT database was categorized according to testosterone levels in the following tertiles: low (<300 ng/dl, $n = 41$), normal (300–600 ng/dl, $n = 57$), and high (>800 ng/dl, $n = 26$). Mean age (\pm SD) was 50.8 (± 12.8). Insulin, hemoglobin A1c, triglycerides, and high sensitivity CRP (hs-CRP) were measured using blood spot assays, which were developed in house and showed good correlations with serum/plasma levels.

Results:

Insulin (4.7 μ IU/ml) and hs-CRP (1.83 mg/liter) were significantly lower in the highest tertile of testosterone levels (> 800 ng/dl) when compared with insulin (6.3 μ IU/ml) and hs-CRP (3.46 mg/liter) concentrations in the lowest tertile of testosterone levels (< 300 ng/dl). No significant difference was observed in HbA1c and triglyceride levels between tertiles.

Conclusion:

We found a higher testosterone level in men to be associated with lower CRP and insulin concentrations, and they may therefore have a lower risk of developing metabolic syndrome and/or atherosclerotic cardiovascular events. The role of testosterone in reducing cardiometabolic risk requires further study.

Technology-Assisted Physical Activity Promotion: Online Accelerometry Data for Research and Clinical Care

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Objective/Introduction:

Physical activity is important for any diabetes regimen. Patients need easily accessible and timely feedback on its duration and intensity to adjust treatment based on real-time information and to understand the complex interrelationships among physical activity, food, insulin, and blood glucose.

Method:

We report a new way to understand and display physical activity information via a Web-based platform using a validated and research-quality accelerometer. The Lifecorder Plus™ (Suzuken, Japan) is a piezoelectric accelerometer highly accurate even when used by sedentary, elderly, or overweight individuals. Every 4 seconds it measures physical activity at nine levels of intensity. It reports the patient's minutes of vigorous activity and calculates daily calories burned. It stores data for 6 months and can hide or display the information.

Result:

The platform supports researchers by allowing patients to remotely upload accelerometer data to a secure Web site. The researcher downloads data in a ready-to-be-analyzed format. New subjects use an accelerometer without a need to eliminate prior patient's data, facilitating multiple use of the same device. Patients use information displayed on the device and the Web site to get detailed information about their physical activity. Information displayed includes graphing of the activity duration and intensity over a daily, weekly, or monthly period. Examples of interventions include monitoring compliance with a therapeutic boot treating foot ulcers and physical activity promotion for patients with type 2 diabetes.

Conclusion/Discussion:

Subsequent versions will integrate glucose values, insulin dosages, and food consumption to give a rich array of critical data. This allows intervention designers to display detailed activity data on a daily grid plotted against continuous glucose and insulin therapy.

Evaluation of a New Continuous Glucose Monitor Calibration Algorithm

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Objective:

This study evaluated the performance of two glucose sensor calibration algorithms that measure interstitial fluid glucose with the use of Medtronic MiniMed's Paradigm® REAL-Time continuous glucose monitor (CGM) and insulin pump.

Method:

Sensor and blood glucose measurements were obtained during the course of a multicenter study evaluating the efficacy of a sensor-augmented pump system in an ambulatory outpatient setting. A total of 138 subjects (98 adults and 40 adolescents) were monitored over a 26-week period of which 55% of the adult population were female and 40% of the adolescent population were male. The mean age for adult and adolescent populations was 40 ± 11 and 14 ± 1.5 years, respectively. Subjects in the study group were required to perform at least four finger stick measurements daily, uploading sensor and blood glucose samples with the Paradigm Link® glucose meter for the duration of the study. A retrospective analysis of the dataset was performed for each glucose calibration algorithm.

Result:

A total of $N = 7193$ sensor downloads for 3 days of use and 90,472 temporally and nonuniformly paired data points (sensor and meter values) were evaluated. Performance metrics were calculated based on International Standards Organization for glucose monitors. A total of 5841 and 15851 hypo- and hyperglycemic events were determined. The new calibration algorithm decreased the overall mean absolute relative deviation by greater than 0.25 to 15.89%, with hypoglycemia sensitivity increased by 50 to 82.3% (91.9% with predictive alerts); however, hyperglycemia sensitivity was decreased only marginally by less than 5 to 82.3%.

Conclusion:

The new calibration algorithm is significantly more robust in detecting hypoglycemia with the error in the 40- to 120-mg/dl range significantly improved while retaining accuracy at high glucose levels.

Enteral Administration of Exenatide-4; Proof of Concept Pharmacodynamic Study in Dogs

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Objective:

Oramed's drug delivery technology is being advanced for the enteral delivery of polypeptides and proteins. We demonstrated previously that Oramed's technology enables the delivery of insulin when administered orally. Here we describe the results of an exploratory study in dogs of enteral delivery of a glucagon-like peptide-1 (GLP-1) analog—exenatide-4, an incretin mimetic with antihyperglycemic actions.

Method:

Four beagle dogs (average weight 10 kg) were used in these experiments. All four dogs had an indwelling cannula residing in the jejunum. The absorption of exenatide was assessed by pharmacodynamic parameters measuring the effect on glucose excursion following oral glucose administration. Control experiments consisted of oral dosing without administration of exenatide-4. The exenatide was administered 30 minutes prior to oral dosing.

Results:

Direct jejunal instillation of the GLP-1 analog significantly curbed postglucose loading (Figure 1).

Discussion:

Exenatide-4 is currently only available as an injectable dosage form. A novel technology demonstrated the feasibility of administering the drug enterally. The enteral route of administration may convey physiological advantages for exenatide and other incretins and incretin mimetics as it replicates the physiological route of incretin secretion from the gut into the portohepatic system.

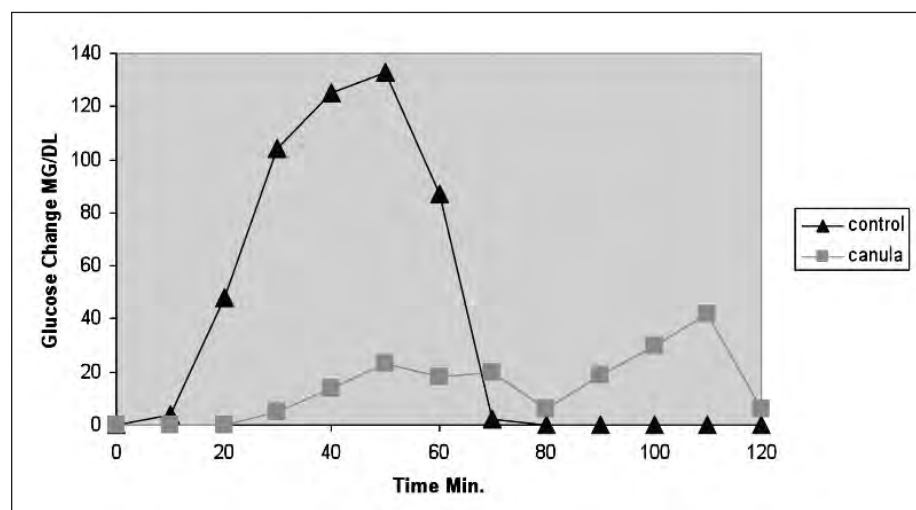


Figure 1. Glucose excursion in control (glucose load no exenatide) vs jejunal exenatide-4 administration 30 minutes after glucose load.

Fuzzy Logic Controller for Insulin Dosing

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Objective:

The objective of this study was testing the feasibility of the fuzzy logic controller (FLC) for an artificial pancreas.

Method:

The FLC uses a dosing rules matrix that visually portrays insulin dosing covering all blood glucose situations. The matrix allows dosing to be customized as a function of any combination of blood glucose (BG), BG rate, and BG acceleration without the mathematical constraints required by other methods. This method provides an intuitive mechanism for significant physician input, allowing for individual customization. The FLC is well suited for control in a nonlinear or poorly behaved system, such as the human glucoregulatory system.

Result:

Four patients were studied in fasting, small meal (SM) [30 grams carbohydrate (CHO)] and large meal (LM) (80 grams CHO) regimens using a FLC with 15-minute BG testing. Comparisons between the patient's treatment for the LM and the FL controller were made. The FLC reduced BG area under the curve (AUC) for all regimens compared to manual control. BG AUC was reduced 28% from 20,647 to 14,835 mg/dl*min over the 180-minute period following a LM. Good control was achieved for SM (BG AUC = 6668 mg/dl*min) and fasting regimens (BG AUC = 3491 mg/dl*min) with low BG requiring treatment in 2 of 12 trials.

Conclusion:

Safe BG levels in fasting and SM studies were maintained by the controller. Better control after a LM may be achieved by more frequent BG sampling (every 5minutes), potential faster-acting, shorter duration insulins, and more customization to individuals. The FLC warrants more investigation as a potential artificial pancreas technology solution.

Self-Monitoring of Blood Glucose Practices in a Suburban Population of Patients with Type 2 Diabetes Mellitus

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Introduction:

Self-monitoring of blood glucose (SMBG) is a tool for assisting with self-management. Patients with type 2 diabetes mellitus (T2DM) were surveyed about their use of SMBG.

Methods:

Surveys were distributed at a free suburban community symposium in California in May 2008 for patients with diabetes and their families. Surveys were completed anonymously. Ninety-five surveys were returned from T2DM patients and were tabulated. Five surveys from patients with type 1 diabetes mellitus and six surveys from patients whose type of diabetes was not specified were not tabulated.

Results:

Duration of diabetes—0–10 (years): 64; 11–20: 21; 21–30: 7; 31–40: 1; 41–50: 1. Medication used—insulin only: 7; insulin plus pills: 19; pills only: 63; no medications: 8. SMBG with a meter—yes: 89; no: 7. Frequency of SMBG tests—more than four/day: 1; four/day: 10; 1–3/day: 52; 4–8/week: 5; 1–3/week: 18; less than 1/week: 5. Response to high or low blood glucose (BG)—adjust food intake: 73; adjust exercise: 27; decrease stress exposure: 15; adjust medication dosage: 15. Received instructions on reacting to high/low BGs?—yes: 70; no: 25. SMBG affects mood?—yes, feels good to do the right thing: 29; yes, creates depression: 20; no effect on mood: 46. Do you rely on SMBG readings or how you feel?—SMBG: 63; feel: 44. Percent of SMBG recorded into a logbook—0–10: 25; 11–20: 0; 21–30: 3; 31–40: 0; 41–50: 3; 51–60: 0; 61–70: 3; 71–80: 2; 81–90: 1; 91–100: 42. Can you identify a situation that probably produces an incorrect reading?—yes: 21; no: 59.

Conclusions:

Most of these T2DM patients self-monitored, interpreted, recorded, and utilized their blood glucose readings to adjust diet, exercise, stress exposure, and medication dosages.

A Personal Digital Assistant-Based Program for Adult Inpatient Management of Diabetes and Hyperglycemia

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Objective:

Hyperglycemia in hospitalized patients is associated with an increased risk for complications, prolonged length of stay, and mortality. Despite published recommendations for inpatient glycemic control, hyperglycemia is a common event. Insufficient knowledge and low confidence levels on the part of physicians and nurses regarding their ability to safely achieve desired glycemic goals may be contributing factors. The goal of this project was to improve inpatient glycemic management by enabling immediate access to information to guide rational insulin therapy.

Methods:

A program for personal digital assistants (PDA) entitled “Guidelines for Adult Inpatient Management of Diabetes and Hyperglycemia” was developed and made available to clinicians. This program can be downloaded to either a Palm or a Pocket PC device.

Result:

The program guides clinicians involved in the care of patients with diabetes or hyperglycemia to information related to inpatient glycemic targets; initiation and adjustment of subcutaneous (SQ) insulin regimens; and descriptions of the available basal, nutritional, and correctional insulins. This program also includes information related to the use of oral diabetes medications, use of insulin pump therapy in the hospital, treatment of hypoglycemia and diabetic ketoacidosis, and transitioning patients from intravenous to SQ insulin, as well as to modifications of therapy for patients receiving high-dose steroids or enteral nutrition.

Conclusion:

By enabling immediate access to information that guides glycemic management of inpatients with diabetes, this PDA program has the potential to improve clinician knowledge and confidence for managing this group of patients. This can result in an increase in the percentage of patients who achieve desired levels of glucose control during periods of hospitalization, thus decreasing risk for complications and length of stay.

Standardized Evaluation of Nine Instruments for Self-Monitoring of Blood Glucose

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Background:

Instruments for self-monitoring of blood glucose (SMBG) should undergo a standardized evaluation including a user test before being marketed. In this study, results from standardized evaluations of nine different SMBG instruments are presented, and the standardized evaluation is discussed.

Methods:

Approximately 80 diabetes patients using three lots of test strips participated in each evaluation. Half of the patients were educated in how to use the meter, and the evaluations were carried out both by medical laboratory technologists (MLT) and by patients. Questionnaires were used to assess the user manual and the user-friendliness of the instrument.

Results:

The imprecision obtained by the patients [coefficient of variations (CVs) of 3.2–8.1%] was generally higher compared to the imprecision by the MLT (CVs of 2.3–5.9%). Three of the nine instruments did not achieve the quality goal based on the recommendation in International Standards Organization 15197 in the hands of the diabetes patients. The bias from the comparison method ranged from –10.4 to +3.2%. There were significant lot-to-lot variations and hematocrit effects for some of the instruments. The temperature difference between the instruments and the test strip deteriorated the quality in one instrument. The user-friendliness was, in general, acceptable.

Conclusions:

The quality of instruments for SMBG seems to have improved, although there are still analytical problems. A standardized evaluation protocol is necessary and should be revised regularly, taking into account the development of new technology and the needs of the patients.

An Automated Blood Glucose Monitoring System for Critical Care

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Objective:

An automated blood glucose monitoring is well recognized to be a valuable tool for achieving tight glycemic control in critical care settings. The aim of the current pilot study has been to clinically evaluate the performance of a recently developed automated blood glucose monitoring system (AGMS) as a precursor to expanded clinical testing and regulatory filing.

Method:

In the past, Cascade Metrix, Inc. had developed a proprietary vascular blood sampling technology platform that was capable of being integrated with a variety of commercially available blood glucose sensors. In the current phase, Cascade has completed the prototype development and evaluation of a compact fully automated blood glucose monitoring system using a test strip-based glucose meter. In this pilot human study, a peripheral intravenous catheter was inserted into the subject's forearm and then connected to the AGMS. Fully automated glucose measurements in venous blood were performed at settings defined through a touch screen interface.

Result:

The total blood consumed for each measurement was negligible, with the bulk being reinfused safely through a patient-dedicated sterilized fluidic assembly. No manual intervention by the nursing staff was necessary during the test period, and the blood sampling system was independent of the subject's arm movements. No problems were seen with thrombus formation. Given that the system used a Food and Drug Administration-approved glucose meter, there was no inaccuracy resulting from the automated blood sampling methodology.

Conclusion:

Cascade's AGMS is setting the stage for an accelerated launch of a fully automated venous blood glucose monitoring system. The system offers significant benefits in terms of ease of use and overall performance. Preparations for carrying out expanded clinical testing in intensive care units at Clarian Methodist Hospital are currently underway.

Structure, Functions and Operation of the TeleDiaFoS Home Telecare System for Patients with Diabetic Foot Syndrome

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Introduction:

Diabetic foot syndrome (DFS) is a leading cause of the non-traumatic lower limb amputations in the developed countries. At first, telemedicine applications in diabetes were related to home telemonitoring of SMBG results and support of the insulin therapy. Recently, telemedicine usage has spread to screening, monitoring, and treatment of the late complications of diabetes such as diabetic retinopathy, cardiovascular disorders and DFS. In the last few years, several video consultation services for DFS patients have been reported which are based on the use of modern mobile phones equipped with digital cameras.

Methods:

The TeleDiaFoS system aimed at monitoring of DFS treatment was designed and developed in IBBE PAS. The TeleDiaFoS consists of: the Central Clinical Server (CCS), the Diabetologist's Workstation, the Podiatrist's Workstation, and a set of the Patient's Modules (PM). PM is a homecare device that is operated by the patient with a simple remote control. Using PM it is possible to scan an image of the sole of the foot and download blood glucose readings and blood pressure values from the meters. The PM can access the Central Clinical Server using a wireless Internet connection to send these data to be evaluated by the physician.

Results and Conclusion:

Validation of the clinical efficacy of DFS treatment supported by the TeleDiaFoS system is currently in progress. The study is organized as a randomized 90-day trial with the study and the control groups each consisting of 10 patients with type 2 diabetes. The results that have been obtained so far indicate that that, from a technical point of view, there are no problems with the system and the quality of the scanned images is superior in comparison to digital photographs.

Evaluation of FreeStyle Navigator in Children and Adolescents with Type 1 Diabetes

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Introduction:

The FreeStyle Navigator CGM (Abbott Diabetes Care, Alameda, CA) provides continuous subcutaneous glucose readings in real time. The present study evaluated accuracy of the Navigator in children and adolescents with type 1 diabetes (T1D) in overnight investigations at a clinical facility.

Methods:

Glucose was measured with the FreeStyle Navigator in six subjects with T1D (male/female 1/5, age 15.1 ± 2.2 years, body mass index 22.8 ± 4.5 kg/m², duration of diabetes 6.6 ± 4.4 years, hemoglobin A1c 9.1 ± 2.4 %, insulin dose 0.92 ± 0.16 U/day/kg, mean \pm SD) on two occasions over 15 hours from 17:00 to 8:00 the following day with dinner at 18:00. The glucose sensor was placed on either the abdomen or the arm and calibrated with capillary blood. Venous whole blood glucose was measured every 15 minutes (YSI 2300 STAT plus analyzer) with a 3-hour delay and corrected to provide reference plasma glucose.

Results:

A total of 697 sensor-reference pairs were analyzed. Error grid analysis (EGA) showed that 87.7% ($n = 611$) and 12.2% ($n = 85$) pairs fell in regions A and B, respectively, and 0.1% ($n = 1$) in region D. Median bias was -0.16 mmol/liter, median relative absolute difference was 8.1%, and 87.7 % of the pairs met the International Standards Organization (ISO) criterion. The ISO criterion was highest during periods of hypoglycemia (100%, <3.89 mmol/liter, $n = 6$) and normoglycemia (92.6%, >3.89 mmol/liter and < 10 mmol/liter, $n = 449$) and lowest during hyperglycemia (78.1%, >10 mmol/liter, $n = 242$).

Conclusions:

Results show high accuracy of the FreeStyle Navigator. As assessed by EGA, the majority of glucose readings led to the correct treatment decisions in children and adolescents with T1D.

Neonatal Glycemic Control: Model Validation and *in Silico* Virtual Patient Trials

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Introduction:

Premature, low-birth-weight infants in the neonatal intensive care unit can lose blood glucose homeostasis due to the immaturity of endogenous regulatory systems and the stress of their condition. Typical treatment relies on glucose restriction before insulin administration due to fear of hypoglycemia. A model of the fundamental glucose regulatory dynamics could enable optimized treatment approaches.

Methods:

An adult critical care metabolic system model is adapted to the unique physiological case of the neonate. Integral-based methods identify time-varying insulin sensitivity and noninsulin-mediated glucose uptake profiles for virtual patient trials. Retrospective clinical for $N = 25$ cases contained 1079 glucose measurements over 3589 total patient hours plus all insulin and nutritional infusion data. Birth weights were all less than 1.5 kg, and gestational age was 23–28.6 weeks. The model is validated for predictions of 1–4 hours forward. Virtual patients are used to develop model-based glycemic control protocols.

Results:

The identified model had a median absolute percentage error of 2.50% [*interquartile range* (IQR): 1.0–5.3%]. Median absolute prediction errors at 1-, 2-, and 4-hour intervals were 5.8% (IQR: 2.6–11.2%), 9.9% (IQR: 4.5–19.3%), and 14.5% (IQR: 6.3–27.2%), respectively. Virtual trial results targeting a 72- to 125-mg/dl range yielded a median blood glucose level of 104 mg/dl (IQR: 90–117). Average insulin usage was 0.069 U/kg/h. These results were compared to clinical values of 144 mg/dl (IQR: 113–178) mg/dl and 0.034 U/kg/h. Average dextrose delivery was 8.9 mg/kg/min. Hypoglycemic events were minimized in virtual trials.

Conclusions:

The model accurately captures and predicts the fundamental dynamic behaviors of the neonatal metabolism well enough for effective potential clinical use in glycemic control. Model-based control can offer improved control with greater nutrition delivery to provide potentially better long-term outcomes.

An Insulin-on-Board Formulation of a Proportional-Integral-Derivative Controller for a Closed-Loop Artificial Pancreas

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Objective:

The proportional-integral-derivative (PID) algorithm is the most commonly used feedback controller in the manufacturing industry and has been used in initial human closed-loop studies. A major problem with PID algorithms is integral action, which can lead to postprandial hypoglycemia.

Method:

We combined a classical PID controller with an insulin-on-board (IOB) calculation to limit the rate of insulin delivery in real time based on residual insulin activity from previously delivered insulin. Residual insulin activity is based on a pharmacodynamic model of insulin action.

Results:

To illustrate the safety and robustness of the proposed approach, we performed *in silico* simulation studies using two different physiologically relevant models of insulin–glucose dynamics: (i) Hovorka and co-workers and (ii) Cobelli and co-workers. The following table provides illustrative results based on the Hovorka model, using a 80-kg subject with moderate insulin sensitivity (1.1 U/h daily basal insulin and 12.5:1 carbohydrate:insulin ratio) consuming three meals/day over a 3-day period. A hybrid closed-loop strategy using a meal bolus given at the onset of the meal and based on total meal carbohydrates has the lowest mean absolute deviation (MAD) with satisfactory minimum and maximum glucose values compared to PID-only strategies (glucose units are milligrams per deciliter).

Controller	MAD	Mean	Min	Max
IOB-PID (with bolus)	24.57	114.57	73.23	199.19
IOB-PID (no bolus)	42.04	136.12	75.69	257.30
PID-only (with bolus)	32.28	92.41	29.95	186.69
PID-only (no bolus)	43.47	93.66	15.50	237.25

Conclusion:

An insulin-on-board-based PID controller combines the benefits of an easy-to-implement control algorithm with a pharmacodynamic model to account for insulin action and yields better results than a classical PID controller and eliminates hypoglycemia in *in silico* studies

Comparison of Control Algorithms for a Closed-Loop Artificial Pancreas Based on *in Silico* Studies and a Patient Population Database

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Objective:

A number of control algorithms for a closed-loop artificial pancreas have been proposed, yet a detailed comparison of the performance of these algorithms on a common *in silico* subject simulator has not been presented.

Method:

Two *in silico* patient simulator models, by Hovorka and colleagues and Cobelli and colleagues, were used. The control algorithms studied include (i) proportional-integral-derivative, (ii) internal model control (IMC), and (iii) model predictive control (MPC). Each of the control algorithms is implemented in several different forms: (i) meal bolus provided by the subject, (ii) feedback only, and (iii) meal detection and meal size estimation. In addition, each algorithm is studied (i) in a classical implementation and (ii) with an insulin on-board (IOB) feature that incorporates a pharmacodynamic model of insulin action.

Results:

Algorithms that incorporate automated meal detection and meal size estimation have better performance than implementations without meal knowledge. Illustrative results for IMC and IOB-MPC are shown in the following table (based on the Hovorka model), where no meal knowledge (feedback only) is compared with meal detection and meal size estimation (results in milligrams per deciliter).

Test for 30 days	MADa	Mean	Min	Max
IOB-MPC: No meal knowledge	44.96	156.30	81.07	323.02
IOB-MPC: Meal detection/estimation	29.77	131.80	68.75	240.20
IMC: No meal knowledge	45.23	198.40	94.90	306.10
IMC: Meal detection/estimation	31.60	123.52	79.24	228.84

^aMean absolute deviation.

Conclusions:

The incorporation IOB, meal detection, and meal size estimation significantly improves the performance of all the control algorithms when there is uncertainty in meal size and when (as in the case of adolescents) meal boluses are frequently missed.

A Modified Euglycemic Clamp Reveals Dynamic Insulin Action and a Mechanism of Postprandial Insulin Sensitization

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Objective:

Few current methodologies can be utilized to study the dynamic action of insulin. The insulin tolerance test (ITT) can be used, however, with major restrictions (number of tests/day, hypoglycemia elicits hormonal counterregulation). A modified hyperinsulinemic euglycemic clamp, the rapid insulin sensitivity test (RIST), was developed to mirror the ITT, but eliminate the related limitations.

Methodology:

The RIST utilizes a vascular sampling shunt, a physiological bolus dose of insulin, and rapid, small volume, whole blood glucose analysis. Multiple RISTs are performed on an animal on the same day. The RIST can be used in both the fasted and the fed state, with the difference indicative of meal-induced insulin sensitization (MIS). The RIST was utilized to elucidate the mechanism of postprandial, hepatic-mediated insulin sensitization. Disruption of this mechanism should inhibit the MIS process.

Results:

RIST correlates to the ivITT $r^2 = 0.84$ and the ipITT $r^2 = 0.87$. Multiple RISTs (4) can be performed in a single day (coefficient of variation = 13%). A multistep postprandial insulin sensitization process, involving hepatic glutathione, hepatic parasympathetic nerves, acetylcholine-activated muscarinic receptors, nitric oxide, and guanylyl cyclase, was revealed. Disruption of any step resulted in an approximate 50% reduction in insulin sensitivity with loss of MIS.

Conclusions:

The RIST, a validated methodology, allows paired experimental protocols via multiple tests per day. The RIST has been utilized in multiple species, including human. The RIST monitors dynamic insulin action and demonstrates that the mechanism of MIS is reliant on a hepatic-mediated insulin sensitization process responsible for 50% of whole body glucose uptake in the fed state. The RIST can demonstrate mechanistic disruption by physiological, pharmacological, and pathological means. A real-time data acquisition RIST methodology is displayed.

Precision and Accuracy of an Improved Version of the Point-of-Care A1cNow+ Device

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Objective:

Point-of-care (POC) hemoglobin A1c (HbA1c) testing can improve diabetes management. An easier-to-use model of the A1cNow+ POC device (Bayer Healthcare, USA) has been released. It is National *Glycohemoglobin* Standardization Program (NGSP) certified for the measurement of HbA1c levels and is *Clinical Laboratory Improvement Amendments* waived for home use. This study assessed the precision and accuracy of the new A1cNow+ device in comparison with another POC HbA1c testing device (DCA 2000, Siemens, Germany) and a *high-performance liquid chromatography* (HPLC) reference laboratory method.

Method:

Lithium–heparin full blood samples from 120 people with diabetes (HbA1c range 5–11%) were divided into aliquots for immediate precision and accuracy testing. Precision was assessed by calculating the coefficient of variation (CV) of repeat measurements ($n = 20$) of four blood samples: two at normal (5.5% and 5.1%) and two at high (11.0 and 9.6%) HbA1c levels. Accuracy was assessed using correlation analysis to compare the HbA1c results of multiple blood samples over a wide HbA1c range obtained with the three assays systems.

Results:

CVs for the normal HbA1c level were 3.6 and 2.75% for the 5.5 and 5.1% HbA1c samples, respectively—inside the NGSP guidelines (<5%). A slightly high CV result (7.2%) at the HbA1c 11% level may be an artifact as the CV result for the HbA1c 9.6% sample was 3.07%, similar to those at normal HbA1c levels. The DCA 2000 and HPLC reference system were within NGSP guidelines at each HbA1c level tested. In accuracy testing, regression coefficients of 0.96 and 0.98 were obtained for comparison of the A1cNow+ with the HPLC and DCA 2000 systems, respectively.

Conclusion:

The A1cNow+ device, a low-investment cost and easy-to-use system for HbA1c monitoring, shows good precision and acceptable accuracy compared with the DCA 2000 and a HPLC method.

Communication Plays a Critical Role in Web-Based Monitoring

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Objective:

The goal of this study was to assess the contribution of online communication to health outcomes of patients with diabetes.

Research Design and Methods: We recruited 109 patients with diabetes who received care at one of three American Indian health clinics to participate in Web-based diabetes monitoring using MyCareTeam. MyCareTeam provided educational modules, glucose meter uploads, and secure online messaging between patients and health care providers (HCP).

Results:

Patient log-ins and number of blood glucose (BG) measures were correlated to the (a) number of messages sent to HCP, (b) total number of messages received from HCP, and (c) number of person-centered messages received from HCP. Correlations are presented in the table.

	Messages sent	Messages received	Person-centered messages received
Log-ins within 1 month	$r = 0.248, N = 109, p < 0.002$	$r = 0.356, N = 109, p < 0.001$	$r = 0.439, N = 108, p < 0.001$
BG measures within 1 month	$r = 0.178, N = 109, p < 0.032$	$r = 0.315, N = 109, p < 0.001$	$r = 0.374, N = 108, p < 0.001$

From these correlations we see that patients who sent more messages also uploaded more BG measures, indicating that they tested their BG more frequently. Person-centered messages seem to be particularly important in motivating the patient to monitor their BG levels and use the Web-based system.

Conclusions:

Online interactions comprise an integral part of a remote monitoring system. Their positive relationship to patients' uploading of medical information implies healthy behaviors in caring for their disease and may lead to positive health outcomes. Online interactions that are personal to the patient provide additional incentive to patient involvement with the system.

Factors Associated with Health Behaviors and Health Outcomes in Patients with Type II Diabetes: Structural Equation Modeling Analyses

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Objective:

There is still controversial and inconclusive evidence regarding the clinical effectiveness of self-management education program on patients with diabetes. The purpose of this study was to analyze the factors related to health behaviors and outcomes of patients with type II diabetes mellitus (T2DM).

Methods:

A 3-year study was conducted to investigate potential improvement in health behaviors and health outcomes of patients with T2DM. By using structural equation modeling (SEM) analyses, 776 patients were enrolled in the study. Based on the PRECEDE-PROCEDE model, a questionnaire including predisposing factors, reinforcing factors, enabling factors, health behaviors, health outcome (hemoglobin A1c, triglycerides), and quality of life was used as the first step of SEM analysis.

Results:

Findings showed that the enabling factor, followed by reinforcing factors and predisposing factors, was related to health behavior. These three factors could explain the 47.4% variance of health behavior, whereas the final model showed that the structure could not fix the PRECEDE-PROCEDE model [$\chi^2/df = 21.663$, $p < 0.001$; normed fit index (NFI) = 0.488, comparative fit index (CFI) = 0.497]. We used the second step SEM to analyze the model of health behaviors and outcomes. There were marked correlations between health outcomes and the seven health-related self-care behaviors (exercise, eating, medication take, monitoring of blood glucose, problem solving, reducing risks, living with diabetes), which have been identified by the American Association of Diabetes Educator as key factors for health outcomes of T2DM. Results showed that health behaviors could predict health outcomes, with $\chi^2/df = 2.540$, $p = 0.000$; NFI = 0.949, and CFI = 0.968.

Conclusion:

Results indicate that significant associations exist between health behavior and health outcomes and among enabling, reinforcing, predisposing factors, and health behavior. However, we found no unique model that could fully predict the health outcome of patients with T2DM.

Long-Term Results of a Subcutaneous Glucose Sensor in Animals

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Objective:

Our ultimate goal is to develop a glucose sensor that can function effectively as a subcutaneous implant for one or more years. The sensor is based on a membrane containing immobilized glucose oxidase and catalase, coupled to an electrochemical oxygen sensor and a similar reference oxygen electrode without enzymes, with the difference signal indicating tissue glucose concentration. An array of sensor pairs is mounted on the face of a hermetically sealed, disc-shaped implant that contains battery-driven potentiostats and a radio frequency telemetry transmitter.

Method:

Devices were implanted subcutaneously in nondiabetic pigs and operated for periods of 2 to 12 months as determined by experiment protocol. Telemetry signals were broadcast and received every 10 seconds to 20 minutes and regular intravenous glucose tolerance tests were performed. Devices were explanted at varying time intervals, tested extensively *in vitro*, and showed insignificant glucose and oxygen sensitivity changes.

Result:

In vivo oxygen sensor signals decayed exponentially by 50 to 95% during the first few weeks after implantation and then stabilized with little further change in sensitivity. After the first 2 weeks, the glucose-dependent difference signal retained near-constant sensitivity to glucose and devices demonstrated periods of extended stable operation where small adjustments in calibration were required only every 3 to 5 weeks. The sensors showed response lags to blood glucose challenges that averaged 8 minutes and remained invariant over the implant period. Histologic examination of tissues at explant showed continuous capillary distribution near the implant interface, a mild inflammation response, and mild dispersed infiltration of white cells.

Conclusion:

With further development, we expect that this system will offer unique advantages as a continuous glucose monitor for the care and treatment of diabetes.

Utility of Continuous Glucose Monitoring Alerts: Time to Detection of Low Glucose

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Objective:

The availability of low glucose alerts helps patients with diabetes who use CGM reduce the risk of hypoglycemia. In addition to accuracy, a key performance metric of these alerts is “time to detection,” the time at which alert occurs vs onset time of a low glucose event. This time-to-detection result is presented, based on clinical trial data of the DexCom Seven.

Method:

Analysis was performed on a previously reported data set of 117 adult subjects with insulin-dependent diabetes (75% type 1) across eight U.S. centers. Each subject wore the continuous glucose monitor (CGM) for 7 days with an 8- to 10-hour in-clinic tracking study on day 1, 4, or 7. Blood glucose was measured with a Yellow Springs Instrument (YSI) every 15–20 minutes. Alert performance was analyzed at a low glucose threshold of 70 mg/dl. The onset of an event was defined as at least one YSI value ≤ 64 mg/dl or two consecutive YSI values ≤ 70 mg/dl (per Clinical and Laboratory Standards Institute guideline). For each event, if at least one CGM value ≤ 70 mg/dl was found in a time window of ± 30 minutes from event onset, the event was detected. If detected, time to detection was calculated as [time of CGM alert] – [time of event onset].

Result:

Of 66 low glucose events, 80% were detected by CGM. On average, the CGM alert preceded the event onset by 10 to 11 minutes. Median [25th, 75th percentile] time to detection was -11 [-21 , -3] minutes. Of the 20% of events not detected, the minimum CGM reading in the ± 30 -minute window was 77 [73, 88] mg/dl.

Conclusion:

CGM low glucose alerts are able to detect the onset of a low glucose event and provide time for patients to act and avoid hypoglycemia.

Proposed Closed-Loop Control Using Fuzzy Logic Controller and Adaptation

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Objective:

The objective of this study was to consider the feasibility of adaptation (learning) of a fuzzy logic controller (FLC).

Method:

FLC uses a dosing rules matrix that visually portrays insulin dosing covering all blood glucose situations. The matrix allows dosing to be customized as a function of any combination of blood glucose (BG), BG rate, and BG acceleration without the mathematical constraints required by other methods. The matrix cells are grouped into one of five groups, rising BG above desired range (DR), flat BG above DR, falling BG above DR, minimal change in BG in DR, and BG below DR. This method provides a mechanism for significant physician input and allows customization for individuals. Fuzzy logic (FL) is very well suited for control in a nonlinear or poorly behaved system, such as the human glucoregulatory system.

Result:

A unique method for adapting a FLC has been developed. The FL dosing matrix allows modification of specific cells within a group of cells if the patient's BG does not meet the desired response outcome. The degree of modification can vary for each group and can be modified up or down repeatedly without affecting the dosing in other groups of the matrix having different traits. To ensure overall dosing coherency, minor adjustments in adjacent cells can also be made, as they may have traits similar to cells identified for modification. The aggressiveness of the modifications can be tailored to the individual, degree of modification (how much), and frequency (how fast).

Conclusion:

The use of FLC may facilitate targeted adjustments without the mathematical constraints imposed by other control methods. This ease of adjustment makes possible the adaptation (learning) of the controller to a subject's changing response to insulin.

Assessment of Glycemic Variability in Continuous Subcutaneous Insulin Infusion Therapy in Type 1 Diabetes Related to Anthropometry and Complication Status

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Objective:

The objective of this study was to assess glycemic variability in type 1 diabetes subjects treated with continuous subcutaneous insulin infusion (CSII) and multiple dose insulin (MDI) regimes.

Method:

Thirty matched subjects with type 1 diabetes on MDI ($n = 16$) or CSII ($n = 14$) were recruited. Following baseline anthropometry and biochemical assessment, subjects had 48 hours of continuous glucose monitoring. Measures of glycemic variability, including standard deviation (SD), mean amplitude of glycemic excursion (MAGE), M value, J index, and mean of daily differences (MODD), were calculated.

Results:

Subjects on CSII had significantly lower mean blood glucose (MBG) (10.2 vs 8.7 mmol/liter), and hemoglobin A1c (HbA1c) (8.8% vs 7.7%) than subjects on MDI. Glycemic variability was significantly lower in the CSII group than in the MDI group, as measured by SD ($p < 0.05$), MAGE ($p < 0.01$), and J index ($p < 0.05$), MODD ($p < 0.05$), but not significantly lower using the M value ($p = 0.0507$). In all subjects, the M value and MAGE were positively correlated with HbA1c. The M value correlated positively with the urine microalbumin:creatinine ratio and correlated negatively with the estimated glomerular filtration rate in all subjects. Glycemic variability and MBG were not significantly different between males and females. No significant correlation was found between glycemic variability and age, body mass index (BMI), duration of diabetes, or retinopathy stage.

Conclusion:

Type 1 diabetic subjects on CSII therapy have a lower HbA1c, MBG, and less glycemic variability than those on MDI therapy. Glycemic variability was found to be correlated positively with HbA1c. An association between glycemic variability and markers of diabetic nephropathy was observed. Glycemic variability was not found to be related to sex, age, BMI, duration of diabetes, or retinopathy stage.

Exposure to Electromagnetic Field of Mobile Phone Can Cause Hyperglycemia

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Objectives:

Mobile phones are low power radio devices that transmit and receive radio frequency radiation at 900–1800 MHz. The widespread use of mobile phones has been going sky-high over the past decade and now its use is an essential part of business, commerce, and society. It has been reported that the number of mobile phone subscribers worldwide has surpassed two billion milestones, which means that every third person on the planet uses a mobile phone. The extensive use of mobile phones has been accompanied by public debate about possible adverse effects on human health. Therefore, the aim of this study was to study the effect of mobile phone radiation and their duration of exposure on the serum fasting blood glucose level in albino rats.

Methods:

In this study, 40 male albino Wistar rats were assigned into five groups containing 8 rats each. The first group was the control, the second group received a 15-minute dose, the third group received a 30-minute dose, the fourth group received a 45-minute dose, and the fifth group received a 60-minute daily dose of mobile phone radiation for a period of 3 months. Blood glucose was determined by an enzyme-linked immunosorbent assay.

Results:

Albino rats, with mobile phone radiation longer than 30 minutes, for the period of 3 months, showed a significant increase in the serum fasting blood glucose level relative to their control group.

Conclusion:

Fasting blood glucose in albino rats was increased, and stratification of results showed a dose effect of duration of exposure of mobile phone radiation on fasting blood glucose. It is suggested that long term and/or excessive use of mobile phones should be avoided by health promotion activities such as group discussions, public presentations, and through electronic and print media sources.

Utilizing Keypad Response Technology to Optimize Diabetes Group Education

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Objective:

The objective of this session is to demonstrate the benefits of utilizing key pad technology in group diabetes education. The exploding epidemic of individuals with diagnosed diabetes presents an extreme challenge of how we empower patients to manage their diabetes effectively. An interactive response system can be utilized to evaluate the collective understanding of an entire class at the point of instruction or to later evaluate individual comprehension. Confidence and conviction can also be evaluated (essential ingredients needed to manage diabetes effectively).

Method:

The method of implementing the interactive keypad response system is facilitated through the use of software integrates with Power Point to create an interactive presentation. Each individual in the class is given a response card keypad the size of a credit card. The class size is approximately 15 to 20 people. A question is posted on the screen. Individuals select answers, and the receiver collects the responses, which are then displayed on the screen. To date, approximately 1100 patients have participated in intensive group education classes. Comprehension scores related to real-life case scenario questions are above 80%. The participants rated their confidence as follows: 42% of participants rated their confidence as “very confident” at the beginning of class and 8% rated their confidence as “not confident at all.” At the end of class, the “very confident” level increased to 57% and the “not confident at all” level decreased to 3%.

Conclusion:

Keypad technology is an effective way to empower patients to manage their diabetes. Utilization of keypad technology gives each patient a voice, increases confidence, and provides immediate feedback in a fun nonthreatening game-like atmosphere.

Long-Term Insulin Delivery to the Retina from Subconjunctivally Implantable Hydrogels: A Potential Adjunctive Treatment for Diabetic Retinopathy

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Objective:

The objective of this study was to develop novel subconjunctivally implantable hydrogels for delivering low doses of insulin to maintain retinal cell viability in diabetic rats.

Method:

Novel hydrogels consisting of thermoresponsive and hydrolytically degradable properties were formulated in dimethyl formamide medium. Fluorescein isothiocyanate (FITC)-labeled insulin or Humalog was loaded during the process of hydrogel synthesis. FITC-labeled insulin from the hydrogels was released in phosphate-buffered saline at 37°C and was monitored by measuring fluorescence intensity. Hydrogels loaded with FITC-labeled insulin were implanted subconjunctivally in rats. Confocal microscopy was used to detect the presence of FITC-labeled insulin in the retina. In order to reconfirm availability of the released insulin from hydrogels, Humalog-specific radioimmunoassay (RIA) was used to detect the Humalog in the retina.

Result:

The designed novel hydrogels produced compact hydrogels with low water content and released FITC-labeled insulin for more than 5 months in phosphate-buffered saline at 37°C. Confocal microscopy confirmed the presence of FITC-labeled insulin after 1 day, 1 week, and 1 month of subconjunctival implantation. RIA also confirmed the presence of Humalog in the retina 1 day after subconjunctival implantation.

Conclusion:

This approach has the potential to deliver low-dose insulin delivery to prevent or treat diabetic retinopathy.

Degradable Nanogels for Controlled Drug Delivery across Ocular Biological Barriers

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Objective:

Many ocular therapeutics lack efficacy because of less efficient delivery due to ocular biological barriers. The present study aims at developing degradable nanogels with enhanced permeability for controlled release of therapeutics to the back of the eye.

Method:

Degradable nanogels, consisting of N-isopropylacrylamide and 2-hydroxyl methacrylate-lactide-dextran macromer, were synthesized in aqueous medium using ultraviolet photopolymerization under stirring. The size and morphology of the nanogels were studied by dynamic light scattering (DLS) and atomic force microscopy (AFM). Fluorescein isothiocyanate (FITC)-labeled insulin was loaded during the synthesis process and released from a 2-mg/ml solution in phosphate-buffered saline (PBS, pH 7.4) at 37°C. Cytotoxicity of the nanogels to R28 and ARPE-19 retinal cells and human brain microvessel endothelial cells (HBMVECs) was studied by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. Permeability of the 100-µg/ml nanogels across the ARPE-19 and HBMVE monolayers was measured and calculated. DTAF-labeled nanogels were injected intravitreally and intravenously into Sprague–Dawley rats.

Result:

DLS and AFM data revealed that the size of the nanogels was around 70–90 nm. Nanogels released FITC-labeled insulin for 2 days in PBS at 37°C. Up to a 1-mg/ml concentration of nanogels did not show any cytotoxicity to the R28 and ARPE-19 cells for at least 1 week. The nanogels were about 10- and 5-fold more permeable than 4 kDa dextran across the ARPE-19 and the HBMVEC monolayers, respectively. Biodistribution of the nanogels to the retina and other ocular tissues and different organs is being assessed.

Conclusion:

The developed degradable nanogels are nontoxic and have the potential to cross the ocular biological barrier and deliver drugs to the retina.

A Web-Based Information System for the Advanced Management of Type 1 Diabetes Patients

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Objective:

A Web-based system has been designed and developed for better glycemic control and improvement of quality of life for type 1 diabetes mellitus (T1DM) patients. The system accelerates the communication between patients and physicians, permitting treatment optimization.

Method:

T1DM patient's data related to glucose levels, insulin intake, diet, other diseases, and physical activity are acquired and transmitted through the Internet to the medical center where the application is installed. The system consists mainly of the following modules: (1) a database module where information related to patient's data, examination results, and comments are stored; (2) a data analysis module, which provides a series of interpretation and analysis tools (based on computational intelligence techniques), in order to detect clinically important patterns and to predict medical events risk factors related to the long-term complications of T1DM; and (3) an insulin advisory (IA) module designed for insulin treatment optimization. The system is available to both the physician via the medical center local area network (wired and wireless) through personal computers and laptops and the patient through the Internet, with appropriate security access rights. In emergency situations the clinician has the ability to connect, through the Internet or cellular network, in order to receive patient's most up-to-day data.

Result:

T1DM patients can access their health status anytime from anywhere, while the smart graph visualization and computational intelligence-based tools allow health care professionals to evaluate a patient's clinical state quickly in either real time or retrospectively. The IA module has already been evaluated *in silico*; evaluation of the entire system is in progress.

Conclusion:

Internet technology, cellular networks, and computational intelligence provide valuable tools for the efficient management of T1DM.

Preoperative Hyperglycemia Prolongs Stay in Hospital after Major Orthopedic Surgery

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Objective:

Reducing hospital length of stay (LOS) after major orthopedic surgery has gained popularity with surgeons, hospital administrators, and third-party payers. Hyperglycemia has been reported to prolong LOS after intensive care unit admission and coronary artery bypass graft surgery. We investigated whether preoperative hyperglycemia (≥ 200 mg/dl) was associated with increased LOS after total hip and knee arthroplasty.

Methods:

After obtaining institutional review board approval, we retrospectively reviewed the medical records of patients undergoing elective total hip or total knee replacement from January 2001 to April 2006. Patients were divided into three groups based on preoperative blood glucose (BG) levels: normal < 110 mg/dl, high 110–199 mg/dl, and very high ≥ 200 mg/dl. Data are reported as geometric mean with 95% confidence interval in parentheses. Data were evaluated using robust regression and robust analysis of variance.

Results:

Data from 7282 patients were included in the study. The median LOS was 3 days (range 1–58). Patients with normal BG stayed on average 3.46 days (3.43;3.49), high BG 3.62 days (3.56;3.67), and very high BG 4.05 days (3.80;4.31). LOS was 8% (4;12; $p < 0.001$) longer in the very high group compared with the normal group. An 8% increase from the median LOS of 3 days translates into 5.8 hours. Age increased LOS by 2% (1;2; $p < 0.001$) per decade of life, body mass index > 40 kg/m² by 4% (1;6; $p = 0.002$), and duration of surgery > 137 minutes by 19% (12;20; $p < 0.001$). Patients with a history of congestive heart failure had 6% (2;10; $p = 0.004$) longer LOS on average. Diabetes increased LOS by 4% (2;5; $p < 0.001$). Females had shorter LOS than males by 4% (3, 5; $p < 0.001$) on average.

Conclusion:

Preoperative BG ≥ 200 mg/dl is associated with increased LOS after major orthopedic surgery. A prospective, randomized, controlled trial is required to determine whether the control of preoperative glucose would decrease LOS in this clinical setting.

A Novel Outcome to Monitor Dynamic Behavior of Plantar Loading: Application in Pre- and Post-Charcot Reconstruction

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Objective:

Dynamically measuring plantar pressure magnitudes during locomotion provides insight into the functional manifestations of foot disorders and yields objective treatment outcome evaluations. However, plantar pressure magnitude varies as a function of gait speed, which challenges the reliability of such measurements. Here, we make initial attempts to develop a novel outcome, which is speed independent and can reliably screen healthy dynamic plantar loading.

Methods:

A timescale normalization scheme was used to moderate the effect of gait speed across different steps' total-foot plantar pressure profiles. To examine whether this distribution was normal, a customized normal distribution curve was created for each trial utilizing the mean and standard deviation values. Then the original plantar pressure distribution was fitted to the customized normal distribution curve using a multiple linear regression approach. This technique yields a regression factor (RF), which represents the similarity of the actual pressure distribution with the normalized distribution.

Results:

In healthy subjects ($N = 8$), the RF >0.3 and was always positive. In preoperative Charcot patients ($N = 3$), the RF <0 ; however, RF was increased postsurgery ($N = 1$), indicating a transition to normal plantar distribution after Charcot reconstruction.

Conclusion:

This investigation suggests a reliable and speed-independent score to demonstrate gait improvement following foot reconstruction. Although this pilot study focused on barefoot pressure evaluation, we believe a similar pattern may be observed in shod case. Further testing involving barefoot as well as in-shoe conditions may elicit a clinical measure and may be integrated into a pervasive health care regimen involving virtual clinics and telemedicine platform. This assessment may be more capable than peak pressure analysis in discriminating pathological and healthy loading during the varied gait speeds utilized during daily activity.

A Potentially Novel Indicator to Predict the Development of Ulcer in Diabetic Patients Based on Fractality of Daily Physical Activity Fluctuation: A Proof of Concept Trial

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Objective:

The output of healthy biological systems reveals a type of complex variability associated with multiscale self-similarity defined as “fractal.” This multiscale complexity appears to degrade with aging and disease, reducing the adaptive capacity of the individual. For example, several studies demonstrated that altered short-term fractal scaling properties of heart rate indicate an increased risk for cardiac mortality, particularly sudden cardiac death in older adults. Here we make initial attempts to investigate whether fractal properties of daily physical activity may predict development of foot ulcers. This hypothesis is based on previous studies, which indicated that poorly organized activity in high-risk patients led to the development of foot ulcers.

Methods:

Daily physical activity was monitored in three healthy subjects during approximately 8 hours using an easy portable body-worn sensor technology: BioHarness™. This simple device enables measuring physiological data (e.g., skin temperature, heart rate, and respiration), as well as activity data (e.g., trunk angle, activity intensity), during a day. To evaluate long-term organization, we estimated the fractal dimension (α) using the detrended fluctuation analysis scheme.

Results:

Preliminary results showed that trunk angle fluctuation, as well as intensity of physical activity, is highly organized in healthy subjects ($\alpha \approx 1$), whereas respiration behavior and localized skin temperature fluctuation are random walk like.

Conclusions:

This preliminary investigation suggests that long-term physical activity organization can be evaluated using a simple wearable tool during the activity of daily living. Further investigations are required to validate the hypothesis and design disease management strategies for dosing physical activity. Results provide a basis to incorporate this novel technology and measurement protocol into a telemedicine health portal for patients with diabetes.

A Novel Tool to Investigate the Role of Feed-Forward Sensory Compensation in Patients Who Suffer from Diabetic Sensory Neuropathy

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Objective:

Instability in people who suffer from diabetic sensory neuropathy has been found to be associated with abnormal somatosensory feedback. However, there is still a paucity of evidence on whether and how neuropathy affects the feed-forward sensory compensatory mechanism. Here we make initial attempts to elucidate the role of feed-forward sensory compensation in postural control and how it is affected due to neuropathy.

Method:

To achieve this goal, we designed a novel biosensor system using microelectromechanical systems technology and a biomechanical model of the human body. This novel tool enables the measurement of three-dimensional movements of body segments in real time, provides visual biofeedback from body joint angles, and enables studying the postural strategy. To evaluate the role of feed-forward sensory compensation in postural control, we adopted a visuomotor transformation (VT) paradigm.

Results:

Preliminary results showed that a healthy subject can adapt quickly to a VT created by mapping the ankle joint position and visual feedback rotated by 30°. While in a patient with distorted sensory feedback, the adaptation is deeply compromised.

Conclusion:

We believe the reason of such quick adaptation to the rotated visual feedback in healthy subject is due to creation of an internal model based on error-dependent learning rules between prior motor action and desired action. However, any sensory impairment might affect the functioning of this internal model. This innovative tool might shed light on the internal architecture of the learning system and provides new opportunities to design intelligent training procedures for the rehabilitation of motor skills lost due to neuropathy. This, in turn, will improve our ability to decrease the risk of falling and to improve the quality of life in people with this devastating malady.

Rapid Prototyping of Microneedles for Transdermal Drug Delivery

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Objective:

One option for the delivery of insulin and other pharmacologic agents for the treatment of diabetes involves the use of microneedles. The use of microneedles for drug delivery was first proposed in the 1970s, and several devices have been demonstrated by researchers over the past decade. We have used two photon polymerization (2PP) to create Ormocer® microneedle arrays for transdermal drug delivery. The two photon-induced polymerization process involves both temporal and spatial overlap of photons to initiate chemical reactions between photoinitiator molecules and monomers within a transparent matrix.

Method:

Three-dimensional microneedle arrays were produced by two photon-induced polymerization of organically modified ceramic materials, 1% Irgacure® 369 photoinitiator, and fillers. Cell viability on ORMOCER® surfaces processed using 2PP was examined using human epidermal keratinocytes. The transdermal drug delivery properties of ORMOCER microneedles were examined using polyethylene glycol (PEG)-amine-coated quantum dots (QD 655) and fluorescein-conjugated biotin molecules.

Result:

The flexibility of the 2PP process allows rapid fabrication of microneedles with designs that meet clinical requirements for the delivery of insulin or other pharmacologic agents. In-plane hollow microneedle arrays and out-of-plane hollow microneedle arrays in various geometries were fabricated using 2PP. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide studies suggest that ORMOCER materials processed using two photon polymerization do not impair human epidermal keratinocyte viability rates. In addition, microneedles may be used to enable the delivery of PEG-amine-coated quantum dots and fluorescein-conjugated biotin molecules through a porcine skin model.

Conclusion:

Results suggest that hollow microneedles may be useful for delivering insulin and other pharmacologic agents that cannot be administered in oral form.

Effect of Ambient Temperature on Analytical Performance of Self-Monitoring Blood Glucose Systems

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Objective:

This study investigated whether analytical quality is influenced by moving self-monitoring blood glucose (SMBG) systems from a lower to a higher temperature or vice versa immediately before measurement (part 1) and whether analytical quality is influenced by using SMBG systems in the lower or in the upper range of the operating temperature range (part 2).

Method:

Measurements performed on SMBG systems kept 1 hour in 5°C or 1 hour in 30°C were compared with measurements performed on SMBG systems kept 1 hour in room temperature (part 1). Parallel measurements were performed in room temperature at 0, 5, 10, 15, and 30 minutes after removal of SMBG systems from 5 or 30°C, respectively. Part 2 was done in the same way, but after 1 hour, parallel measurements were performed once in 10°C and room temperature and once in 39°C and room temperature. Heparinized venous blood adjusted with glucose to 5 and 20 mmol/liter was used for all the measurements.

Results:

Five SMBG systems measured 14–25% too high results and two SMBG systems measured 16–21% too low results immediately after removal of the SMBG systems from 5 and 30°C, respectively. However, with one exception the effect was <10% after 10 minutes. Two SMBG systems measured 10% too low results in the lower range. One of these systems measured 10% too low results in the upper range also while another system measured 15% too high results.

Conclusion:

Moving SMBG systems from one temperature zone to another immediately before measurement affected five of out of eight SMBG systems. Using SMBG systems in the lower or in the upper range of the operating temperature range affected three SMBG systems.

Improving Diabetes Care and Outcome via Telemedicine: Preliminary Data from Addressing Diabetes in Tennessee Project

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Objective:

The prevalence rate of diabetes in Tennessee has increased by 64% in the last decade to 8.5%, with an estimated diabetes-related mortality rate of 40%. The rising prevalence and shortage of physicians, especially in rural areas, contribute to a poor outcome in diabetic patients. The goal of the Addressing Diabetes in Tennessee (ADT) project is to evaluate the efficacy of telemedicine-based diabetes management program in improving quality of care and outcome in rural areas

Method:

ADT is a prospective interventional study in five rural communities with high diabetes-related mortality rates. The proposal was discussed with the management and medical staff of the regional hospitals. Diabetic patients aged ≥ 18 years, with hemoglobin A1c (HbA1c) $\geq 8.0\%$, who consented to the study were recruited. ADT has three components: (1) patient education; (2) quarterly group health visits with an endocrinologist and certified diabetes educator, during which recommendations to optimize care are made; and (3) a secure, Web-based electronic health record to facilitate outcomes tracking and communication among providers. Data will be collected to assess changes in the process of diabetes care and outcomes following 6 and 12 months of intervention.

Results:

Preliminary data show that 20 patients have been enrolled, 75% of whom are females; the average age is 56.6 ± 12.4 years. The mean HbA1c level is $9.7 \pm 1.7\%$, with an average duration of diabetes of 12 ± 10 years. There was associated hypertension and dyslipidemia in 60 and 82% of patients, respectively; 55% had all three cardiovascular risk factors. All participants (100%) were satisfied with the services provided by the ADT project.

Conclusion:

A telemedicine-based diabetes management program promises to be a satisfying means of improving diabetes care and outcome in patients at high risk for cardiovascular disease.

A Benchtop Closed-Loop System Controlled by a Bio-Inspired Silicon Implementation of the Pancreatic β Cell

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Background:

The normal pancreatic β -cell membrane depolarizes in response to increasing concentrations of glucose in a bursting pattern. At <7 mM, the cell is electrically silent. The bursting pulse width increases as glucose rises >7 mM until a continuous train of bursting is seen at >25 mM. A bio-inspired silicon β cell has been developed using analogue electronics to implement the membrane depolarization of the β cell. The “silicon β cell” is an ultralow power, miniaturized (5×5 mm) device that produces a bursting output identical to that characterized in electrophysiological studies.

Objective:

The goal of this study was to demonstrate the ability of the silicon β cell to control a closed-loop system *in vitro*.

Method: A platinum disc glucose oxidase electrode is used to sense glucose concentration in a water bath. Glucose oxidase electrochemical electrodes form hydrogen peroxide, producing a concentration-dependent current. Current from the electrode is passed to the β cell, which bursts in response to changing analyte concentration and the bursting output is converted to a voltage that drives a syringe pump loaded with a 50-ml syringe containing water. Glucose is added to the water bath, increasing the β -cell burst pulse width, leading to activation of the syringe pump.

Results:

On adding glucose to the water bath the silicon β cell bursts with a pulse width proportional to concentration. Activation of the syringe driver infuses water into the water bath, returning the glucose concentration to <7 mM at which the silicon β cell is electrically silent.

Conclusion:

This is the first *in vitro* demonstration of closed-loop insulin delivery utilizing the silicon β cell, an implementation of β -cell electrophysiology in analogue electronics.

Closed-Loop Insulin Delivery Utilizing Insulin Feedback: Preliminary Clinical Results

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Objective:

We have previously described the use of insulin feedback as an additional component for a closed-loop algorithm to regulate blood glucose, basing it on the effect of insulin inhibiting insulin secretion in the β cell. We present the preliminary results of clinical testing of said algorithm.

Method:

Seven subjects with type 1 diabetes have completed the algorithm test. Prior to the algorithm testing subjects wore a continuous glucose monitoring system for 3 days. Subjects were admitted to the clinic on the evening prior to the start of closed-loop control. Control was initiated around 06:30 and lasted 30 hours. Meals were served at 7:00, 12:00, and 18:00, with a snack at 21:00. A 2-unit premeal bolus was given manually at the start of each meal.

Results:

The average (over all subjects) of the mean glucose (each subject) during closed loop was 109 ± 12 mg/dl versus 121 ± 21 mg/dl during open loop. The 25–75 percentile range was 91 ± 10 to 134 ± 11 mg/dl during closed loop versus 93 ± 19 to 163 ± 26 mg/dl during open loop. During the open-loop period the percent of sensor values in the range of 70–180 mg/dl was 69.2%, <70 mg/dl was 12.1%, and >180 mg/dl was 18.7%. During closed loop these were 86.7, 9.8, and 3.5%, respectively. There were five instances of hypoglycemia (<50 mg/dl) during closed loop for a rate of 0.58 hypoglycemic episodes per day. During the open-loop period there were 18 hypoglycemic episodes, for a rate of 0.85 episodes per day. For the sensors used in closed loop the mean/median relative absolute difference was $12.6 \pm 2.8/10.3 \pm 2.5\%$.

Conclusion:

While the study has not been completed, results obtained to date are very encouraging. A significant advantage over previous studies is that the amount of the premeal bolus is independent of the carbohydrate content of the meal.

Do Differences in Sleep Architecture Exist between Persons with Type 2 Diabetes as Compared to Nondiabetic Controls?

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Objective:

It has been shown previously that suppression of slow-wave sleep (SWS) markedly reduced insulin sensitivity and led to an impairment of glucose tolerance. We sought to investigate whether differences in sleep architecture exist between type 2 diabetic patients and nondiabetic controls referred to our sleep laboratory because of suspected sleep apnea.

Method:

A retrospective case-control study analyzing overnight polysomnographic recordings of 22 type 2 diabetic patients [4 females/18 males, aged 58.4 ± 5.3 years, body mass index (BMI) 34.9 ± 6.7 , apnea-hypopnea index (AHI) 29.2 ± 21.7 /hour] and 22 nondiabetic controls (4 females/18 males, aged 56.6 ± 5.5 , BMI 32.6 ± 4.5 , AHI 30.1 ± 22.2 /hour) were matched individually for gender, age, BMI, and severity of sleep-related breathing disorders. All recordings were scored manually using standard criteria. Primary end points included macro- and microarchitectural features derived from sleep staging and waveform analysis, including the amount of time in each sleep stage.

Result:

We found significantly reduced deep sleep (SWS, nonrapid eye movement stages 3 and 4) in diabetic patients as compared to nondiabetic controls ($3.9 \pm 5.8\%$ vs $8.4 \pm 4.5\%$; $p = 0.014$). Rapid eye movement sleep was increased significantly in cases as compared to nondiabetic controls ($24.1 \pm 11.9\%$ vs $13.8 \pm 6.8\%$; $p = 0.005$). Notwithstanding the subjects were also matched for the degree of sleep-related breathing disorders, the arousal index was significantly higher in persons with diabetes (44.3 ± 19.1 /hour vs 35.7 ± 12.4 /hour; $p = 0.037$).

Conclusion:

Although reduced amounts of deep sleep are typical of aging and sleep-related breathing disorders, results indicated that decreased SWS was more pronounced in persons with type 2 diabetes as compared to nondiabetic controls independently of obesity. Given the functional links between sleep and clinical conditions, early recognition of altered sleep architecture might help detect persons at increased risk for type 2 diabetes with a possibility to intervene.

Internet-Based Portal Communications as a Value-Added Tool for Providers and Patients in the Management of Diabetes

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Background:

With Internet use increasing among all age and socioeconomic groups, it is important to develop effective Internet communications in medicine. Secure, Internet-based diabetes management tools that use data relevant to providers and patients demonstrate value in the virtual management of diabetes. UPMCHealthTrak is an Internet portal that provides communications between provider and patient, results review, health maintenance alerts, and the ability to manage medication refills and appointment access.

Objective:

The objective of this project was to evaluate the perceived value of UPMCHealthTrak to patients in contrast to Internet tools used in daily life. In addition, the study examined typical barriers to patient Internet use for medical self-management, such as the perceived nonwillingness to pay for portal services.

Methods:

Methods included facilitated focus groups of providers and patients. Patients, users and non-users, were solicited by a third party who administered standard questions to each group. A validated survey with questions regarding valuation of portal services, perceived ease of use, and usefulness was administered to patients using UPMCHealthTrak.

Results:

Results indicate that both providers and patients find value in UPMCHealthTrak. Patients varying in age, socioeconomic group, and degrees of nonmedical Internet experience expressed a willingness to pay for services. Communications between providers and patients create a perceived value to patients interacting with providers in a collaborative patient care model.

Conclusion:

In conclusion, this study showed that aforementioned barriers to Internet-based chronic care tools such as a nonwillingness to pay for services, security concerns, and lack of provider engagement are not valid reasons to abandon Internet development. Patients using the Internet to manage their care value tools developed using standard practices in other industries for the management of all aspects of life.

Noninvasive Ultrasonic Glucose Sensing on Pigs (~200 Pounds) Using a Lightweight Cymbal Transducer Array

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Objective:

To prevent complications in diabetic patients, the proper management of their blood glucose levels is essential. Because conventional glucose meters require pricking fingers or other areas of the skin, a noninvasive method of monitoring glucose level is desired. A previous study conducted using a lightweight (<22 grams) cymbal transducer array demonstrated ultrasonic transdermal glucose sensing on hyperglycemic rats. With a similar intensity and frequency, the goal of this study was to determine noninvasively the glucose level of pigs having a size similar to overweight humans.

Method:

A total of 43 experiments were performed with eight pigs (~200 pounds). A cymbal array with a standoff (reservoir) that held saline solution was attached to the axillary area of the pig. Biochemical glucose sensors were placed in the reservoir. The array was operated at 20 kHz ($I_{\text{sptp}}=100 \text{ mW/cm}^2$) for 10 or 20 minutes. After the exposure, concentrations of glucose diffused through the skin were determined by the biochemical sensors. For comparison, blood samples were collected from the ear vein and glucose levels were determined by a commercial glucose meter.

Result:

After 20 minutes of ultrasound exposure, the average glucose level determined by the cymbal array and biochemical sensors was $175 \pm 39 \text{ mg/dl}$; after 10 minutes of exposure, it was $127 \pm 60 \text{ mg/dl}$. In comparison, blood glucose levels, as measured by the glucose meter, were similar ($p > 0.4$) to those determined by the sensors: 166 ± 20 and $131 \pm 11 \text{ mg/dl}$, respectively.

Conclusion:

Results indicate the feasibility of using the cymbal array for noninvasive glucose sensing on pigs that have a similar size to overweight humans. Further studies on ultrasound conditions, such as frequency, intensity, and exposure time, will be continued for effective glucose sensing.

Stochastic Model-Predictive Control of Type 1 Diabetes Mellitus: Anticipating the Next Meal with Random Meal Profiles

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Introduction:

Recent clinical investigations of model-predictive control of type 1 diabetes mellitus (T1DM) via the subcutaneous (SC)–SC route have shown that meal profile information describing the historic timing and size of meals is critical for optimal management of blood glucose. However, if model-predictive methods are to be used outside of the clinical setting, then they must accommodate the random nature of patient behavior.

Methods:

Working toward stochastic model predictive control (SMPC) of blood glucose, we developed an algorithm that optimally accommodates random meal timing. Assuming that the next meal, if taken, will involve a given amount of carbohydrates and having access to a *random* meal profile that describes the conditional probability of the meal arriving within the next update interval, our algorithm computes optimal insulin injections in anticipation of the next meal. The algorithm employs a linear discrete-time, input–output model of insulin–glucose kinetics.

Results:

The algorithm was tested *in silico* using a computer simulation environment containing *in silico* images of 300 subjects with T1DM. The anticipatory behavior of the algorithm depends strongly on the meal profile. Certainty about meal timing results in aggressive preprandial insulin injection, while uncertainty implies a more reactive response.

Conclusions:

SMBC and adaptive statistical methods for characterizing random patient behavior are likely to be key ingredients in safe and effective model-predictive control of T1DM.

An Agent Model of Continuous Glucose Monitoring Adoption

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Objective:

Continuous glucose monitoring (CGM) devices, while available commercially and approved as a supplement to self-monitoring blood glucose (SMBG), have not found widespread use among the type 1 diabetes mellitus (T1DM) population. It is reasonable to speculate that CGM will be more widely adopted after approval to replace SMBG. However, establishing the business case for new CGM innovations/products is difficult given the lack of predictive tools that address the adoption patterns of new health care technologies.

Methods:

We developed an agent-based model to predict rates of CGM adoption (with or without Food and Drug Administration approval for replacement), reflecting the diverse perspectives and complex interactions of relevant actors, including patients, doctors, insurance companies, and CGM device manufacturers. The model was implemented as a NetLogo simulation, supported with data that reflect the properties of all agent types and their interactions. We used regression analysis within various demographic groups to gain insight into the model's predictions about CGM adoption rate, focusing on subpopulations whose behaviors can be explained with $R^2 \geq 0.7$.

Results:

We found that price, CGM effectiveness, calibration frequency, and doctor experience constitute the variables that are significant ($p < 0.05$) for the demographic groups studied. Higher socioeconomic classes are less price sensitive and can focus more on the quality and comfort of CGM. Younger patients are more tech-savvy and are consequently more likely to adopt CGM.

Conclusions:

Agent-based models can shed light on the complex process of technology adoption within the health care sector, including CGM adoption within the T1DM community. Such models may encourage the development of new products that ultimately reduce cost and improve overall quality of care.

Insights in Subject Recruitment for Clinical Trials of Diabetes Technologies in Disease Management Settings: Preliminary Data from the Diabetes Remote Monitoring Evaluation Study

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Objective:

The goal of this study was to provide insights into recruitment of a randomized clinical trial of a diabetes remote-monitoring technology in a disease-management (DM) setting.

Methods:

Most randomized clinical trials are done in a clinic setting with face-to-face encounters between physicians and patients. New models of evaluation are needed to scientifically evaluate the care provided with remote monitoring and in DM settings and to understand criteria for successful participation in a telephonic model. In the ongoing Diabetes Remote Monitoring Evaluation study, subjects 18–64 years of age with diabetes mellitus contacted by two DM companies are being randomized to standard DM or DM combined with remote monitoring. Outcomes of interest include changes in glycemic control and low-density lipoprotein levels, patient engagement with diabetes treatment plan—medications and lifestyle recommendations, and utilization costs. Remote monitoring consists of a cell phone, a OneTouch® Ultra2® glucometer, and a Bluetooth cradle. Eligibility is determined via administrative claims, a telephone survey to ascertain interest, and laboratory data. Screening failures are being tracked to understand barriers to study participation.

Results:

Between April 1, 2008 and June 9, 2008, 539 subjects met the claims criteria, were sent letters, and were reached for telephone clinical trial enrollment by a DM nurse. Common barriers cited for nonparticipation in the study include time commitment necessary, value from participating, and not wanting to change meter type because of the perceived hassle factor, such as cost of strips and doctor visits for prescriptions.

Conclusion:

Obtaining high levels of participation in clinical trials of telephonic or remote monitoring in a DM setting requires an expanded knowledge and awareness of patients' needs. Analysis of responses is allowing us to modify procedures to maximize recruitment in a DM setting.

Assessments of Insulin Analogs in Clinical Samples by Means of Preanalytical Three-Dimensional Free-Flow Electrophoresis Technology

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Background:

Parallel determination of insulin analogs in the presence of endogenous insulin in the plasma of diabetic patients is a major diagnostic challenge. Only one specific immunoassay for insulin lispro is available commercially and all other analogs show different degrees of cross-reactivity with different assays for regular human insulin.

Method:

We performed this proof-of-concept investigation to explore the eligibility of protein separation by free-flow electrophoresis (FFE), a new quantitative preanalysis method, prior to insulin measurement as a means to solve this problem. Plasma from healthy subjects and patients was drawn, centrifuged, and spiked with the different available insulin analogs to achieve therapeutic concentrations (20–100 $\mu\text{U/ml}$). For protein separation, the samples were diluted and directly applied and separated by FFE. The FFE principle is based on a continuous electrophoretic separation process in a thin layer of buffers flowing continuously through a flat chamber in a laminar fashion. The absence of any kind of solid separation matrix prevents unspecific adsorption of analytes and allows fast and native separation conditions. A special adapted protocol for isoelectric focusing gave highly reproducible separations of the complex serum protein mixture into a 96 fraction format. After identification of the FFE characteristics of the insulin analogs, their individual FFE fractions were collected quantitatively and subjected directly to a chemiluminescence assay for regular human insulin, which is cross-reactive to all insulin analogs (Invitron, Cardiff, UK).

Results:

In these pilot experiments, insulin lispro had the same FFE running characteristics as regular human insulin and did not separate. All other insulin analogs, except detimir (aspart, glulisine, and glargine), could be separated quantitatively from regular human insulin with acceptable assay characteristics (e.g., insulin glargine, intra-assay variability: 4–6%, inter-assay variability: 5–8%). Quantification of insulin glargine in clinical trial samples from patients with type 2 diabetes with residual β -cell function was possible and achieved clinically plausible results.

Conclusion:

FFE is a reliable laboratory preanalysis method that allows for separation and quantification of insulin analogs when present in combination with other insulins in a quality suitable for clinical trials.

Laboratory Study on the Influence of Hematocrit Levels on Blood Glucose Meter Readings

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Background:

Measurement of blood glucose by means of self-measurement blood glucose (SMBG) meters is a routine procedure in the daily life of patients with diabetes mellitus. The devices have to provide accurate and reliable results, as they are used frequently for therapeutic decisions, e.g., selection of insulin doses. However, based on the underlying measurement technology, SBGM results may be subject to influences by interfering substances and conditions, such as hematocrit (HCT), maltose, vitamin C, and others.

Methods:

This experiment investigated the influence of high and low hematocrit levels on the readings of different blood glucose meters and point-of-care (POC) devices (SBGM: FineTouch/Terumo; Ascencia Contour/Bayer, Precision Xceed/Abbott Medisense, Accu-Chek Aviva/Roche Diagnostics; POC: StatStrip/Nova Biomedical, SuperGL/Müller; reference method: COBAS/Roche Diagnostics). Laboratory samples were spiked with glucose to achieve three different blood glucose concentrations (55, 150, and 380 mg/dl). Cell-free plasma or erythrocytes were added to achieve three different HCT levels (28, 42, and 57%) for each glucose sample. Two readings were performed with each sample with the reference methods, and eight readings were performed with each of the SBGM meters. Results were compared to the COBAS device (glucose oxidase method), which had successfully and very accurately passed all quality assurance workshops from the United States and Germany [Clinical Assessment Program and Richtlinien der Bundesärztekammer (Guidelines of the German Federal Medical Society)].

Results:

Only two devices showed readings that were unaffected by the hematocrit values as expressed by their mean absolute percent deviation with 28, 42, and 57% HCT and the slope of the HCT/deviation curve over all individual measurement values: StatStrip (5.2%/6.8%/4.6%/0.02) and FineTouch (6.5%/5.0%/7.6%/0.04). All other devices showed increasing or decreasing deviations with increasing HCT (SuperGL: 7.6%/9.4%/14.2%/0.23; Ascencia: 5.9%/5.9%/22.8%/0.59; Accu-Chek: 16.2%/14.5%/11.1%/−0.18; Precision: 5.3%/11.0%/37.5%/1.12; all $p < 0.001$ vs StatStrip or FineTouch).

Conclusions:

Results indicate that only the point-of-care device StatStrip and the SBGM FineTouch showed a stable and reliable blood glucose reading performance independent from the hematocrit values. All other devices, including one POC device, showed partly very pronounced deviations. These findings should be taken into account when blood glucose meters are selected in medical units or for patients where deteriorations of HCT are likely to happen (e.g., intensive care units, kidney centers, dialysis patients).

Clinical Data Validation of an Improved, Physiologically Relevant Critical Care Glycemic Control Model

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Introduction:

Stress-induced hyperglycemia is prevalent in critical care. Tight glycemic control is associated with significantly improved clinical outcomes. Providing tight control is difficult because of evolving patient condition and drug therapies. Model-based/derived methods (e.g., SPRINT) have shown significant mortality reductions. This research validated an improved metabolic control model and its parameters based on predictive capability for use in real-time glycemic control.

Methods:

A clinically validated metabolic system model that includes two-compartment dextrose absorption and a maximal endogenous glucose production (EGP_{max}) was validated using clinical data from SPRINT. The physiologically based model offered better prediction and control in clinical application. Integral-based methods identified patient-specific, time-varying insulin sensitivity, with a grid search over EGP_{max} and noninsulin-mediated glucose uptake, pG. Other model constants were validated population values from previous studies. Optimal EGP_{max} and pG were identified based on prediction error to determine optimal population values or ranges for critical care patients.

Results:

The per-patient median 1-hour forward prediction error was 4.5% [interquartile range (IQR): 3.8–5.6]. Median pG = 0.006 min⁻¹ (IQR: 0.002–0.010) and median EGP_{max} = 0.8 mmol·min⁻¹ (IQR: 0.5–1.5). Virtual trials targeting 80–110 mg/dl using these population values had a median blood glucose of 103 mg/dl (IQR: 90–119).

Conclusions:

Model-based glycemic control is a function of model quality. A more physiologically relevant model was presented and validated. Results indicated that noninsulin-dependent glucose removal, pG, is far less patient specific than EGP_{max}. Median prediction errors were less than the 7–12% measurement error. Results confirmed that the updated model is suitable for further use in glycemic control design.

Numerical and Clinical Accuracy of a Continuous Glucose Monitoring System during Intravenous Insulin Therapy in the Intensive Care Unit

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Objective:

Intensive insulin therapy (IIT) in critically ill patients has been shown to be beneficial. Glycemic control with the use of IIT demands frequent monitoring and can be cumbersome. Continuous glucose monitoring systems (CGMS) have been approved as an adjunctive device to complement, not replace, standard glucose monitoring. This study was designed to evaluate whether a real-time CGMS (DexCom™, STS) can be similarly beneficial in assisting with the glycemic control in the intensive care unit (ICU).

Methods:

Ten patients (six males) were enrolled in this 7-day sensor study (7 from the surgical ICU and 3 from the burn ICU). The patients were on IIT for at least 2 hours prior to sensor insertion. The sensor was inserted in the abdominal subcutaneous tissue, and the receiver was blinded to the nursing staff. Mean age and body mass index were 60.6 ± 3.8 years and 39.35 ± 3.9 kg/m². DexCom accuracy was analyzed separately for the Johnson and Johnson (J & J) calibration finger sticks, Roche Accu-Chek finger sticks, and Hitachi 917 analyzer measurements on plasma.

Results:

The range for the 767 data points was 39 to 464 mg/dl. The number and percentage of measurements for the DexCom and references using Clarke error grid analysis are as follow.

		Zones					
		A	B	C	D	E	A+B
J & J	N (%)	86 (63.2)	40 (29.4)	2 (1.5)	8 (5.9)		92.6
Accu-Chek	N (%)	289 (52.8)	210 (38.4)	6 (1.1)	40 (7.3)	2 (0.4)	91.2
Hitachi 917	N (%)	35 (41.7)	35 (41.7)	5 (6.0)	8 (9.5)	1 (1.2)	83.4

Conclusions:

A high percentage of measurements in the A+B zones confirms clinical usefulness of CGMS as an adjunct to complement conventional glucose monitoring methods in the ICU and supports further trials of their use in the ICU.

Screening of Glycemic Attributes of *Trichosanthes dioica* Leaves *in Vivo*

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In continuation of previous work on *Trichosanthes dioica*, the aim was to screen glycemic attributes of the aqueous extract of *T. dioica* Roxb. (Cucurbitaceae) leaves in normal as well as various diabetic models. The variable doses of 250, 500, and 750 mg kg⁻¹ body weight (bw) of the extract were administered orally to normal and streptozotocin-induced sub- and mild-diabetic rats in order to define its glycemic potential. The dose of 500 mg kg⁻¹ bw was identified as the most effective dose, which brings down the blood glucose level (BGL) by 32.9% ($P < 0.001$) at 6 hours during fasting blood glucose studies in normal rats. However, a glucose tolerance test showed a maximum reduction of 30.9% ($P < 0.001$) in BGL at 5 hours in normal rats with the same dose, whereas the reduction observed was by 40.3 and 88.6% ($P < 0.001$) in sub- and mild-diabetic rats, respectively, at 3 hours of glucose administration only. This evidence clearly indicates that the aqueous extract of *T. dioica* leaves has good hypoglycemic potential along with a high antidiabetic profile.

Antidiabetic Potential of *Psidium guajava* Fruit Peel

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Objective:

This study dealt with critical evaluation of the glycemic potential of the aqueous extract of the *Psidium guajava* unripe fruit peel on the blood glucose level (BGL) of normal and streptozotocin-induced mild and severely diabetic rats as an extension of previous work carried out on the *P. guajava* ripe fruit peel.

Method:

The hot aqueous extract was filtered, concentrated under reduced pressure, and then lyophilized to get a powder. Male albino Wistar rats of approximately the same age group were selected for the experiment. Blood glucose levels were measured by the glucose oxidase method.

Results:

A maximum fall of 21.2% ($P < 0.001$) and 26.9% ($P < 0.001$) after 3 hours of glucose administration during a glucose tolerance test was observed in BGL from a dose of 400 mg kg⁻¹, identified as the most effective dose, in normal and mild diabetic rats, respectively. In severely diabetic rats, a maximum fall of 20.8 and 17.5% ($P < 0.001$) in fasting blood glucose and postprandial glucose levels and 50% ($P < 0.01$) in urine sugar levels was observed with the same dose. However, hemoglobin increased by 5.2% ($P < 0.01$) and body weight by 2.5% ($P < 0.05$) after 21 days of treatment.

Conclusion:

Normal, mild, and severely diabetic models showed hypoglycemic as well as antidiabetic effects with the unripe fruit peel aqueous extract. The strong median lethal dose experiment also showed a great margin of safety. The increased hemoglobin and body weight are additional advantages of the extract.

New Strategies of Laser-Induced Breakdown Spectroscopy-Based Validation of Glycemic Elements for Diabetes Management

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Objective:

Diabetes being a global burden is a big challenge for medical science. The antidiabetic efficacy of the medicinal plant cannot be ignored in order to develop drugs without toxicity and side effects. The present study was aimed at exploring scientifically the glycemic potential of *Withania coagulans* and *Cajanus cajan*.

Method:

The effect of variable doses of both extracts on the blood glucose level (BGL) of normal and diabetic models has been studied and the results were compared with the reference drug glipizide. The recent laser technique called laser-induced breakdown spectroscopy (LIBS) has been used to assess the major and minor elements, present in them, responsible for their glycemic management.

Result:

The dose of 1000 mg kg⁻¹ body weight of *W. coagulans* showed a maximum fall of 20.9 and 37.8% ($p < 0.001$) in the blood glucose level (BGL) of normal and mild diabetic rats, respectively, during the glucose tolerance test. However, the same dose of *C. cajan* showed a significant rise of 17.0 and 50.7% ($p < 0.001$) in the BGL of normal and mild diabetic rats, respectively. LIBS results clearly demonstrated that the higher content of Mg and Ca in *W. coagulans* in comparison to *C. cajan* is responsible for its significant role in diabetes management, whereas the concentration of other elements, such as H, O, N, and C, are nearly the same in both extracts.

Conclusion:

From this study, it can be stated conclusively that the specific proportion of the concentrations of Mg and Ca in *W. coagulans* and *C. cajan* is collectively responsible for their glycemic potential.

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

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Background:

The pharmacodynamics (PD) and pharmacokinetics (PK) profiles of current insulin analogs are still slow compared to normal physiology. Among other effects, this results in large postprandial blood glucose excursions in insulin-dependent diabetic subjects (IDDS).

Objective:

In this study the effect of the InsuPatch device on the PD and PK profiles of insulin analogs was tested. The InsuPatch is a novel device intended to accelerate insulin delivery when used with insulin pumps by locally warming the infusion site without heating the insulin itself.

Method:

To evaluate the effect of the device on the insulin PD profile, a euglycemic clamp protocol was used with and without the device. At time $t = 0$, a bolus of 0.15 IU/kg was infused followed by glucose infusion to maintain the euglycemic level. The effect of the device on postprandial glucose excursions was tested by comparing postmeal glucose levels with and without the device in a meal tolerance test protocol. At time $t = 0$, a bolus of 0.15 IU/kg was infused followed by oral intake of a standardized liquid meal. The effect of the device on insulin PK was evaluated by comparing the insulin concentration in both protocols with and without the device.

Results:

The main benefits of using the device are a reduction of 39% in the time to peak action of insulin, an increase of 37% in the available insulin in the blood during the first hour postinjection, and a reduction of 25% in the average glucose level during the first 2 hours postmeal. These results suggest that the InsuPatch may be used to improve glycemic control in IDDS.

Point of Care Measurement of Blood Ketones in a Diabetes Clinic

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Objective:

The objective of this study was to evaluate routine blood ketone testing in a pediatric diabetes clinic.

Methods:

During 6 months, 1788 diabetic children were seen for 3007 visits at the Barbara Davis Center in Denver. Blood β -hydroxybutyrate (B-OHB) and glucose using Precision Xtra[®] (Abbott Laboratories) and hemoglobin A1c (HbA1c) using DCA 2000[®] (Bayer) were measured at the point of care using one finger poke. Patients with elevated B-OHB were given a corrective dose of insulin and fluids.

Results:

Among 127 newly diagnosed children, B-OHB was >3 mmol/liter in 17%, 1.6–3.0 in 20%, and 0.6–1.5 in 20%. Elevated B-OHB levels were associated with higher HbA1c ($p < 0.001$), but not age, gender, body mass index (BMI), or current blood glucose level; 10/127 patients had a blood glucose below 200 mg/dl (range 68–197), but elevated B-OHB (0.7–3.6). During 2880 visits of 1661 returning patients, the distribution of B-OHB levels was, respectively, 0.4, 0.9, and 3.3%, with 95% of the tests in the normal range (<0.6). Elevated B-OHB levels were associated with higher HbA1c, shorter duration of diabetes, and higher current blood glucose ($p < 0.0001$ all), but not age, gender, or BMI. Only 10% of patients with B-OHB >1.5 and 17% of those with B-OHB 0.7–1.5 were using insulin pumps compared to 32% of those with normal levels ($p < 0.0002$). While 96/107 (90%) of cases with elevated B-OHB had BG >290 , HbA1c $>9.4\%$, diabetes duration <10 weeks, or age <4 , this was true for 47% of all visits, making routine B-OHB testing a more practical approach.

Conclusions:

Testing blood, rather than urine ketones, in the setting of a pediatric diabetes clinic saves an estimated 7 minutes in check-in time/patient and identifies 67% of newly diagnosed and 5% of the returning patients who need an immediate corrective insulin dose.

Using Data Integration and Online Analytical Processing to Identify Gaps in Diabetes Self-Management Education Services in Western Pennsylvania

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Background:

Diabetes self-management education (DSME) is a critical component in the clinical management of diabetes. Although DSME is recognized as important, the number of patients who receive DSME is disproportionately small. Several barriers to receiving DSME exist, including awareness and access.

Objective:

The objective of the University of Pittsburgh Diabetes Information Management System (UP-DIMS) project was to create a data warehouse and clinical object layer for data integration, management, and data mining. This program enables one to track location, utilization, and financial data for DSME services at the University of Pittsburgh Medical Center (UPMC) diabetes centers throughout western Pennsylvania.

Method:

UP-DIMS is a Windows-based user interface with an underlying relational database developed for the unique requirements of a diabetic patient. The application works in conjunction with other UPMC information systems and stores patient pertinent information. Visualization of data contained within the data warehouse is facilitated by a clinical object layer that integrates data into records of information by patient. This gives the investigator a view of data that is consistent with how it is used and analyzed. To further assist the researchers with interrogation of the data warehouse, we have employed online analytical processing to “slice and dice” data for analysis. This technology is also useful for analyzing the quality of data.

Conclusion:

The UP-DIMS system affords the unique opportunity to identify gaps in service; provide a mechanism to track the effectiveness of marketing strategies designed to increase awareness, penetration, and development; and monitor financial data for reimbursement practices while evaluating patient clinical outcomes. This system has large-scale applicability in tracking other areas of diabetes services and other disease states.

A Systematic Review of Health Monitoring Technologies for Individuals with Type 1 or 2 Diabetes at Risk for Cardiovascular Complications

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Background:

The objective of this study was to determine the strength of evidence for the effectiveness of health monitoring technologies and devices in adults and youth (7–14 years) with type 1 or 2 diabetes who are at risk of developing cardiovascular complications. Also examined were factors that affect device acceptance and adherence to protocols by both patients and practitioners.

Methods:

Online databases (MEDLINE, EMBASE, CINAHL, PsycINFO, EBM Reviews), specific journals, reference lists, and grey literature sources were searched for the years 1985–2008 (May) for all types of study designs in English. Selected studies were independently evaluated and assessed with an instrument for determining the methodological quality of both randomized and nonrandomized studies and ranked according to levels of evidence. Specific study characteristics, interventions, and outcome measures data were extracted and presented in evidence tables. Statistical analyses and meta-analyses of randomized controlled trials (RCTs) were conducted where feasible.

Results:

The following types of studies and totals were conditionally selected: 26 RCTs, 29 non-RCTs, 2 meta-analyses, 9 systematic reviews, and 1 technical review. The predominant types of devices and interventions used in selected RCTs included pedometer, accelerometer- and exercise-based programs, blood glucose and blood pressure monitoring devices, and wireless-, Web-, or mobile-enabled health management systems.

Conclusions:

Initial results from the literature searches highlighted gaps within the research. New health monitoring technologies or devices could provide potentially beneficial results for individuals with diabetes (e.g., global information systems or imaging technologies). Results of the literature search indicated a need for additional controlled trial research related to a range of devices for monitoring health outcomes and complications associated with diabetes and cardiovascular complications. Evidence-based conclusions from this research synthesis are forthcoming.

Acknowledgment:

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Improving Diabetes Care: Development of a Diabetes Simulator

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Objective:

The incidence and severity of the complications that accompany diabetes can be reduced considerably if diabetic patients receive effective treatment leading to good glycemic control. Education of patients and health-care providers is therefore considered to be a fundamental part of diabetes care. For this purpose, computer simulation programs can be used. The goal of this project was to develop a diabetes simulator that incorporates a mathematical model predicting glucose profiles after a change in carbohydrate intake and insulin dose.

Method:

The developed glucose–insulin model incorporates a combination of different mathematical models from literature: the classical minimal model of Bergman, the β -cell secretion model of Steil, the model of subcutaneous insulin injection of Berger and Rodbard, the gut model of Natalucci, and a renal excretion model of Lehmann. Model parameters were estimated using continuous glucose monitoring system (CGMS) data. These data were measured in 11 healthy normoglycemic subjects (age = 59 ± 2 years; body mass index = 27.8 ± 1.4 kg/m²).

Result:

The glucose–insulin model was able to predict glucose concentrations in healthy persons. Our predicted glucose profiles were within the ± 1 SD of measured glucose concentrations. This model was implemented in a user-friendly user interface.

Conclusion:

Preliminary results of this study are encouraging to further develop the diabetes simulator. By adapting the glucose–insulin model to diabetes, we will be able to provide patient-specific trainings to diabetes patients. These trainings may help these patients manage their disease and live a safe life with minor diabetes complications. Consequently, the cost of diabetes may be reduced.

Temporal Data Mining Approaches for the Analysis of Blood Glucose Monitoring Data of Intensive Care Unit Patients

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Objective:

This work tackled the problem of investigating the phenomena underlying blood glucose (BG) dynamics in critically ill patients by analyzing retrospectively collected data through statistical and data mining techniques.

Method:

We considered 596 intensive care unit (ICU) patients treated by the Mediterranean Institute for Transplantation and Specialized Therapies, Palermo, Italy, from August 2006 to February 2008 (median ICU stay: 3 days). A set of 22 parameters was monitored for all the patients; BG was monitored by BG finger stick and venous measurements. In addition to standard statistical analysis, we applied a novel method to cluster time series data according to their qualitative behavior: data were clustered if they showed similar trends over the same time intervals.

Results:

Using temporal abstraction clustering, we divided the patients into two main groups based on the initial trend of the glucose-monitored values. We identified 287 patients starting with a decreasing trend and 259 patients starting with an increasing trend. The median time spans of the increasing and of the decreasing periods were found to be significantly different ($p < 0.01$); the higher duration was associated with the decreasing period. The basal glucose values in the two groups were found to be statistically different ($p < 0.05$) with the higher BG value associated with the decreasing group. The average values of the insulin intakes of the two groups over the increasing or decreasing periods were found not significantly different. In the second period the two groups showed a significantly different ($p < 0.01$) average risk profile (computed as proposed by Kovatchev and colleagues), with the decreasing group being less risky.

Conclusion:

The analysis suggests a crucial role of the initial BG response and its potential predictive value for assessing future patients' risk.

Weight, Lipid Profile, and Serum Glucose Changes in Drug-Naive First Episode Schizophrenia

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Objective:

Schizophrenia, one of the most devastating diseases known to humankind, has been helped immensely by the advent of second-generation antipsychotics, which have come at a considerable cost—problems of weight gain, altered lipid profiles, and glucose parameters. Most studies in the past have been limited by several confounders. This study examined the effects of olanzapine, risperidone, or haloperidol on weight, lipid profile, and serum glucose in a drug-naive population compared with a healthy matched control group.

Method:

Newly diagnosed consecutive patients with first-episode schizophrenia seen during the period from June to October 2006 at our referral psychiatric institute were recruited for an extensive prospective randomized, double-blind controlled study that assessed lipid profiles, weight, and serum glucose and compared with a matched healthy control group. Inclusions started in June 2006 and patients were followed for a period of 6 weeks.

Results:

Analysis of 99 patients showed significant differences ($p < 0.001$) between the control group and the treatment group at end points along with a significant increase in weight ($p < 0.001$), fasting blood sugar ($p = 0.01$), 2-hour postprandial blood sugar ($p < 0.001$), triglyceride ($p < 0.001$), high-density lipoprotein ($p = 0.04$), cholesterol ($p < 0.001$), low-density lipoprotein, and very low-density lipoprotein ($p < 0.001$) from baseline to end points between the groups. Olanzapine caused the most significant changes compared with risperidone and haloperidol.

Conclusion:

Results confirmed clinically significant and substantial changes in weight, lipid profile, and serum glucose induced by antipsychotic treatment in drug-naive patients with first-episode schizophrenia. Early monitoring of patients on atypical antipsychotics can possibly play an important role in early detection and hence prevention of these changes.

Telemedicine-Supported Health Care Delivery in an Integrated Diabetes Health Care Network

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Objective:

It was the aim of this project to demonstrate the feasibility of improving diabetes control in conventional diabetes care by implementing the innovative Karlsburg Diabetes Management System (KADIS®) in combination with continuous glucose monitoring (CGM) and the telemedicine-based communication system TeleDiab® in an integrated diabetes health care network.

Method:

Based on a contract for integrated health care provision (IV contract) with the German health care insurance company BKK Taunus, KADIS-based decision support was implemented into an integrated health care network to facilitate information exchange among patients, physicians, and health care professionals under daily life conditions. The interactive diabetes management system KADIS enables individualized evaluation of the metabolic situation (metabolic fingerprint) and simulates online trended the outcome of treatment recommendations. The metabolic fingerprint visualizes the relationships between daily glucose profiles and causal endogenous and exogenous factors and enables evidence-based identification of “weak points” in glycemic control. The outcome of KADIS-based support in routine diabetes care was evaluated by comparing hemoglobin A1c (HbA1c) levels and 24-hour glucose profiles before and after the intervention.

Result:

At present there are 485 diabetic patients permanently included into the integrated diabetes health care network treated by 132 general practitioners and 30 diabetes specialists. Application of KADIS-based decision support reduced HbA1c after 12 months of follow-up significantly by 0.4% (7.3 to 6.9%) after 6 months in routine diabetes care. The reduction in HbA1c was related to improved 24-hour glucose profiles and weight reduction by 0.6 kg/m² (30.2 to 29.6).

Conclusions:

Application of KADIS in combination with telemedicine-based communication in integrated health care networks has high potential for improving diabetes care and management considering daily life conditions.

Reliability and Usability of SoloSTAR® Disposable Pen in Everyday Clinical Practice: Evaluation by German Health Care Professionals and Patients with Diabetes Mellitus Using Insulin Glulisine

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Objective:

The goal of this study was to evaluate the reliability, usability, and safety of the new SoloSTAR® disposable pen in clinical practice when used by patients with type 1/type 2 diabetes.

Methods:

In this 6- to 8-week, national, noninterventional study, patients were prescribed the insulin glulisine SoloSTAR pen. Both patients and health care professionals (HCPs) participated in interviews and rated SoloSTAR on a scale of 1–6 (with 1 being very good and 6 being unsatisfactory). Patients were asked to proactively contact their HCPs or the manufacturer, sanofi-aventis, if they had any questions or product technical complaints (PTCs) regarding SoloSTAR use and to report adverse reactions/events (AR/AE).

Results:

Across 528 centers, 709 HCPs and 2445 trained patients (mean 4.6 patients/center) participated. Most HCPs (95.1%) had previously trained patients to use SoloSTAR. Of HCPs, 58.1% spent 5–10 minutes and 24.0% spent <5 minutes training their patients. HCPs gave an overall rating of 1.35 ± 0.52 (mean \pm SD); 98.0% would recommend SoloSTAR. Patient characteristics ($n = 2445$; type 1: 458; type 2: 1960) were 50.1/49.1% male/female, (mean) age 59.3 years, weight 88.0 kg, and body mass index 30.4 kg/m^2 . Most (73.0%) were insulin treated (39.9% were on basal-bolus therapy) and had experience with disposable (44.2%) and/or reusable (62.3%) devices, while the remainder were new users. Few patients (2.9%) raised questions, including reading the display (1.0%), insulin dispensation (0.9%), attaching (1.0%) or removing (0.4%) the needle, dose adjustment (0.8%), and safety testing (0.5%). Unconfirmed PTCs were reported by only 0.5% of patients. No pens were returned for inspection. One patient reported an AR, and three patients reported an AE. Patients gave an overall rating of 1.49 ± 0.63 , and 97.2% would continue using SoloSTAR.

Conclusions:

SoloSTAR was well accepted by HCPs and patients, with a low incidence of technical problems or concerns reported by patients.

Supported by sanofi-aventis, Germany.

Reliability and Usability of SoloSTAR® Disposable Pen in Everyday Clinical Practice: Evaluation by German Health Care Professionals and Patients with Diabetes Mellitus Using Insulin Glargine

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Objective:

The goal of this study was to evaluate the reliability and usability of the SoloSTAR® disposable pen in everyday clinical practice.

Methods:

This was a 6- to 8-week observational study conducted in patients with type 1/2 diabetes mellitus who were prescribed the insulin glargine SoloSTAR pen and were offered training for use. After SoloSTAR use, patients and prescribing health care professionals (HCPs) rated the pen on a scale of 1–6 (with 1 being very good and 6 being unsatisfactory). Patients were asked to report adverse events (AEs), adverse reactions (ARs), and product technical complaints (PTCs).

Results:

Across 1098 centers, 1703 HCPs and 5983 patients took part. Of HCPs, 93.2% trained patients to use SoloSTAR before the study; 57.3 and 23.4% spent 5–10 minutes or <5 minutes, respectively. Of HCPs, 97.7% recommended SoloSTAR [overall rating, 1.39 ± 0.51 (mean \pm SD)], citing handling, dose adjustment, and injection force as appealing features. Demographics of patients (type 1/2 diabetes = 792/5139) were 51.1/48.9% male/female, mean age 62.7 years, weight 85.5 kg, and body mass index 29.8 kg/m². Of the patients, 35.1% were insulin naive; the remaining patients had prior experience with disposable (49.8%) or reusable (56.2%) insulin pens. In everyday use, 25.4% of patients performed safety checks before each injection; 22.3% once/pen and 15.5% once/week. Few patients (3.5%) raised questions about SoloSTAR use, including insulin dispensation (0.9%), reading display/attaching needle (both 0.8%), and dose adjustment (0.7%). Reports of ARs, AEs, and PTCs were low (0.15, 0.3, and 0.6%, respectively). Before each injection, 61% of patients did not change needles; 3.2% patients reported complaints regarding clogged needles. Overall, 97.4% of patients would continue using SoloSTAR [overall rating 1.53 ± 0.61 (mean \pm SD)].

Conclusions:

The SoloSTAR disposable pen was very well accepted, with patients reporting a very low incidence of technical problems or concerns.

Supported by sanofi-aventis, Germany.

Comparison of Pharmacokinetic and Pharmacodynamic Effects of Nasulin™ and Lispro in Type 2 Diabetic Patients

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Introduction:

This exploratory study in type 2 diabetic patients examined the pharmacokinetics and pharmacodynamics of CPEX Pharmaceuticals' insulin formulation, Nasulin™, designed for intranasal administration.

Methods:

Eighteen type 2 diabetic patients (16 males, 2 females; body mass index <40 kg/m²) received two doses of intranasal insulin (25 and 50 IU) and one dose of lispro (5 IU) in a randomized design just prior to a high protein boost challenge. Serum insulin, C-peptide, and plasma glucose were measured in the 4 hours following dosing.

Results:

At both Nasulin doses, the glucose area under the curve₀₋₁ (AUC₀₋₁) values were less than for lispro. Nasulin AUCs over the first hour were comparable (25 IU) or slightly higher (50 IU) than lispro. T_{max} values demonstrated more rapid absorption from the nasal mucosa.

Dose	Glucose ^a AUC ₀₋₁	Insulin ^b AUC ₀₋₁	Insulin T _{max} (minutes)	Insulin C _{max} (mIU/liter ^c)
N 25U	42.5 (20.8)	31.5 (20.4)	30	61.6 (39.5)
N 50U	43.9 (13.9)	45.2 (26.6)	42	82.8 (47.9)
Lispro 5U	52.3 (23.3)	32.4 (28.0)	78	79.9 (68.5)

^aBaseline adjusted mean values (SD) in mg*h/dl.

^bBaseline adjusted mean values (SD) in mIU*h/ml.

^cBaseline adjusted mean values.

Conclusion:

Nasulin demonstrated better glucocodynamic effect during the first hour. Despite similar or slightly better AUCs for Nasulin, this improved early glucocodynamic effect is due to its more rapid absorption. C_{max} values should have been influenced only minimally by endogenous insulin for Nasulin during the first hour.

Information Management Systems as Part of an Integrated Diabetes Self-Management Approach That Can Improve Diabetes Outcome in Different Patient Populations

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Objective:

To achieve near-normal hemoglobin A1c (HbA1c) and blood glucose values, patients may need new information management tools to support their self-management efforts. We have been involved in the development of several new tools and have completed proof-of-concept studies.

Method and Result:

AC 360 View pilot studies on 30 orally treated type 2 diabetes mellitus patients provided insights for the use of the AC 360 View paper tool, designed to structure and visualize a series of seven-point blood glucose (BG) profiles in primary care physician settings. Ninety-six percent of patients completed the BG profiles accurately, and 90% were willing to repeat this process at least once per quarter or also more often if necessary. With these new profile data, 77% of the primary care physicians changed their therapeutic decisions and 86% stated that these BG profile data were of equal or higher value than HbA1c data. The AC Advisor study investigated AC Advisor Insulin Guidance Software on a handheld medical device in 121 type 1 diabetes mellitus (T1DM) patients on multiple daily injection therapy in a randomized controlled clinical trial. The experimental group had a sustained and significant decrease in HbA1c of 0.71% during a 12-month Rx period, with a higher number of patients achieving target HbA1c values when compared to the control group. The AC Pocket Compass Study introduced a handheld medical device designed to support patients on insulin pump therapy. Twenty-seven reasonably controlled (HbA1c baseline 7.9%) T1DM patients on continuous subcutaneous insulin infusion were included in this noncontrolled clinical trial. With only 2 hours of training at baseline, HbA1c improved significantly over the 3-month treatment period by $0.33 \pm 0.48\%$. In the subgroup with baseline HbA1c $>7.5\%$, a larger decrease in HbA1c was observed ($0.41 \pm 0.57\%$).

Conclusion:

Information management systems contributed to a significant drop in HbA1c and a larger number of patients reaching treatment target. Future studies on larger number of subjects are likely to be of value to investigate the benefits of information management systems further.

Modeling and Simulation of Transient Sensitivity Attenuation in Continuous Glucose Sensors

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Objective:

Continuous glucose sensors (CGS) experience transient sensitivity attenuation (TSA), posing significant barriers to hypoglycemia detection and closed-loop control. Current models/simulators of CGS behavior cannot account for these events. We propose a model and a simulation method that faithfully reproduce these transient losses of sensitivity.

Methods:

We augmented a previously reported diffusion model (Rebrin, Bergman) to include a multiplier function $P(x)$ modeling TSA: $IG' = P(x) \cdot (1/t) \cdot [BG(x) - IG(x)] - a \cdot IG(x)$, where BG is plasma glucose and IG is interstitial glucose. This attenuation term reduces the impact of the BG-IG gradient on diffusion dynamics. Minutely CGS and 30-minute Yellow Springs Instrument (YSI) BG data from seven overnight data collection sessions were used to estimate diffusion parameters and TSA frequency, length, and intensity. CGS traces were simulated with reference BG and model parameters drawn from estimations of population distributions.

Results:

Nocturnal TSA events occurred in all sessions. Sensor estimates of BG often fell below 15 mg/dl of the YSI value with more intense TSA events occurring less frequently. The attenuation function $P(x)$ recreated variable-length and variable-intensity TSA accurately. Twenty-four hours of CGS simulations with simulated TSA proved qualitatively indistinguishable from *in vivo* traces. Sensors traces with maximally intense TSA behaved exponentially.

Conclusions:

This method of TSA modeling/simulation accurately reproduces the characteristics of *in vivo* loss of sensitivity. Real-time parameter fitting may facilitate TSA detection and compensation. More realistic sensor-error simulations will aid in the testing of closed-loop glucose control algorithms.

Acknowledgment:

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Development and Implementation of a Standardized Online Lifestyle Intervention Coaching Protocol for Diabetes Prevention

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Objective:

Our objective was to translate an intensive in-person coaching protocol from an evidence-based lifestyle intervention into an online standardized protocol.

Method:

We developed and implemented an online lifestyle coaching protocol to provide tailored behavioral support for virtual lifestyle management (VLM), our online translation of the Diabetes Prevention Program's lifestyle intervention. Coaches reviewed participation, self-monitoring, lesson completion, and self-reported barriers to healthy eating and physical activity. Active participants were sent brief secure messages each week during the 16 weekly lessons and then biweekly messages during the 8 monthly lessons. Coaching notes included standardized elements and tailored advice. VLM was piloted on 50 medically eligible patients from an urban academic internal medicine setting with a body mass index (BMI) ≥ 25 kg/m², at least one weight-related cardiovascular risk factor, and Internet access. We examined online coaching data for the subsample of 19 patients who completed the 1-year program.

Results:

Participants were predominantly female (76%), with a mean age of 51.9 years (SD 10.8), and a BMI of 36.8 kg/m² (SD 6.8). The VLM program was successful (7.1 kg weight loss at 9 months). Of the subsample who completed the program, most had participated regularly throughout the year (mean active weeks = 38.6, SD 16.4). The average number of total messages per patient (patient queries, coach replies, technical and evaluation-related communication) was 68.1 (SD 39.9). The average number of coaching notes per patient was 28.4 (SD 12.9).

Conclusion:

VLM was designed to provide a time-efficient and high-quality intervention program for promoting diabetes prevention in primary care. Standardized online lifestyle coaching provided behavioral support and tailored advice to help patients achieve their dietary and physical activity goals.

A New Quantitative Image-Based Atlas of All Human Foot Bones in Diabetic Foot Diseases

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Objective:

Diabetic foot disease (DFD) is the leading cause of diabetes-related hospital admissions and culminates in >80,000 lower extremity amputations annually. Amputations are often the result of adult-acquired neuropathic foot deformities resulting from accelerated bone mineral density (BMD) loss, leading to rapid and severe destruction of foot architecture. Improved methods for monitoring bone loss in diabetes are desperately needed.

Method:

We developed a new precise, quantitative, image- and atlas-based method for measuring whole-bone and subregional volumetric BMD for all 26 bones of the human foot based on high-resolution computed tomography. To acquire subregion densities, three-dimensional (3D) atlases were constructed from segmented surfaces of each bone and represented as hierarchical tetrahedral meshes partitioned into subregions of interest. Each bone atlas can be elastically registered onto segmented bones of future images, thus placing all registered bones within a common coordinate frame for comparison. The registration allows (1) visualization of 3D bone density distributions over time and between subjects and (2) precise quantification of volume and BMD changes for the whole bone as well as within each partitioned region.

Result:

Whole-bone and subregional estimates of error (% root mean square error of cross-validation RMSEcv) for BMD and volume were $\leq 1.6\%$, yielding highly precise estimates between repeat scans. Talus BMD and volume changes over 9 months in a subject recovering from acute Charcot neuroarthropathy increased 9.6 and 16.7% BMD and volume, respectively (whole talus); talus head/neck subregion increased 12.2 and 21%, respectively, compared to talus body increasing 8.9 and 15.3%, respectively.

Conclusion:

Semiautomated atlases of whole-bone and important subregions of all foot bones provided highly precise, quantitative outcomes for clinical trials investigating therapeutic interventions and for monitoring DFD progression in diabetes.

Self-Monitoring of Blood Glucose (SMBG) in Type 1 Diabetes Patients with Insufficient Metabolic Control: Intervention Focused on SMBG Lowers Hemoglobin A1c

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Objective:

The goal of this study was to evaluate the effect on hemoglobin A1c (HbA1c) of a structured intervention focused on self-monitoring blood glucose (SMBG) in type 1 diabetes patients with insufficient metabolic control (HbA1c $\geq 8\%$) using a randomized clinical trial design.

Methods:

One hundred thirty-four outpatients with type 1 diabetes, multiple injection therapy with insulin and HbA1c $\geq 8\%$ were recruited and randomized into one group receiving a focused and structured 9-month and five-visit SMBG intervention ($n = 59$) and one group receiving regular outpatient care based on guidelines and a local established clinical practice ($n = 64$). The study was performed at one outpatient clinic and research facility at Stavanger University Hospital, Norway.

Results:

Hemoglobin A1c values (mean% \pm SD) at the study start were similar: 8.65 ± 0.10 in the intervention group and 8.61 ± 0.09 in the control group. The two groups were comparable (age, gender, body mass index, complication rate, and treatment modality) at study start and had mean diabetes duration and SMBG experience of 19 and 20 years, respectively. At study end, a decrease in HbA1c was observed in the intervention group ($p < 0.05$) and the HbA1c was 0.6% lower compared with the control group ($p < 0.05$). No increase in the number of minor or major hypoglycemia episodes was observed in the intervention group during the study period.

Conclusions:

A simple, structured, and focused SMBG intervention resulted in an improved metabolic control in patients with longstanding diabetes type 1 and HbA1c $\geq 8\%$. The intervention was based on general recommendations from American Diabetes Association and World Health Organization, realistic in format, and is possible to apply in a regular outpatient setting.

Biologic and Analytic Variations of Glucose Determined from Serial Intensive Care Unit Patient Testing Indicate Inferiority of Blood Glucose Metered Glucose Compared to Blood Gas Glucose Measurements

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Objective:

We demonstrated that accurate estimates of biologic variation (BV) could be derived from serial differences of repeated tests. BV can be compared to analytic variation (AV). BV/AV ratios of 4 and 1.33 indicate optimally precise and minimally acceptable testing, respectively. We extended this work to intensive care unit (ICU) glucose testing.

Method:

Over 5 months, 264 General Systems ICU patients treated at the University of Alberta Hospital had both arterial blood glucose measured by one of two radiometer ABL800 FLEX analyzers and capillary or arterial blood glucose measured by 1 of 16 nurse-operated LifeScan SureStepFlexx® blood glucose meters (BGM). We tabulated the glucose measurements of paired inpatient blood samples drawn within 8 hours of each other for both the BGM and the radiometer systems. We calculated the standard deviations of duplicates (SDD) of the inpatient pairs grouped by 1-hour intervals. For both systems, SDDs were regressed against time with extrapolation to zero time representing the sum of BV and short-term AV. Substitution of experimentally derived radiometer AV permitted the calculation of BV of the ICU patients. Substitution of the calculated BV into the BGM regression permitted calculation of the AV of the BGM.

Results:

The BV of the ICU patient glucose was 8.5%. The AV of the radiometer and BGM was 2.2 and 8.9%, respectively.

Conclusion:

The BV/AV ratio indicated that the radiometer is optimally precise (the analytic error contributes only 3% to the glucose variation); the BGM demonstrated inferior performance with its imprecision contributing 40% to the glucose variation.

Inspiratory Efforts Achieved in Use of the Technosphere Insulin Inhalation System

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Objective:

The Technosphere[®] insulin (TI) inhalation system comprises TI powder premeasured into unit dose cartridges and the patient-friendly, reusable, breath-powered MedTone[®] inhaler. This high-resistance system uses a patient's inspiratory effort to affect TI powder deagglomeration and promote subsequent deep lung delivery. This study reported on flow and pressure data achieved by patients with diabetes using the MedTone system.

Method:

MedTone inhalers containing empty cartridges were adapted with pneumotach measuring devices to capture inhalation profiles. The measuring apparatuses had negligible impact on the nominal MedTone system resistance level of .117 kPa[^].5/LPM. Each of 56 subjects inhaled twice to mimic TI clinical study dosing instructions. Achieved inhalation profiles were characterized by peak inspiratory flow (PIF), peak inspiratory pressure (PIP), and average pressure drop from the time of PIP to 4 seconds (P_{AVG}).

Results:

The achieved mean PIF (\pm SD) in all subjects was 26.74 (\pm 6.06) LPM after the first inhalation and was similar to the mean PIF of 26.25 (\pm 6.23) LPM achieved after the second inhalation. Mean PIP (\pm SD) achieved by subjects was 8.49 (\pm 2.86) kPa and 8.1 (\pm 2.99) kPa, and mean average pressure drop P_{AVG} (\pm SD) in all subjects was 6.53 (\pm 2.24) kPa and 6.09 (\pm 2.08) kPa after the respective inhalations.

Conclusion:

Patients with diabetes demonstrated consistent inspiratory efforts over two inhalations using the MedTone system. The achieved PIFs and PIPs demonstrated the capacity of this population to obtain sufficient inspiratory effort necessary for delivery of TI using the MedTone inhaler. Adequate and sustained postpeak pressures were also revealed, supporting maximal *in vivo* TI delivery inhalation maneuvers.

Use of Continuous Glucose Monitoring to Minimize Hypoglycemia during Tight Glycemic Control in the Intensive Care Unit

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Objective:

The objective of this study was to use continuous glucose monitoring (CGM) to reduce hypoglycemia during tight glycemic control in the cardiac intensive care unit (ICU).

Methods:

Children aged 3 and under, enrolled in a randomized prospective trial of euglycemia following cardiac surgery (TECS), were studied with CGM (Medtronic Guardian® REAL-Time) using standard of care (SOC; $N = 63$) or insulin intervention (INT; $N = 57$). In the INT group, insulin was titrated in response to the prevailing glucose concentration, its history, and its rate of change (respectively, proportional, integral, and derivative terms). Therapy recommendations were made based on sensor glucose readings at intervals of 0.5 to 1 hour, with changes in therapy made following confirmatory blood glucose measurements with a bedside glucometer. Target glucose was 80–110 mg/dl, and intravenous (IV) glucose was administered if the glucose was anticipated to fall below 60 mg/dl.

Results:

With INT, glucose levels achieved target sooner (4.8 hours vs 14 hours; $p = 0.0036$) and were maintained within target longer (48% vs 28% of time; $p < 0.0001$) compared with SOC. The mean absolute relative difference between the sensor and the glucometer was 16.8%, with regression slope (0.68 ± 2) and intercept (34 ± 2 mg/dl) different from 1 and 0 ($p < 0.05$ both). To compensate for the slope less than 1, the predictive CGM alarm threshold was increased from 60 to 70 mg/dl. At the higher alarm threshold, 6 of 13 hypoglycemic excursions (BG < 60 mg/dl) in 46 subjects were detected. In three cases, hypoglycemia was prevented by giving IV glucose in response to a predictive alarm. Median time to correct hypoglycemia was 38 minutes (range 5–241 minutes).

Conclusions:

Continuous glucose monitoring during tight glycemic control in the ICU can reduce the risk of hypoglycemia and aid in the titration of insulin and glucose.

Intensive Care Unit Insulin Delivery Algorithms: Why so Many? How to Choose?

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Objective:

Studies showing improved outcomes with tight glycemic control in the ICU have resulted in numerous insulin delivery algorithms being proposed. The objective of this study was to determine under which conditions an algorithm can be expected to perform better.

Methods:

Dose-response curves and dynamic responses to persistent hyperglycemia were calculated for the Portland (P), University of Washington (UW), Yale (Y), Glucommander (GM), and proportional-integral-derivative (PID) algorithms.

Results:

All five algorithms increased insulin in response to persistent hyperglycemia, but the underlying mechanism did not alter the dose response in the P and PID protocols, whereas it increased the sensitivity to glucose in the GM, UW, and Y protocols.

Conclusions:

The gradual rise in insulin delivery in response to persistent hyperglycemia, observed in all algorithms, can be expected to bring subjects to target glucose irrespective of differences in insulin sensitivity. However, as the mechanism used to affect the rise did not alter the dose response in the PID or P protocols, these algorithms can be expected to take longer to achieve target glucose in the presence of insulin resistance. The increased sensitivity to glucose observed with GM, UW, and Y algorithms should allow the algorithms to maintain the same time to normalization, provided that insulin resistance is not associated with a slower insulin effect. If the effect is slower, the algorithms may be prone to hypoglycemia. Therefore, if the time for insulin to act is not expected to change, algorithms that adjust sensitivity may be preferred. If both insulin sensitivity and the time for insulin to act are expected to change, algorithms that increase insulin without changing their sensitivity to glucose may be preferred.

Detection of Qualitative Glycemic Control Differences as a Function of Baseline Hemoglobin A1c in Pediatric Type 1 Diabetes Mellitus Patients Treated with Pump Compared to Insulin Injections Using Group Functions Derived by Discrete Fourier Transformation of Continuous Glucose Monitoring Data

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Objective:

Calculated averages may mask differences in subgroups. Continuous glucose monitoring (CGM) provides detailed information about glucose fluctuations, but this information is often lost in trial analysis. The objective of this study was to illustrate a methodology developed to compare 24-hour glycemic control between treatment groups as a function of baseline hemoglobin A1c (HbA1c).

Methods:

This was a post-hoc analysis of data from a DirecNet study randomizing type 1 diabetes mellitus to standard care or use of the GlucoWatch Biographer reporting no effect of injection route. Insulin injection methodology mean function estimates were based on a 12 cycle Fourier approximation of each CGM 24-hour tracing, applying a multivariate linear model to all Fourier coefficients. Estimates at quartile baseline HbA1c were obtained as predicted values from the multivariate model. Twenty-four-hour injection methodology comparisons used parametric bootstrap of the maximum absolute deviation between the curves.

Results:

Consistent with the published results of the study, there were no overall difference in 24-hour glucose between continuous subcutaneous insulin infusion (CSII) and insulin injections (INJ) (data not shown). Patients with baseline glycemic control at the lower quartile HbA1c = 7.3% had lower glucose on CSII compared to INJ, particularly during the morning. Final HbA1c values were $7.5 \pm 0.1\%$ CSII and $7.7 \pm 0.1\%$ INJ. In contrast, there were no differences between CSII and INJ in 24-hour glucose in patients at the higher baseline quartile of HbA1c = 8.5% and end HbA1c at 8.6 ± 0.1 and $8.3 \pm 0.1\%$ for CSII and INJ, respectively.

Conclusion:

Employing Fourier transformation of CGM as part of an integrated multivariate model allows formal comparison of glycemic control in any defined time interval providing more detailed information than an HbA1c. Well-controlled T1DM on CSII achieved better glycemic control during morning hours compared to INJ.

Postprandial Glucose Levels and Hypoglycemia in Japanese Type 1 Diabetes Patients Monitored by Continuous Glucose Monitoring

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Background:

Little information is available regarding postprandial glycemic excursions and hypoglycemia in Japanese type 1 diabetes (T1D) patients.

Method:

The study participants comprised 17 T1D patients who were on intensive insulin therapy with rapid-acting insulin plus basal insulin. Twenty-four-hour mean glucose levels/their standard deviations (SD), glucose levels before each meal, the highest glucose levels within 4 hours of each meal, the time to peak glucose levels from the beginning of each meal, and postprandial glycemic excursions, as well as duration of hypoglycemia (<70 mg/dl), were measured using continuous glucose monitoring (CGM).

Results:

The characteristics of the study participants (5 males/12 females) were as follow [median (25–75%)]: age, 32.0 (26.5–50.5) years; body mass index, 21.8 (19.0–23.4) kg/m²; duration of T1D, 8.8 (4.7–20.3) years; urinary C-peptide, 0.80 (0.50–6.05) µg/day; hemoglobin A1c after 2 months of CGM, 6.6 (6.0–9.0) %; total insulin dosage, 40.0 (33.0–48.0) IU/day; and basal/total insulin ratio, 0.33 (0.21–0.45). Mean glucose levels/their SD over 24 hours were 127 (106–167) mg/dl /45 (39–63) mg/dl. Premeal glucose levels before breakfast, lunch, and supper were 122 (88–183)/127 (78–191)/79 (94–136) mg/dl. The highest postprandial glucose levels measured after each meal were 244 (166–297)/229 (167–263)/182 (152–216) mg/dl. Differences between premeal and the highest postprandial glucose levels for each meal were 95 (50–124)/67 (50–123)/71 (50–105) mg/dl. Time intervals from the start of each meal to the highest postprandial glucose levels were 95 (45–133)/60 (42–108)/75 (53–123) minutes. Hypoglycemia was observed in 88.2% of the patients and lasted for 145.0 (47.5–372.5) minutes.

Conclusion:

Glucose levels peaked in Japanese T1D patients 60 to 95 minutes postprandially, but in less than 2 hours. The largest glucose excursions were observed after breakfast. Special attention should be paid to episodes of hypoglycemia, which were observed to last for more than 2 hours.

Blood Glucose Monitoring Should Not Be a Risk Factor for Hepatitis B Virus Infection

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Objective:

In long-term care (LTC) settings where blood glucose monitoring (BMG) equipment is shared among residents without either adequate disinfection between every use or use of equipment dedicated to each resident, multiple opportunities for blood borne pathogen transmission can occur. In 1990 and 2005, the Centers for Disease Control and Prevention (CDC) published recommendations for providing safe diabetes care in LTC settings, yet outbreaks of hepatitis B virus (HBV) infection continue in these settings. Here, we summarize these outbreaks and highlight the role that diabetes technology can play in prevention.

Method:

We reviewed reports to CDC of outbreaks of HBV infection in LTC settings—nursing homes and assisted living facilities that have been investigated in the past 10 years.

Results:

We identified 15 outbreaks of HBV infection at U.S. LTC facilities between 1999 and 2008. During these outbreaks, 97 residents acquired incident HBV infection and 4 (4.1%) died as a result of their infection. Infections clustered almost exclusively among diabetics. Each outbreak was attributed to unsafe BGM practices that exposed HBV-susceptible residents to blood-contaminated BGM equipment used previously on a resident with chronic HBV infection. The predominant unsafe BGM practices identified were the sharing of finger stick and glucometers among diabetic residents without adequate cleaning between each use.

Conclusion:

Through lack of awareness or failure to follow published recommendations, HBV infection outbreaks continue to occur in LTC settings. Because of underreporting, the scope of the problem is likely much greater. Engineering controls, such as the development of BGM equipment that can withstand frequent disinfection and noninvasive glucose monitoring methods, could reduce unnecessary HBV and other blood borne infectious morbidity and mortality that currently burden diabetic residents in LTC settings.

Very Brief Weaning to Extensively Hydrolyzed Cow Milk Formula Is Sufficient for Type 1 Diabetes Prevention in Nondiabetic Mice

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Objective:

Factors influencing the development of type 1 diabetes (T1D) continue to be of great interest. In T1D-permissive rodents, one diabetogenic event maps to weaning with commonly used complex foreign protein diets; weaning to severely hydrolyzed cow milk proteins prevents T1D. We investigated the minimal delay of exposure to intact foreign protein diets necessary for T1D protection.

Methods:

Three groups of nondiabetic female mice were weaned (20 days) to either standard chow or rodent-modified/pelletized infant formulas (Nutramigen™, Alimentum™) for 3–37 weeks. Prediabetes progression was monitored [blood glucose, insulinitis, irumahalperi-islet Schwann (pSC) death, T-cell autoreactivity].

Results:

Chow-fed mice developed T1D at high incidence (>85%). Hydrolysate-fed mice were protected from T1D ($p < 0.001$), but not from loss of T-cell tolerance ($p > 0.05$). The first islet infiltrates appeared at the same time in all animals, but halted at the pSC border in hydrolysate-fed mice, with little evidence of pSC death for several months. Subgroups of mice were crossed to normal chow at varied ages. Surprisingly, long-term T1D protection was observed after crossover at 40 days of age, i.e., after only a 3-week exposure to hydrolysates, providing the first hard datum for the hydrolysate-sensitive event in T1D progression. Alimentum and Nutramigen provided equivalent T1D protection throughout ($p > 0.05$).

Conclusions:

The time window where complex foreign protein diets promote prediabetes progression is narrow (3 weeks). T1D protection does not affect initiation of islet inflammation nor loss of tolerance, but rather its progression to pSC destruction. These data from two commercial infant formulas add to the promise of human T1D prevention efforts in the ongoing Trial to Reduce IDDM in the Genetically at Risk aimed at translating such animal experiments to humans.

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Role of Diabetes Interface Device in Clinic Settings

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Objective:

The objective of this study was to demonstrate improved clinical decision making based on more efficient detailed gathering of self-monitoring of blood glucose (SMBG) data and trend analysis with use of a new device, Intelligent Diabetes Interface (IDI), enabled to interface 14 different blood glucose monitors with electronic medical records (EMR), in ambulatory care settings.

Method:

The IDI device is a USB human interface device that uploads blood glucose readings from 14 different blood sugar monitors and transfers it to the EMR via a USB port. Data then are analyzed using a custom reporting tool that allows the provider to better monitor patient's glucose readings. The device was tested at an endocrinology practice for 3 weeks. The IDI device was used to import data from patients who brought in their blood sugar monitors. Data were then compared with manual readings of blood glucose meters or log books to the time taken with the IDI device. Nursing staff, providers, and patients were interviewed for a 3-week study design. The following devices were downloaded during the study period: OneTouch Ultra, OneTouch Ultra2, FreeStyle, FreeStyle Flash, Accu-Chek Active.

Result:

Ease of use for clinical staff and patient satisfaction was observed. Other effects noted were improved staff efficiency, improved patient satisfaction, higher quality of office visits, and dramatically improved clinical decision making.

Conclusion:

The analysis of such SMBG data is crucial in determining the most likely causes of lack of blood glucose control (looking for trends), selection of best possible therapy, and monitoring effects of therapy. This will enhance the quality of care for long-term diabetes mellitus management. This process can be performed simultaneously with patient check in and does not require extra staff. Data are available at the time of patient examination and can be physically demonstrated to the patient, thereby enhancing patient involvement in clinical decision making. Along with other features of EMR, this can allow higher quality of physician–patient interaction at the time of office visit. Overall, higher quality office visits with added efficiency are realized using such a unique device. This data analysis report can be a codable function for which reimbursement is potentially possible.

Because patients are not required to maintain glucose logs, use of this device definitely increases patient compliance.

A Miniaturized Multianalyte Sensor for Simultaneous Detection of Glucose, Lactate, and Oxygen

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Introduction:

A revolutionary, miniaturized multianalyte sensor for continuous metabolic monitoring that can detect glucose, lactate, and O₂ without interference from other species or chemical cross talk is reported. Nanotechnology is used to fabricate the O₂ sensor to allow low voltage (−0.1 V) operation, where interferences from endogenous species are minimal. Semipermeable membranes were used to modulate analyte diffusion, and an outer inflammation suppressing coating was used to prevent a negative tissue response. This groundbreaking multianalyte sensor has application to diabetes care, as well as weight management and obesity.

Methods:

Glucose- and lactate oxidase-modified working electrodes were utilized for amperometric detection of glucose and lactate, respectively. Oxygen was detected by electrochemical reduction, using a nanocomposite-modified electrode (operating at −0.1 V). A variety of semipermeable membranes were developed for each sensor to extend their linear ranges well beyond normal physiological levels (hypo as well as hyper).

Results:

Controlled growth of various polyelectrolytes and hydrogel membranes, using layer by layer (LBL) and dip coating, has enabled modulation of analyte diffusion coefficients over two orders of magnitude. For example, using LBL-grown membranes and a subsequent hydrogel layer, the Michaelis–Menten constant of glucose has been increased from 2 mM to 11 and 17 mM, respectively. Similar results were obtained for lactate and O₂. The multianalyte sensor has been tested *in vitro*, and each sensing element exhibited functionality in excess of 3 months.

Conclusions:

The multianalyte sensor displays exceptional sensitivities, linearities, response times, and *in vitro* lifetimes with no interference or cross talk (which until now have been a major roadblock to multianalyte sensor development). Together with our inflammation and fibrosis controlling outer membranes, this multisensor is poised to revolutionize diabetes care and weight management.

Interpreting the GLYCENSIT Procedure Used in the Assessment of Glucose Sensors

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Objective:

The GLYCENSIT procedure (www.esat.kuleuven.be/GLYCENSIT) has been introduced as a new method to evaluate the reliability of blood glucose meters and glucose monitoring systems. This work demonstrated the practical use of this new assessment method with three hypothetical examples.

Method:

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 the International Organization for Standardization (ISO) criterion, 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.

Result:

The practical relevance of the GLYCENSIT procedure is discussed in some detail. Since *overestimated* measurement behavior may result in potentially dangerous false negatives (e.g., failure to measure true hypoglycemic events) and since *nonpersistent* measurement behavior avoids the use of a conversion factor, persistently *underestimated* measurement behavior over the full glycemic range is preferred (tested in phase 1). Next, the relative number of errors against the ISO criterion reveals the accuracy of the sensor device under study (tested in phase 2). Finally, statistical tests will only be meaningful if sufficient amounts of data are available, presented by probability level P that is computed in phase 3. In that phase, the computed tolerance intervals are used to illustrate the range in which the value, which would have been obtained with the reference device, lies with a certain probability P when a new test measurement is introduced.

Conclusion:

These hypothetical examples help interpret statistically based GLYCENSIT results correctly and show potential shortcomings of currently existing evaluation methods.

Procedure for Assessing and Comparing Different Blood Glucose Control Algorithms Applied in the Intensive Care Unit

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Objective:

In order to maintain normoglycemia in the intensive care unit (ICU), many authors are developing (semiautomated) blood glucose control or insulin infusion titration algorithms. We introduce a specific procedure to assess and compare different algorithms and illustrate the pitfalls that may falsify algorithm assessments.

Method:

Reviewing the available literature returned that studies that compare the performance of different insulin titration algorithms applied to the critically ill should rely on the “similarity conditions”: the duration of algorithm application and the blood glucose sampling frequency should be similar among patient groups. Further, validated ways of measuring blood glucose should be used as the quality of the glucose measurements influences the level of glycemic control and the efficiency of the selected assessment measure.

Result:

A practical procedure that can be used for adequately evaluating/comparing different insulin infusion algorithms in the ICU is proposed. The “similarity conditions” are taken into consideration such that the influence of different blood glucose sampling frequencies and/or different durations of algorithm application on the assessment of a blood glucose protocol is limited. The HyperGlycemic Index and the Glycemic Penalty Index are found to be efficient measurement tools and the pitfalls originating from (inaccurate) glucose measurements are discussed.

Conclusion:

This work introduced a practical procedure for the assessment of (semiautomated) blood glucose control algorithms. The proposed procedure takes into account potential pitfalls.

Comparison of Sagittal Abdominal Diameter and Waist Perimeter Measured at Four Different Anatomical Sites for Prediction of the Homeostasis Model Assessment–Insulin Resistance Index in Adult Men

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Objective:

This study evaluated the effectiveness of four different measurements of the sagittal abdominal diameter (SAD) and the waist perimeter (WP) in predicting the risk of insulin resistance.

Method:

One hundred thirty-eight Brazilian men (20–59 years old), apparently healthy, were evaluated. The SAD was measured at the narrowest waist (SAD1), at the largest diameter (SAD2), at the umbilical level (SAD3), and at the midpoint between the iliac crests (SAD4). The WP was measured at the narrowest waist (WP1), immediately above the iliac crest (WP2), at the umbilical level (WP3), and at the midpoint between the last rib and the iliac crest (WP4). Insulin resistance was evaluated by the homeostasis model assessment–insulin resistance index, considering the percentile 75 as the cutoff point. Statistical analysis consisted of Spearman correlation coefficient and receiver operating characteristic (ROC) curves, with calculation of areas under the curve (AUC).

Result:

The SAD1 showed stronger correlation and greater AUC ($r = 0.482/AUC = 0.739 \pm 0.049$) than results for the SAD2 ($r = 0.458/AUC = 0.726 \pm 0.05$), the SAD3 ($r = 0.477/AUC = 0.726 \pm 0.05$), and SAD4 ($r = 0.458/AUC = 0.716 \pm 0.05$) ($p < 0.001$), whereas the WP4 showed stronger correlation and greater AUC ($r = 0.464/AUC = 0.746 \pm 0.05$) than the WP1 ($r = 0.434/AUC = 0.736 \pm 0.05$), the WP2 ($r = 0.453/AUC = 0.728 \pm 0.05$), and WP3 ($r = 0.455/AUC = 0.738 \pm 0.05$) ($p < 0.001$).

Conclusion:

The SAD measured at the narrowest waist and the WP measured at the midpoint between the iliac crest and the last rib showed better efficiency in predicting the insulin resistance risk. Further investigations in other extracts of the population and in other ethnic groups should be undertaken in order to facilitate the adoption and the use of these insulin resistance indicators in a standardized way, as there are different recommendations in the literature for these two measures.

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The Ability of Anthropometric Indicators for Prediction of the Homeostasis Model Assessment–Insulin Resistance Index in Adult Men

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Objective:

This study assessed the ability of anthropometric indicators to predict the insulin resistance (IR) risk.

Methodology:

One hundred thirty-eight healthy Brazilian men (20–59 years old) were evaluated. The anthropometric indicators studied were waist perimeter (WP), sagittal abdominal diameter (SAD), conicity index (CI), waist-to-height ratio (WER), body mass index (BMI), waist-to-hip ratio (WHR), waist-to-thigh ratio (WTR), and sagittal index (SI). The IR was evaluated by the homeostasis model assessment–IR index, considering the percentile 75 as the cutoff point. Statistical analysis consisted of Spearman correlation coefficient and receiver operating characteristic (ROC) curves, with calculation of areas under the curve (AUC).

Result:

The correlation coefficients and the AUC found were SAD ($r = 0.482$ and $AUC = 0.739 \pm 0.049$), WP ($r = 0.464$ and $AUC = 0.746 \pm 0.049$), CI ($r = 0.370$ and $AUC = 0.682 \pm 0.052$), WER ($r = 0.406$ and $AUC = 0.702 \pm 0.054$), BMI ($r = 0.377$ and $AUC = 0.696 \pm 0.049$), WHR ($r = 0.379$ and $AUC = 0.687 \pm 0.053$), WTR ($r = 0.345$ and $AUC = 0.659 \pm 0.053$), and SI ($r = 0.350$ and $AUC = 0.636 \pm 0.054$) ($p < 0.001$), respectively. The anthropometric indicators of central obesity, especially WP and SAD, have shown greater ability to predict IR risk, as they showed the strongest correlations and the largest AUC. According to the literature, this result can be explained by the strong correlation of these two measures with the amount of visceral fat, which is directly associated with the development of cardiometabolic complications as IR.

Conclusion:

Use of the WP and the SAD as alternative instruments for the IR prediction in clinical practice is advisable. However, further studies assessing other samples, including women, adolescents, elderly, and other ethnicities, should be conducted, enabling their use as alternative tools to assess the IR risk and hence to prevent diseases in the whole population.

Acknowledgment:

This work was supported by FAPEMIG and CNPq.

The Ability of Biochemical Lipid Profile Indicators in Identifying High Levels of the Homeostasis Model Assessment–Insulin Resistance Index in Adult Men

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Objective:

This study investigated the effectiveness of biochemical lipid profile indicators as alternative instruments in identifying high levels of the homeostasis model assessment–insulin resistance (HOMA-IR) index in men.

Method:

One hundred thirty-eight healthy Brazilian men (20–59 years old) were evaluated. The lipid profile biochemical indicators analyzed were triglycerides (TG), total (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and TC/HDL-C and TG/HDL-C ratios. The IR was evaluated by the HOMA-IR index, considering the percentile 75 as the cutoff point. Statistical analysis consisted of Spearman correlation coefficient, receiver operating characteristic (ROC) curves, and calculation of areas under the curve (AUC).

Result:

The TG/HDL-C ratio showed the strongest correlation and the greater AUC ($r = 0.334$ and $AUC = 0.724 \pm 0.046$, $p < 0.001$) respectively, followed by the HDL-C ($r = -0.313$ and $AUC = 0.716 \pm 0.052$, $p < 0.01$), the TG ($r = 0.261$ and $AUC = 0.048 \pm 0.674$, $p < 0.01$), and CT/HDL-C ratio ($r = 0.259$ and $AUC = 0.655 \pm 0.05$, $p < 0.01$). Results for TC and LDL-C showed no statistical significance ($p > 0.05$). Increased efficiency of the TG/HDL-C ratio in predicting high levels of the HOMA-IR index, compared to the other biochemical indicators, can be attributed to the frequent dyslipidemia present in individuals with IR, characterized by low HDL-C levels and high TG levels, as well as small and dense LDL-C particles and increased postprandial lipoproteins remnants.

Conclusion:

The TG/HDL-C ratio is an alternative and easy access instrument to assess IR in clinical practice, providing diseases prevention in adult male population. However, further studies assessing women, adolescents, elderly, and other ethnic groups should be conducted.

Acknowledgment:

This work was supported by FAPEMIG and CNPq.

Novel Approach to Stochastic Modeling and Prediction of Continuous Glucose Data

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Objective:

It is known from a variety of studies that tight glycemic control will help prevent or least delay comorbidities of diabetes. The American Diabetes Association recommends an average blood glucose value of 110 mg/dl (6.1 mM) as being optimal. A tool to help the diabetes patient control blood glucose levels by making suggestions on food intake, insulin dosing, and so on is highly desirable. This, however, requires highly personalized and adaptive tools. The key element is the prediction of glucose on a timescale of hours.

Method:

Data from subcutaneous continuous glucose measurements of six patients with diabetes type 1 were collected (body mass index 24.3 ± 2.4 , age 37 ± 12 , all diagnosed with diabetes type 1 at least 10 years ago). The patients were asked to keep a diary with scheduled monitoring of diet, emotional status, and activities. The patients were additionally monitored with an activity monitor; in some cases, insulin pump data were also available. Various statistical methods for analysis of multivariate time series have been explored.

Result:

Physiological signals are notoriously difficult to analyze. These signals typically exhibit long-range dependence and a number of other properties, which make accurate prediction problematic. We showed that glucose data have all these properties. We applied a number of standard mathematical and statistical techniques to the problem of prediction. We confirmed that classical autoregressive stochastic models are sufficiently accurate only on relatively short (30 minutes) prediction horizons. We identified a class of stochastic models that are more suitable for modeling and predictions of continuous glucose data.

Conclusion:

Successful prediction of blood glucose requires application of nonlinear or nonstationary mathematical models. First results will be presented.

Development of Noninvasive Continuous Glucose Estimation Models for Free-Living Conditions

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Objective:

Monitoring blood glucose levels continuously is a key component of treating diabetes and preventing complications such as heart disease, blindness, nerve damage, and kidney failure. We examined the ability of the BodyMedia's SenseWear Pro3 wearable armband to estimate blood glucose values in a noninvasive and continuous manner in free-living conditions.

Methods:

This study was performed on 15 individuals who were either diagnosed with type II diabetes or were prediabetic. For each subject, data were obtained by a Medtronic MiniMed continuous glucose monitor (CGM) for a period of 3 days. During the trial, finger stick readings for blood glucose levels were also obtained four to six times per day. All subjects wore the armband on the back of the upper left arm during the trial. The armband measured movement, heat flow, skin temperature, galvanic skin response, and electrical activity and estimated energy expenditure and heart rate. A food log was also maintained and used for developing the glucose estimation models. Variables for modeling were personalized for each subject. Next, equations for estimating blood glucose values were developed from data and evaluated using by-subject cross-validation.

Results:

The absolute average error between estimated glucose values and CGM values was 21.1 ml/dl (14.1%) and the correlation between values was 0.77. The correlation between model estimates and finger stick glucose values was 0.87 and the average error was 21.30 ml/dl (15.7%). A Clarke error grid analysis between model estimates and Medtronic CGM values yielded 97.33 % points falling in zone A and B (81% in zone A).

Conclusion:

This study suggested that the armband may provide the capability to monitor blood glucose level changes continuously during free-living conditions.

Hunger Assessed by Subjective Appetite Scores and Hypoglycemic Events in Continuous Subcutaneous Insulin Infusion Therapy and Multiple Dose Insulin Injection Therapy in Type 1 Diabetes Mellitus

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Objective:

No studies have investigated appetite in type 1 diabetes mellitus (T1DM) subjects on continuous subcutaneous insulin infusion (CSII) or multiple dose insulin injection (MDI) therapy. Compared with MDI, CSII is associated with reduced 24-hour insulin requirements, less weight gain, and fewer hypoglycemic episodes. This study examined hypoglycemic events and appetite in patients on CSII and MDI and assessed the relationship among appetite, interstitial glucose levels, and food intake.

Method:

Eighteen T1DM subjects on MDI and 15 T1DM subjects on CSII were recruited to have continuous glucose monitoring (CGMS) for 48 hours. Appetite was assessed subjectively using visual analogue hunger scores (VAS) before and after each meal during the monitoring; all food and drink were recorded.

Results:

The CSII and MDI groups were matched for age and duration of T1DM, although hemoglobin A1c was significantly lower in the CSII group ($p < 0.05$). Hypoglycemic events over the study period were similar for the CSII and MDI groups. Overall subjective hunger scores were significantly higher in CSII subjects ($p < 0.0001$) and both before and after meals. Subjective hunger scores were significantly negatively correlated with interstitial glucose levels ($p < 0.0001$) and significantly positively correlated with kilocalorie intake ($p < 0.0001$). Interstitial glucose was the same premeals but significantly lower postprandially in the CSII group.

Discussion:

Higher hunger scores among the CSII subjects could be because of their lower mean blood glucose levels. Supporting this hypothesis, a significant negative correlation exists between interstitial glucose levels and subjective appetite.

Conclusion:

Significantly higher hunger scores found in the CSII group could not be attributed to differences in hypoglycemic events, but may be because of better overall glycemic control, including the postprandial period.

Glucose Control for Type 1 Diabetes Mellitus Based on Iterative Learning Model Predictive Control

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Objective:

Continuous glucose monitoring (CGM) technology has evolved to a mature state for use in closed-loop glucose control. Frequent glucose readings, together with the repetitive nature of the daily eating habits, can promote glycemic control through a novel combination of iterative learning control (ILC) and model predictive control (MPC).

Methods:

An *in silico* study of subjects with type 1 diabetes mellitus (T1DM) based on the model by Dalla Man and colleagues was performed in MATLAB® (The MathWorks, Inc., Natick, MA). A unique combination of ILC and MPC was used to develop the control algorithm (ILMPC). An ARX model was used as the subject-specific model for the control algorithm. The ILC exploits the daily patterns and MPC augments the ILC control law to compensate for disturbances and irregularities.

Results:

The proposed method was validated on an *in silico* diabetic subject who followed a daily pattern of three meals at 7 am, noon, and 6 pm of 20, 40, and 60 grams of carbohydrates, respectively. In less than 10 days, the algorithm converged to the desired glucose range of 80–150 mg/dl. The method has been proven to be robust to random variations in both meal timing of ± 40 minutes and meal size of $\pm 50\%$ of the nominal values, where 97% of glucose concentrations are in the 60- to 180-mg/dl range. The algorithm was tested on several of the patients in the study by Dalla Man and colleagues.

Conclusions:

This novel combination that learns an individual's lifestyle can be used in a future artificial β cell. This algorithm does not rely on the subject's inputs. Thus the algorithm is appealing for closed-loop systems, particularly for children and adolescents.

Avoidance of Interference from Acetaminophen and Ascorbic Acid in an Amperometric Glucose Microsensor: A Study in Type 1 and Type 2 Diabetes

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Objective:

Oxidizable compounds can interfere with glucose sensor accuracy by creating a glucose-like current. We developed a multilayered glucose sensor that contains a selectivity layer designed to reject acetaminophen and ascorbic acid. We hypothesized that such a device would respond to glucose while preventing a response to these interferents. *In vitro* testing verified minimal interference from many interferents.

Methods:

Subjects with type 1 or insulin-treated type 2 diabetes wore two miniaturized sensors (330 μ M diameter) that had been subcutaneously inserted into the abdomen during the prior day. For the first 6 hours, the sensors were tested for accuracy in the absence of interfering compounds. At minute 360, either acetaminophen (APAP, 1000 mg, 10 sensors) or ascorbic acid (AA, 1000 mg, 8 sensors) was given orally. The sensor function was then followed for an additional 4 hours. Serum levels of acetaminophen or ascorbic acid were drawn every 30–60 minutes until minute 600. The Yellow Springs Instrument glucose analyzer was used to measure reference glucose.

Results:

The serum level of APAP rose quickly, peaked 60 minutes after administration, and stayed elevated until the end of the study. The level of AA rose more slowly and peaked 240 minutes after administration. Sensor accuracy is expressed in terms of mean absolute relative difference (ARD) and median ARD.

	Control	APAP	Control	Ascorbic acid
ARD (%), mean \pm SD	12.1 \pm 9.3	11.8 \pm 10.3	17.4 \pm 17.9	8.9 \pm 8.3
ARD (%) median	9.8	8.5	12.9	6.3
<i>n</i> (data pairs)	301	147	218	97

Sensors performed with a high degree of accuracy, both before and after administration of APAP or ascorbic acid.

Conclusion:

Inclusion of a selectivity membrane within the multilayered membranes of a glucose sensor prevented clinically significant interference from the two major interferents, despite elevated serum levels of those compounds. Allowing oral administration of APAP or ascorbic acid will add to patient acceptance.

Noninvasive Continuous Glucose Monitoring for Diabetic and Critically Ill Patients

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Objective:

This work presented the use of the noninvasive NBM device (OrSense Ltd.) for continuous glucose monitoring. Two groups participated in the study: patients in an intensive care unit (ICU), where glycemic control is associated with less morbidity and mortality, and home patients with type 1 and 2 diabetes.

Method:

OrSense technology is based on measuring the time-dependent optical transmission resulting from a temporary occlusion of the finger's blood flow. The NBM probe was placed on the patient's finger for up to 24 hours, with readings every 10 minutes. In the first group there were 14 ICU patients from the Rabin Medical Center, while in the home scenario group there were 25 sessions (from 15 patients). Reference values were measured every 30–60 minutes using a blood gas analyzer (for the ICU group) or a self-monitoring glucometer (home group).

Result:

The ICU group produced a total of 208 paired glucose points (NBM vs reference). The median relative absolute difference (RAD) was 7.3%, and a Clarke error grid showed that 95.2% of the measurements fell within zones A (74.5%) and B (20.7%). For the home group, with 1068 paired glucose values, the median RAD was 12.3, and 95.1% of the points fell within the A+B regions (zone A: 66.7% and zone B: 28.4%). Use of the device did not cause any discomfort for subjects, was safe, and well tolerated.

Conclusion:

This study indicated the potential use of the noninvasive NBM for continual, accurate, safe, and easy-to-use blood glucose evaluation. The information gained by the device is of clinical utility for people with diabetes at home and for patients in ICU and other hospital departments.

Validation of Simulation Environment Utilizing Clinical Data Collected during Overnight Closed-Loop Glucose Control in Children and Adolescents with Type 1 Diabetes

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Objective:

The goal to this study was to validate the *in silico* simulation environment designed to support the development of the artificial pancreas for overnight closed-loop glucose control in children and adolescents with type 1 diabetes (T1D).

Methods:

A virtual population of 18 subjects with T1D was used to simulate a 15-hour-long clinical study with a model predictive controller (MPC). The protocol of the simulated study reflected the real clinical trial conducted in 12 children and adolescents with T1D. At 18:00 virtual subjects had a meal containing the mean carbohydrate (CHO) intake recorded in the real study (87 grams CHO) accompanied by a prandial insulin bolus. A closed-loop glucose control was run from 20:00 to 08:00 the next day. Subcutaneous glucose was measured in real time by a continuous glucose monitoring (CGM) device. CGM glucose was provided every 15 minutes to MPC, which in turn advised on subcutaneous insulin infusion rate adjustments.

Results:

Starting blood glucose during the simulated study was designed to match that of the real study [9.8 ± 3.1 mM vs 9.5 ± 3.7 mM, $p =$ nonsignificant (NS); mean \pm SD]. CGM glucose at the start of closed-loop control (12.2 ± 4.0 mM vs 10.6 ± 3.0 mM, $p =$ NS) and mean overnight CGM glucose (7.6 ± 1.2 mM vs 7.8 ± 1.4 mM, $p =$ NS) were similar during simulated and real studies. Time spent in the 3.9 to 8.0 mM target glucose range was not significantly different at 69 (62–78)% vs 63 (49–78)% [median (interquartile range)] ($p =$ NS). Kovatchev's low blood glucose (BG) index [0.5 (0.2–0.9) vs 0.3 (0.0–1.0), $p =$ NS] and high BG index [3.4 (1.3–6.8) vs 3.7 (0.6–6.8)], $p =$ NS) were also similar during real and simulated studies.

Conclusions:

MPC performance was comparable during real and simulated studies, providing rationale for the use of the simulation environment to forecast the outcome of future closed-loop studies in subjects with T1D.

Glucose Underestimation by the FreeStyle Navigator System: Effect on Overnight Closed-Loop Insulin Delivery Assessed by Simulations

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Introduction:

The FreeStyle Navigator[®] continuous glucose monitoring system may transiently underestimate plasma glucose (PG). These “dropouts” are believed to occur when pressure is applied to the transmitter, such as may occur when lying on the device. Dropouts typically last on the order of 15 minutes or less, although longer ones have been observed. Adopting *in silico* study design, we evaluated the effect of dropouts on overnight closed-loop insulin delivery with model-predictive control (MPC).

Methods:

Dropouts from 194 nights were analyzed and classified into quartiles based on severity: Q1 represented the least and Q4 the most significant dropouts. Forty-one representative data sets, spanning quartiles, were chosen. Data sets were incorporated into a metabolic simulator, which included 18 synthetic subjects with type 1 diabetes, resulting in 738 simulated nights of MPC-driven insulin delivery.

Results:

Based on PG, time in target (3.9–8.0 mM) was comparable for Q1–Q3 at ~80% and lower for Q4 at 67%. Kovatchev’s low blood glucose index was not affected by dropouts and was between 0.5 and 1.0 for all quartiles; Kovatchev’s high blood glucose index increased from ~1.7 for Q1–Q3 to 2.8 for Q4. This reflected the increase in mean PG from ~6.8 mM for Q1–Q3 to 7.5 mM for Q4. Adopting a 3.5 mM threshold, the ratio of PG to sensor glucose (SG) alarms was reduced from 0/10 in Q1 to 7/34, 2/27, and 5/150 in Q2, Q3, and Q4, respectively. Overall, there was one alarm per 53 nights based on PG and one alarm per 3.3 nights based on SG.

Conclusions:

FreeStyle Navigator dropouts are expected to lead to false-positive hypoglycemia alarms during closed-loop insulin delivery at a rate of approximately two per week. This does not affect safety and efficacy except for mildly elevated glucose, which follows from reduced insulin delivery during the worst dropouts.

In Silico Monte Carlo Virtual Trials of a Model-Based Adaptive Type 1 Diabetes Mellitus Control Protocol

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Objective:

The goal of this study was to test an *in silico* type 1 diabetes control protocol while accounting for realistic physiological variability and measurement and delivery error.

Methods:

A Monte Carlo (MC) analysis uses clinically reported variations in physiological parameters, subcutaneous insulin absorption and delivery, nutritional carbohydrate counting intake, and self-monitoring of blood glucose (SMBG) error to test robustness. The model-based protocol was tested repeatedly on a 40 patient virtual cohort over 1.4M patient hours. The analysis was repeated for SMBG frequency of 2–10/day. Long-term hemoglobin A1c (HbA1c) was estimated from clinically reported formulas to assess performance.

Results:

The protocol controlled 100% of the cohort to American Diabetes Association-recommended HbA1c with a SMBG frequency of 6/day. Peak control was achieved at a SMBG frequency of 8/day. A small but significant decrease in time in the 72- to 144-mg/dl band and a consequent increase in mild and severe hypoglycemia occurred at a SMBG frequency of 10/day. Time spent in the 72- to 108-mg/dl band was not significantly different to a no error and no variability simulation. Cohort HbA1c was reduced for all SMBG frequencies. Hypoglycemia increased over the no error simulation, as expected. The difference in the 95% confidence band for time in severe (≤ 54 mg/dl) and mild (≤ 71 mg/dl) hypoglycemia spanned an acceptable (1–6%) or 0.24–1.44 hours/day versus the no error simulation for the 6/day SMBG frequency.

Conclusions:

A MC simulation tool predicts long-term glycemic control outcomes to test an adaptive control protocol in conditions of realistic variability and error. The protocol was shown to be robust, remaining effective and safe from hypoglycemia compared to perfect no error or variability simulations and clinical cohort control data. The protocol utilized the most commonly used forms of intervention (SMBG and multiple daily injections) and is thus applicable for most type 1 diabetes mellitus individuals.

Novel Nanogels Containing β -Cyclodextrin and Poly(β -aminoester) for Controlled Release of Insulin across the Blood–Brain Barrier

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Objective:

Studies have shown that insulin deficiency in the brain caused by type I diabetes could promote brain damage and causes Alzheimer's disease and other dementias. The objective of this project was to develop novel cationic and biodegradable nanogels for controlled delivery of insulin across the blood–brain barrier (BBB) toward the goal of increasing the insulin availability to brain cells to improve memory.

Method:

A series of β -cyclodextrin-based nanogels with tertiary amine groups and/or quaternary amine groups were synthesized using the Michael addition reaction and sequentially quaternizing the tertiary amine groups using CH₃I. The structure, particle sizes, and degradation of the nanogels were characterized using attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR), nuclear magnetic resonance, dynamic light scattering (DLS), and atomic force microscopy (AFM). Fluorescein isothiocyanate (FITC)–insulin was loaded into the nanogels after the synthesis. The release of insulin from the nanogels was conducted in phosphate-buffered saline solution (PBS, pH 7.4) at 37°C by monitoring the fluorescent intensity of the release medium outside of the dialysis membrane. Cytotoxicities of the nanogels at concentrations of 10, 100, and 500 mg·ml⁻¹ to bovine brain microvessel endothelial cells (BBMVECs) and human brain microvessel endothelial cells (HBMVECs) were studied by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. The BBB permeability of the nanogels alone at 100 μ g·ml⁻¹ and with FITC–insulin (5 μ M) at 300 mg·ml⁻¹ was investigated using a model BBB consisting of a BBMVEC or HBMVEC monolayer.

Result:

The sizes of these nanogels were in the range of 20–400 nm, measured by DLS and AFM. ATR-FTIR results showed that these nanogels degrade with time in PBS through the cleavage of ester bonds in the nanogels. The release of insulin from the nanogels follows zero order up to 4 days with 80% of the payload released. The nanogels were not toxic to BBMVECs or HBMVECs at a concentration up to 500 μ g·ml⁻¹. The permeability of nanogels across the model BBB was 40% higher than that of dextran control with a molar weight of 4 kDa. The nanogels enhanced the permeability of FITC–insulin across the BBB about 20%.

Conclusion:

The developed novel biodegradable β -cyclodextrin–poly(β -aminoester) nanogels have great potential for sustained release of insulin across the BBB for the treatment of Alzheimer's disease and other dementias.

Improvement of Continuous Glucose Sensors Using the InsuPatch Device

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Background:

Current continuous glucose monitors (CGM) based on interstitial fluid (ISF) measurement are not accurate enough for replacing blood glucose measurements. Major limitations of the CGM accuracy are the delay of glucose transport between the blood and ISF compartments and variations of the glucose transport parameters between the two compartments.

Objective:

The InsuPatch device—a disposable heating patch developed by Insuline Medical—was tested for improving the accuracy of ISF-based CGM by local warming of the tissue around the CGM. This warming increases and stabilizes the blood perfusion at the measured tissue and also stabilizes the transport parameters of the glucose between the blood and the ISF compartments.

Method:

To evaluate the effect of the InsuPatch device on CGM measurements, two CGM system (Guardian® MiniMed Medtronic) sensors were used in a crossover study over four subjects. In each subject the first day of the study was used for attachment and calibration of the sensors. Then, four glucose excursions were carried out over 2 days, where the InsuPatch device was applied to a different sensor in each glucose excursion. For each glucose excursion the delays of the two glucose peaks of the two sensors relative to the reference glucose peak were calculated.

Results:

The result obtained for 12 glucose peaks shows an average delay of the reference CGM of 17.5 minutes (STD 3.8 minutes) and of 13.1 minutes (STD 3.4 minutes) with the InsuPatch device. Addition of the InsuPatch device reduced the delay between the CGM ISF glucose peak and the blood glucose peak by 25% ($p < 0.007$).

Conclusion:

The result suggests that the InsuPatch device may be used to reduce delay and improve the accuracy of CGM.

Performance Evaluation of a Blood Glucose Monitor That Requires No Coding: The OneTouch® Vita™ System

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Objective:

Improvements to blood glucose monitoring systems aim to simplify the testing process, reduce or eliminate errors, and provide additional information for patients with diabetes. New systems must continue to demonstrate high-quality analytical performance. The new OneTouch® Vita™ system offers a no-code testing process and proven technology found in the OneTouch® Ultra® test strip. Comparative laboratory and clinical studies were conducted with the new and established systems to evaluate their precision and accuracy.

Method:

Within-run precision in blood, total precision with controls, and system accuracy with capillary blood were tested using three lots of OneTouch Vita test strips and one lot of OneTouch Ultra strips. Accuracy was evaluated across a wide glucose range using finger tip samples from 139 subjects. Reference plasma glucose values were obtained using the Yellow Springs Instrument 2300. All studies were designed in accordance with requirements published by the International Organization for Standardization (ISO) 15197.

Result:

Precision testing (within-run and total) with both meter systems produced coefficients of variation (CVs) of <5% for all sample types and glucose levels. Within-run precision testing with blood showed CVs of ≤ 3.1 and $\leq 4.7\%$ for the OneTouch Vita and OneTouch Ultra systems, respectively. Total precision with control samples gave CVs of ≤ 3.0 and $\leq 3.6\%$ for the two systems. Consensus error grid analysis showed equivalent clinical accuracy with 98.4 and 98.2% of results within zone A. Both systems met the ISO acceptability requirements for system accuracy.

Conclusion:

The OneTouch Vita system provided a simple no-code testing process and performance equivalent to the OneTouch Ultra and OneTouch Ultra2 systems.

Hydrostatic Effects on Continuous Subcutaneous Insulin Infusion Pump Delivery Performance

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Objective:

This study quantified the hydrostatic effects on continuous subcutaneous insulin infusion (CSII) pumps during basal and bolus insulin delivery and pump suspension.

Methods:

We tested insulin infusion pumps from Medtronic, Smiths, and Insulet using a rapid-acting insulin analog and infusion tubing. Three pumps from each manufacturer were tested. Each pump was filled and primed with Novolog per the manufacturer's instructions. We measured the change in the fluid level displayed in an in-line graduated pipette (100 μ l) when the pump was moved in relation to the end of the tubing, first while suspended and then while delivering insulin. Pumps were compared during bolus doses of 1 and 5 units and during basal insulin delivery for 1-hour durations with rates of 1.0 and 1.5 units per hour.

Results:

The most pronounced differences were seen during basal delivery in the CSII pumps using 80- to 100-cm tubing. For the 1-U/h rate, differences ranged from 47% less to 37% more than the expected dose when the pipettes were above or below the pump, respectively. For the 1.5-U/h rate, differences ranged from 16% less to 16% more than expected doses when the pipettes were above or below the pump, respectively.

Conclusions:

Movement of a conventional CSII pump in relation to its tubing resulted in significant changes in insulin delivery. The siphon effect in the tubing may affect the accuracy of insulin delivery, especially the pediatric population where low basal rates are used. Such fluctuations arise when the height of the pump, relative to the cannula, changes as a result of normal daily use. This effect had been reported previously when syringe pumps were moved in relation to infusion sites but has not been reported with CSII devices.

Non-Invasive Glucose Measurement Using Infrared Spectroscopy

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Objective:

To evaluate the accuracy of glucose measurement using infrared spectroscopy

Methods:

Thirty healthy adults participated in the study. Venous blood glucose samples were drawn from the participants. Their thumbs were scanned simultaneously using infrared (NIR) spectroscopy to obtain NIR spectra.

Results:

We used the NIR spectra (wavelength 1100 -1600nm) and the blood glucose level (BGL) ranged from 4-8 mmol/L to calibrate the partial least squares (PLS) model. The total number of samples was 30 and the data was divided into 2 sets. One set of data (60% of the total number of samples, 18 subjects) was randomly selected for calibration purpose, in which PLS was performed to maximize the correlation between predicted value and the reference value; the remaining data set (40% of the total number of samples, 12 subjects) was then fitted to the calibration model for cross-validation. Each time, a subset of calibration samples (15 out of 18 samples) was taken for training. The training procedure was repeated 100 times and the predictor matrix was obtained with the mean of the training results. The correlation of the calibration set in cross-validation was $R = 0.79$. 100% of the data points fell within Zone A.

Conclusions:

The model provides an accurate estimation of blood glucose non-invasively.