

Abstracts

Acree	Assessment of a Patient-Level Diabetes Education Elective for First-Year...	A1
Ahn	Continuous Glucose Monitoring Using Near-Infrared Fluorescent Carbon and...	A2
Albanese-O'Neill	Ketone Monitoring Frequency and Methods in Type 1 Diabetes Subjects	A3
Aloi	eGlycemic Management System Provides Safe and Effective Glycemic Control for...	A4
Andreatta	Optimization of Core Sensor Components for an Osmotic Pressure Sensor for...	A5
Bailey	Accuracy and User Performance Evaluation of a New Blood Glucose Monitoring...	A6
Baram	Development of a New Glucose Dehydrogenase Mutant That Is Free of Xylose...	A7
Benesch	ClampArt: Improved Algorithm for Automated Glucose Clamps	A8
Blaabjerg	Development of a Hypoglycemia Alarm Based on Electroencephalography	A9
Bode	Patient-Level Assessment of Cough with Technosphere Inhaled Insulin in Patients...	A10
Bondia	Coordination of Insulin and Glucagon Delivery in Bihormonal Artificial Pancreas...	A11
Breton	Calibration of the Dynamical Tracking eA1c Algorithm with Reference HbA _{1c} ...	A12
Carlson	Safety Analysis of a 90-Day Implantable Continuous Glucose Monitoring System...	A13
Cembrowski	Biologic Variation of Intensive Care Unit Patient Capillary Glucoses Monitored...	A14
Ching	Bidel's Glucagon Emergency Management Autoreconstitution Device...	A15
Christiansen	Accuracy and User Performance Evaluation of a New Blood Glucose Monitoring...	A16
da Silva	Personalizing the Model Predictive Controller Aggressiveness for the Artificial...	A17
Dagliati	Metformin Exposure Patterns Are Related to Type 2 Diabetes Nephropathy	A18
Datye	Timing of Meal Insulin Delivery and Its Relation to Missed Insulin Doses	A19
David	Serum Total Homocysteine as a Potential Predictor for Increased Risk for...	A20
Daya	Planar Microwave Sensor for Noninvasive Blood Glucose Sensing	A21
de Bock	Performance of a Hybrid Closed-Loop Insulin Delivery Algorithm with Insulin...	A22
Docherty	Basal Glucose Is Just the First Measured Point . . . Right?	A23
Dungan	Messaging via Electronic-Medical-Record-Based Patient Portal: Effect on Glucose...	A24
Emilion	Screening Obese Women with Prediabetes from Classes of Serum...	A25
Esenaliev	Noninvasive Glucose Monitoring with Novel High-Resolution Ultrasound Technique	A26
Famulla	Recombinant Human Soluble Insulin Julphar Insulin R Is Bioequivalent to...	A27
Feldman	Pramlintide versus Liraglutide: Assessing Incremental Benefits of Adjunctive...	A28
Feng	Controller Performance Assessment of Model-Based Artificial Pancreas Control...	A29
Fischer	Glooko: Mobile, Unified Platform for Diabetes Management, Combined with Nurse...	A30
Frank	An Estimation of Glucose Uptake during Exercise	A31
Freckmann	ISO 15197:2013: Evaluation of Two Improved Blood Glucose Monitoring Systems	A32
Fuller	Evaluation of Glucometer Test Strips for the Presence of Potential Pathogens...	A33
Gal	Simplifying Calibration Practice for Home Use Noninvasive Glucose Monitoring...	A34

Abstracts

Gal	Simplifying Calibration Practice for Home Use Noninvasive Glucose Monitoring...	A35
Garcia	A Novel, Time-Invariant, Intuitive Metric for Assessing Glycemic Variability	A36
Godavarty	Optical Classification of Diabetic Wounds: Preliminary Sensitivity and Specificity...	A37
Gómez	Long-Term Follow-Up of Sensor-Augmented Pump Therapy with Low-Glucose...	A38
Groat	Characterizing Self-Management Behaviors of Type 1 Diabetes Patients on Insulin...	A39
Groat	Introducing a Method to Retrospectively Compare Insulin Dosing Recommendations	A40
Grosman	Hybrid Closed Loop in Monitored Outpatient Conditions	A41
Gu	In Vitro and In Vivo Performance of a Multianalyte Sensor	A42
Hajnssek	The SPIDIMAN Single-Port System: Combining Continuous Glucose Monitoring...	A43
Hansen	Insulin-to-Carbohydrate Ratio and 24-h Urinary Glucose Excretion to Assess...	A44
Haselwood	Toward a Sensor and Model for Cortisol as Feedback in the Bioartificial Pancreas	A45
Hauzenberger	Systematic Study to Optimize Insulin Delivery through a Continuous Subcutaneous...	A46
Henderson	Finger Stickin' Good: Improved Glycemic Control in Cardiovascular Surgery...	A47
Herrero	<i>In Silico</i> Evaluation of Ultra-Fast-Acting Insulins Using the Bioinspired Artificial...	A48
Hodish	Scalable and Durable Optimal Glycemic Control in Insulin Users	A49
Howsmon	Infusion Set Fault Detection via Monitoring of Real-Time Data over Sliding Windows	A50
Huber	Performance of a Blood Glucose Monitoring System in a Point-of-Care Setting	A51
Jacobs	Use of a Bihormonal Artificial Pancreas System with Exercise Announcement in...	A52
Kastellorizios	Cytotoxicity of Photopatternable Hydrogels for Implantable Glucose Sensors	A53
Kastellorizios	GlucoWizzard: An Injectable, Wireless Biosensor for Continuous Glucose Monitoring	A54
Kastellorizios	Multianalyte Monitoring <i>via</i> Implantable Biosensors Predicts Exhaustion	A55
Kircher	Automated Insulin Delivery "In the Wild"	A56
Knab	The Importance of Multiple Sensors in Continuous Glucose Monitoring	A57
Kovatchev	Hemoglobin A _{1c} and Self-Monitored Average Glucose: Validation of the...	A58
Kudva	Acute Effect of Low-Dose Pramlintide on Islet and Gastrointestinal Peptides in...	A59
Laguna Sanz	Adaptive Blood Glucose Predictions Using Untrained Models: a Performance...	A60
Lajara	Evaluation of Insulin Delivery with V-Go Combined with a Glucagon-Like...	A61
Lajara	Using the V-Go Disposable Insulin Delivery Device in Patients Prescribed High...	A62
Lande	Widespread Clinical Experiences Validating a Blood-Based Artificial Pancreas	A63
Leal	Online Detection of Sensor Faults from Continuous Glucose Monitoring, Meal, and...	A64
Lee	MT-Diet: Automated Diet Assessment Using Myo Wristband and Thermal Images	A65
Little	The Use of Insulin Pump Technology to Advance Safe and Effective Care	A66
Lucisano	Late-Breaking Human Clinical Results from a Second-Generation Long-Term Fully...	A67
Mader	Glycemic Control by Using GlucoTab in Insulin-Naive and Insulin-Treated...	A68
Magee	mHealth Blood Glucose Monitoring Solution Enables Timely Targets Attainment	A69

Abstracts

Melish	Pharmacokinetic Study of Mixed-Diet Glucose Concentration Responses in Type 1...	A72
Mould	Pharmacokinetic and Pharmacodynamic Modeling Predict Concentrated Biphasic...	A73
Murase	Resistance to Acetaminophen Interference of the Direct Electron Transfer-type...	A74
Nguyen	U-Strip Transdermal Insulin Patch	A75
Nunlee-Bland	Technology Use Enhances Body Mass Index Reduction in African American...	A76
Oser	Using Blogs to Support Caregivers of Patients with Type 1 Diabetes: A Pilot Study	A77
Otto	Evaluating a Novel Glycemic Pattern Recognition Algorithm for Alerting to Risk of...	A78
Pery	Performance of a Smartphone-Linked Blood Glucose Assessment Platform	A79
Pesl	Clinical Pilot Study Assessing the Postprandial Outcome of an Advanced Bolus...	A80
Pesl	Performance of an Automated Revision Algorithm for a Personalized Bolus...	A81
Pohl	Mixture of Insulin Monomers, Dimers, and Hexamers Demonstrated by...	A82
Reiterer	Is There a Recipe for Comparability of Mean Absolute Relative Difference Values...	A83
Renard	Multicenter Assessment of Usability and Safety of a Model Predictive Control...	A84
Resalat	Incorporating an Exercise Detection, Grading, and Hormone Dosing Algorithm into...	A85
Rigla	Artificial-Intelligence-Augmented Telemedicine Applied to the Management of...	A86
Rollins Sr.	Automatic Insulin Delivery System Approach Capable of Tight Control	A87
Ruan	Night-to-Night Variability of Basal Insulin Requirements in Adults with Type 1...	A88
Sacchi	Predicting Microvascular Complications from Type 2 Diabetes Retrospective Data	A89
Samadi	Meal Detection and Carbohydrate Estimation Algorithm Based on Continuous...	A90
Sartori	Comparison of the Nova Biomedical StatStrip Glucose Meter to an Isotope Dilution...	A91
Schwartz	Augmenting the Detection and Prediction of Blood Glucose Control Problems with...	A92
Shehata	New Technology for Metformin Hydrochloride Mucoadhesive Microparticles...	A93
Shomali	Data Science Framework for Mobile Health Engagement and Outcomes	A94
Simon	MyDiaText: Short Message Service Technology for Behavioral Health in Patients...	A95
Skowronski	Circulating Levels of Protease Activity during a Meal Tolerance Test in Type 2...	A96
Smajada	Interference Test Results for an Osmotic Pressure Sensor for Interstitial Glucose...	A97
Sode	First Three-Dimensional Structure of Fungus-Derived Glucose Dehydrogenase...	A98
Stewart	High Compliance = Good Control? Compliance of the Stochastic Targeted...	A99
Sundarapperuma	Perspectives on Diet during Postpartum Periods in Mothers with Gestational...	A100
Terrazas	Improving Meal Detection Using a Smartwatch and Accelerometer	A101
Thavareesan	Smartphone-Based Patient Health Care Management System	A102
Tiangco	Progress toward Passive Transdermal Glucose Sensing Based on a Glucose-Binding...	A103
Uyttendaele	Insulin Sensitivity Profile as a Marker for Reduced Outcome in the Neonatal...	A104

Abstracts

Vahlsing	Combination of Microdialysis and <i>Ex Vivo</i> Glucose Sensing by Infrared...	A105
Valenzuela	Early Results Support Efficacy and Clinical Efficiency of Diabetes Management...	A106
Veiseh	Long-Term Glycemic Control Using Polymer Encapsulated Human-Stem-Cell...	A107
Vettoretti	Simulation of Patient Decision Making to Test Safety and Effectiveness of...	A108
Vettoretti	Simulation of Patient Decision Making to Test Safety and Effectiveness of...	A109
Visentin	Modeling the Effect of Liraglutide in Type 2 Diabetes Mellitus with the Type 2...	A110
Voge	Usage and Perceptions of Type 1 Diabetes Devices	A111
Voskanyan	Feasibility of Use of Novel Stable Soluble Glucagon Analog ZP-GA-1 in Artificial...	A112
Waki	Telehealth System: Smartphone-Based Self-Management for Diabetes Patients	A113
Walker	Accuracy of a Blood Glucose Monitoring System as It Relates to the ISO...	A114
Walker	Evaluation of a Blood Glucose Monitoring System in Comparison with Global...	A115
Wang, G.	Autonomous Shape-Memory-Alloy-Based Actuator Reaching Subcutaneous Blood...	A116
Wang, Y.	Comparison of Point-of-Care Blood Glucose Monitoring System Performance...	A117
Wang, Y.	Development of a Primary Isotope Dilution Mass Spectrometry Traceable...	A118
Wilson	Glucosense: A Low-Cost Glucose Meter System for Resource-Poor Settings	A119
Woodley	Cytotoxic Effect of Three Commercial Rapid-Acting Insulin Analogs on Four...	A120
Xenakis	Characterization of the Information Technology Utilization and Experiences of...	A121
Yablonski	Human Kinetic Approach to Improving Conformability in PaQ, a 3-day Wearable...	A122
Yan	Simulation Study on Insulin Sensitivity Factor Changes for Patients with Illness/Stress	A123
Yavelberg	Accuracy of Select Wearable Technology for Varying Exercise Modalities and...	A124
Zhao	Pilot Study of Oral Insulin Enteric-Coated Soft Capsules Research and...	A125
Zhong	Continuous Glucose Monitoring Accuracy Improvement Using the Autocalibration...	A126
Zhong	Real-World Assessment of Undetected Glycemic Excursion Events in Type 2...	A127
Zhong	Real-World Performance of a Predictive Low-Glucose Management Algorithm	A128
Zijlstra	Dance 501 Inhaled Human Insulin Has a Dose-Linear Response and Similar...	A129
Zijlstra	Demonstration of Very High Compliance and HbA _{1c} Benefit of a Long-Term...	A130
Zijlstra	Faster-Acting Insulin Aspart Using Continuous Subcutaneous Insulin Infusion...	A131
Zijlstra	Particle Size Does Not Impact the Pharmacokinetic Response of a Novel Inhaled...	A132

Assessment of a Patient-Level Diabetes Education Elective for First-Year Pharmacy Students Utilizing Hands-On Diabetes and Coexisting Disease State Point-of-Care Screening Tools

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Objective:

Utilizing the Diabetes Empowerment Education Program intended for non-health-care providers, this course teaches first-year students the tools needed to understand and educate patients about diabetes and several related disease states. Through hands-on training and practice, students learn how to screen patients for diabetes, cholesterol, and blood pressure.

Methods:

Diabetes Education and the Patient is a three-credit-hour elective course that is open to first-year PharmD students as an elective course. The program addresses the AADE7 self-care behaviors through eight modules. In addition to the modules, students are required to participate in two health care screening events in which they are able to practice the skills and techniques learned throughout the course. Within the modules, students are trained to utilize screening tools for cholesterol, A1C, and blood glucose testing. In addition, students also master manual blood pressure skills through practice with other students.

Result:

Course assessment includes student evaluations, oral and written assignment rubrics, reflections, and informal verbal feedback. Students were given patient-level pre- and posteducation training tests. Test scores improved from an average of 67.5% on the pretest to 91.8% on the posttest. Through analysis of pretest data, the area of diabetes diagnostics was the weakest, with an average of only 40%. Diabetic pathophysiology was identified as having the highest score on the pretest, with an average of 75%. However, the posttest revealed a low score of 86% and a high score of 97% in all question categories.

Conclusion:

Typically, diabetes is not taught in the curriculum until the third-year pharmacotherapy course, in which they receive 6–8 h of didactic lecture and classroom activities. Although blood pressure and blood glucose skills are taught during the first year, A1C and cholesterol screening equipment is not utilized in the curriculum until the third year in the Introductory Pharmacy Practice Experience course. This innovative diabetes course provides students with the skills and tools needed to counsel patients on diabetes, cholesterol, and lifestyle changes during their early experiential education rotations. With the hands-on activities included in the diabetes elective course, students may also gain the confidence during the first year of pharmacy school to become more involved with health fairs and patient education activities.

Continuous Glucose Monitoring Using Near-Infrared Fluorescent Carbon and Corona Phase Molecular Recognition Molecular Sites for Glucose

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Objective:

Developing a continuous glucose sensor with which individuals can monitor and control the potential life-threatening effects of diabetes mellitus remains a heavily researched challenge. Herein, we present our work developing a new class of glucose sensors for long-term continuous blood glucose monitoring based on glucose-responsive near-infrared fluorescent nanoparticles utilized as a subcutaneous tattoo, which enables external, noninvasive, optical signal detection.

Method:

A novel composition of phenylboronic acid polymer was complexed with near-infrared fluorescent single-walled carbon nanotubes (SWNT) to generate unique glucose recognition sites using a technique we term corona phase molecular recognition (CoPhMoRe). The resulting glucose nanosensors were encapsulated within two different form factors, a dialysis membrane (~1.5 cm) and liquid core-hydrogel shell particles (~200 μm), and implanted subcutaneously in mice for long-term stability test and continuous glucose monitoring. The modulation of the fluorescent signal was monitored noninvasively and compared with the blood glucose levels measured by the commercially available continuous glucose monitor.

Result:

Our in vitro studies demonstrated notable instantaneous and reversible fluorescence responses to varying glucose concentrations over the hypoglycemic to hyperglycemic range. In vivo studies confirmed the stability and biocompatibility of the sensors for over 4 weeks, with no signs of inflammation. The preliminary glucose challenge tests showed promising results of correlations between changes in glucose concentration and modulation of the fluorescence emission intensity.

Conclusion:

We developed a new class of glucose sensors using SWNT complexed with novel CoPhMoRe sites for glucose recognition. These sensors were successfully implanted subcutaneously in mice and enabled noninvasive continuous glucose monitoring over long time periods, providing great promise for long-term glucose sensing tattoo implants.

Ketone Monitoring Frequency and Methods in Type 1 Diabetes Subjects

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Objectives:

Clinical recommendations advise self-monitoring of blood or urine ketones during hyperglycemia and illness to allow for early diagnosis of ketonemia or ketonuria and to reduce the risk of diabetic ketoacidosis (DKA). The purpose of this study was to characterize ketone management in persons with type 1 diabetes (T1D) who completed an online questionnaire between February and August of 2014 as part of the T1D Exchange registry.

Methods:

We analyzed data from 3,737 participants or parents of participant's ages 3–88 years (median 23 years; median T1D duration 11 years; 56% female; 90% non-Hispanic white). A linear regression model was used to analyze the association between ketone checking and age.

Results:

Thirty percent (1,129) reported checking ketones at least once in the last 30 days. Among these 1,129 subjects, checking ketones was more common among younger participants (59% <18 years vs. 15% ≥18 years; $P < 0.001$). Checking ketones most or all the time when glucose level is above 300 mg/dL was reported by 30% of 61 <6-year-olds, 36% of 644 6–12-year-olds, 36% of 580 13–17-year-olds, 14% of 808 18–25-year-olds, and 7% of 1,644 ≥26-year-olds and checking most or all the time when nauseated or vomiting by 87, 81, 73, 42, and 18%, respectively. Among participants who reported a method for checking ketones, 81% reported checking with urine, 13% blood, and 7% urine and blood.

Conclusions:

Checking ketones is infrequent when the blood glucose is high or when nausea or vomiting occur, particularly in adults. The reported rate of monitoring is unacceptably low and suggests a need for more robust diabetes education to improve adherence to ketone monitoring guidelines and to reduce the risk for DKA in patients with T1D.

eGlycemic Management System Provides Safe and Effective Glycemic Control for Stroke Patients Requiring Subcutaneous Insulin in the Hospital Setting

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Objective:

Admission hyperglycemia (>130 mg/dL) and persistent inpatient hyperglycemia (>48 h) have been predictors of poor patient outcomes, including higher mortality, higher rates of in-hospital complications, and longer length of stay in patients with acute ischemic stroke. This study evaluated the glycemic outcomes of patients using eGlycemic Management System subcutaneous (eGMS-SQ) for subcutaneous insulin management versus standard subcutaneous orders (SSO) in patients with acute ischemic stroke.

Method:

The study evaluated 40 patients with type 2 diabetes mellitus at Sentara Health System who required subcutaneous insulin to manage hyperglycemia. Qualifying patients were treated with eGMS-SQ or SSO with a target of 120–160 mg/dL. The efficacy and safety of each was evaluated by the following: 1) percentage of blood glucose (BG) between 71 and 180 mg/dL, 2) percentage of BG >180 mg/dL, 3) percentage of hypoglycemic events <40 and <70 mg/dL, 4) average BG, and 5) average length of stay (LOS).

Result:

Patients ($n = 20$) treated with eGMS-SQ had a starting BG of 232 mg/dL, average BG 149 mg/dL, and 74.7% of readings in target, and hypoglycemia <70 mg/dL was 2.1% and hypoglycemia <40 mg/dL was 0.0%. Average LOS using eGMS-SQ was 5.3 days. Patients ($n = 20$) treated with SSO had a starting BG of 235 mg/dL, average BG on eGMS-SQ of 169 mg/dL, and 56.8% of readings in target, and hypoglycemia <70 mg/dL was 4.4% and hypoglycemia <40 mg/dL was 0.5%. Average LOS using SSO was 6.4 days.

Conclusion:

These results suggest that eGMS-SQ can effectively and, more importantly, safely control and maintain glucose control for patients with acute ischemic stroke. A higher percentage of patients reached target glucose levels and had over 50% less hypoglycemia <70 mg/dL, and a lower LOS was observed.

Optimization of Core Sensor Components for an Osmotic Pressure Sensor for Interstitial Glucose Assessment ANDR15123D

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Background:

A new interstitial glucose sensor based on an osmotic pressure sensor technology is currently under development by Lifecare, Norway (Sencell). In the sensor core, competitive binding of glucose versus dextran to specific binding sites of the plant lectin concanavalin A (Con A) is used to induce an osmotic pressure signal, which is in close correlation to interstitial glucose content. Molecular weight of dextran and environmental temperature are supposed to influence the reproducibility and stability of the sensor signal. The purpose of this experiment was to identify the most suitable dextran size and to assess stability of the sensor signal over months at 21 and 37 °C.

Methods:

A working laboratory model of the core sensor technology was developed to perform the chemistry optimization experiments. After confirmation of proper sensor operation, three different molecular weight versions of dextran were applied (10, 40, and 70 kDa) in a standardized experiment, and sensor sensitivity was tested over a glucose range from 2 to 30 mmol/L. Influence of glucose concentrations on chamber fluid viscosity was tested at different Con A:dextran concentration ratios (6:1, 3:1, and 1:1). In addition, the stability of the sensor signal was tested after 3 months of storage at 21 and 37 °C.

Results:

Lowering of the Con A concentration decreased the influence of glucose on the viscosity of the active fluid most likely because the number of intermolecular bonds between dextran and Con A is reduced. In addition, decreasing the molecular Con A:dextran ratio from 6:1 to 1:1 resulted in a significant reduction of glucose on active fluid viscosity and enhanced the amplitude of the osmotic pressure sensor signal. The combination of 40 kDa dextran in a 1:1 molecular ratio to Con A provided the most optimal sensor signal and was chosen for further stability experiments. When experiments were carried out at 21 vs. 37 °C, they led to comparable results. Stability of the active fluid at 37 °C was confirmed by the experimental data. In addition, there was no signal of a loss of Con A integrity when assessed by ultraviolet-visible spectroscopy.

Conclusions:

The results of our experiments and numerical simulations enabled us to optimize the composition of the active chamber fluid and to calculate the absolute osmotic pressure that will be measured for a given concentration of glucose. In addition, our results indicate that the sensor is working with a stable performance when stored for 3 months at body temperature of 37 °C.

Accuracy and User Performance Evaluation of a New Blood Glucose Monitoring System in Development for Use with Contour Plus Test Strips

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Objective:

We evaluate the accuracy of a new blood glucose monitoring system (BGMS) in development for use with Contour Plus test strips in the laboratory and clinical settings. The BGMS features an easy-to-use wireless-enabled blood glucose meter that links to a smart mobile device via Bluetooth connectivity.

Method:

In the laboratory study, fingertip blood samples from 100 subjects were tested in duplicate using each of three test-strip lots. BGMS results were compared with YSI reference results and assessed per ISO 15197:2013 accuracy criteria (i.e., $\geq 95\%$ of results within ± 15 mg/dL [glucose < 100 mg/dL] or $\pm 15\%$ [glucose ≥ 100 mg/dL] of the reference result). In the clinical study, 134 subjects with diabetes, who had never used this BGMS previously, enrolled at two clinical sites. The primary objective was to evaluate BGMS accuracy using subject fingertip self-tests based on ISO 15197:2013 accuracy criteria (see above).

Result:

In the laboratory study (glucose range, 37–526 mg/dL), 99.0% (594/600) of BGMS results met the accuracy criteria; additionally, 96.3% (578/600) of results were within ± 10 mg/dL or $\pm 10\%$ of the YSI reference result. In the clinical study (glucose range, 44.3–474.5 mg/dL), 99.3% (133/134) of subject fingertip self-test results met the accuracy criteria; moreover, 95.5% (128/134) of results were within ± 10 mg/dL or $\pm 10\%$ of the YSI reference result.

Conclusion:

The BGMS exceeded ISO 15197:2013 accuracy criteria in the laboratory (section 6.3) and in a clinical setting when used by untrained subjects (section 8).

Development of a New Glucose Dehydrogenase Mutant That Is Free of Xylose Interference

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Background:

Current blood glucose (BG) meters using glucose dehydrogenase (GDH) have been reported to be influenced by xylose concentrations, resulting in a profound bias of the BG measurement result. With more xylose replacing glucose as sweetener in “functional” food, this interference may become more important in future clinical routine.

Methods:

We used our proprietary Provolution process to generate several variants of GDHs from a bacterial source. All variants were screened using not only biochemical assays, but also electrochemical assays in order to identify the most suitable candidates. Mutants were tested both in vitro and with physiological fluids. In tests that involved physiological fluid, heparinized whole blood was freshly drawn from healthy volunteers and diabetic patients and manipulated to contain different glucose concentrations (0, 1, 3, 5, 10, 20, and 30 mmol/L) and different xylose concentrations (0, 1, 3, 5, 10, 20, and 30 mmol/L). The samples were tested with SmartZyme electrodes, and the resulting signals were analyzed in order to conclude the interference percentage of the original sample.

Results:

The commercial GDH showed approximately 20% interference with xylose at all tested glucose ranges. The finally selected mutant candidates showed no xylose interference; the signal resulting from xylose with this mutant was below the signal-to-noise ratio.

Conclusions:

By means of the Provolution technology, we have been able to develop a GDH mutant that showed no interference with xylose in a laboratory setting. Clinical studies are now warranted to demonstrate the suitability of this GDH mutant for glucose sensing devices, like self-monitoring BG systems and continuous glucose monitors.

ClampArt: Improved Algorithm for Automated Glucose Clamps

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Objective:

In contrast to manual techniques, automated glucose clamps (e.g., using the Biostator) offer the advantage of a bias-free assessment of the pharmacodynamic properties of blood-glucose-lowering agents and a minute-by-minute adaptation of glucose infusion rates (GIRs), thereby keeping blood glucose (BG) concentrations very close to the clamp target level. However, the Biostator algorithm leads to pronounced oscillations of both BG and GIRs, requiring mathematical smoothing procedures for the determination of time-related parameters. As ClampArt, our novel automated clamp device, offers the option to modify the clamp algorithm, we compared the unmodified Biostator algorithm (UBA) and a potentially improved clamp algorithm (ICA) regarding GIR/BG oscillations and clamp quality.

Methods:

We analyzed 90 clamps using the UBA and 44 clamps with ICA performed in 67 patients with type 1 or type 2 diabetes. BG target was 5.5 mmol/L (100 mg/dL), and the clamp duration was 12 h after a single dose of 0.2 U/kg insulin aspart in all clamps. After applying a Fourier filter (band-pass filter 0.01 to 0.1), we compared the oscillations (coefficient of variation [CV] of GIRs and BG) and control deviation (mean absolute relative deviation of BG from the clamp level) as parameters of clamp quality between UBA and ICA.

Results:

ICA showed significantly lower oscillations in both GIRs and BG versus UBA (CV GIR 48.1 ± 21.9 vs. $85.1 \pm 79.4\%$, $P = 0.0029$; CV BG 4.4 ± 1.2 vs. $6.6 \pm 2.9\%$, $P < 0.0001$). Control deviation did not change (1.1 ± 0.6 vs. $1.1 \pm 2.5\%$, not significant).

Conclusion:

ICA substantially improved clamp quality over UBA, in particular oscillations in both GIRs and BG, which were reduced by 43 and 33%, respectively, and variation of control deviation is reduced by 76%. This improved algorithm will be used in future ClampArt experiments.

Development of a Hypoglycemia Alarm Based on Electroencephalography

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Objective:

Hypoglycemia is associated with increased activity in the low-frequency bands in the electroencephalogram (EEG). The objective of this research is to develop a hypoglycemia alarm device with an automated EEG algorithm predicting hypoglycemia in patients with type 1 diabetes and hypoglycemia unawareness.

Methods:

Patients with type 1 diabetes were exposed to insulin-induced hypoglycemia terminated at nadir due to significant hypoglycemic symptoms or at blood glucose levels below 1.8 mmol/L for adults or 2.2 mmol/L for children. In addition, the alarm device was tested during everyday activities in adults with type 1 diabetes, enabling detection of spontaneous hypoglycemic events. EEG was recorded and analyzed real-time using an automated EEG algorithm.

Results:

For adults, the hypoglycemia-associated EEG changes remained stable across age groups, duration of diabetes, sleep stage, and hypoglycemia awareness status. Furthermore, the hypoglycemia-induced EEG changes were unaffected by recent antecedent hypoglycemia. Spontaneous events of hypoglycemia during everyday activities were detected in time for the patient to take appropriate action, avoiding progression to severe events. In children, the automated EEG algorithm developed in adults was able to detect hypoglycemia prior to blood glucose nadir in awake state during daytime. During sleep, the current version of the EEG algorithm was unable to distinguish hypoglycemia from deep sleep patterns.

Conclusions:

Due to the consistency of the hypoglycemia-induced changes in the EEG in adults, it seems possible to develop a hypoglycemia alarm device with a general algorithm for detection of hypoglycemia, based on EEG recordings and real-time data processing. This is currently being tested in clinical trials.

Patient-Level Assessment of Cough with Technosphere Inhaled Insulin in Patients with Type 1 Diabetes Mellitus

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Objective:

Technosphere insulin inhalation powder (TI) is a dry powder formulation of regular human insulin adsorbed onto Technosphere microparticles for oral inhalation in patients with diabetes. Cough is an adverse event that is reported with the use of TI. Here we describe the characteristics and the outcomes of patients reporting cough.

Method:

This patient-level analysis of a 24-week, phase 3 study in patients with type 1 diabetes mellitus (T1DM) assessed the characteristics of those who self-reported cough while using TI delivered via the Gen2 inhaler. Details regarding cough were collected in a cough-specific case report form.

Results:

One hundred seventy-four patients (mean age 37 years; 56% female) were included in the analysis, and cough was reported by 31.6% ($n = 55$) of patients; it was considered mild (73%), dry (82%), intermittent (69%), and occurred within 10 min of inhalation (89%). Cough was reported to start in week 1 of initiating TI for a majority of patients reporting cough (62%). There was no difference ($P > 0.05$ for all) in patients who reported cough versus those who did not in terms of age (39 vs. 36 years), sex (female, 56% vs. 56%), TI dose (average dinner dose at baseline, 0.45 vs. 0.61 U/kg), A1C at 24 weeks (7.90 vs. 7.75%), incidence of any confirmed hypoglycemia (76 vs. 83%), or pulmonary function at study end (forced expiratory volume in 1 s/forced vital capacity ratio, 83 vs. 81%). Ten patients (5.7%) discontinued due to cough, which resolved within 1–2 days of discontinuation.

Conclusion:

This analysis found that the characteristics of patients with T1DM who reported cough with TI but continued treatment were similar to those who did not report cough, with comparable safety and efficacy outcomes.

Coordination of Insulin and Glucagon Delivery in Bihormonal Artificial Pancreas through Habituating Control

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Objective:

Current approaches to bihormonal control in an artificial pancreas consider independent controllers for insulin and glucagon delivery, whereas physiological secretion of both hormones is interlinked. Bihormonal control can be posed as a multiple-input single-output control problem, with inputs differing significantly in their dynamics and cost of manipulation. Habituating control addresses this class of control problems, leading to coordination schemes among the different hormones delivery. This work aims at analyzing the benefits of insulin and glucagon delivery coordination in the framework of habituating control.

Method:

An habituating control scheme was implemented consisting of a discretized central controller designed from a given plant factorization. This central controller computes the “control effort” required for tight glucose control (virtual control action), which is then distributed among insulin and glucagon signals following a given coordination law. Different coordination laws were obtained based on different plant factorizations. In silico performance of the resulting control schemes were evaluated using the University of Virginia/Padova simulator and compared to an independent proportional-derivative controller for glucagon delivery, as currently used.

Result:

Current bihormonal control approach efficiently avoided hypoglycemia. However, coordinated action significantly improved postprandial control, with a reduction of time in hyperglycemia in approximately 50% while avoiding hypoglycemia. For equivalent closed-loop performance, factorization of faster input-output dynamics led to more efficient hormone coordination in terms of amount delivered.

Conclusion:

Bihormonal artificial pancreas performance may benefit from the coordination of insulin and glucagon delivery. These results justify the need for an increased understanding of the insulin and glucagon interplay that will translate to a more faithful bioinspired approach for bihormonal control.

Calibration of the Dynamical Tracking eA1c Algorithm with Reference HbA_{1c} Values: Performance in Type 1 and Type 2 Diabetes

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Background:

We previously introduced the eA1c, a new approach to real-time tracking of average glycemia and estimation of HbA_{1c} from infrequent self-monitoring of blood glucose data. Tested in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), the eA1c procedure yielded mean average relative deviations (MARDs) between 6.5 and 8%. We now present improved performance using calibration with one or two reference HbA_{1c} values.

Methods:

Reanalysis of previously published 12-month data from 120 patients with T1DM and 3-month data from 375 patients with T2DM, age (T1DM/T2DM) 39/55 years, baseline HbA_{1c} 8.0/7.5%, duration of diabetes 20.3/8.7 years. In the unstructured type 1 data surrogate fasting blood glucose and seven points profiles were obtained by time-of-day bins. Initial calibration was obtained using an additive offset to account for 33% of the previously published hemoglobin glycation index. Secondary calibration was performed by minimizing the weighted sum of square between previous two references and linear transform of uncalibrated eA1c values. Accuracy was assessed using MARD, days of reference measurements were excluded, and calibration was applied causally (no a posteriori calibration).

Results:

With one-point calibration, correlation between eA1c and HbA_{1c} improved from (T1DM/T2DM) $r = 0.75/0.78$ to $0.81/0.84$, and its deviation from reference from MARD = 8.1/6.6 to 6.6/6.1%. Two-point calibration further improved performance to correlation $r = 0.82/0.85$ and MARD = 5.4/6.0%. Using the longer T1DM data, we assessed eA1c performance 3, 6, and 9 months following the second calibration; accuracy remained improved with MARD = 3.6, 4.0, and 4.7%, respectively.

Conclusions:

The eA1c procedure can be significantly improved by one- or two-point calibration schemes in both T1DM and T2DM. Accuracy was improved nearly twofold and slowly deteriorated during the 9 months following a second calibration, but MARD remained below 5%.

Safety Analysis of a 90-Day Implantable Continuous Glucose Monitoring System in the PRECISE Study

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Objective:

A new implantable continuous glucose monitoring (CGM) system consisting of a fluorescence-based glucose sensor, body-worn smart transmitter, and smartphone application has been developed. The small cylindrical sensor has been designed to be inserted subcutaneously and provides 90 days of continuous measurements. Besides demonstrating functionality of the CGM system, a pivotal study was designed to demonstrate safety of the system through 90-day postinsertion use by measuring incidence of device or procedure related adverse events (AEs).

Method:

The full 81-subject study was evaluated at 90 days with a total of 44 subjects crossing the 90-day time point. In each subject, two sensors were inserted bilaterally in the upper arm, and a smart transmitter was placed over each sensor for communication. During the investigation, AEs in the clinic and during home use were documented. The primary investigator and the medical monitor independently evaluated each AE.

Result:

A total of 17 AEs in 12 (14.8%) subjects were identified as device or procedure related by the medical monitor. They included four cases of transmitter adhesive patch skin reactions, three cases of site infections, two cases of insertion procedure problem during training, two cases of insertion site pain, and one case each of depression, ingrown hair, pain in forearm muscle, numbness in hand, nausea, and headache. None of these AEs were serious or unanticipated. All AEs were resolved or stable at the study analysis point.

Conclusion:

Clinical data from a 90-day pivotal study of an implantable fluorescence-based CGM system have demonstrated that the system is safe for use in subjects with type 1 or type 2 diabetes mellitus.

Biologic Variation of Intensive Care Unit Patient Capillary Glucoses Monitored with Hematocrit-Independent Strips (2012–2015) Compared to That Monitored with Hematocrit-Dependent Whole Blood Glucose Strips (2009–2010)

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Objective:

We have devised a numerical technique to derive accurate estimates of biologic variation (BV) of most laboratory tests from the serial differences of series of repeated tests. We have applied this work to intensive care unit (ICU) glucose testing to determine whether our selection of the Roche maltose-independent, hematocrit-independent whole blood glucose measured on the Roche Inform II decreased the variation of glucose in ICU patients whose capillary glucose values were previously monitored by the LifeScan OneTouch blood glucose meter (BGM).

Method:

We tabulated the glucose measurements of paired inpatient University of Alberta Hospital General Systems ICU samples drawn within 3 h of each other and ranging between 6 and 12 mmol/L for both the Inform II and LifeScan systems. We calculated the standard deviations of duplicates (SDDs) of the inpatient pairs grouped by 0.5 h intervals. For both systems, the SDDs were regressed against time with extrapolation to zero time, representing the sum of BV and a much smaller analytic variation (AV). Substitution of 4 and 2.5% for the AV of the LifeScan and Roche systems permitted calculation of the BV for the two meter systems.

Results:

Over 13 months, 2009–2010, the BV of the ICU patient glucose was 6.8% for the LifeScan (11.1 tests/patient). For the Roche BGM system, the ICU patient glucose BV was 4.6% ($P < 0.001$; 7.6 tests/patient), 6.4% (not significant; 7.3 tests/patient), and 5.9% ($P < 0.01$; 7.0 tests/patient) for 12-month periods 2012–2013, 2013–2014, and 2014–2015, respectively.

Conclusion:

The decreased BV of the Roche system and the associated marked decrease in BGM testing is consistent with improved glucose control using the Roche BGM compared to the LifeScan BGM.

Biodel's Glucagon Emergency Management Autoreconstitution Device Demonstrates Superior Usability Compared to Marketed Glucagon Kits in Human Factors Study

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Objective:

Biodel conducted a formative human factors study for its autoreconstitution glucagon emergency management (GEM) rescue device and compared it to marketed glucagon kits.

Method:

A study with 24 participants in three groups (experienced, naive, and bystander) conducted a simulated emergency rescue dose of glucagon. The first group (experienced) consisted of eight first responders and caregivers experienced with the glucagon kits. The second group (naive) consisted of eight first responders and caregivers not experienced with glucagon kits. The third group (bystander) consisted of eight adults with no relationship to a diabetes patient and naive to glucagon kits. The experienced group performed a rescue with a glucagon kit, then four were trained on the GEM device and four self-trained using the GEM instructions. They returned 1 week later and performed a rescue with the GEM device. In the naive group, four participants were trained on the GEM device and four self-trained using the instructions. They returned 1 week later and performed an unaided rescue with the GEM device. The bystander group participants performed a rescue with the GEM device and with a glucagon kit without any training.

Result:

Eighty-seven percent of participants successfully delivered a full dose of glucagon using the GEM device compared to 6% for glucagon kits. The average dose delivery time was 48% faster with the GEM device compared to the glucagon kits. Successful delivery of a full dose of glucagon with the GEM device was comparable in trained (87%) and untrained (88%) participants.

Conclusion:

The GEM device was used accurately and in a time-sensitive manner by first responders, caregivers, and laypersons with or without training or previous experience administering glucagon.

Accuracy and User Performance Evaluation of a New Blood Glucose Monitoring System in Development for Use with Contour Next Test Strips

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Objective:

We evaluate the accuracy, in the laboratory and clinical settings, of a new blood glucose monitoring system (BGMS) in development for use with Contour Next test strips. The BGMS features an easy-to-use wireless-enabled blood glucose meter that links to a smart mobile device via Bluetooth connectivity.

Method:

A laboratory study was conducted. Fingertip blood samples from 100 subjects with diabetes were tested in duplicate using each of three test-strip lots. Accuracy was assessed per ISO 15197:2013 accuracy criteria (i.e., $\geq 95\%$ of results within ± 15 mg/dL [glucose < 100 mg/dL] or $\pm 15\%$ [glucose ≥ 100 mg/dL] of the YSI reference result). In a two-center clinical study, 375 subjects with ($n = 332$) or without ($n = 43$) diabetes, who had never used this BGMS previously, enrolled. The primary objective was to assess accuracy of the BGMS using fingertip self-test results based on ISO 15197:2013 accuracy criteria (see above). Secondary objectives included accuracy per Food and Drug Administration Draft SMBG Guidance 2014 Section C (i.e., 95% of results within $\pm 15\%$ and 99% within $\pm 20\%$ of the laboratory method across the entire tested range).

Result:

All 600 laboratory readings (glucose range, 36–643 mg/dL) met ISO 15197:2013 accuracy criteria. In the clinical study, among subjects with diabetes (glucose range, 32–458 mg/dL), 99.4% (327/329) of subject fingertip self-test results met ISO 15197:2013 accuracy criteria. Considering both subjects with and without diabetes, 99.5% (370/372) of fingertip self-test results were within $\pm 15\%$, and 99.7% (371/372) were within $\pm 20\%$ of the laboratory method.

Conclusion:

The BGMS exceeded ISO 15197:2013 accuracy criteria in the laboratory and a clinical setting and exceeded FDA Draft 2014 criteria in a clinical setting.

Personalizing the Model Predictive Controller Aggressiveness for the Artificial Pancreas: A Trade-Off Analysis

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Objective:

The University of California, Santa Barbara–developed zone model predictive control minimizes an asymmetric input cost function with parameters that penalize differently positive (greater than basal) or negative (lower than basal) control inputs. The configuration of the cost function by using these parameters has a direct effect on the occurrence of hypo- and hyperglycemia events. The goal of this work is to determine appropriate the upper and lower limits of controller aggressiveness to cover a useful spectrum of controller responses within which a user can choose, depending on personal preferences.

Method:

The controller tuning was evaluated on the University of Virginia/Padova metabolic simulator with 10 repetitions of 10 adult patients for a three-unannounced-meals scenario (50, 75, 100 g of carbohydrate). The input cost high (ICH; associated to positive inputs) tuning range was [100,1E5], and the input cost low (ICL; negative inputs) was [10,1E3]. The performance of the controller was evaluated by the average time (percentage) in hyperglycemia (>180 mg/dL) and hypoglycemia (<70 mg/dL).

Result:

The controller tuned to minimize occurrence of hyperglycemia is obtained for ICH = 800 and ICL = 500, with an average time of 23.8% in hyperglycemia and 1.03% in hypoglycemia. The opposite controller, designed to avoid hypoglycemia, is obtained for ICH = 5E4 and ICL = 10, with 0.14% time in hypoglycemia and 31.7% in hyperglycemia.

Conclusion:

The proposed controller settings present suitable configurations depending on the daily circumstances of a patient, who would be able to choose the aggressiveness of the controller based on his personal preferences and lifestyle. A person more prone to hypoglycemia could tune the controller to its conservative settings, and other patients could choose to tune the aggressiveness up in certain critical periods of the day, such as the postprandial periods.

Metformin Exposure Patterns Are Related to Type 2 Diabetes Nephropathy

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Objective:

The integration of heterogeneous data sources may provide the ability to identify patterns of medication use and possibly associated clinical phenomena in type 2 diabetes (T2D). Drug exposure patterns can be used as a marker for adherence to a drug regimen and ultimately for clinical outcomes. We used a state-of-the-art data warehouse environment and analytic tools to determine how a patient’s actual dosing corresponds to a prescribed regimen, compared to diabetic nephropathy.

Method:

Within the European-Union-funded MOSAIC project, we collected primary and secondary data of 943 T2D patients. We determined daily doses defined on prescriptions (DDD) as a proxy for dosing regimens. We used DDD to build metformin exposure profiles for each patient from the date of diagnosis until transfer to an endocrinologist’s care, in 1-month intervals. In order to assess adherence to the drug regimen, we calculated the proportion of days covered (PDC) as the number of months covered by prescription refills over the observation period since diagnosis. PDC of less than 90% indicated irregular adherence. We included PDC values in a multivariate predictive model for nephropathy.

Result:

The mean observation time was 28.3 months (standard deviation [SD] = 30.3). Mean PDC was 71.8% (SD = 25.6); an irregular purchasing pattern of metformin was found to be related to a higher risk of developing nephropathy (odds ratio = 2.8; $P < 0.01$). The area under the curve for the model, validated with a leave-one-out strategy, is 0.683.

Conclusion:

This result suggests that missing adherence to diabetic drug regimens is associated with adverse outcomes, in this case nephropathy. Using data sources and information technologies, we can provide clinicians with better information about diabetes management and patients’ activities.

Timing of Meal Insulin Delivery and Its Relation to Missed Insulin Doses

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Objective:

This study examines the relationship between timing of meal insulin delivery and missing insulin doses in adolescents and young adults with type 1 diabetes (T1D).

Method:

This analysis includes 9,343 participants with T1D between the ages of 13 and 25 years with T1D duration of at least 1 year (mean age 17 ± 3 , mean duration 7.9 ± 4.7 years, 48% female, 81% non-Hispanic white) who are participating in the T1D Exchange clinic registry. Participants were asked when they give mealtime insulin (ranging from several minutes before a meal to not regularly given). The association between timing of meal insulin and missing at least one insulin dose per week was evaluated in a logistic regression model.

Result:

Among the 9,343 participants, 15% reported administering insulin at least several minutes before meals, 35% immediately before meals, 10% during meals, 24% after meals, 10% depending on glucose level prior to meal, and 3% not administering mealtime insulin on a regular basis. Approximately 47% of pump users reported taking insulin before a meal compared with 52% of injection users. Missing an insulin dose ≥ 1 time per week was reported by 62% of participants who took insulin before meals (either a few minutes or right before) compared with 78% among those who did not administer insulin before meals ($P < 0.001$).

Conclusion:

Timing of the meal bolus was found to be significantly associated with the probability of missing at least one meal bolus a week. The T1D Exchange has previously shown that giving insulin before a meal is associated with better glycemic control. We demonstrate that premeal insulin is associated with fewer missed meal doses, which may account for some of this improvement.

Serum Total Homocysteine as a Potential Predictor for Increased Risk for Cardiovascular Disease among Type 2 Diabetes Mellitus Patients

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Background:

Serum total homocysteine (tHcy) is positively associated with type 2 diabetes mellitus (T2DM) while its association with diabetic nephropathy has not been fully established. As a growing health issue, increased tHcy with T2DM may be a powerful indicator for developing cardiovascular disease (CVD).

Method:

Serum tHcy was measured among respondents with managed and unmanaged T2DM, with and without nephropathy, spanning different durations. Values were correlated with lipid profile (total cholesterol [TC], triglycerides [TG], high-density lipoproteins [HDL], and low-density lipoproteins [LDL]), creatinine, glycosylated hemoglobin (HbA_{1c}) and estimated glomerular filtration rate (eGFR). Serum tHcy was measured using AU400, while lipid profile, creatinine, HbA_{1c}, and eGFR were measured using Vitros, D-10 Hemoglobin A_{1c} Program, and the modification of diet in renal disease equation, respectively. Statistical evaluation was performed using SPSS.

Results:

Seventy-four respondents were chosen; 22 composed the managed group, 32 for the unmanaged group, and 20 controls. Elevation of tHcy was significantly correlated with the duration of T2DM, indicating that regardless of management, the mean homocysteine of those with at least 10 years of T2DM is significantly higher ($P < 0.001$) as compared to those with 5 to 9 and <5 years. tHcy was not associated with diabetic nephropathy. Those with unmanaged T2DM had significantly lower ($P < 0.001$) eGFR and significantly higher ($P < 0.001$) LDL, TG, HbA_{1c}, and creatinine levels compared with the managed group, regardless of duration. LDL was significantly correlated ($r = 0.232$; $P = 0.0047$) with tHcy; 1 $\mu\text{mol/L}$ of tHcy leads to 2.6 mg/dL increase of LDL. There was no association for TC and HDL, although those who have unmanaged diabetes are 4.8 times [95% confidence interval: 1.1–30.3] more likely to have HDL below the normal range versus the managed group.

Conclusion:

This indicates that tHcy, with at least 10 years duration of T2DM, regardless of management, is a strong independent factor for the progression of CVD.

Planar Microwave Sensor for Noninvasive Blood Glucose Sensing

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Objective:

This paper presents a proof of concept study of a planar stripline-type microwave sensor as a point-of-care system for continuous monitoring of blood glucose.

Method:

The microwave planar spiral stripline sensor is designed at 1,800 MHz and is based on the principal of resonance. On pressing the sensor with a finger or thumb, the overall capacitance of the resonator changes, which changes the resonance frequency. This change in resonance is the measure of change in permittivity of blood, which is related to the concentration of glucose in blood. The sensor was calibrated by running parallel testing in the pathology laboratory of a local hospital on 70 patients. To increase the accuracy, a pressure sensor was incorporated in the sensor, and the glucose level was predicted using a fuzzy c-means clustering algorithm.

Result:

The sensor was tested on 70 patients and was found to have accuracy of +20%. The sensing range of the sensor is from 80 to 300 mg/dL. Efforts are in progress to increase the accuracy and sensing range.

Conclusion:

Glucose sensor presented here is microwave-integrated-circuit compatible and can be integrated into the cell phones. Results of this proof of concept testing phase promise a paradigm shift in the pathology for diabetes with further optimization in the design.

Performance of a Hybrid Closed-Loop Insulin Delivery Algorithm with Insulin Limits Designed for Home Use, Under Serial Hypoglycemic Challenges

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Objective:

We assess a hybrid closed-loop algorithm with maximum basal insulin limits in scenarios likely to induce hypoglycemia.

Method:

Type 1 diabetes patients were commenced on a Medtronic hybrid closed-loop system (HCL) for a 4-day in-clinic study: day 1, carbohydrate ratio 25–35% more aggressive; day 2, overreading glucose sensor by 20% + aggressive carbohydrate ratio; day 3, exercise (45 min stationary cycling at 55% VO_2 max minutes) + overreading glucose sensor + aggressive carbohydrate ratio; and day 4, aggressive carbohydrate ratio. Primary outcome was hypoglycemic events (plasma glucose <63 mg/dL or symptomatic hypoglycemia with plasma glucose <70 mg/dL).

Result:

Seven studies are completed. Data are shown as median and interquartile range, or mean \pm standard deviation. Twelve hypoglycemic events occurred. Four on day 1, four on day 2, two on day 3 (one pre- and one postexercise). The remaining two events occurred in one participant: one on day 3 after 130 min of open loop (HCL exited due to sensor failure) and one during exercise shortly after. There was no overnight hypoglycemia. All hypoglycemia was preceded by no algorithm-calculated insulin delivery (median 60 [55, 71] min). Median time hypoglycemia followed an insulin bolus for carbohydrate was 138 (74, 118) min. Mean plasma glucose was 144 ± 12.6 mg/dL. Time in target plasma glucose range (60–180 mg/dL) was $77.1 \pm 10.7\%$. Time spent <60, 180–270, and >270 mg/dL was 1.8 ± 1.4 , 20.0 ± 11.3 , and $1.0 \pm 1.5\%$, respectively.

Conclusion:

There was no overnight hypoglycemia despite several hypoglycemia stimuli. Although it is hard to generalize since sensors were overcalibrated, hypoglycemic risk appears to be related to food boluses and an aggressive carbohydrate ratio. It is likely carbohydrate counting accuracy will still be important in HCL.

Basal Glucose Is Just the First Measured Point . . . Right?

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Objective:

Assuming measured fasting glucose (G_0) equals true basal glucose (G_B) is common in model-based insulin sensitivity (SI) tests. This study determines the impact of a model-identified G_B versus the first sampled fasting, G_0 .

Method:

Fourteen participants with established type 2 diabetes mellitus in a 24-week dietary intervention study were given an insulin-modified intravenous glucose tolerance test at weeks 0, 12, and 24. The validated dynamic insulin sensitivity and secretion test (DISST) model was used to identify SI, V_G , and, additionally, G_B (three-parameter identification) versus a typical two-parameter approach. SI values and identified G_B versus measured G_0 are compared using nonparametric statistics.

Result:

SI from the three-parameter DISST identification was median (interquartile range) 3.36×10^{-4} (2.30 – 4.95×10^{-4}) $L \cdot mU^{-1} \cdot \min^{-1}$ and significantly lower than the typical two-parameter identified values: 6.38×10^{-4} (4.87 – 9.39×10^{-4}) $L \cdot mU^{-1} \cdot \min^{-1}$ ($P < 0.001$). Identified G_B values were lower and more consistent across all weeks than measured fasting G_0 for all tests and by week ($P < 0.001$), although they were well correlated ($r = 0.70$). The three-parameter approach provided significantly better fit with lower error and yielded lower SI values more in-line with expected values based on participant physiology. The changes in identified S_I also tracked changes in participant state over the 24-week trial better.

Conclusion:

This analysis suggests model-identified G_B is a stable and important metric for the assessment and modeling of glucose data from individuals with type 2 diabetes.

Messaging via Electronic-Medical-Record-Based Patient Portal: Effect on Glucose Control

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Objective:

The objective is to determine if the use of electronic messaging through an electronic medical record (EMR)-based patient portal is associated with improved glycemic control among patients with diabetes.

Method:

Patients who were seen over a 1-year period between January 1, 2013, and December 31, 2013, at a university endocrinology clinic with a diagnosis of diabetes (diagnosis code 250.xx) were identified using the institution's Information Warehouse. The association between electronic messaging and HbA_{1c} was further characterized using multivariable linear regression models.

Result:

A total of 3,616 patients were identified, 1,207 who had activated the patient portal but were not using the messaging function (portal group), 867 who were active and using electronic messaging (message group), and 1,542 patients who had not activated the patient portal (inactive group). The message group was younger and more likely to be Caucasian and have type 1 diabetes compared with the inactive group. The HbA_{1c} was 7.7 ± 1.5 , 8.4 ± 1.9 , and $8.2 \pm 1.8\%$ among the message, portal, and inactive groups, respectively ($P < 0.0001$). After controlling for age, gender, race, and type of diabetes, electronic messaging was associated with a 0.19% (standard error 0.04%) lower HbA_{1c} compared with the inactive group and a 0.25% (standard error 0.04%) lower HbA_{1c} compared with the portal group ($P < 0.0001$ for both).

Conclusion:

Electronic messaging was associated with better glycemic control, even after controlling for electronic portal access and other variables.

Screening Obese Women with Prediabetes from Classes of Serum 25-Hydroxyvitamin D and Serum Parathormone Levels among African Migrants Living in Paris

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Background:

It has been postulated that vitamin D may affect glucose homeostasis. We hypothesized that taking into account fasting plasma glucose concentrations in estimation of a serum 25-hydroxyvitamin D threshold below which parathyroid hormone concentrations increase could be useful to identify part of our sample usually called outliers.

Methods:

Measurements of serum 25-hydroxyvitamin D and serum parathormone were taken between February and June 2008 among 165 adult African migrant women living in Paris. All were calcium sufficient. We used receiver operating characteristic analysis to identify serum 25-hydroxyvitamin D/parathormone threshold. Analysis of variance was performed with Wilcoxon test. We used machine learning model.

Results:

A threshold of serum 25-hydroxyvitamin D of 65 nmol/L and serum parathormone of 44 ng/L was found with a sensitivity of 86%, a specificity of 83%, and a total predictive value of 98%. We identified 15% of the sample as a particular class of obese and prediabetic women with high levels of serum 25-hydroxyvitamin D and serum parathormone.

Conclusions:

Estimation with capillary glucose measurement instead of fasting plasma glucose could be a less costly method to screen glucose and vitamin D status among African migrant women. Estimating vitamin status and glucose status in other samples of the population might be of interest.

Noninvasive Glucose Monitoring with Novel High-Resolution Ultrasound Technique

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Background:

Noninvasive, continuous blood glucose monitoring is very important for management of diabetes. For the last four decades, a number of university groups and companies have proposed and tested various noninvasive glucose monitoring techniques. Despite these enormous efforts, limited success has been achieved and noninvasive glucose monitor development remains one of the most challenging and important biomedical problems. We proposed, patented, and tested a novel technique for noninvasive continuous glucose monitoring. It is based on detection of high-resolution ultrasound signals reflected from tissues including skin.

Method:

Glucose-induced (mostly osmotic) changes in tissue can be detected with the high-resolution ultrasound technique that can be used for noninvasive glucose measurements. We developed and built high-resolution ultrasound systems with specially designed, ultrasensitive probes. We used oral glucose tolerance test or meal intake to test the systems in diabetic (both type 1 and type 2) and nondiabetic subjects. Blood glucose reference values were measured with commercially available invasive glucose meters. The probes were placed on the outer wrist area, and ultrasound signals were recorded continuously. System calibration was performed with one or two blood samples to provide real-time, continuous, noninvasive blood glucose concentrations.

Result:

High-resolution ultrasound measurements allowed for precise (1 ns) measurement of skin signal position and shift, which was linearly dependent on glucose concentration in the range of 56 to 400 mg/dL. Calibrated systems provided noninvasive glucose concentration values that closely followed the reference glucose concentration in the physiologic range. The accuracy of the noninvasive glucose monitors was approaching that of invasive glucose meters.

Conclusion:

The obtained results suggest that the proposed high-resolution ultrasound technique may provide noninvasive continuous blood glucose monitoring in diabetic and nondiabetic patients.

Recombinant Human Soluble Insulin Julphar Insulin R Is Bioequivalent to Huminsulin Normal, a European Union– Marketed Soluble Insulin

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Objective:

We compared the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the recombinant human soluble insulin Julphar Insulin R (test) and Huminsulin Normal (reference) in a randomized, double-blind, crossover study performed in full compliance with the European guidelines for biosimilar insulins.

Method:

Twenty-six healthy subjects (24 male/2 female, age 38.4 ± 9.9 years (mean \pm standard deviation), body mass index 24.5 ± 2.3 kg/m²) received a single subcutaneous dose (0.3 U/kg) of test or reference under automated euglycemic glucose clamp conditions (ClampArt, clamp level 5 mg/dL below fasting blood glucose, clamp duration 12 h postdose) with a washout period of 3–14 days between dosings.

Result:

Test and reference showed superimposable serum insulin (ins) and glucose infusion rate (GIR) profiles. Bioequivalence was proven for the primary PK end points ($AUC_{ins\ 0-12\ h}$ 1.02 [0.99; 1.04], geometric least squares means ratio test/reference [90% confidence interval (CI)]; $C_{ins\ max}$ 1.02 [0.96; 1.09]) as well as for the primary PD end points ($AUC_{GIR\ 0-last}$ 1.03 [0.96; 1.11], treatment ratio [95% CI]; GIR_{max} 1.04 [0.97; 1.12]), as the CIs did not exceed the prespecified range of 0.8 to 1.25. Bioequivalence criteria were also fulfilled for a number of additional end points ($AUC_{ins\ 0-4\ h}$ 1.04 [0.98; 1.12]; $AUC_{ins\ 0-6\ h}$ 1.02 [0.97; 1.08]; $AUC_{GIR\ 0-4\ h}$ 1.05 [0.95; 1.17]; $AUC_{GIR\ 0-6\ h}$ 1.05 [0.96; 1.14]; $AUC_{GIR\ 6-last}$ 1.00 [0.86; 1.13]). Both insulins were well tolerated, and no injection-site reactions were observed.

Conclusion:

Julphar Insulin R and Huminsulin Normal show very similar PK/PD properties. This study demonstrated bioequivalence between both insulins.

Pramlintide versus Liraglutide: Assessing Incremental Benefits of Adjunctive Therapy to Closed-Loop Insulin Delivery

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Objective:

Closed-loop (CL) insulin delivery effectively maintains blood glucose (BG) overnight but struggles when challenged with meals. Therefore, pramlintide and liraglutide were assessed as adjuncts to CL insulin delivery. The objective of this analysis was to compare the relative effect of each adjunctive agent on glycemic excursions and insulin requirements during CL.

Research Design:

Two studies, one evaluating adjunctive pramlintide, the other liraglutide, were compared. Ten subjects (six female; age 16–23 years; A1C $7.2 \pm 0.6\%$) completed two 24-hour sessions, one on CL alone and one on CL plus 60 μg pramlintide (CLP), after a 3–4 week outpatient dose escalation. Eight subjects (seven female; age 19–27 years; A1C $7.4 \pm 1.0\%$) underwent the identical protocol with 1.8 mg liraglutide (CLL) after similar 3–4 dose escalation. Timing and content of meals during CL were identical within experiments; meals were not announced.

Results:

Mean BG levels were lower during CLL than CLP (131 ± 27 vs. 145 ± 28 ; $P < 0.005$). Overall reduction in magnitude of glycemic excursions was greater with liraglutide than pramlintide (24 ± 4 vs. 13 ± 5 mg/dL; $P = 0.09$). However, differences by individual meal were noted, with breakfast and dinner favoring CLL and lunch favoring CLP. Pramlintide delayed the time to peak BG excursion (CLP 2.6 ± 1.5 vs. CLL 1.6 ± 0.8 h; $P < 0.005$). Reductions in meal-related insulin requirements were similar in both studies (CLP 1.5 ± 1.9 vs. CLL 2.1 ± 2.1 U/meal; $P = 0.51$).

Conclusions:

Adjunctive liraglutide during CL was associated with lower mean BG and greater reduction in magnitude of prandial BG excursions than pramlintide and had less effect on delaying postprandial glucose appearance. Differences in lunchtime BG excursion may be due to carryover effect of pramlintide. Given its once-daily dosing regimen, liraglutide appears to be the preferable adjunct to CL insulin delivery.

Controller Performance Assessment of Model-Based Artificial Pancreas Control Systems

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Objective:

Many artificial pancreas control systems are based on models that predict glucose concentrations. The performance of these control systems depends on the accuracy of the models and may be affected when large dynamic changes in the human body or changes in equipment performance would move the operating conditions away from those used in developing the models used in designing the control system. The objective for this paper is to develop a controller performance assessment (CPA) module to evaluate the performance of model-based controllers and initiate controller retuning if there is significant performance deterioration.

Method:

The CPA module has six indexes that capture different aspects of model and controller performance, which can be analyzed to determine the specific component of the controller that caused performance deterioration. These indexes are used to diagnose four different kinds of control system errors, and the diagnosis results are used for controller retuning.

Result:

Thirty subjects in the University of Virginia/Padova metabolic simulator and data from five clinical experiments are used to evaluate the performance of the CPA module. The results indicate that a controller with the proposed CPA module keeps glucose concentration variations in the desirable range for a larger percentage of time and provides more reasonable insulin suggestions than a controller without controller retuning guided by the CPA module.

Conclusion:

The performance of an artificial pancreas control system is not always at the optimal condition. The proposed index-based CPA module can improve the controller performance by monitoring and retuning the controller in an artificial pancreas system.

Glooko: Mobile, Unified Platform for Diabetes Management, Combined with Nurse Coaching, Lowers HbA_{1c} and Improves Quality of Life

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Objective:

While benefits of remote coaching between clinical visits for patients with diabetes are documented, the added effect of technology that enables remote access to diabetes data, analytics, and patterns between clinical visits has not been thoroughly studied. The aim of this study was to evaluate whether Glooko, a mobile and web-based diabetes management platform, in combination with remote nurse coaching, results in improved health outcomes for patients and satisfaction for patients and health care providers.

Method:

Blood glucose (BG) readings analysis and satisfaction surveys were used to quantify the efficacy of Glooko's diabetes management platform. Because Glooko downloads historical BG readings taken prior to study initiation, we used a retrospective analysis where each patient was their own control ($n = 40$). A patient met the inclusion criteria if they had a compatible smartphone and HbA_{1c} $\geq 8.5\%$, hypoglycemia unawareness, and/or were a new insulin start as determined by the clinic staff. At least, patients were required to use Glooko to upload their BG data weekly and nurses were expected to review the data every 2 weeks. Each patient call consisted of data analysis, medication reconciliation, and communication about treatment adjustments and quality of life, which were recorded in surveys and the electronic health record.

Result:

Participants showed positive health outcomes after 90 days; over 35% of participants saw at least 10% reduction in average BG level and BG variability. Survey responses showed improvements in quality of life for patients and work satisfaction for providers. The average time per call was <15 min per 2-week period.

Conclusion:

This study demonstrated that remote patient monitoring, using a combination of Glooko and limited coaching, yielded positive health outcomes and improved overall satisfaction.

An Estimation of Glucose Uptake during Exercise

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Objective:

We aim to develop a model that can estimate the exercise enhancement in insulin action of healthy (nondiabetic) exercising patients during an oral glucose tolerance test. This model provided quantitative estimates for the contribution of three mechanisms of glucose uptake: insulin-mediated uptake, glucose-mediated uptake (mass action), and exercise-induced uptake.

Method:

Triple-tracer isotope dilution techniques were used to estimate the rate of appearance and the endogenous glucose production during rest and exercise in the postprandial period. The data were analyzed and interpreted through a novel modified model of glucose uptake based on the classical oral minimal model.

Result:

During a 75-min period of exercise that commences 2 h after a meal is ingested, approximately 37% of glucose uptake is exercise induced and independent of an increase in insulin concentration. The remaining uptake is estimated to be 29% from insulin-mediated uptake and 34% glucose mediated.

Conclusion:

Exercise has a significant ability to induce glucose uptake independent of an increase in plasma insulin concentration. In order for closed-loop controllers to provide accurate and safe insulin dosing, it is necessary to include the effects of exercise.

ISO 15197:2013: Evaluation of Two Improved Blood Glucose Monitoring Systems

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Objective:

Accurate results obtained with blood glucose monitoring systems (BGMSs) are essential for patients with diabetes to control their therapy. The tightening of system accuracy requirements introduced by the new international standard ISO 15197:2013 necessitates improvements in BGMS technology. The two investigated BGMSs had been updated with an improved algorithm and were tested for compliance with ISO 15197:2013 system accuracy criteria.

Method:

We performed an accuracy evaluation of two improved BGMSs (Contour and Contour TS, Bayer Consumer AG, Basel, Switzerland) following ISO 15197:2013, section 6.3. Blood glucose values of 100 subjects determined with the BGMSs were compared to results obtained with a hexokinase method (Cobas Integra 400 plus). Three test-strip lots of each system were tested, and the number of values that fall within the stipulated limits of ISO 15197:2013 (± 15 mg/dL at glucose concentrations < 100 mg/dL and $\pm 15\%$ at glucose concentrations ≥ 100 mg/dL) was calculated.

Result:

Between 98.5 and 100% of the results measured with Contour and between 99 and 99.5% of Contour TS results were within ± 15 mg/dL and $\pm 15\%$ of the comparison measurement results. For Contour 99.8% and for Contour TS 100% of values were within zone A of the consensus error grid. The remaining one value for Contour (0.2%) was within zone B. Relative bias ranged from -2.6 to -2.1% for Contour and from -2.7 to -0.6% for Contour TS.

Conclusion:

Both improved systems fulfilled the accuracy requirements of ISO 15197:2013. Regarding the key role of self-monitoring of blood glucose in diabetes therapy, adequate accuracy is essential for improving diabetes management.

Evaluation of Glucometer Test Strips for the Presence of Potential Pathogens, Including Methicillin-Resistant *Staphylococcus aureus*, *Clostridium difficile*, and Vancomycin-Resistant Enterococci

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Objective:

This study analyzed open containers of unused point-of-care (POC) glucometer test strips for the presence of potential pathogens, including common agents of health-care-associated infections in the United States, namely, methicillin-resistant *S. aureus* (MRSA), *Clostridium difficile* (CD), and vancomycin-resistant enterococci (VRE).

Methods:

Open blood glucose test-strip containers were collected from POC locations, including outpatient clinics (pediatric and adult) and inpatient units (critical care and noncritical care) and the emergency department, and transported to the microbiology laboratory. Remaining test strips were counted, and the containers were filled with 5 mL of thioglycollate broth and incubated for 48 h at 37 °C. Aliquots from each bottle were subjected to real-time polymerase chain reaction (PCR) for MRSA, CD, and VRE and subcultured to selective and differential media for identification of any potential pathogens using standard microbiological procedures.

Results:

Two hundred containers were tested, 42 were negative by both PCR and culture for any microorganisms. Of the remaining 158 containers, only 1 tested positive by PCR for MRSA. All other PCR testing yielded negative results. However, numerous microorganisms (215) were detected via conventional culture methods to include 52 vials that were polymicrobial. Isolates recovered included coagulase-negative staphylococci (109), *Enterococcus* sp. (not VRE) (29), *S. aureus* (not MRSA) (25), *Bacillus* sp. (24), alpha-hemolytic streptococci (23), and one isolate of group D streptococci, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus* sp., and MRSA, respectively. The number of remaining strips (1 to 48) had no significance on isolates recovered nor did location of retrieved containers.

Conclusion:

Seventy-nine percent of the containers tested were colonized with one or more microorganisms. Although only one microorganism was recovered using PCR for MRSA, VRE, and CD, numerous microorganisms (215) were detected via conventional culture methods. The number of test strips remaining in the container was not related to the number of microorganisms recovered.

Simplifying Calibration Practice for Home Use Noninvasive Glucose Monitoring Device: Shortening Procedure Duration

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Background:

GlucoTrack, a noninvasive blood glucose monitoring device for home use, requires calibration, using an invasive reference device, prior to its first use. Calibration establishes a baseline for physiological change detection in each individual and is required to be performed biannually. Currently, calibration takes ~2 h and requires a minimum of seven invasive measurements. In order to simplify the calibration practice, a shorter calibration scheme, with less invasive measurements required, was developed.

Method:

The new short-calibration algorithm was developed offline on the data set collected from 53 type 2 diabetes subjects (~4,300 paired GlucoTrack and invasive measurements readings) during clinical trials. The developed short-calibration duration is ~30 min, requiring only three paired GlucoTrack and invasive measurements. The validity of the new calibration algorithm was evaluated (offline) in an independent data set consisting of 117 type 2 diabetes subjects (~8,200 paired readings). The performances obtained with the original real-time calibration were compared to performances obtained when the short-calibration algorithm was applied to the same data. The performances using both calibrations were evaluated based on Clarke error grid (CEG) and mean absolute relative differences (MARDs).

Results:

Performance evaluation using a real-time original calibration algorithm showed 94.7% of points in CEG's clinically acceptable zones (A+B) and 31.2% in MARD, whereas using the short (offline) calibration, 95.7% of points were in CEG's A+B zones and MARD was 24.2%.

Conclusions:

Applying the short-calibration procedure not only reduces procedure complexity, but also improves the device's performances. These results support the validity of the newly developed calibration scheme for type 2 diabetes patients. Ultimately, practicing a shorter, simpler, and less-painful procedure is expected to positively affect device usability and user satisfaction.

Simplifying Calibration Practice for Home Use Noninvasive Glucose Monitoring Device: Reference Device Aspects

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Objective:

GlucoTrack is a CE Mark–certified noninvasive blood glucose monitoring device for home use. GlucoTrack’s measurement of glucose is indirect; thereby it requires individual calibration, using an invasive reference device. Currently, calibration is done in-clinic, using a point-of-care (POC) clinical-use invasive device as a reference. In order to simplify calibration practice, we evaluated the possibility of using users’ own invasive device as a calibration reference.

Method:

GlucoTrack performances were evaluated in clinical trials. At the beginning of the trials, each subject was calibrated using HemoCue Glucose 201 RT System as a reference (real-time calibration). Each HemoCue reading was accompanied by a simultaneous measurement with a common home-use blood glucose meter (FreeStyle Freedom Lite), which complies with ISO 15197. FreeStyle readings were then used for an offline calibration. GlucoTrack performances following both calibrations were evaluated versus HemoCue.

Results:

Analysis was performed on data collected from 204 diabetic subjects of various demography (14,205 data points). Real-time calibration, using HemoCue as a reference device, yields a mean absolute relative difference (MARD) of 29.5%, while 95.5% of points fall in the clinically acceptable A+B zones of the Clarke error grid. Offline calibration, using the FreeStyle reference, yields a MARD of 29.9% and 95.8% of points in A+B zones, similar to the results when HemoCue was used as a reference.

Conclusions:

GlucoTrack performances remain similar when using either a home-use device for calibration or a POC device. This allows a conventional device (complying with ISO 15197) to be used as a reference device for GlucoTrack calibration. Calibration, using subjects’ home glucose meters, becomes more flexible, accessible, and practicable. This is expected to have a positive impact upon GlucoTrack acceptability by users.

A Novel, Time-Invariant, Intuitive Metric for Assessing Glycemic Variability

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Objective:

High levels of glycemic variability are still observed in most patients with diabetes with severe insulin deficiency. Glycemic variability may be an important risk factor for acute and chronic complications. Although numerous methods have been proposed for assessment of glycemic variability, there is no consensus on the optimum method for routine clinical use. We propose a novel and intuitive metric, the topological glycemic variability index (TGVI), for assessing glycemic variability using continuous glucose monitoring (CGM) data.

Method:

The TGVI measures glycemic variability by analyzing the length of the CGM temporal trace normalized to the duration under evaluation. We applied this metric to data from six clinical studies for the G4 Platinum CGM system (Dexcom, San Diego, CA). The TGVI was also applied to data from a study of an artificial pancreas, comparing results from open loop and closed loop in adolescents and in adults.

Result:

The new metric for glycemic variability index, TGVI, was able to clearly differentiate between diabetic and nondiabetic subjects; between subjects with diabetes with low, moderate, and high glycemic variability based on interquartile analysis; as well as between subjects on open- versus closed-loop control.

Conclusion:

A new metric for the assessment of glycemic variability has been shown to be applicable to a broad range of subjects with diabetes. The new metric includes equal weighting of the amplitude and frequency of glycemic fluctuations and may be a more effective tool in assessing glycemic variability than other extant methods that emphasize either the amplitude or frequency only.

Optical Classification of Diabetic Wounds: Preliminary Sensitivity and Specificity Analysis

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Objective:

Of the nearly 246 million people diagnosed with diabetes worldwide, an estimated 15% of all patients suffering with diabetes will develop diabetic foot ulcers (DFUs). About half of these DFUs will become infected, resulting in 20% of patients left to face some form of a lower extremity amputation. To date, clinicians use visual inspection of the wound site during its standard 4-week healing process via monitoring of surface granulation. In many cases, surface granulation is not an implication of internal healing. There is a need to develop on-site, low-cost imaging tools that can objectively classify healing from nonhealing wounds.

Method:

Herein, a portable, low-cost, noninvasive, and non-contact-based near-infrared optical scanner (NIROS) was implemented to optically differentiate healing from nonhealing DFUs. Noncontact, nonradiative real-time imaging was performed on diabetic subjects with foot/leg ulcers. The near-infrared optical images acquired from the foot were processed to obtain optical contrast ratio between the wound and its background under various conditions of imaging location, selection of wound and background regions, and analysis by different researchers (to remove operator variability). Statistical analysis was carried out to determine the sensitivity and specificity of the imaging approach to classify healing from nonhealing wounds.

Result:

Preliminary analysis from 21 wounds showed a sensitivity of 90% and a specificity of 98% in differentiating a wound as healing or nonhealing. The optical classification was based on the differences in the optical contrast between the wound and its peripheries.

Conclusion:

A portable NIROS demonstrated its capability to classify a healing from nonhealing wound. Future work will involve systematic weekly assessment of wounds to determine healing area with time.

Long-Term Follow-Up of Sensor-Augmented Pump Therapy with Low-Glucose Suspend Function in Type 1 Diabetes Patients with High Risk of Hypoglycemia

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Objective:

We assess the efficacy and safety of long-term use of sensor-augmented pump therapy with low-glucose suspend (SAP-LGS) in type 1 diabetes (T1D) patients with high risk of hypoglycemia.

Method:

The study was an observational prospective cohort study from August 2010 until February 2015 of T1D patients who started SAP-LGS. The main indication was hypoglycemia and poor metabolic control. Demographic and clinic variables were registered as well as A1C levels at the beginning, 3-month, and 1-year follow-ups.

Result:

Ninety-four T1D patients with hypoglycemia were included with an average baseline of A1C of $8.84 \pm 1.93\%$. The mean follow-up was 2.2 years (range 4.5–1.02 years); sensor was used 80–100% of the time. At the end of the follow-up, the decrease of A1C was statistically significant at $7.3 \pm 1.03\%$ ($P < 0.0001$); this decrease was found at the third month A1C $7.6 \pm 1.7\%$ ($P < 0.0001$). Incidence of severe hypoglycemia decreased in the last year to 0.02 episodes per patient per year ($P = 0.0032$). Only 2% of the patients presented severe hypoglycemia, which is statistically different from the baseline ($P < 0.0001$), and 12% of patients remained with hypoglycemia unawareness ($P < 0.0001$) after initiating therapy. The patient proportion at the beginning with A1C at less than 7% was 16%; 87% of them had severe hypoglycemia. At the end of the follow-up, 44.7% had A1C less than 7%; only 4.8% of the patients had severe hypoglycemia ($P < 0.0001$).

Conclusion:

SAP-LGS therapy reduces the frequency of severe hypoglycemia and unawareness of hypoglycemia in T1D patients with failure to adhere to multiple daily injections and at a high risk of hypoglycemia. This allows better metabolic control in a safe way. This effect was observed early and was maintained during the follow-up time.

Characterizing Self-Management Behaviors of Type 1 Diabetes Patients on Insulin Pump Therapy

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Objective:

Very little is known about patient insulin dosing behaviors in relationship to alcohol and exercise. Identifying patterns of behavior could assist clinicians in developing decision aids in support of improving glycemic control. The purpose of this study was to analyze patient insulin dosing decisions occurring in conjunction with alcohol intake and exercise.

Methods:

We recruited nine subjects with type 1 diabetes on insulin pumps, seven of whom used continuous glucose monitoring systems (CGMSs). Participants were interviewed regarding their perception of how exercise and alcohol affect glucose control. They were asked to keep a 30-day journal on the duration and intensity of exercise performed and the type and amount of alcohol consumed. After 30 days, stored glucose, carbohydrate, and insulin data were downloaded. Participants' reported behaviors with insulin dosing in the setting of alcohol and exercise were compared with data stored on their pump/CGMS devices.

Result:

Over 1,000 subject interactions with the bolus wizard were analyzed. There were 186 events associated with exercise and 81 related to alcohol. How subjects compensated for alcohol and exercise varied among subjects. Subjects varied between sometimes or never entering alcohol-associated carbohydrates into the bolus wizard. Some subjects accounted for exercise when making decisions regarding insulin boluses, while others did not, and within-subject inconsistency was also noted. We observed that subjects' actual behaviors regularly diverged from their reported alcohol and exercise compensation techniques.

Conclusion:

Alcohol and exercise can affect glycemic control. However, how patients dosed their prandial insulin in response to alcohol and exercise behaviors was inconsistent. Further study is needed to understand these inconsistencies and to develop improved strategies to help patients make better treatment decisions.

Introducing a Method to Retrospectively Compare Insulin Dosing Recommendations

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Objective:

We introduce a method to compare the performance of insulin dosing algorithms and exemplify the method by comparing in terms of postprandial control the evidence-based iDECIDE algorithm accounting for carbohydrates, alcohol, and exercise against insulin bolus recommendations made by the proprietary algorithm of the type 1 diabetes (T1D) patients' devices.

Method:

We recruited nine T1D patients on insulin pump therapy. Patients kept a 30-day journal to track exercise performed and alcohol consumed. Glucose, carbohydrate, insulin dosing, exercise, and alcohol data were downloaded and entered into the iDECIDE algorithm. The prandial insulin dose recommended by iDECIDE was compared with that made by the insulin pump. We considered that a recommendation was more favorable if it was more likely to cause blood glucose to be within the patient's target range 3 h after dosing. Two doses were equivalent if they were equal or had a variation of less than 10%.

Result:

We analyzed over 1,000 patient events. Equivalent prandial insulin doses were suggested in 61% of the interactions. In 23% of cases, iDECIDE outperformed the insulin pumps, while the pumps outperformed 16% of the time. In the cases where iDECIDE outperformed, hypoglycemia could have been avoided in 26% of events. In over 50% of the reported exercise events, iDECIDE would have appropriately dosed insulin or suggested a proper amount of carbohydrates to consume before exercising.

Conclusion:

By using a detailed method to compare algorithms instead of the standard technique of computing number of hypoglycemic cases avoided, we hope to better calibrate the iDECIDE algorithm and to learn from differences between patients' actual reactions versus expected reactions to exercise and alcohol as reported by evidence resulting from controlled studies.

Hybrid Closed Loop in Monitored Outpatient Conditions

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Objective:

Medtronic's Android-based hybrid closed-loop (HCL) system was tested in nine type 1 diabetes (T1D) patients (mean age 53.3 years, duration of diabetes 22.6 years, HbA_{1c} 7.2%) in monitored outpatient settings to assess its efficiency and reduction of risk during automated insulin delivery with and without personalized parameter adaptation.

Method:

Subjects spent 4 days and 3 nights under HCL control (611 h total) for postprandial glucose control assessment after three types of meals: with precise carbohydrate (CHO) content prepared by Metabolic Kitchen (MK), a dietician-estimated CHO content (D), and CHO content estimated by subjects (control). Timing and CHO content of all meals were matched. Out of 611 h, 36% of time, HCL parameters were set to default values based on total daily dose of insulin; 64% of time, a personalized adaptation was implemented.

Result:

The increments in 3 h postprandial sensor glucose (SG) values were 6.0 ± 31.5 vs. 6.8 ± 28.3 mg/dL, with control and D meals, respectively ($P = 0.76$), and 18.1 ± 39.2 vs. 13.9 ± 36.0 mg/dL with control and MK estimations, respectively ($P = 0.16$). During HCL control, 79.5% of time, subjects' SG values were in the 70–180 mg/dL range and 0.9% were below the 70 mg/dL range. Notably, the percentage of time in the 70–180 mg/dL range was further improved when HCL parameters were individually adapted (from 67.7% at baseline to 86.1%).

Conclusion:

The HCL system demonstrated significant glycemic efficacy and safety in T1D patients. Personalized adaptation further improves glycemic outcomes. Meal bolus estimation based on precise CHO counting didn't significantly reduce postprandial glucose excursions. The HCL system manifests significant efficacy and safety in T1D patients.

In Vitro and In Vivo Performance of a Multianalyte Sensor

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Objective:

The aim of this work was the development and in vitro and in vivo evaluation of a multianalyte sensor capable of monitoring glucose, lactate, and oxygen simultaneously.

Method:

Multianalyte sensors with three amperometric sensing elements (glucose, lactate, and oxygen) were developed. The sensors were equipped with a wireless transmitter capable of transmitting multiple sensor signals simultaneously. The sensors were tested in vitro (in phosphate-buffered saline) and in vivo (rat model). For in vivo testing, the trends of the three analytes were monitored and recorded in response to external stimuli: 1) glucose injection, 2) increase in isoflurane level, and 3) death after pentobarbital injection.

Result:

The sensor was able to monitor the trends of glucose, lactate, and oxygen simultaneously. No crosstalk between the different sensing elements was observed. Following intraperitoneal glucose injection, glucose increased while oxygen decreased slightly. The signal of both glucose and oxygen sensing elements decreased after increase in the anesthesia level from 2 to 3%. The injection of pentobarbital led to further decrease of both oxygen and glucose signals, which is consistent with observations for individual sensors in rats following death. Lactate levels were affected to a smaller extent compared with glucose and oxygen, as lactate levels are known to be stable during inactivity.

Conclusion:

The multianalyte sensor presented here is capable of measuring and transmitting individual analyte trends without interference or cross talk. The current study on multianalyte sensors paves the way for the development of a miniaturized fully implantable wireless multianalyte biosensors for better diabetes management and monitoring of physical activity.

The SPIDIMAN Single-Port System: Combining Continuous Glucose Monitoring and Insulin Infusion

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Objective:

In order to improve glycemic control in type 1 diabetes patients, we aimed to develop a new technology combining continuous glucose monitoring and insulin infusion in a single-port system for simultaneous glucose measurement and insulin delivery.

Method:

In contrast to current artificial pancreas systems, where patients have to carry two separate devices—a glucose sensing device and an insulin pump—the SPIDIMAN single-port system integrates two luminescence-based sensors as thin coatings directly on the cannula of an insulin infusion set. The read-out device is placed on the patch of the insulin infusion set, and the sensor signals are read out transcutaneously via contactless near-infrared radiation. The system calculates glucose concentrations using an enzymatic glucose sensor for tissue glucose measurements and a reference oxygen sensor to detect tissue oxygen levels.

Result:

In a proof-of-principle study, we showed successful frequency-domain measurements in the near-infrared region in skin and subcutaneous tissue. Subsequent *in vivo* experiments in pigs demonstrated a good correlation of measured subcutaneous glucose concentrations and reference blood glucose values but also that measured glucose concentrations are not affected by simultaneous insulin delivery at the same site. In the first clinical trial in humans, we successfully monitored glucose with our new single-port SPIDIMAN system to test *in vivo* sensor performance including hypo- and hyperglycemic episodes.

Conclusion:

Our single-port SPIDIMAN system integrates a new sensing technology to measure glucose with simultaneous subcutaneous insulin delivery and could thus become the heart of an artificial pancreas to reach a new milestone in diabetes management.

Insulin-to-Carbohydrate Ratio and 24-h Urinary Glucose Excretion to Assess Insulin Dose Adjustments in Type 1 Diabetes Mellitus Subjects Treated with Dapagliflozin

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Objective:

We hypothesized that 1) individual insulin-to-carbohydrate ratios (I/C), adjusted with 24-h urinary glucose excretion (UGE) data, can derive an insulin dose effect equivalent to the glucose amount excreted in urine after 7 days treatment with the sodium-glucose cotransporter-2 inhibitor dapagliflozin (DAPA) in subjects with type 1 diabetes mellitus (T1DM) and 2) the UGE:insulin dose equivalent can guide insulin dose adjustment during treatment with DAPA.

Method:

Day 7 data on total daily insulin dose (TDD), UGE, and fasting serum beta-hydroxybutyrate (BOHB) were obtained from study NCT01498185, a 14-day study of DAPA (1, 2.5, 5, and 10 mg/day; $n = 15$ /arm) as add on to insulin in subjects with T1DM. The insulin prediction factor $450 = \text{TDD} \times \text{I/C}$ (for adults on short-acting insulin) was applied to derive I/C. UGE:insulin dose equivalent was calculated as $\text{UGE}:\text{I/C}$ and expressed as percentage of TDD.

Result:

At day 7, mean observed reductions in TDD were 16, 11, 19, and 17% for the 1, 2.5, 5, and 10 mg DAPA groups, respectively. There was good agreement with the calculated mean UGE:insulin dose equivalents, which were 11, 13, 18, and 22% across groups, respectively. At day 7, BOHB slightly correlated with the observed reduction in TDD ($r = 0.19$) across groups. In subjects with $\leq 20\%$ reduction in TDD ($n=41$), the maximal value of BOHB was 1.00 mmol/L. In subjects with $>20\%$ reduction in TDD ($n=26$), the maximal value of BOHB was 2.15 mmol/L.

Conclusion:

Insulin dose reduction in T1DM at/after the initiation of DAPA treatment should probably not exceed 20%. Further reduction may offset the glycemic benefit of UGE and elevate BOHB and could potentially increase the risk of ketoacidosis.

Toward a Sensor and Model for Cortisol as Feedback in the Bioartificial Pancreas

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Objective:

A means of quantifying biomolecules, such as hormones, for use as feedback in a bioartificial pancreas system has been called for by many prominent members of the field. It is the goal of this work to begin development of a sensor and model to quantify an important hormone, cortisol, as a novel marker for diabetes management.

Method:

The main focus has been to develop an electrochemical immunosensor that can reliably quantify cortisol in a rapid, if not continuous manner. Several electrochemical techniques have been used to fulfill this purpose, including cyclic voltammetry (CV), amperometric-it (amp-it), square wave voltammetry (SWV), and impedance spectroscopy (EIS). These techniques were run on serial dilution samples of cortisol (suited for the concentration sensitivity range of each technique) in ethanol/chloroform/phosphate-buffer saline solutions with 100 mmol/L ferricyanide as a redox mediator. The resulting calibration curve models of cortisol concentration versus measurand have been completed for each of the electrochemical techniques.

Result:

It was found that though the CV, amp-it and SWV techniques provided useful information regarding the electroactivity of cortisol, EIS was found to be the most sensitive and potentially useful for the desired application: a lower limit of detection of 257.52 pg/mL and a responsivity of 4.03 pg/mL per ohm measured at 1465 Hz. Whereas the enzyme-linked immunosorbent assay (ELISA) provided a lower limit of detection of 312.05 pg/mL and a responsivity of 252 pg/mL per arbitrary unit of optical density measured.

Conclusion:

The EIS technique shows promise for rapid quantification of cortisol in purified solutions. This 90-s assay, which rivals ELISA, will continue to be optimized (for blood samples) as input to a nonlinear control integrated into a bioartificial pancreas system.

Systematic Study to Optimize Insulin Delivery through a Continuous Subcutaneous Insulin Infusion Catheter

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Objective:

A pilot study is being performed in six ambulatory humans scheduled for a surgical abdominoplasty to compare histology and cytokine expression profiles of the tissue surrounding Teflon continuous subcutaneous insulin infusion (CSII) catheters inserted 4, 3, and 2 days and 2 h prior to surgery. The results will help formulate a hypothesis, why insulin absorption into the circulation becomes more variable 2–4 days after catheter insertion.

Method:

Two CSII catheters (Quick-set) are inserted into the subcutaneous abdominal tissue of six ambulatory humans 4, 3, and 2 days and 2 h prior to elective plastic surgery to remove excess skin and subcutaneous tissue. Tissue surrounding CSII catheters is removed and stained with hematoxylin and eosin, reticulin, and trichrome as well as CD31, CD68, and D240 to determine morphological changes and number/location of capillaries, lymph vessels, and inflammatory cells in the tissue. RNA is isolated from the second CSII catheter-tissue specimen from each time period and quantitative real-time PCR carried out to measure changes in expression of interleukin (IL)-1b, IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-a, transforming growth factor (TGF)-b, and CD68.

Result:

Data from six patients will be included in the final abstract. Tissue from the first patient showed mechanical impact of catheter insertion and neutrophil recruitment after day 3. Capillaries and lymphatic vessels remained at a normal density over 4 days. We could not detect macrophages by immunohistochemistry, but CD68 gene expression increased 3× over 3 days. While IL-6 and IL-10 showed only a slight increase in expression by day 4, levels of IL-1b, IL-8, TGF-b, and TNF-a were 3–6× higher than in unaffected tissue.

Conclusion:

This is the first human study to show the soft tissue's immune response to CSII catheter insertion. The results from the histological, immunohistochemistry, and molecular analysis may help us understand why insulin absorption from a CSII catheter becomes more variable after 2–4 days of implantation.

Finger Stickin' Good: Improved Glycemic Control in Cardiovascular Surgery Patients Provides Cost Savings through Reduction in Point-of-Care Tests

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Objective:

Glucose control with intravenous (IV) insulin has been shown to provide up to \$2,700 in cost savings per patient undergoing cardiovascular surgery with a target of 100–140 mg/dL. This study focuses on cost savings achieved with point-of-care (POC) test-strip reduction by achieving glycemic targets quickly and safely.

Method:

A retrospective, observational study was conducted comparing Glucommander (GM) IV to standard insulin infusion by paper protocol (SII) at a community-based hospital involving 627 adult patients undergoing cardiovascular surgery with a glycemic target <180 mg/dL. This study was conducted over a 9-month period with 3 months before GM as control (206 patients) and 6 months with GM as active (421 patients). POC test-strip use and reduction of hypoglycemia were analyzed to compare cost and efficiency of the two methods.

Result:

Hypoglycemia <40 and <70 mg/dL was 0.46 and 1.86% for SII and 0.0 and 0.8% for GM, respectively. Percentage of patient-day in target range for SII was 81 versus 91% for GM. Hyperglycemia >180 mg/dL was 16.33% for SII versus 8.11% for GM. Time to glucose target was 5.3 h faster for GM (3.1 h) compared with SII (8.4 h). The average number of POC tests with SII was 50.4, and 35.1 for GM. The cost savings from treatment with GM was \$69.30 per patient, totaling \$29,175.30.

Conclusion:

GM had 57% fewer hypoglycemic events <70mg/dL and 30% less POC utilization per patient. Patients treated with GM had faster time to target, less hyperglycemia, and more patient-days in target. These data suggest that it is possible to achieve better glycemic control with GM, which correlates to cost savings.

In Silico Evaluation of Ultra-Fast-Acting Insulins Using the Bioinspired Artificial Pancreas

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Objective:

Currently available rapid-acting insulin analogs (RAIs) are not fast enough to provide good postprandial glycemic control in a fully automated artificial pancreas (AP) system (no user intervention required). Therefore, most of the existing AP systems incorporate a premeal insulin bolus to minimize postprandial glucose peaks. The advent of ultra-fast-acting insulin (UFI), showing an even more rapid onset of action and a shorter duration of action after subcutaneous administration, opens the door to a fully automated closed-loop AP system. This in silico study evaluates the benefits of using UFIs in a closed-loop glucose control setting.

Method:

For validation, the University of Virginia-Padova simulator was used. The bioinspired artificial pancreas (BiAP) controller without meal announcement was used over a 1-week simulation period in 10 adult and 10 adolescent virtual cohorts. For comparison, standard glucose metrics were used: mean glucose (G), percentage of time in glucose target 70–180 mg/dL (%inT), percentage of time below target (%<T), percentage of time above target (%>T), and risk index (RI). The parameters of the insulin absorption model of the University of Virginia-Padova simulator were adjusted to model the dynamics of a UFI with a peak action time of 30 min.

Result:

When compared with an RAI, the utilization of a UFI within the BiAP controller improved all the evaluated glycemic metrics ($P < 0.05$) but %<T in the adult cohort. In adults, G 133.8 ± 5.9 vs. 127.5 ± 6.1 ; %inT 88 ± 7 vs. 92.8 ± 5.6 ; %<T 0.85 ± 1.2 vs. 0.59 ± 0.94 ; %>T 11 ± 6 vs. 6.5 ± 4.8 ; and RI 3.1 ± 1.1 vs. 2.1 ± 1.0 . In adolescents, G 153.8 ± 16.3 vs. 139.7 ± 11.9 ; %inT 68.9 ± 12.6 vs. 80.9 ± 11.6 ; %<T 2.3 ± 1.7 vs. 1.2 ± 1.3 ; %>T 28.8 ± 11.3 vs. 17.9 ± 10.3 ; and RI 7.4 ± 3.5 vs. 4.6 ± 2.7 .

Conclusion:

UFIs have the potential to significantly improve glycemic control in a fully automated AP system.

Scalable and Durable Optimal Glycemic Control in Insulin Users

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Objective:

The outcome of insulin therapy has been persistently disappointing, where the majority of users sustain elevated glycated hemoglobin (HbA_{1c}). Studies have shown that this therapy can be successful if combined with frequent dosage adjustments to narrow the gap between the initially prescribed and the individual therapeutic dosage. Additionally, due to constant variations in insulin demands, frequent titration is needed to maintain optimal control while avoiding hypoglycemia. In reality, insulin titration is done sporadically. Provider-based frequent insulin titration is not feasible since it requires special expertise and time that exceeds health care systems' resources.

Method:

We have implemented a scalable and practical solution in Europe that does not place any additional burden on the health care system. The insulin guidance service is available by prescription and relies on d-Nav, a handheld device. d-Nav provides patients with an insulin dose recommendation for each injection. Similar to the approach providers use during clinical encounters, d-Nav analyzes stored glucose patterns and titrates insulin dosage without providers' supervision. It does not necessitate patient behavior modifications. The service nurse specialists provide patients with ongoing support and clinical triage. We report interim glycemic outcomes in long-term users.

Result:

A total of 178 patients have been managed for >6 months. During enrollment, average (\pm standard deviation) HbA_{1c} was 9.3 (\pm 1.4), after a year 7.4 (\pm 1.0), and at 2 years 6.9 (\pm 0.9). Hypoglycemic burden was stable and low.

Conclusion:

Global implementation of such a service has the potential to transform the standard of care by optimizing long-term glycemic control. It may prevent morbidity and save resources in the growing population that requires lifelong insulin therapy. Such a service can only be successful if it does not increase the burden on health care systems.

Infusion Set Fault Detection via Monitoring of Real-Time Data over Sliding Windows

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Objective:

From continuous glucose monitors (CGMs) and continuous subcutaneous insulin infusion (CSII) pumps to fully closed-loop artificial pancreas systems, advanced technology for type 1 diabetes management seeks to improve the safety of people living with this disease. However, even with the newly integrated CGM/CSII systems, fault detection for the infusion system has not received much attention. Therefore, we have developed an algorithm based on an individual's average glucose and average plasma insulin over sliding windows that alarms an individual when a fault in the insulin infusion set has likely occurred.

Method:

The developed algorithm is trained retrospectively on data from 62 insulin set insertions from 20 patients in a study that assessed the effect of inserting infusion sets in lipohypertrophic sites. An alarm is determined when thresholds on the following quantities are exceeded: 1) the integrated difference between the average CGM reading in the short and long windows, 2) the normalized difference between average estimated plasma insulin in the short and long windows, 3) the glucose slope in the short window, and 4) the number of CGM readings in the short window.

Results:

With the chosen operating parameters, the sensitivity of and number of false positives generated by the proposed fault detection algorithm are 75% and 0.4/day, respectively. Although false positives are usually not desired, they may help patients improve their overall glycemic control in open loop. Furthermore, preliminary closed-loop data suggest that this algorithm can be used under both scenarios and may even offer more desirable alarm statistics under closed loop.

Conclusion:

The algorithm developed is able to effectively alert patients to possible infusion set failures in open loop. Ongoing studies conducted in real time under closed-loop conditions will give further credence to the proposed fault detection algorithm.

Performance of a Blood Glucose Monitoring System in a Point-of-Care Setting

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Objective:

We assess the performance of the Contour XT (XT) blood glucose monitoring system (BGMS) in a point-of-care (POC) setting when tested by laboratory personnel in accordance with ISO 15197:2013 accuracy criteria and national quality control guidelines for POC.

Method:

This is a single-center study conducted in Switzerland using 105 excess venous blood samples coming for routine laboratory procedures. Each sample was tested thrice, using three different strip lots, yielding 315 pairs of measurements (BGMS and hexokinase reference method). Compliance with Swiss (QUALAB) and German (Rilibäk) POC guidelines was assessed by daily control measurements with three XT BGMSs and two control solutions for each strip lot.

Result:

Glucose concentrations ranged from 2.2 to 28.4 mmol/L. The overall accuracy of XT BGMS according to ISO limits was 98.41%. For samples with glucose levels <5.551 mmol/L ($n = 42$) and ≥ 5.551 mmol/L ($n = 63$), 96.3 and 100% of BGMS measurements satisfied ISO accuracy criteria, respectively. Parkes error grid analysis revealed 99.4% of results for the BGMS to be in zone A, while 0.6% fell in zone B. Using the newly developed surveillance error grid analysis, 97.46% of measurements fell within the no-risk zone. The relative differences of measurements using control solutions (26 control tests per strip lot) were within the limits defined by QUALAB (errors within $\pm 10\%$ of control solution target values) and Rilibäk (errors within $\pm 11\%$ of target value) POC guidelines.

Conclusion:

This study demonstrates that XT BGMS fulfills the ISO 15197:2013 accuracy limits under routine hospital conditions, as well as stringent Swiss and German quality control requirements for the POC setting.

Use of a Bihormonal Artificial Pancreas System with Exercise Announcement in Type 1 Diabetes to Prevent Hypoglycemia

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Objective:

We developed and tested a wireless bihormonal artificial pancreas system that adjusts dosing after an exercise announcement to reduce exercise-related hypoglycemia.

Method:

Adult subjects with T1D underwent three 20 h sessions: open loop (OL), closed loop (CL), and CL with exercise announcement (CLX). Exercise announcement stopped insulin for 30 min, then 50% reduction for 60 min, and increased glucagon by twofold for 1.5 h. Parameters were selected via *in silico* testing. G4 sensor values were pushed to a Google Nexus phone that sent delivery commands to t:slim pumps for subcutaneous insulin and glucagon infusion. After an overnight stay, subjects exercised for 45 min at 60% of maximum heart rate. Subjects were given two meals and wore a Zephyr heart rate monitor and accelerometer.

Result:

Twelve subjects participated in 36 20-h studies. Hypoglycemic events were reduced from 10 during OL, to 6 during CL, to 1 during CLX ($P < 0.01$, CLX vs. OL). The CLX reduced the number of hypoglycemia events versus CL ($P < 0.05$). Seven, five, and one subjects had a hypoglycemic event that required carbohydrates during the OL, CL, and CLX ($P < 0.05$ for CLX vs. OL). Mean glucose was 156 mg/dL for OL, 145 mg/dL for CL, and 149 mg/dL for CLX. Mean insulin delivery was similar across conditions. The mean amount of glucagon delivered was higher during the CLX (286 μg) compared with CL (180 μg ; $P < 0.01$).

Conclusion:

Automated insulin and glucagon delivery effectively controlled glucose levels and prevented hypoglycemia. Incorporating exercise announcement that adjusted insulin and glucagon delivery significantly reduced hypoglycemic events compared with standard CL. Incorporating an exercise announcement or automatic exercise detection into the design of the artificial pancreas is advantageous for preventing hypoglycemia.

Multianalyte Monitoring via Implantable Biosensors Predicts Exhaustion

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Objective:

Our aim is to develop a biosensor platform capable of continuous real-time monitoring of metabolic level changes to predict exhaustion during physical exercise. Monitoring of more than one analyte simultaneously is necessary to provide a holistic view of the metabolic changes that lead to exhaustion. This approach to metabolic monitoring is of great importance to diabetic patients, especially when undertaking intense physical activity since it can allow prediction of imminent metabolic changes and enable the individual to take preventive measures.

Methods:

Our previously developed coil-type electrochemical sensors were implanted transcutaneously in normal and diabetic rats, and a wireless dual transmitter collected data continuously from glucose and lactate sensors. Microdialysis samples were taken from both the jugular vein and subcutaneous tissue and analyzed for glucose and lactate via a YSI analyzer were used as a control. Forced exercise was performed on a treadmill (IITC Life Sciences).

Results:

Glucose and lactate trends indicated two major metabolic events following commencement of exercise: 1) rest to exercise transition and 2) exhaustion. Individually, glucose and lactate monitoring revealed only one of these two events. When glucose and lactate changes over time are combined, the result is a multianalyte biomarker, which is more informative than independent assessment of the single analytes. Additionally, the observed trends are more sensitive in the subcutaneous tissue (an implantation-friendly peripheral tissue) compared with the blood. This unexpected observation was confirmed in normal as well as type 1 diabetic rats.

Conclusions:

With the current work, we have extended the capabilities of our biosensor platform by incorporating lactate monitoring and identifying an appropriate multianalyte biomarker. These findings can be implemented in new multianalyte continuous monitoring technologies for more accurate insulin dosing, as well as for exhaustion prediction studies based on objective data rather than the subjects' perception.

Gluowizzard: An Injectable, Wireless Biosensor for Continuous Glucose Monitoring

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Objective:

Biorasis Inc. and the University of Connecticut are developing a totally implantable continuous glucose monitoring device. Gluowizzard is engineered at the smallest possible footprint ($0.5 \times 0.5 \times 0.5$ mm). This miniaturization is made possible by utilizing light for powering as well as wireless communication. The objective of this study was to optimize sensor parameters and provide in vitro and in vivo proof of concept.

Methods:

Gluowizzard uses a first-generation Clark-type enzymatic sensor based on three-electrode (working, reference, and counter) electrochemical transduction for detecting glucose levels. An integrated circuit is used to interact with the glucose sensing element and transmit data wirelessly through the skin to a proximity communicator. The sensors were tested both in vitro (in phosphate-buffered saline) and in vivo in normal rats. Blood glucose concentrations were used as a reference.

Results:

Gluowizzard showed a linear response over a wide glucose range in vivo and in vitro. Interestingly, the sensor sensitivity increased after 4 days of implantation. Implanted sensors were successfully used to monitor glucose trends in the subcutaneous tissue of rats, which closely followed the changes in blood glucose levels.

Conclusions:

This study provided proof of concept for the in vivo functionality of Gluowizzard, an injectable, wireless glucose biosensor. The sensors showed a linear response over a wide glucose concentration range both in vivo and in vitro. Moreover, blood glucose levels correlated with trends obtained from Gluowizzard, which is paramount for tight glucose control and diabetes management.

Cytotoxicity of Photopatternable Hydrogels for Implantable Glucose Sensors

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Objectives:

The function and lifetime of implantable electrochemical-based continuous glucose monitoring (CGM) devices depend on the stability of glucose oxidase (GO_x), the enzyme responsible for glucose detection. Polyethylene glycol (PEG)-ylated hydrogels offer an opportune venue to minimize biofouling, while retaining their highly hydrated state to prevent enzyme denaturation. Here we report the cytotoxicity studies of a novel PEGylated hydrogel capable of being photocrosslinked in its fully hydrated state. This hydrogel allows for CGM sensors with long-term stability and optimal performance.

Methods:

A PEGylated copolymer was synthesized via a free-radical polymerization using an azobisisobutyronitrile initiator. This PEGylated copolymer was crosslinked into hydrogel nanoparticles and suspended in cell culture media with concentrations from 0.01 to 100 $\mu\text{g/mL}$. Subsequently, mouse dermal fibroblasts (cell line L929) were incubated for 72 h with various nanoparticle concentrations. Cell viability was assessed via CellQuanti-Blue Cell Viability Assay Kit from BioAssay Systems (Hayward, CA).

Results:

Typically, nanoparticle cytotoxicity studies are conducted at very low concentrations (down to parts-per-billion levels) and for only 24- or 48-h incubation periods. In this study, cells were exposed to high nanoparticle concentrations for 72 h. It was determined that these PEGylated copolymer nanoparticles show no cytotoxicity for up to 72 h for the entire concentration range.

Conclusions:

Our studies indicate that photopatternable PEGylated hydrogels are ideal matrices for covalent immobilization of GO_x enzyme, enabling the fabrication of CGM devices. In this study we demonstrate that these photocrosslinked hydrogel nanoparticles are not cytotoxic and therefore pose no threat to the local tissue. Long-term in vivo studies are currently underway to determine the ultimate stability of these photopatternable CGM devices.

Automated Insulin Delivery “In the Wild”

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Objective:

Automated insulin delivery “in the wild” is more challenging than in hospital clinical research centers, diabetes camps, or hotels where health care professionals and engineers are closely standing by. Challenges include sensor changes/calibrations, system start-up/shutdown, continuous glucose monitor (CGM) communication errors, infusion set changes, insulin refills, and battery changes. Each of these challenges could occur for arbitrarily long periods of time. Furthermore, a normally operating CGM can produce physiologically impossible glucose values, such as following sensor calibration.

Method:

Our artificial pancreas autodosing mode control module enables closed-loop insulin dosing only when interfacing subsystems are operating normally and the CGM signal is physiological. The software module turns off automated insulin dosing and reverts to the user’s preprogrammed basal when something is wrong. The system resumes automated dosing when the problems are resolved.

Result:

The automated insulin doses at any time depend only on current CGM, rate, and acceleration and do not depend on prior insulin administration. This means that our fuzzy logic dosing controller can tolerate arbitrarily long challenges and time gaps in the CGM data input stream. Insulin on board (IOB) is taken into account 1) by the expertise model of the fuzzy logic dosing controller and 2) in the glucose prediction module. The prediction module uses the IOB and CGM histories to calculate the glucose predictions. If low blood glucose is predicted, automated insulin dosing is suspended until CGM begins rising.

Conclusion:

The modular system architecture and design of the dose safety controller enables automated insulin delivery “in the wild.”

The Importance of Multiple Sensors in Continuous Glucose Monitoring

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Objective:

Targeted glucose control (TGC) may improve outcomes in critically ill patients by reducing the incidence of hypoglycemia and the severity of stress hyperglycemia. Automated TGC requires high-frequency intervention and rapid measurement of glucose, achievable via continuous glucose monitors (CGMs). The efficacy of TGC is directly related to the measurement quality of the CGM. We explored whether a single sensor is sufficient to achieve TGC in the intensive care unit.

Methods:

Composite blood glucose (CBG) profiles, dynamically weighted linear combinations of duplicate CGM signals from critically ill patients ($n = 8$), were regressed against low-frequency reference finger sticks, from which a distribution of CGM error derivatives was calculated. Integration of random samples from the distribution generates error trajectories, which, when added to CBG profiles, simulate a CGM. Simulated CGMs are used singly and in duplicate for moving horizon estimation (MHE) of blood glucose.

Results:

CBG profiles follow reference finger stick measurements within $\pm 5\%$. Stochastic simulations show that 88% of actual CGM error trajectories fall within the 95% confidence envelope of the simulations. MHE using a single simulated noisy sensor results in blood glucose estimates with a mean absolute relative deviation (MARD) of 13.80%, but the use of two sensors recovers MARD to a clinically acceptable 10.29%.

Summary:

Blood glucose profiles are reconstructed from noisy CGM data and used to create a model of sensor error. Blood glucose estimates from simulated noisy single sensor measurements result in a MARD beyond an acceptable clinical level, whereas the use of two CGMs allows for estimation of blood glucose with a clinically acceptable MARD. TGC with a single CGM is insufficient for high-quality control in critically ill patients.

Hemoglobin A_{1c} and Self-Monitored Average Glucose: Validation of the Dynamical Tracking eA1c Algorithm in Type 1 Diabetes

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Background:

We previously introduced the eA1c, a new approach to real-time tracking of average glycemia and estimation of HbA_{1c} from infrequent self-monitoring of blood glucose (SMBG) data, which was developed and tested in type 2 diabetes. We now validate eA1c in type 1 diabetes and assess its relationship to the hemoglobin glycation index (HGI), an established predictor of complications and treatment effect.

Methods:

Reanalysis of previously published 12-month data from 120 patients with type 1 diabetes, age 39.15 (14.35) years, 51/69 males/females, baseline HbA_{1c} 7.99% (1.48%), duration of diabetes 20.28 (12.92) years, and number SMBG/day 4.69 (1.84). Surrogate fasting blood glucose was generated by selecting the average of SMBG values between 5:00 a.m. and 8:00 a.m. on any given day; seven-point daily profiles were derived from these unstructured SMBG data similarly in seven time-of-day bins over the past 2 weeks. We then applied the previously reported eA1c method without any changes. Following the literature, we calculated $HGI = HbA_{1c} - (0.009 * \text{Fasting Blood Glucose} + 6.8)$.

Results:

The correlation of eA1c with reference HbA_{1c} was $r = 0.75$, and its deviation from reference was mean absolute relative deviation = 7.98%; 95% of all eA1c values fell within $\pm 20\%$ from reference. The HGI was well approximated by a linear combination of the eA1c calibration factors: $HGI = 0.007552 * q1 + 0.007645 * q2 - 3.154$ ($P < 0.0001$); 73% of low- versus moderate high HGIs were correctly classified by the same factors as well.

Conclusions:

The eA1c procedure developed in type 2 diabetes to track in real time changes in average glycemia and present the results in HbA_{1c}-equivalent units has now been validated in type 1 diabetes. The eA1c calibration factors are highly predictive of the HGI, thereby explaining partially the biological variation causing discrepancies between HbA_{1c} and its linear estimates from SMBG data.

Acute Effect of Low-Dose Pramlintide on Islet and Gastrointestinal Peptides in Type 1 Diabetes Mellitus

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Introduction:

Postprandial hyperglycemia continues to be a challenge even with closed-loop control systems for the management of type 1 diabetes (T1D). Pramlintide improves postprandial hyperglycemia by delaying gastric emptying and decreasing postprandial glucagon. To better understand the mechanism of its effects, we explored the impact of prandial pramlintide administration on other islet hormones and gastrointestinal peptides.

Methods:

We conducted a mixed-meal study including 75 g of labeled glucose given as Jell-O in our clinical research unit in 12 (6 M) C-peptide-negative T1D patients (age 44.4 ± 14.1 years, HbA_{1c} $7.5 \pm 1.1\%$, body mass index 28.9 ± 5.7 kg/m²) on continuous subcutaneous insulin infusion (CSII) investigating glucose kinetics, islet hormones, and gastrointestinal (GI) peptides with and without 30 µg pramlintide subcutaneous administration at time zero. Patients with active GI disease were excluded from the study. We measured integrated area under curve (iAUC) for plasma glucagon-like peptide-1 (GLP-1), ghrelin (total and active), somatostatin, and leptin up to 120 min.

Results:

Whereas pramlintide decreases postprandial glucose excursion from 0–120 min ($P < 0.001$), it had no effect on it from 0–360 min. iAUC 0–120 min for GLP-1 (mean 163.6 ± 1208.7 vs. 200.4 ± 1922.0 pmol/L*min), total and active ghrelin (mean 4584.4 ± 4531.5 , -506.7 ± 2042.9 vs. $-8,943.5 \pm 9,713.9$, $-1,621.4 \pm 5,185.3$ [pg/mL]*min) somatostatin (mean 14.2 ± 345.0 vs. -181.9 ± 463.1 pmol/L), and leptin (mean -250.3 ± 358.1 vs. -66.4 ± 202.1 [ng/mL]*min) were not different between the two study conditions.

Conclusions:

Low-dose pramlintide acutely decreases postprandial glucose excursion in T1D on CSII with no effect on any of the islet and GI peptides measured.

Adaptive Blood Glucose Predictions Using Untrained Models: a Performance Comparison on the Continuous Glucose Monitor Rate of Change

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Objective:

Accurate model predictions are a key requirement for efficient glucose control and ultimately for a fully functional artificial pancreas for type 1 diabetes. It is common to evaluate the prediction capabilities of trained models by comparing them to the performance of a zero order holder (ZOH) predictor. Reports in literature show that most current glucose prediction models perform only marginally better than a ZOH in average. In this work, we assess the performance of an adaptive physiology-based untrained prediction model for longer prediction horizons and its dependence on the rate of change (ROC) of a continuous glucose monitor (CGM).

Method:

A three-state physiology-based minimal bilinear model is used in combination with an unscented Kalman filter (UKF) for glucose prediction based on data from a CGM. The UKF corrects the models state estimation and simultaneously adapts one of its parameters. The predictions are tested on a previously available clinical data set ($n = 64$). Prediction horizons tested range from one to nine samples ahead.

Result:

Glucose periods with ROC between -1 and 1 mg/(dL·min), accounting for more than 80% of the data samples, are better predicted using the ZOH. For ROC greater than 1 mg/(dL·min) or less than -1 mg/(dL·min), the combination of model + UKF yields superior predictions than the ZOH. The residuals are 8 and 10% smaller than the ZOH residuals for the four- and eight-steps-ahead predictions, respectively.

Conclusion:

The untrained combination of model + UKF surpasses the predictions of a ZOH for distant prediction horizons and rapidly changing CGM signals. High gradient CGM periods are critical stages, usually involving great uncertainty, in which to assess a controller's performance. Improving glucose predictions in these periods is crucial for improved glycemic outcomes under closed loop.

Evaluation of Insulin Delivery with V-Go Combined with a Glucagon-Like Peptide-1 Receptor Agonist in Patients with Suboptimally Controlled Type 2 Diabetes Mellitus

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Objective:

Combining insulin therapy with glucagon-like peptide-1 (GLP-1) has been associated with improvements in A1C and lower insulin requirements in patients with type 2 diabetes mellitus. No data have been published to evaluate if switching insulin delivery to V-Go, a disposable insulin delivery device, would impact A1C results in patients not achieving glycemic goals with insulin therapy + GLP-1.

Method:

Electronic medical records were queried to identify patients with an A1C >7.0% switched from previous insulin therapy + GLP-1 to insulin delivery with V-Go + GLP-1.

Result:

Thirty patients were identified: 13 patients administering basal insulin only + GLP-1 (mean A1C $9.1 \pm 1.3\%$, weight 104 ± 25 kg, insulin total daily dose [TDD] 65 ± 28 U/day, duration of diabetes mellitus [DM] 13 ± 7 years) and 17 patients administering basal-bolus insulin + GLP-1 (mean A1C $9.1 \pm 1.5\%$, weight 111 ± 17 kg, TDD 147 ± 63 U/day, duration of DM 13 ± 6 years). When switched to V-Go both groups demonstrated significant reductions in A1C ($P = 0.002$). Mean changes in A1C (95% confidence interval) for those on basal insulin at baseline and basal-bolus at baseline were -1.9 ($-0.8, -3.0$) and -1.4 ($-0.6, -2.2$), respectively. Insulin was significantly reduced for those in the basal-bolus group, 147 to 70 U/day ($P < 0.0001$). Redistribution of the TDD with V-Go proved beneficial in the basal-insulin-only group, where the TDD was reduced from 65 to 59 U/day.

Conclusion:

Delivering insulin with V-Go + GLP-1 resulted in significant reductions in A1C and lower insulin requirements in patients previously administering insulin using traditional injection methods. Improvements contributed to convenience and efficiency of insulin delivery and adherence to regimen; however, further studies are needed.

Using the V-Go Disposable Insulin Delivery Device in Patients Prescribed High Insulin Doses: A Comparison of Clinical Results between High and Moderate Insulin Dose Groups

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Objective:

We evaluate the change in insulin requirements and glycemic control for patients with uncontrolled type 2 diabetes mellitus prescribed high insulin total daily doses (TDDs) compared with moderate doses when switched to V-Go. No data have been published evaluating what clinical impact baseline TDD has when using V-Go.

Method:

Electronic medical records queried to identify patients switched from previous insulin therapy to insulin delivery with V-Go. Patients ($n = 104$) were stratified by moderate baseline doses (<100 U/day) or high baseline doses (≥ 100 U/day) and compared using units per kilogram.

Result:

Sixty-six patients with a baseline insulin TDD <100 U/day (0.70 ± 0.27 U/kg) (mean A1C $9.3 \pm 1.4\%$, weight 92 ± 20 kg) and 38 patients with a baseline TDD ≥ 100 U/day (1.37 ± 0.37 U/kg) (mean A1C $9.5 \pm 1.6\%$, weight 106 ± 19 kg) were evaluated. Baseline characteristics were similar for all variables including age (57 years) and diabetes duration (14 years). Baseline insulin dose was significantly greater for those prescribed ≥ 100 U/day ($P < 0.0001$). Following a 6-month average duration using V-Go, both groups had significant reductions in A1C and units per kilogram insulin requirements. Mean changes in A1C (95% confidence interval) were similar for those on <100 and ≥ 100 U/day at baseline -1.5 ($-1.2, -1.9$) and -1.7 ($-1.1, -2.3$), respectively. Despite significant differences in baseline insulin doses, both groups had almost identical TDD using V-Go: 0.59 vs. 0.64 U/kg ($P = 0.25$). Those prescribed ≥ 100 U/day at baseline decreased TDD from 143 to 67 U/day ($P < 0.0001$).

Conclusion:

Patients prescribed high doses of insulin before switching to V-Go experienced similar A1C reductions administering similar insulin rates to those prescribed moderate insulin doses at baseline.

Widespread Clinical Experiences Validating a Blood-Based Artificial Pancreas

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Objective:

Told since the 1980s that directly and continuously accessing blood over a lifetime is impossible, research and development teams worldwide have been attempting to plug their artificial pancreases into remote subcutaneous or other time-delaying tissues. In light of the difficulties encountered, including having to predict the future of a volatile diabetes patient, a direct blood-based artificial pancreas (BBAP) deserves another look.

Method:

This presentation reviews widespread clinical data that reflect on a potential wearable BBAP.

Result:

The Biostator bedside blood-based console, Food and Drug Administration–approved since the 1980s, has demonstrated platinum standard capability to “place a clamp” on blood glucose. Arteriovenous fistula (AVF) is the gold standard for intermittent hemodialysis access. In case of AVF failure, accessory vein obliteration, which routes all fistula flow through one least damaged outflow vein, has been demonstrated to markedly improve that vessel’s function and durability. It is not a great stretch to project that a virgin in situ debranched vein fistula graft (VFG), revised or replaced as needed, might serve a lifetime. It is also not a stretch to recognize that point compression over the VFG makes atrioventricular differential pressure accessible to perfuse an extracorporeal device. Widespread physician and patient acceptance of AVF for hemodialysis and similar acceptance for the more cosmetic VFG, for a BBAP, is likely.

Conclusion:

The diabetes community has agreed for 95 years on the desirability of a practical, reliable, accurate means to automatically assess and administer insulin and other medications, to thereby eliminate life-threatening hypoglycemia and reduce the devastating and costly complications of hyperglycemia and also reduce costs through steady, nonsequestering, and nondegrading medications administration directly into the blood.

Online Detection of Sensor Faults from Continuous Glucose Monitoring, Meal, and Insulin Delivery Information

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Objective:

Continuous glucose monitoring (CGM) faults, even if of limited time duration, can expose diabetic patients to severe risks and deteriorate effectiveness of automated insulin therapies. Typical faults originated by mechanical sources include occasional spikes and temporary attenuations induced by, e.g., pressure made by the patient lying or sleeping on the sensor. In this work, an online method based on a geometric mean support vector machine (GSVM) is used to detect such failures by exploiting CGM, meal, and insulin delivery information.

Method:

One hundred virtual patients were generated by using the University of Virginia/Padova type 1 diabetic patient simulator. For each patient, 7 fault-free days of closed-loop control with three meals per day were simulated starting from midnight. Then several artificially generated fault episodes were added at random time instants. For each fault type, different amplitudes (-7.5 , -10 , -15 , -20 , -25 , and -30 mg/dL) and durations (5, 10, 20, 30, 40, 50, and 60 min) were considered. An individualized GSVM model was trained offline using past CGM sensor readings, rate of appearance of glucose and insulin. Then the model and inputs were used online to detect sensor faults. The first 4 data days were used for training. The remaining 3 days were used for testing, simulating an online scenario.

Result:

GSVMs with radial basis function kernel were tuned and validated using fivefold cross-validation. From all patients, 75,940 fault-free readings and 10,160 failures readings were obtained for testing, and 92.8% accuracy, 94.0% specificity, and 83.4% sensitivity were reported. Regarding amplitude, sensitivity was between 89.0 and 93.0%, except for 7.5 mg/dL (57.6%) and 10 mg/dL (72.3%). Regarding duration, sensitivity was around 83.0%, except for 5 min (94.1%), 10 min (92.2%), and 60 min (78.0%).

Conclusion:

The method shows good sensitivity by detecting CGM faults for mid and large amplitudes (above 10 mg/dL) and for duration faults lower than 60 min.

MT-Diet: Automated Diet Assessment Using Myo Wristband and Thermal Images

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Objective:

Diet monitoring and control is an important factor for individuals with diabetes. Manual self-monitoring techniques for diet suffer from drawbacks such as low adherence, underreporting, and recall error. Camera-based applications that automatically extract type and quantity of food from an image of the food plate can potentially improve adherence and accuracy. However, state-of-the-art systems have fairly low accuracy for identifying cooked food (only 63%). To overcome these drawbacks, we introduce an automated diet assessment system, MT-Diet, that can identify cooked food with an accuracy of 88.5%.

Method:

MT-Diet is a smartphone-based system that interfaces a thermal sensor and a Myo wristband with a smartphone. Using this system, a user can take both thermal and visual images of her food plate with just one click. While eating the Myo device monitors hand movements and estimates number of bites taken by the user. We used a database of 80 frozen foods to evaluate three core components: 1) food segmentation, separating food items from the plate, 2) food identification, determining type of food, and 3) food intake measurement.

Result:

MT-Diet food segmentation methodology is fully automatic and requires no user input as opposed to recent works, and the accuracy was 92.5%. The accuracy of food identification using a support vector machine with color, texture and histogram of gradients features is 88.5%. The accuracy of detecting a bite using accelerometer data from Myo device was 91.37%.

Conclusion:

MT-Diet can potentially be an inexpensive, real-time, easy-to-use, and fully automated diet monitoring system. The tool can also be used to conduct clinical studies to develop models of meal patterns that can be incorporated to design a better artificial pancreas.

The Use of Insulin Pump Technology to Advance Safe and Effective Care

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Objective:

Traditionally insulin pump download software was developed for endocrinologist or patient use in assessing glycemic patterns. Upon admission, patients are fearful of losing the control they have achieved with the pump if the hospital directs them to remove it due to prescriber lack of insulin pump knowledge. Our institution developed a process for obtainment of pump settings using pump software for home medication list and appropriate physician medication order entry. Our goal was to use the technology to support more precise use of pump dosing by providers versus discontinuing the pump and ordering basal-bolus dosing.

Method:

A multidisciplinary team revised current policy to support the new practice. Diabetes champions were educated on the use of the software to obtain individual patient insulin dosing data. A reference manual was created for each inpatient unit and the emergency department. Education was provided for all prescribers, and dedicated computers for software download were identified.

Result:

Data were collected on 80 patients over 12 months. The average blood glucose level during hospitalization improved over the average preadmission blood glucose level. Hypoglycemic and hyperglycemic events decreased with the continued use of the insulin pump. Preadmission insulin dosing was maintained throughout the hospitalization for most patients. Patient lack of knowledge related to insulin pump management was identified and provided opportunities for targeted education.

Conclusion:

The ability to review preadmission insulin pump data resulted in more accurate insulin dosing and improved glycemic control and provided baseline information for the purposes of medication reconciliation.

Late-Breaking Human Clinical Results from a Second-Generation Long-Term Fully Implanted Continuous Glucose Monitoring System

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Objective:

A human clinical study is underway to verify safety and tolerance of a second-generation long-term fully implanted (no skin-attached elements) continuous glucose monitoring system (the GlySens ICGM system). The study is also designed to provide data to characterize the response properties and calibration characteristics of the implanted sensor and to evaluate how such properties vary over a 6-month implant duration.

Method:

A GlySens Model 100 ICGM sensor was subcutaneously implanted in each of nine human subjects in a minor outpatient surgical procedure utilizing local anesthesia. Subjects self-monitored blood glucose four times per day, and meter-stored finger stick values were downloaded during regular clinical visits. Glucose clamp procedures inducing euglycemic, hyperglycemic, and hypoglycemic levels over a 12-h period were performed at monthly clinic visits. For comparison, YSI plasma glucose measurements and, in some cases, Dexcom G4 continuous glucose monitor recordings were obtained throughout each clamp. Monthly subject interviews, including a standardized survey questionnaire (response scale -2 = negative, 0 = neutral, 2 = positive), were conducted to assess tolerance of the device.

Result:

Interim analysis at 12 weeks postimplant was as follows: Subject survey response scores were 1.1 ± 0.8 (average \pm standard deviation). Example ICGM sensor with last calibration 3 weeks prior to clamp had 13.5% MARD at clamp, 3.2-min lag. Comparison Dexcom G4 calibrated at clamp had 14.6% MARD at clamp, 12.3-min lag.

Conclusion:

Interim study results indicate that the implanted ICGM sensor is well tolerated and can remain appropriately responsive to glucose excursions in human diabetes patients over extended periods. The demonstration by implanted sensors of multiweek calibration stability confirms the suitability of the ICGM system for long-term monitoring with minimal need for user system maintenance.

Glycemic Control by Using GlucoTab in Insulin-Naive and Insulin-Treated Hospitalized Patients with Type 2 Diabetes Mellitus

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Objective:

Preliminary results demonstrate that the GlucoTab system is able to safely establish glycemic control in hospitalized patients with type 2 diabetes. The aim of the current analysis was to compare the efficacy of GlucoTab to establish glycemic control in insulin-naïve (IN) versus insulin-treated (IT) patients in the hospital setting.

Method:

GlucoTab is a tablet-based decision-support system for glycemic management in the hospital setting based on a basal-bolus algorithm. GlucoTab was used in one surgical and three medical wards. GlucoTab was used to calculate initial total daily dose (TDD), consecutive TDD adjustments (50% basal and 50% bolus insulin), and mealtime insulin. Blood glucose (BG) measurements and insulin injections were performed four times daily (three premeal, bedtime).

Result:

Data from two clinical trials were pooled for the current analysis. Forty-two IN (19 female, age 68 ± 11 years, HbA_{1c} 74 ± 27 mmol/mol, body mass index 29.1 ± 6.9 kg/m², diabetes duration 11 ± 9 years) and 121 IT patients (48 female, age 68 ± 10 years, HbA_{1c} 66 ± 21 mmol/mol, body mass index 30.2 ± 6.1 kg/m², diabetes duration 16.2 ± 10.2 years) were analyzed. Mean BG was 148 ± 30 mg/dL (IN) vs. 159 ± 32 mg/dL (IT; $P = 0.06$). We found no statistically significant differences in hypoglycemia (<60 mg/dL, 0.47% IN vs. 0.65% IT; $P > 0.5$) and insulin doses when comparing IN vs. IT: TDD 41.0 ± 18.4 units (basal insulin 17.8 ± 7.3 units; bolus insulin 23.2 ± 11.1 units) vs. TDD 53.0 ± 36.4 units (basal insulin 22.9 ± 17.9 units; bolus insulin 29.9 ± 18.4 units; $P > 0.1$).

Conclusion:

The use of GlucoTab established good glycemic control both in IN and IT patients. IN patients had on average lower mean BG levels with comparable rates of hypoglycemic episodes. Glycemic control was established with a 23% lower TDD in this group.

mHealth Blood Glucose Monitoring Solution Enables Timely Targets Attainment

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Objective:

We assess the impact of an mHealth cellular-enabled blood glucose (BG) meter in an intervention targeting improved glycemic control among high-risk uncontrolled type 2 diabetes mellitus (T2DM) patients.

Method:

Adults with T2DM and A1C $\geq 9.0\%$ from five primary care practices in a health care system are consented to enter a 6–12 week intensive medication management and survival skills self-management education intervention. A Food and Drug Administration–approved BG monitoring system (Telcare BGM) with cellular connectivity that autotransmits BGs via a cloud-based data repository to patient and provider portal dashboards is provided. Customized feedback messages are generated in response to each finger stick BG (FSBG) result. The Certified Diabetes Educator (CDE) accesses the dashboard to review individual time-stamped FSBGs, weekly averages, and trends daily and contacts patients frequently to review results and make adjustments to diabetes medications and/or lifestyle based upon BG levels, until glycemic targets are attained. Patient and CDE mHealth solution user experience is being evaluated.

Result:

To date, 23 patients have completed the 3 months of intervention. All used the mHealth system successfully and report increased compliance with FSBG testing, knowing that CDE is actively monitoring results, and satisfaction with the technology. CDEs report that smart meter use facilitates timely BG management, including immediate intervention for significant hyper- and hypoglycemia, and saves time compared with collating BG results in traditional ways. Mean A1C was 11.4% (9.2–19.6%) at baseline and 8.4% (5.1–12.2%) at 3 months. Nineteen BG < 70 mg/dL were recorded ($> 50\%$ accrued to one patient). There was one instance of BG < 40 mg/dL.

Conclusion:

Real-time monitoring of FSBG can be transformational from a clinical perspective and supports timely DM medications management and attainment of glycemic control.

Detectability of Confounding Effects in Glycemic Diary Data from In Silico Patients with Diabetes

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Objective:

There are a number of influences that can have a significant impact on glycemia but have sufficiently low incidence rates to be ignored by most attempts to model the glucose excursions of individuals with diabetes. This research aims to determine how much data are required to model specific parameters that capture these confounding effects.

Method:

A type 1 diabetes patient model was used to simulate glucose for a year and included weekly instances of exercise and monthly instances of high emotional stress. The data were sampled at a rate of six samples per day and mimicked finger-prick error. Identified values for insulin sensitivity and the magnitude of glycemic effect of exercise and stress were measured in increasing ranges of data in a Monte Carlo analysis.

Result:

As the range of data increased, the identified model parameters became more accurate to the parent model values. Since insulin sensitivity had a consistent effect on glycemia, it achieved a coefficient of variation (CV) <10% prior to 7 days of data. The confounding effects of stress and exercise had CVs within 10% after approximately 100 and 150 days, respectively.

Conclusion:

This research has shown the length of diary data required to quantify patient-specific effect sizes for some confounding glycemic effects in diabetes. However, this in silico analysis must be repeated in heterogeneous cohort of diabetes to capture the interpatient effect-size variability.

Perceived Knowledge and Attitudes of Certified Diabetes Educators Regarding Genetic Testing for Type 2 Diabetes Mellitus

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Objective:

The purpose of this study is to identify the relationship between knowledge and attitudes of genetic testing for type 2 diabetes mellitus among registered nurses that are Certified Diabetes Educators (CDEs).

Method:

Data were collected from 2,000 registered nurses who are CDEs using a mailed survey. Three instruments were used to collect data: demographics and background data, perceived knowledge of genetic testing scale, and attitudes toward genetic testing instrument.

Result:

Participants were predominantly females aged 50 years and older with a bachelor's to a master's degree. Years as a CDE were evenly spread from 1–30 years. Participants were also predominantly used in diabetes education 75–100% of the time. Those reporting to have had no previous genetic training were greater than those who did. Means of the complete perceived knowledge tool and mean of the favorable and reserved attitudes subscale were correlated. There were no significant correlations found.

Conclusion:

The purpose of this study was to examine the perceived knowledge of CDEs regarding genetic testing for type 2 diabetes mellitus. The lack of significant findings suggests that future research involves more investigation into nursing education regarding the types, amounts, and specifics of genetic training that nurses receive. Other recommendations would be for more longitudinal studies of CDE knowledge and attitudes as chronic disease and genetics information grows. Also, further examination of the independent study variable may be warranted to examine what types of relationships exist between the statements.

Pharmacokinetic Study of Mixed-Diet Glucose Concentration Responses in Type 1 Diabetes Patients on Closed-Loop Pump Therapy

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Objective:

The aim is to 1) characterize pharmacokinetic data concerning seven type 1 diabetes patients exposed to high- and low-fat dinner meals (constant carbohydrate and protein) followed by a high-carbohydrate breakfast the following day, 2) quantitate glucose uptake and disposal using frequently sampled data to better understand closed-loop pump systems, and 3) demonstrate the usefulness of this analytic tool.

Method:

The method is based on deconvoluting rising and equilibrium portions of the grouped frequently sampled data curves to achieve a near linear glucose concentration posthepatic glucose input then used to derive fractional rate constants for endogenous and combined endogenous-exogenous glucose uptakes (K_a). From this is generated exogenous glucose disappearance (K_d), volume of distribution (V_d), and fraction remaining after first pass hepatic glucose uptake (Fr_{xRem}). This model is applied the Wolpert data. Data for each meal was analyzed using an Excel spreadsheet.

Result:

K_a and K_d for all the meals were less than the minimal normal value of 0.012/min for K_a with the high-fat meal having the lowest input, K_a , and K_d values. Fr_{xRem} was inversely related to the rate of glucose appearance. The closed-loop controller functioned best with the low-fat meal but imperfectly responded to the high-carbohydrate breakfast. Clearances (Cl) were calculated for each meal Cl high-fat < Cl low-fat.

Conclusion:

The model infers pharmacodynamics of insulin and related hormones through the pharmacokinetic description of glucose concentration changes. The data can be used to adjust the closed-loop system. More accuracy would be achieved had more data related to glucose disposable been recorded. Although applied to grouped data, the analysis can assess individual patient continuous glucose monitor data.

Pharmacokinetic and Pharmacodynamic Modeling Predict Concentrated Biphasic Insulin BIOD-531 Is Suitable for Twice or Three-Times Daily Dosing with No Dose Accumulation

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Objective:

BIOD-531 is a U-400 formulation of recombinant human insulin containing EDTA, citrate, and MgSO₄ with a biphasic time-action profile characterized by ultra-rapid onset and a basal duration of action. Mathematical models of pharmacokinetic (PK) and pharmacodynamic (PD) data from three clinical trials were used to project an appropriate dosing paradigm for multidose clinical trials and to facilitate prediction of short- and long-term PD responses to BIOD-531.

Method:

Population-based models were created using PK/PD data from three clinical trials: 1) a PK/euglycemic clamp study ($n = 12$) in nondiabetic obese volunteers, 2) a PK/standardized meal challenge study ($n = 12$) in patients with type 2 diabetes and moderate insulin resistance, and 3) a PK/standardized meal challenge study ($n = 12$) in patients with diabetes and severe insulin resistance. Because BIOD-531 demonstrated ultra-rapid absorption in all three clinical trials, a controller model was developed to project the PK/PD relationship after meals. Simulations were used to project long-term glycemic profiles in large numbers of patients.

Result:

Circadian effects appear to influence insulin absorption from the subcutaneous space and the PD response to insulin. Steady state is achieved after a second dose of BIOD-531. BIOD-531 when dosed twice or three-times daily is projected to achieve sustained glucose lowering during the day. BIOD-531 is not likely to be associated with accumulation of insulin when dosed twice or three-times daily.

Conclusion:

Mathematical modeling predicts the biphasic profile of BIOD-531 can be utilized to successfully achieve control of mealtime glucose excursions and provide 24-h basal coverage when dosed twice or three-times daily.

Resistance to Acetaminophen Interference of the Direct Electron Transfer-type Continuous Glucose Monitor Sensor

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Objective:

Amperometric continuous glucose monitor (CGM) sensors typically monitor glucose by applying the amount of voltage necessary to oxidize the substrates of enzymatic reactions. We have been developing direct electron transfer (DiET) technology for a third generation of CGM sensor utilizing glucose dehydrogenase (GDH) complex from *Burkholderia cepacia*. The electron transfer subunit of the GDH confers the ability to transfer electrons directly to an electrode, which contributes to success in reduction of the working potential. Besides, it is widely known that several interfering exogenous substances exist in blood and in interstitial fluid and consequently cause positive bias to sensor glucose readings. The aim of this study is to evaluate the effect of acetaminophen on the third-generation CGM sensor signals, which use DiET technology.

Method:

Laboratory-manufactured sensors based on DiET technology were used in this study. Sensor working potential was +0.2 V (vs. Ag/AgCl). To evaluate the effects of acetaminophen on the sensors, interfering species were added into glucose solution at the maximum possible in vivo concentration. The sensors were subject to initialization following a predetermined procedure prior to the interference examination.

Result:

Change in sensor signals toward 100 mg/dL glucose was less than 1% at the presence of 30 µg/mL acetaminophen in the glucose solution and determined to be negligible.

Conclusion:

The presence of acetaminophen with the maximum possible in vivo level concentration is negligible toward the sensor signals of the third-generation CGM sensor.

U-Strip Transdermal Insulin Patch

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Objective:

With a fast growth of diabetes and a need of noninvasive insulin delivery, an ultrasonic transdermal patch system, called U-Strip, was developed. It was designed to deliver insulin, such as lispro, into the bloodstream with the aid of ultrasound. The system was tested for its delivery capability through a volunteer's skin into the bloodstream and therefore could be a viable alternative to insulin injection.

Method:

In the HPT-6A clinical trial of the U-Strip desktop system, five prediabetic males with glucose levels between 140 and 200 mg/dL were connected to a U-Strip desktop and then fitted with a transducer block, which held a transdermal patch cap loaded with 100 U insulin, mounted over the right side of the volunteers' abdomens. The duration for patches A and B was 4 h using 50/50 sawtooth/square wave setting and 5 h using 80/20 sawtooth/square wave setting, respectively. Both patches were weighed before and after being attached on the abdomens. A total of 23 blood draws were collected for pharmacokinetics analysis.

Results:

The average of number of units of insulin delivered from a patch A for all five volunteers was 36.02 U and that of patch B was 28.53 U. The total glucose reductions on volunteers 1, 2, 3, 4, and 5 were 43, 44, 90, 78, and 50 points, respectively. The blood test results showed that the pancreatic insulins of all five volunteers were substantially decreased within 9 h.

Conclusion:

This study has demonstrated glucose reductions via ultrasonic noninvasive transdermal delivery. The U-Strip also led to a fast relaxation of the insulin output from the volunteers' pancreas during the 9-h study.

Technology Use Enhances Body Mass Index Reduction in African American Young Adults at Risk for Developing Type 2 Diabetes

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Objective:

The objective of the study was to evaluate reduction in body mass index (BMI) in young African American adults at risk for developing type 2 diabetes who were overweight/obese, using communications and networking technologies.

Method:

African Americans ages 18–24 years with a family history of type 2 diabetes were recruited. Height and weight were measured and BMI calculated. Subjects with a BMI of 25 or greater participated in a 10-week healthy lifestyle program. Informed consent was obtained. Subjects were randomized either into a technology only or in-person weekly group visits. Both groups received the same Group Lifestyle Balance Program curriculum. However, smartphone text messages, Fitbit pedometer steps that interfaced with the NoMoreClipboard personal health record and Numedics Disease Management software and using Moodle software for the online Group Lifestyle Balance Program curriculum, were monitored remotely by the research team for the technology group progress. At the completion of the 10-week course, participants were weighed and postintervention BMI was calculated. Means and standard deviations were calculated. The study was approved by the Howard University Institutional Research Board.

Results:

A total of 69 participants have completed the study with 40 (5:35, M:F) in the nontechnology arm and 29 (4:25, M:F) in the technology arm. There was a significant decrease in BMI in both nontechnology and technology arms ($P = 0.009$ and 0.003 , respectively). The technology arm had a slightly more decrease in BMI of -0.680 ± 1.128 vs. -0.398 ± 0.911 in the nontechnology arm.

Conclusion:

The use of technology to promote healthy BMI change in a young adult African American population at risk for developing diabetes may be beneficial and as equally effective as in-person group visits.

Using Blogs to Support Caregivers of Patients with Type 1 Diabetes: A Pilot Study

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Objective:

The self-management demands of type 1 diabetes mellitus (T1DM) on patients and their caregivers are immense. Sources of real-time support have been limited. This study aimed to understand how blogs—online interactive journals—discuss the barriers and facilitators of T1DM self-management and may be “anytime” sources of support for caregivers. Previously, there has been little data on the content or use of blogs as support mechanisms.

Method:

Three T1DM caregiver blogs were retrospectively analyzed using grounded theory qualitative methods from January 2012 to August 2014 in reverse chronological order. Blogs were imported into qualitative software (NVivo 10, QSR) and coded according to content until no new concepts were identified. Coded data were analyzed to identify 1) medical misinformation and 2) frequently overlapping codes and emergent themes across the data set.

Result:

Virtually no medical misinformation was identified upon clinician review. Emergent themes include 1) blogs provide significant T1DM caregiver peer support, based on stated reasons to blog, affirmations of topics discussed, and comments made; 2) T1DM's 24/7/365 self-management burden affects the whole family and causes exhaustion/lost sleep for caregivers; 3) everyone's T1DM is different, and hypo/hyperglycemic events may cause unpredictability to schedules and plans; and 4) the memory of T1DM diagnosis recurs frequently but a new sense of normal emerges.

Conclusion:

Blogs may be convenient, cost-effective sources of support for T1DM caregivers that health care professionals can recommend. They allow users to share stories and develop a sense of community in a factual, supportive way. As one blogger wrote, “I want you to know, that I started this blog for me. . . and now I want you to know I write it now just as much for you.”

Evaluating a Novel Glycemic Pattern Recognition Algorithm for Alerting to Risk of Severe Hypoglycemia in the Next 24 Hours

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Objective:

Severe hypoglycemia is often preceded by recent hypoglycemia and glycemic variability that compromises the patient's counter-regulatory, hormonal, and symptomatic defenses. In this study we evaluated the utility of a novel method (method 1) of identifying this pattern and compared it with other potential methods for identifying risk of severe hypoglycemia.

Method:

We optimized method 1 in a test data set and then evaluated it with comparative methods in an independent validation data set of 297 diabetes patients (242,253 blood glucose [BG] readings, T1 = 129, T2 = 162, NA = 6, HbA_{1c} [standard deviation] = 8.17% [1.4%]). Comparative methods included commonly used BG variability measures and hypoglycemia counts, as well as previously published algorithms that include risk-based BG transformations such as the low BG index and average daily risk range.

Result:

At the default alert frequency, method 1 predicted 28.9% of BG \leq 40 mg/dL (biochemical severe hypoglycemia [BSH]) and was 9.37 times more likely to be followed by BSH in the next 24 h versus baseline. Method 1 demonstrated advantages in predictive capacity across a range of alert frequencies versus the comparative methods, as elucidated by an analysis of the partial area under the receiver operator characteristic curve.

Conclusion:

Method 1 provides useful information about the risk of BSH in the next 24 h and shows advantages over other methods of predicting hypoglycemia risk. Further study will inform how alerting patients to periods of increased risk can lead to reductions in BSH.

Performance of a Smartphone-Linked Blood Glucose Assessment Platform

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Objective:

Successful self-care by people with diabetes mellitus requires ongoing assessment of blood glucose levels. New technology included in blood glucose testing platforms led to new performance requirements for these systems from the International Standards Organization (ISO) in 2013. The Dario blood glucose monitoring system (DBGMS) that includes a smartphone reporting platform meets these ISO 2013 performance requirements for accuracy and precision as reported here.

Method:

Seventy-eight adult diabetes patients donated 100 fresh whole blood capillary and venous samples. We tested whole blood glucose levels with three different test-strip lots, each lot tested by two different meters, compared with a YSI glucose analyzer at values between 50 and 400 mg percent, and assessed glucose measurement stability and repeatability at prespecified glucose levels in conformance with ISO 2013 guidelines. Further, we reported our comparative analysis with the YSI standard on a consensus error grid and a system accuracy plot.

Result:

We demonstrate 99% precision in whole blood at five different glucose concentrations, stability of measures and accuracy reports on the consensus error grid were 100% within zones A and B, and system accuracy plot was within the 95% limits, all of which meets or exceeds ISO 2013 requirements.

Conclusion:

DBGMS meets and exceeds ISO 15197:2013 criteria for accuracy and precision of glucose testing systems.

Clinical Pilot Study Assessing the Postprandial Outcome of an Advanced Bolus Calculator for Diabetes When Used for Meals with Exercise and Alcohol

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Objective:

Structured educational programs for insulin dosing provide support for people with type 1 diabetes on how to adapt insulin-to-carbohydrate ratios for meals with exercise or alcohol. The objective of this work is to analyze changes in the insulin-to-carbohydrate ratios and the resulting postprandial outcomes after a 6-week pilot study using the adaptive advanced bolus calculator for diabetes (ABC4D).

Method:

Ten subjects used ABC4D for insulin bolus advice continuously over 6 weeks where exercise and alcohol were manually announced on the smartphone-based system. After each week, ABC4D adapted the insulin-to-carbohydrate ratios for both exercise and alcohol scenarios under supervision of the research team. We have analyzed changes in the insulin-to-carbohydrate ratios at the end of the study and the 6-h postprandial glucose excursion for each scenario when ABC4D has been used for meals with either exercise or alcohol and where the bolus advice has been followed.

Result:

The final insulin-to-carbohydrate ratios showed an increase from 1 U:10.2 ± 3.4 g carbohydrate to 1 U:11.1 ± 3.8 g carbohydrate and from 1 U:11.2 ± 2.3 g to 1 U:14.2 ± 7.1 g carbohydrate for meal scenarios with alcohol and exercise, respectively. Analyzing the resulting postprandial outcome showed a trend to reduce the number of hypoglycemic excursions (<3.9 mmol/L) per subject for meal scenarios with alcohol from 0.3 ± 0.7 to 0.1 ± 0.3. Compared to the initial 3 weeks, hypoglycemia was completely eliminated for scenarios with exercise (0.4 ± 0.7 to 0.0 ± 0.0) in the final 3 weeks of the study.

Conclusion:

Personalized adaptations to the insulin-to-carbohydrate ratio performed by ABC4D reduced the amount of insulin given at meal scenarios involving exercise and alcohol with potential improvements in postprandial hypoglycemia.

Performance of an Automated Revision Algorithm for a Personalized Bolus Advisory System

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Objective:

The advanced bolus calculator for diabetes (ABC4D) is a personalized insulin bolus advisory system that is able to adapt its parameters over time, aiming to improve glycemic control. For safety reasons, performed adaptations are supervised by clinical experts who use their judgment to determine which scenarios are eligible to be used for adaptations and ensure that changes to insulin therapy are clinically safe. We have developed and tested an automated revision algorithm that aims to achieve similar performance to clinical experts to help them in their decision making and reduce the requirement for remote supervision.

Method:

We have tested the performance of the automated revision algorithm during a 6-week pilot study of the ABC4D system for revising the glycemic outcome of 718 meal scenarios. The algorithm analyzed each scenario for validity, such as checking for missing sensor data, snacks, and correction boluses shortly after the meal, which would exclude the scenario from automatic adaptation. Clinical experts were able to review the suggested meal scenario eligibility generated by the algorithm.

Result:

Overall, 679 (94.6%) of all 718 suggestions generated by the automated revision algorithm agreed with the decision of the clinical expert. The remaining 5.4%, where there was discordance between the algorithm and clinical review of the meal scenario eligibility, were due to input errors by the user requesting a bolus advice (e.g., requesting multiple recommendations for one meal), user interventions (e.g., correction bolus) that were unnoticed by the clinician, or artifactual glucose data.

Conclusion:

The presented automated revision algorithm achieves similar performance compared with clinicians reviewing insulin bolus advice. This is of clinical importance when adopting personalized bolus calculators that automatically adapt their parameters.

Mixture of Insulin Monomers, Dimers, and Hexamers Demonstrated by Sedimentation Velocity Analysis Supports Biphasic Ultra-Rapid-Acting and Basal Profile of Concentrated Human Insulin Formulation BIOD-531

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Objective:

BIOD-531, a U-400 recombinant human insulin formulated with EDTA, citrate, and MgSO₄, is associated with an accelerated onset of action and a basal duration profile. Accelerated absorption may be due to rapid dissociation of insulin hexamers into smaller monomer/dimers in the subcutaneous space. In this study, sedimentation velocity analysis was used to evaluate the extent of insulin hexamer dissociation for BIOD-531 versus Humulin U-500R (U-500).

Method:

Sedimentation velocity analysis was conducted with a Beckman-Coulter XL analytical ultracentrifuge, and the weight-averaged sedimentation coefficient (WASC) in svedbergs (S) was determined for each concentration of BIOD-531 (insulin concentration range of 13.35–0.17 mg/mL) and U-500 (18.2–0.21 mg/mL). The WASC includes multiple forms of insulin; monomers are ~1 S, and hexamers are ~3 S. Shifts to lower S values indicate dissociation of the insulin hexamers.

Results:

The WASC was 4.1 S for undiluted BIOD-531 (13.35 mg/mL), suggesting the presence of a mixture of hexamers and dodecamers. Dilution of BIOD-531 indicated the particle size shifted toward smaller structures (dimers/monomers), with the final dilution of 0.17 mg/mL = 1.6 S. In contrast, the WASC for U-500 remained in the 3 S hexamer range across all dilutions.

Conclusion:

The rapid dissolution of a proportion of BIOD-531 into smaller monomeric/dimeric insulin structures supports the clinical ultra-rapid absorption profile of BIOD-531; the secondary basal phase may be due to the continued presence of some larger forms of insulin including hexamers. Data demonstrating the predominance of hexamers at all dilutions of U-500 support the slow absorption and prolonged basal duration of action of this formulation.

Is There a Recipe for Comparability of Mean Absolute Relative Difference Values from Clinical Performance Evaluation of Continuous Glucose Monitoring Sensors?

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Objective:

The most widely used measure for the performance of continuous glucose monitoring (CGM) systems is the mean absolute relative difference (MARD). However, different MARD values have been published for the same CGM system, which was explained by the fact that MARD does not reflect only the performance of the CGM system, but is heavily influenced by the study design. As study protocols will never be identical, the aim of this publication is to define conditions under which comparability is given.

Method:

We first examine by a Monte Carlo simulation how reliable a MARD is (quantified by its confidence interval) according to the number of measurements, the choice of the reference (or comparison) quantity, and the properties of paired points. The results of this Monte Carlo study (performed using CGM data from a clinical trial with 12 patients) are then used to define simple rules to fix the key study parameters according to the desired confidence.

Result:

A critical precondition is a sufficient number of data points in all clinically relevant blood glucose ranges. An irregular distribution of points (e.g., fewer values in euglycemia and more in hyperglycemia) can be taken into account subsequently and, if so, will not affect MARD. The choice of the comparison method is critical, as it defines a reliability threshold that cannot be improved independently from the number and distribution of points.

Conclusion:

As CGM systems are continuously improving, and their difference will become smaller, a proper performance assessment of the continuous glucose readings is necessary. This is achievable using the MARD, but care must be taken to ensure comparability of results already at the study design phase.

Multicenter Assessment of Usability and Safety of a Model Predictive Control Algorithm with Enhanced Hypoglycemia Minimizer for Closed-Loop Insulin Delivery in Patients with Type 1 Diabetes: A Randomized Control Crossover Inpatient Clinical Trial

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Objective:

The primary goal of closed-loop insulin delivery (CLID) is automated glucose control with reduced hypoglycemia in patients with type 1 diabetes (T1D). We assessed a new model predictive control algorithm with enhanced hypoglycemia minimizer (MPC+eHM) in an inpatient clinical trial.

Method:

Fourteen T1D patients (12 male/2 female, age 47.0 ± 9.9 years, body weight 75.9 ± 11.9 kg, diabetes duration 23.6 ± 11.7 years, HbA_{1c} $7.4 \pm 0.7\%$) were included in a randomized crossover trial including two 24-h sessions starting at 10:00, either with patient-managed wearable Medtronic Veo insulin pump (open loop) or CLID driven by the MPC+eHM algorithm. Continuous glucose monitoring (CGM) by a Dexcom G4 Platinum device was blinded to the patient (open loop) or connected to a smartphone running the algorithm. CLID was manually changed according to algorithm proposals every 15 min. Each session included three standardized meals (70 g carbohydrate at 12:00 and 19:00, 40 g carbohydrate at 08:00) and a 30-min moderate exercise at 16:00. Meal insulin was delivered 10 min before meals according to patient decision or following meal announcement to the algorithm. Glucose control was assessed on CGM data.

Result:

Overall glucose control was similar during both sessions with percentage of time in the 70–180 mg/dL range of $66.0 \pm 20.8\%$ (CLID) vs. $59.1 \pm 21.8\%$ and mean blood glucose level of 151 ± 27 vs. 141 ± 43 mg/dL, respectively. Interestingly, percentage of time <70 mg/dL was reduced during CLID: 3.9 ± 3.7 vs. $13.5 \pm 13.6\%$, more specifically from 23:00 to 07:00, 0.0 ± 0.2 vs. $21.6 \pm 27.8\%$ ($P = 0.0002$). Number of patients with at least one event <70 mg/dL from 23:00 to 07:00 was 1/14 vs. 8/14 ($P = 0.0065$).

Conclusion:

This first clinical inpatient assessment of our MPC+eHM algorithm demonstrates its usability and safety, including a reduction of nocturnal hypoglycemia. Ongoing refinements of the algorithm will target improvement in minimization of hyperglycemia.

Incorporating an Exercise Detection, Grading, and Hormone Dosing Algorithm into the Artificial Pancreas Using Accelerometry and Heart Rate

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Objective:

We test an exercise detection algorithm in adult subjects with type 1 diabetes (T1D) and demonstrate the importance of including dosing adjustments during exercise in a bihormonal closed-loop algorithm during *in silico* testing.

Method:

Thirteen adults with T1D underwent 20-h open-loop sessions with 45-min exercise routines at 60% maximum heart rate. Accelerometry and heart rate obtained from a Zephyr BioPatch was entered into a validated model that estimates energy expenditure. This was compared with measurements taken during a maximum VO_2 test. Additionally, we utilized a model of insulin and carbohydrate metabolism coupled with a validated exercise model to help determine dosing adjustments that best limit hypoglycemia during and after exercise.

Result:

Separation of exercise and no exercise was obtained (sensitivity 97.2%, specificity 99.5%), though energy expenditure showed only moderate correlation ($r^2 = 0.55$). During exercise, glucose levels drops were greater than expected by the glucoregulatory model without exercise. The exercise model allowed more accurate estimation of the change in glucose. We found that hypoglycemia was minimized if insulin infusion was shut off for 30 min after exercise, then reduced to 50% of calculated rates for another 60 min, and glucagon doses were allowed to double.

Conclusion:

A detection algorithm accurately detects and potentially can grade exercise for use in a bihormonal system to appropriately adjust insulin and glucagon dosing to limit exercise-related hypoglycemia.

Artificial-Intelligence-Augmented Telemedicine Applied to the Management of Diet-Treated Gestational Diabetes

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Objective:

Gestational diabetes (GD) confers an increased risk of complications as well as future type 2 diabetes. The implementation of the International Association of Diabetes and Pregnancy Study Groups/American Diabetes Association diagnosis criteria implies a huge increase in GD prevalence and, consequently, a significant increase in its management-related burden. We assess the safety and efficacy of an artificial intelligence (AI)-augmented telemedicine system (ruled-based reasoning) that includes a blood glucose (BG) classifier (C4.5 Quinlan decision tree) in comparison with the standard care in the management of GD while insulin is not required.

Method:

A randomized (2:1) controlled trial was performed. After downloading BG data and informing on ketonuria status and diet transgressions, the patient immediately receives (short message service) an evaluation including a proposal for diet adjustment when needed. Doctors are only alerted when the analysis concludes that insulin would be required.

Result:

We present the results of the 76 patients (50 users of the AI telemedicine system) who have completed the study. At baseline, groups were comparable regarding all the clinical variables tested. Patients download data every 3.4 (2.8–4) days, with a median of BG data transmitted = 106 (60–226). Mean number of BG values per day, mean BG and the percentage of BG values above 140 mg/dL, prepartum HbA_{1c}, as well as all the perinatal outcomes tested were similar between groups. The system performed 21 automated diet changes. Median number of face-to-face visits for diet-treated patients was 4.1 (4–7.5) for control group and 0 (0–0) for the active group ($P < 0.001$). An ad hoc questionnaire demonstrated a high degree of user satisfaction with the system.

Conclusion:

The AI-augmented telemedicine application developed can safely reduce the GD burden, guiding diet-treated patients without health caregiver intervention.

Automatic Insulin Delivery System Approach Capable of Tight Control

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Objective:

An automatic insulin delivery system (AIDS) must be capable of tight glucose control for major disturbances. Thus our objective is to present our novel AIDS approach that seeks to directly nullify the effects of eating, activity, and stress, resulting in a substantial reduction on the variability of blood glucose concentration (BGC).

Method:

Feedforward control (FFC) has the potential to completely cancel the effects of any disturbance that is measured and effectively modeled. This work applies a novel FFC modeling method and control algorithm to nullify critical disturbances that cause large variation in BGC. By removing the effects of these disturbances, the AIDS has the potential of controlling BGC as tightly as the human pancreas.

Result:

In this work, 11 cases of 2 weeks of free-living data collection on subjects with type 1 diabetes are modeled with 13 input variables. The activity variables were collected using the SenseWear Pro3 Body Monitoring System. For a FFC model, the critical performance measure is the correlation of the measured BGC and the fitted BGC (r_{fit}). The average r_{fit} values of the 11 cases for training, validation, and testing were 0.64, 0.63, and 0.61, respectively. The closeness of the values for each of the three sets is an indication that the models did not significantly overfit the data on unmeasured disturbances. The potential impact of this fit is a reduction of approximately 90% the variability of BGC as measured by the standard deviation from the target value.

Conclusion:

Thus an AIDS based on this FFC approach has the potential to reduce the variation of BGC to the level of those without diabetes.

Night-to-Night Variability of Basal Insulin Requirements in Adults with Type 1 Diabetes during 12-Week Closed-Loop Insulin Delivery

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Objective:

We evaluate night-to-night variability of basal insulin requirements (BR) in adults with type 1 diabetes (T1D) during closed-loop insulin delivery.

Method:

A multicenter, randomized crossover study involved 33 subjects with T1D (15 females, age 40 ± 9.5 years, body mass index [BMI] 25.4 ± 4.4 kg/m², HbA_{1c} $8.5 \pm 0.6\%$) who applied sensor-augmented pump therapy on two occasions, with or without day-and-night closed loop, in free-living home settings over 12 weeks. We retrospectively analyzed overnight (23:00 to 07:00) insulin delivery during the closed-loop period. The BR for each closed-loop night were expressed as the percentage of the total amount of basal insulin administered on that night over what was preprogrammed on the insulin pump and delivered during the open-loop period. Coefficient of variation of BR (CV_{BR}) was calculated to represent individual variability of overnight BR. Correlations were sought between subjects' baseline characteristics (gender, age, BMI, HbA_{1c}, duration of diabetes, duration of insulin pump use) and CV_{BR} .

Result:

We analyzed data from 2,065 closed-loop nights. The CV_{BR} was 31% (22, 39%; $n = 32$, mean [95% confidence interval]) with the lowest variability CV_{BR} of 24% (with the corresponding BR of 137% [73, 201%]) and the highest CV_{BR} of 40% (BR 124% [28, 221%]). Significant correlation was found between gender and CV_{BR} , which suggests a larger variability in BR in male subjects (33 vs. 28%, male vs. female; $P = 0.014$). No other significant correlations were observed.

Conclusion:

Overnight insulin requirements vary considerably between nights in adults with T1D during long-term use of closed loop insulin delivery. Male subjects appear to have more variable overnight BR than females.

Predicting Microvascular Complications from Type 2 Diabetes Retrospective Data

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Objective:

We present the development and evaluation of predictive models for type 2 diabetes microvascular complications. Traditionally, such models are based on prospective data collected at diagnosis and provide risk factors without presenting a validation to assess predictive performance. In this study, models are based on retrospective data collected at the first hospital visit and validated using area under the curve (AUC) measures.

Method:

Within the European Union–funded project MOSAIC, clinical and administrative data of 943 patients followed by the Fondazione Maugeri Hospital (Pavia, Italy) and by the local health care agency of Pavia were integrated in a data warehouse, relying on the i2b2 infrastructure. On this data, we built logistic regression and naive Bayes models to predict the onset of retinopathy, neuropathy, or nephropathy at 3, 5, and 7 years from the first visit at the hospital. Considered variables are gender, age, time since diagnosis, body mass index (BMI), HbA_{1c}, hypertension, and smoking. The predictive power of our approach is estimated with a leave-one-out cross-validation.

Result:

Selected variables for a single complication across different temporal thresholds show high consistency. Variables included in the models are HbA_{1c} for all models, gender for neuropathy (5 and 7 years), time since diagnosis and hypertension in all models for retinopathy and neuropathy, BMI for all the nephropathy models, and smoking for nephropathy (3 and 5 years) and for neuropathy (3 years). AUC on leave-one-out cross-validation varied between 0.832 (logistic regression applied to retinopathy) and 0.647 (logistic regression applied to neuropathy).

Conclusion:

We developed and validated models for microvascular complications prediction exploiting retrospective data. These models are intended to help physicians, suggesting which patients are more likely to develop a microvascular complication and might need closer control.

Meal Detection and Carbohydrate Estimation Algorithm Based on Continuous Glucose Monitoring Data for Use in Artificial Pancreas Systems

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Objective:

Automatic handling of the deviation of blood glucose concentration (BGC) from the control target range as a result of meal effects is one of the biggest challenges of artificial pancreas (AP) systems, particularly when the controller is not informed about the mealtime and its carbohydrate amount by manual announcement. In this study, a trend analysis based algorithm is proposed to estimate the time and amount of carbohydrate intake at meals (snacks) based on continuous glucose monitoring (CGM) data and subcutaneous insulin delivery data from an insulin pump.

Method:

Frequent data of subcutaneous glucose concentration from a CGM are used to describe a meal's effect on glucose variation. The algorithm has three steps. The noise of measured glucose is filtered in the first step. The filtered glucose signal is interpolated to have a glucose value every minute. In the second step, the meal's effect on BGC variation is modeled by qualitative variables by using qualitative trend analysis, which transforms glucose concentration time series to a sequence of nonoverlapping segments. A member of small set of qualitative variables is assigned to describe each segment. Each qualitative variable has a different combination of first and second derivative signs. The mealtime is detected by the sequence and patterns of these qualitative variables. To estimate the carbohydrate content of meal, in the third step, within the 10 min after detection time, the carbohydrate amount is counted every minute using measured glucose and estimated insulin on board. Subcutaneous insulin delivery data and insulin action curve are used to estimate insulin on board.

Result:

The algorithm is tested on data of three different type 1 diabetes patients participating in clinical experiments. Sensitivity, defined as the ratio of the number of correctly identified meals and snacks to the total number of meals and snacks, is 0.84. False positive ratio, defined as the ratio of false detections per day, is 0.93. The average increase in BGC between the beginning of a meal and the time it is detected varies within the range of 15–31 mg/dL for three different patients. The largest change until detection was observed to be 55 mg/dL, which belongs to a patient whose change in blood glucose is rapid.

Conclusion:

An AP control system equipped with meal detection and carbohydrate estimation module has the potential to make more appropriate insulin decisions and has better performance in blood glucose regulation. The meal estimator can also be useful in warning patients who do not use an AP about forgotten meals and their estimated carbohydrate contents.

Comparison of the Nova Biomedical StatStrip Glucose Meter to an Isotope Dilution Mass Spectrometry Hexokinase Glucose Method in Oncology and Renal-Insufficient Patients: Demonstration of Utility in Critically Ill Patients

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Objective:

In an institutional-review-board-approved study, remnant whole blood specimens from oncology and/or renal-insufficiency patients were used to compare whole blood glucose analyses on a Nova Biomedical StatStrip glucose meter to plasma glucose on a Roche Cobas c8000 isotope dilution mass spectrometry (IDMS) traceable hexokinase method. We present the results of 78 oncology patients and 36 renal-insufficient patients.

Method:

Arterial or venous whole blood remnant specimens collected for blood gas analyses were obtained. Whole blood glucose was measured on two different Nova Biomedical StatStrip glucose meters in a blinded fashion. The remaining remnant specimen was centrifuged at $\sim 1,500$ g for 5 min at room temperature. The fresh plasma aliquot was analyzed in duplicate on a Roche Cobas c8000 analyzer using the hexokinase IDMS reference method. Data analysis was performed following the Clinical and Laboratory Standards Institute POCT 12-A3 (2013).

Result:

Per POCT 12-A3, 12/12 oncology specimens were within ± 12 mg/dL and 66/66 specimens were within 12.5%. For the renal-insufficiency patients with whole blood creatinine ≥ 2.0 mg/dL, 7/8 specimens were within ± 12 mg/dL and 25/27 specimens were within 12.5%. One specimen was >600 mg/dL, which is the instrument's upper limit of linearity. Additionally, a surveillance error grid was prepared. For both the oncology and renal-insufficiency patients, one data pair demonstrated only a slight, lower risk.

Conclusion:

The use of the Nova Biomedical StatStrip blood glucose meter system is appropriate for use in patients being treated for cancer and/or in those who are renal insufficient. Mean bias of the meters is 0.22 and 2.11%, respectively.

Augmenting the Detection and Prediction of Blood Glucose Control Problems with Physiologic Sensor Data

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Objective:

For ten years, Ohio University researchers have been building intelligent software tools for managing patients with type 1 diabetes (T1D) on insulin pump therapy. These systems leverage data from insulin pumps, continuous glucose monitoring (CGM) systems and patient-entered life events to detect and predict blood glucose control problems. Newly available fitness bands provide additional signals indicative of patient activity via physiologic sensors. The objective of this preliminary study was to see if these signals could be integrated to potentially improve system accuracy.

Method:

An N-of-1 study was conducted. The subject was a well-controlled, middle-aged male physician with T1D on insulin pump therapy with CGM. For 9 weeks, he provided his device data, entered life events via a smartphone interface, and wore a commercially available fitness band. Galvanic skin response (GSR), heart rate, and skin and ambient temperature signals from the band were juxtaposed with insulin, blood glucose, and life event data and displayed via custom visualization software. Once a week, the subject met with his physician and researchers to review and analyze the consolidated data.

Result:

Preliminary results, based on data visualization, were encouraging in that marked patterns could be seen in the data. The most pronounced pattern was a sharp rise in GSR with hypoglycemia. When hypoglycemia followed significant outdoor winter exercise, there was a concomitant rise in GSR and heart rate with a drop in skin and ambient temperature.

Conclusion:

Newly available physiologic sensor signals show early promise for facilitating the automated detection and prediction of blood glucose control problems. Even subtle data patterns could potentially be leveraged by machine learning algorithms. A larger follow-up study is planned for the near future.

New Technology for Metformin Hydrochloride Mucoadhesive Microparticles Preparation Utilizing Büchi Nano-Spray Dryer B-90

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Objective:

Currently, nanoparticles acquired a high interest in both research and pharmaceutical technology fields. Nanoparticles offer several advantages for well-known drugs, including new routes of administrations and sustained release effect. Recently, Büchi launched its latest fourth-generation nano-spray dryer B-90 used for nanoparticle production. B-90 offers an elegant technology combining particle engineering and drying in one step. In our laboratory, we successfully developed a new formulation for metformin hydrochloride mucoadhesive nanoparticles utilizing B-90 technology.

Method:

Gelatin or sodium alginate, naturally occurring polymers with mucoadhesive properties, solely or in combination, were used in our formulation trials. Preformulation studies (atomization head mesh size, flow rate, head temperature, polymer solution viscosity, and surface tension) and postformulation characters (particle size, flowability, surface scan, and dissolution profile) were evaluated. Finally, hypoglycemic effect of the selected formula was evaluated in streptozotocin-induced diabetic rats. Spray head with a 7 μm hole, flow rate of 3.5 mL/min, and head temperature of 120 °C were selected. Polymer viscosity was less than 11.5 cP with surface tension less than 70.1 dyne/cm.

Result:

Discrete, nonaggregated particles and free flowing powders with particle size was less than 2,000 nm were obtained. Gelatin and sodium alginate combination in ratio 1:3 were successfully sustained the in vitro release profile of the drug. Hypoglycemic evaluation of the previous formula showed a significant reduction of blood glucose level over 24 h.

Conclusion:

B-90 technology can open a new era of nanoparticle preparation, offering a convenient dosage form that can enhance compliance of type 2 diabetes patients.

Data Science Framework for Mobile Health Engagement and Outcomes

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Objective:

Knowledge about patient behavior is a critical element for managing chronic medical conditions such as type 2 diabetes. Until recently, data about what patients are doing outside their physicians' offices were limited. Mobile health technology has the potential to collect and process new sources of data, which can then be used to provide real-time coaching to patients and clinical decision support for providers. Our aim was to use data science tools to extract knowledge from patient-generated data in a mobile health platform.

Method:

The first mobile prescription therapy, WellDoc's BlueStar, was created and launched in 2014 for patients with type 2 diabetes. This platform was designed to collect data that would not otherwise be available to providers. Users interact with the product on their smartphone or via a web portal on their personal computer. An active engagement with the product was defined as entry of data such as self-monitoring of blood glucose (SMBG), exercise, carbohydrate intake, or medication administration. A passive engagement with the product included watching a video or reviewing the logbook. In this analysis, user data were de-identified in accordance with the HIPAA Privacy Rule. The number and type of user engagements were examined as well as user attributes such as age, diabetes medication regimen, and type of insurance. Preliminary outcomes such as improvements in SMBG and reduction in A1C were also studied. These data were used to illustrate the utility of our data science framework.

Result:

We conceptualized a data framework for mobile health that includes 1) driver metrics, which are measurable factors that influence results and include enrollment, usage, and satisfaction data, and 2) results metrics, which examine outcomes such as improved quality of care, improved diabetes control, and potential health care cost savings. From March 2014 to May 2015, we identified 1,036 diabetes patients who were prescribed BlueStar, enrolled and activated their accounts, and used the product for over 30 days. We characterized 161,602 active engagements from this population. We also demonstrate a high degree of user satisfaction. We report here significant improvements in SMBG values over time, fewer hypoglycemia SMBG entries, as well as significant reductions in A1C for those users who entered multiple A1C values. User attributes, which are associated with usage and outcomes, were identified.

Conclusion:

This mobile health data framework allows us to monitor the process of deploying a mobile prescription therapy product, in this case BlueStar. The driver metrics demonstrate a high degree of user engagement and satisfaction. The result metrics demonstrate improved glycemic outcomes. As mobile health products evolve, there will be growth in their potential for patient coaching and provider clinical decision support based on real-world data and not just the sparse information available at a patient visit.

MyDiaText: Short Message Service Technology for Behavioral Health in Patients with Type 1 Diabetes

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Objective:

MyDiaText is a cloud-based short message service (SMS) text messaging platform designed to improve behavioral health outcomes by encouraging adolescents to become more involved in their health management. By engaging directly with this demographic, MyDiaText engages youth to utilize SMS to integrate diabetes as part of their daily lives.

Method:

The MyDiaText SMS platform engages patients by sending and receiving messages at least once a day and incentivizing participation with a points-based gamification system. MyDiaText also periodically solicits self-reported ratings of their health from patients to measure health perceptions and administers short questionnaires to test knowledge and allow users to accumulate additional points. All of these data are displayed using real-time visualizations feedback and by texts relayed directly to the users via SMS using the SMS service Twilio.

Results:

The completed pilot data of the MyDiaText system included 22 patients, recruited from the Children's Hospital of Philadelphia. Over the pilot period of 30 days, these patients participated by sending 368 messages to the system, recording ratings and responses. Ninety-five percent of respondents liked the cadence of messages (approximately 10 per week), while 86% enjoyed earning points through the gamification aspect. MyDiaText also archived all messages it did not understand to focus the development of new content areas and responses.

Conclusion:

The MyDiaText pilot reported good participation and received 95% response of positive feedback from users, validating the concept and identifying areas for additional features and improvements in the technology. The pilot of this technology provides a good foundation for the SMS-based behavior health practice in treating type 1 diabetes patients, as well as promising in other areas of patient engagement and behavioral health.

Circulating Levels of Protease Activity during a Meal Tolerance Test in Type 2 Diabetes Mellitus

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Objective:

This study aimed to elucidate the effect of a high-calorie meal on circulating levels of proteases in type 2 diabetes mellitus (T2DM) patients using a novel assay that allowed for the rapid detection of matrix metalloproteinase 2/9 (MMP-2/-9), elastase, and trypsin activity in untreated whole blood.

Method:

Three groups of patients, T2DM ($n = 10$), pre-T2DM ($n = 10$), and normal ($n = 10$), received a standardized high-calorie meal. Blood samples were taken for 5 h at nine different time intervals (0, 15, 30, 45, 60, 90, 120, 180, and 300 minutes). MMP-2/-9, elastase, and trypsin activities were measured using a novel assay based on charge-changing fluorescently labeled peptides.

Result:

Base activity levels of MMP-2/-9 and elastase in the blood of T2DM and pre-T2DM groups were significantly elevated compared with normal group ($P < 0.01$). MMP-2/-9 and elastase activities were elevated in T2DM relative to pre-T2DM, but the difference was not significant ($P > 0.01$). Trypsin activity was higher in pre-T2DM than in other groups, but the difference was not significant ($P > 0.05$). Variation in protease activity over the 5 h after the meal was distinct for each group, with pre-T2DM experiencing the most variation, followed by T2DM.

Conclusion:

This study showed for the first time the detection of MMP-2/-9, elastase, and trypsin activities directly in untreated whole blood samples of T2DM. MMP-2/-9 and elastase activities were elevated in the blood of T2DM patients compared with normal individuals after a meal. Elevated circulating protease activity may be involved in the molecular mechanisms underlying the development of diabetes.

Interference Test Results for an Osmotic Pressure Sensor for Interstitial Glucose Assessment

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Background:

An implantable osmotic pressure sensor for interstitial glucose assessment is currently under development by Lifecare, Bergen, Norway (Sencell). A working laboratory sensor prototype model has been developed, which can be used for initial optimization experiments and further developmental tasks. The purpose of this experiment was to evaluate the stability of the glucose sensor signal against a potential influence of other carbohydrates.

Methods:

For each test, the sensor was equilibrated with 2 mmol/L glucose prior to addition of the potentially interfering substances in high physiological concentrations. The following carbohydrates and concentrations were tested: α -D-Mannose (100 μ mol/L), xylose (1.5 mmol/L), maltose (10.5 mmol/L), fructose (120 μ mol/L), and transferrin (5 g/L). In case of a measurable impact of the carbohydrate on the sensor signal, at least one more carbohydrate concentration below the initial concentration was to be tested.

Results:

There was no impact of mannose, xylose, fructose, and transferrin in the tested concentrations on the osmotic sensor signal. A measurable interference was observed with maltose at concentrations of 10.5 and 5 mmol/L. With 5 mmol/L maltose, the observed increase in the osmotic pressure signal amounted to ~9% (10.5 mmol/L, ~17%). However, such maltose concentrations are unlikely to be seen in the interstitial fluid under physiological conditions in human subjects.

Conclusions:

The results of our pilot experiments show that the osmotic sensor technology using the competitive binding of glucose to concanavalin A vs. dextran in a core sensor chamber is not influenced by the majority of the tested potentially interfering carbohydrate molecules. The only interfering carbohydrate was maltose, which was tested in highly supraphysiological concentrations. However, the potential impact of maltose on the final product will have to be tested in an appropriately designed clinical experiment in the later development process.

First Three-Dimensional Structure of Fungus-Derived Glucose Dehydrogenase: Knowing Enzyme for Glucose Monitoring

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Objective:

Fungus-derived glucose dehydrogenases harboring flavin adenine dinucleotide (FAD) as the cofactor (GDHFAD) are currently the most advanced and popular enzyme used in glucose sensor strips manufactured for glycemic control by diabetic patients. In spite of current emergent focus on the use of this enzyme, its biochemical information, including the structural information, is limited. In this study, we aim to elucidate the three-dimensional (3D) structure of GDHFAD and obtain biochemical properties of this unique enzyme, which are inevitable for the precise understanding of the glucose sensor, and acknowledge the benefit and drawback of using this enzyme.

Method:

Fungus GDHFAD was recombinantly prepared, and the purified protein solution was concentrated for crystallization. A single crystal mounted in a CryoLoop was directly flash cooled in a stream of evaporating nitrogen, and X-ray diffraction data were collected using an ADSC Quantum 315r detector on the BL5A in the Photon Factory (Tsukuba, Japan). Thus, obtained structures were superimposed with previously reported glucose oxidase 3D structures to elucidate regions, cavities, and residues responsible for each enzyme property.

Result:

The X-ray structures of the binary complex of enzyme and reduced FAD at a resolution of 1.78 angstrom, and the ternary complex with reduced FAD and D-glucono-1,5-lactone at a resolution of 1.57 angstrom were obtained. The absence of residues that recognize the sixth hydroxyl group of glucose, and the presence of significant cavity around the active site, may account for this enzyme activity toward xylose.

Conclusion:

The 3D structure of the fungus GDHFAD was elucidated. The structural information will contribute to the further engineering of GDHFAD for use in more reliable and economical biosensing technology for diabetes management.

High Compliance = Good Control? Compliance of the Stochastic Targeted Glycemic Control Protocol

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Objective:

Critically ill patients often experience stress-induced hyperglycemia, which has been shown to result in increased morbidity and mortality. Safe, effective glycemic control (GC) can reduce mortality and improve outcomes but is only effective if strong compliance is observed within the clinical practice. This study examines insulin-nutrition dosing compliance for stochastic targeted (STAR), a tablet-based protocol designed to easily adapt to variable clinical practice.

Methods:

STAR offers a choice of 1–3 h interventions, allowing GC workload to be chosen. Clinical staff are also able to enter an intervention at any point in time, ensuring flexibility to the clinical staff's needs. Clinical staff can also change the intervention, if clinical needs change. All interventions and changes are recorded. STAR has been the standard of care in the Christchurch intensive care unit since 2011, from this data (22,901 h; 287 patients), the hourly insulin dosing compliance of STAR was analyzed.

Results:

Compliance was 99.6 and 99.5% for insulin bolus and infusion recommendations, respectively, and 96.8% for feed rate recommendations. While maintaining high protocol compliance, STAR maintained GC performance, 84.8% of time in the 4.4–8.0 mmol/L target band and safety, and 1.06% of patients experienced severe hypoglycemia.

Conclusions:

STAR provides an adaptive tablet-based GC protocol, designed for ease of use in a dynamic clinical environment. As a result, it demonstrated excellent clinical compliance, and very safe and effective GC performance can be attributed this very high clinical compliance.

Perspectives on Diet during Postpartum Periods in Mothers with Gestational Diabetes Mellitus, Nurses in the Postnatal Ward, and Midwives in the Antenatal Clinic

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Objective:

We aim to understand the perspectives of nurses in postnatal wards, midwives in antenatal clinics, and mothers regarding physical activity and diet of gestational diabetes mellitus (GDM) mothers in postpartum periods.

Methodology:

Three nurse midwives and three public health midwives were invited for this study from selected districts. Gampaha, Colombo, and Galle were the selected districts. Semistructured in-depth interviews were conducted to collect data. Thematic analysis was undertaken to determine underlying themes.

Result:

Six key themes emerged from the data: 1) experience of myths and tradition of food and food habits, 2) lack of motivation to practice, 3) time pressure, 4) negligence, 5) lack of knowledge, and 6) social influence. In addition to that, stigma and lack of family support were identified as barriers to implement lifestyle modification, especially among women in rural areas.

Conclusions:

This study provides insight into the tradition, myths, and barriers of pregnant mothers diagnosed with GDM and the experience of health care workers. It emphasizes the importance of health education not only for mothers but also for their family members and society and provides insight into the challenges and opportunity for preventing future diabetes risk reduction. To improve adherence to management plans, these women required educational counseling and intervention that are culturally appropriate and aimed at either low or high quality of life.

Improving Meal Detection Using a Smartwatch and Accelerometer

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Objective:

Meals pose a large challenge for both automatic and manual control of blood glucose. The difficulty of detecting meals and the less-than-perfect rate of meal announcement/bolusing makes meals more challenging. This work explores using a smartwatch and an accelerometer to improve meal detection. These devices should cause minimal burden since the accelerometer could reside in the insulin pump. Specifically, we will show that the position and orientation of the wrist correlate when people are eating. This in turn can be used to prompt the user for a meal announcement or increase the sensitivity of a continuous-glucose-monitor-based meal detector.

Method:

We use an LG w100 smartwatch on the dominant wrist that provides three-dimensional (3D) compass, accelerometer, and gyroscope data. We also use a torso-mounted activity monitor device (Zephyr BioHarness) that provides 3D accelerometer data. We fuse the sensor data using quaternions and a Kalman filter to estimate wrist orientation and wrist position relative to the torso. Since most meals require 1) the dominant hand to come near the mouth, 2) repeated vertical motions, and 3) an upward and inward wrist orientation, we can use the wrist position and orientation to estimate the likelihood that food is being consumed.

Results:

We will verify our methods by collecting sensor data and meal logs from subjects and comparing the generated meal signal with the meal logs.

Conclusion:

We can leverage smartwatch data to improve glucose control via better meal detection.

Smartphone-Based Patient Health Care Management System

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Objective:

I proposed and developed a smartphone-based patient health care management system that would help persons to monitor their blood glucose level on a daily basis and to transfer such data to their health care service providers' database whenever they visit their physician.

Method:

This proposed system utilizes an Android-operating-system-based smartphone application and a database server to save each individual's data such as blood glucose level, reading time, daily meal details, special symptoms, allergies, prescription renewal dates, and drugs intake details.

Results:

This system allows users to conveniently record their measured health care data in their smartphones in a most convenient way and to track their long-term health condition changes. Each time a person visits his or her physician, the data stored in their smartphone gets transferred to the health care service providers' database wirelessly and enables the physician to easily get a clear picture of the patient's health progress. Doctor's instructions, prescriptions, guidelines, and appointment details all can be written to the application in the smartphone and transferred to the health care service providers' database wirelessly, and the patient can review them leisurely. This system also enables users to check their wellness progress by representing their recorded data in the form of graphs and charts and can alert them on their prescription renewal dates. When patients record their daily health care data, if the system notices any serious variation in the recorded data, it will automatically send a short message briefly describing the abnormality in the data.

Conclusion:

In this project, I have developed a patient health care management system for collecting, storing, and reviewing patient data in Android smartphones and transferring such data via Bluetooth to the doctors' or health care service providers' database. This system has been implemented using the Java programming language, XML language, SQLite, and MySQL. In this system, many advanced features have been included such as data storage, alarm services, graph plotting, and short message service also.

Progress toward Passive Transdermal Glucose Sensing Based on a Glucose-Binding Protein

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Objective:

The ability to measure the levels of glucose in premature neonates is a critical part of good clinical care. Commercially available glucose sensing methods require breaking the skin and collecting blood for testing. On the other hand, there are no Food and Drug Administration–approved noninvasive glucose testing methods in the US market today. The purpose of this work is to study the possibility of passively collecting transdermal glucose and then measuring the extracted glucose with a fluorescent glucose biosensor. We foresee the use of this noninvasive technology in the neonatal intensive care unit.

Method:

Skin samples from Yucatan female pigs (9 months old) were used for the skin diffusion experiments. The dermatomed skin ranging from 200–350 μm was placed in a PermeGear in-line flow-through diffusion cell (maintained at 37 $^{\circ}\text{C}$). Phosphate-buffered saline (PBS) and glucose (2, 5, and 20 mmol/L to mimic hypo-, normo-, and hyperglycemic conditions, respectively) were allowed to flow in a bottom chamber at a constant rate of 0.8 mL/min . Skin is mounted in the diffusion cell apparatus with the outer surface of the stratum corneum facing the sample chamber. The chamber was loaded with 250 μL of PBS. Glucose in the flow solution was allowed to diffuse to the PBS for 15 min. The extracted glucose was then assayed with the fluorescent glucose-binding protein (GBP). The fluorescence intensities were measured using a 96-well plate on a SpectraMax M5 plate reader.

Result:

The fluorescence intensity of GBP labeled with the fluorophore badan increases with increasing glucose concentration. The linear range for the determination of glucose is up to 20 $\mu\text{mol/L}$. The concentration of glucose in the transdermal samples range from 1.30 ± 0.05 to 4.0 ± 0.10 $\mu\text{mol/L}$. As expected, the cumulative amount of glucose increases with the concentration of glucose in the flow-through. This shows that glucose passively diffused from the skin can be measured using the GBP over the hypo- to hyperglycemic range.

Conclusion:

Results show that the flow-through diffusion system is a promising tool to develop the noninvasive glucose sensing system. Future experiments will be dedicated to the optimization of the transdermal glucose sensing system and modeling.

Insulin Sensitivity Profile as a Marker for Reduced Outcome in the Neonatal Intensive Care Unit

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Objective:

Hyperglycemia in neonatal intensive care units is associated with mortality and morbidity. This trial aims to use machine learning methods to provide a prediction of outcomes in hyperglycemic neonates based on model-based metabolic (glycemic control) data as a noninvasive marker.

Method:

Glycemic control data from 44 patients (4,499 h) under the STAR-NICU or STAR-GRYPHON model-based glycemic controllers from Christchurch Women's Hospital were used. Predictive models were built using attributes from hourly, patient-specific, model-based insulin sensitivity. Among these patients, 12 contracted sepsis, 8 suffered from intraventricular hemorrhage (IVH), and 8 died. The methods used were classification trees and K-nearest neighbors. The efficacy of the models was assessed evaluating sensitivity, specificity, and accuracy.

Result:

Mean insulin sensitivity was different among different subgroups: 7.51×10^{-4} , 5.47×10^{-4} , 2.42×10^{-4} , and 7.50×10^{-4} L/mU/min for patients who were septic, had IVH >grade 1, nonsurvivors, and survivors, respectively. Variability assessed as interquartile range was also different between groups, with 1.00×10^{-4} , 4.99×10^{-5} , 4.22×10^{-5} , and 9.09×10^{-5} L/mU/min, respectively. It was possible to predict mortality with 85% sensitivity after the first 15 h and (later proven) sepsis with sensitivity of 80% within 20 h.

Conclusion:

A clinically validated model-based insulin sensitivity measure and its variability may provide information about patient condition and possible outcome, despite modeling limitations. This study emphasized the potential of machine learning to provide information on degrading patient condition and worsened outcome as an alert to provide more intensive care.

Combination of Microdialysis and Ex Vivo Glucose Sensing by Infrared Spectrometry with Online Recovery Rate Determination

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Objective:

Blood glucose monitoring has been realized by biosensors in combination with microdialysis, using either intravascularly or subcutaneously implanted catheters. However, a drawback is variable recovery rates, which can be observed especially for the latter devices. For continuous sensing, infrared spectrometry has been suggested, since besides glucose, other clinically relevant analytes can be simultaneously determined that are important, e.g., for intensive care patients.

Method:

Perfusates with either acetate or mannitol have been investigated as recovery markers. The latter substance is suggested for application with tunable quantum cascade lasers, rendering only a limited wavenumber interval when compared with Fourier transform infrared spectrometers. Despite the overlap of mannitol and glucose spectra, their simultaneous accurate quantification was successful.

Result:

In contrast to the previously used acetate, an almost linear dependency of mannitol loss and glucose recovery was realized for all microdialysis catheters tested, which provides a straightforward correction of any dialysis recovery rate variation during patient monitoring.

Conclusion:

The combination of microdialysis with infrared spectrometry provides a calibration-free assay for accurate continuous glucose monitoring, as reference spectra of dialysate components can be a priori allocated.

Early Results Support Efficacy and Clinical Efficiency of Diabetes Management Decision-Support Software for Blood Glucose Control

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Objective:

The benefit of drug therapy to persons with diabetes has been well established in clinical trials in terms of reducing cardiovascular risk, microvascular complications, and mortality. However, treatment adherence and treatment effectiveness continue to be challenges in diabetes management. Use of software algorithms to simulate the effect of antidiabetic medications on an individual's glucose profile should allow for more targeted decision making by the clinician. This study evaluates whether adding decision-support software that allows for modeling the anticipated effect of medication adjustments leads to improved glycemic control and a perceived benefit by health care providers and patients with diabetes.

Method:

We conducted a randomized, controlled, open-label, multicenter study to assess the effect of using decision-support software (Rimidi) on hemoglobin A_{1c} and time to A1C goal. The study population consists of patients with type 2 diabetes (ages 18–80 years) and a starting A1C >9% referred to pharmacist-directed medication management services by their primary care physician.

Result:

Preliminary data show 50% of subjects using Rimidi achieved goal within 3 months, with a mean absolute drop in A1C of 2.5% and, in those cases, a corresponding A1C <7%, with the largest change occurring in the first 30 days. In the usual care arm without Rimidi, an equivalent percentage reached goal, without the dramatic lowering of A1C.

Conclusion:

The initial results support the need to complete full enrollment for the study given the powerful and immediate impact of Rimidi on A1C results within the first 30 days. A full data analysis will delineate the full range of benefits for clinical results as well as patient engagement and satisfaction in using technology to empower better outcomes.

Long-Term Glycemic Control Using Polymer Encapsulated Human-Stem-Cell-Derived β -Cells in Immune Competent Rodents

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Background:

The transplantation of glucose-responsive, insulin-producing cells offers the potential for restoring glycemic control in diabetic patients.

Method:

Pancreas transplantation and the infusion of cadaveric islets are currently implemented clinically, but their utility is limited by both the adverse effects of lifetime immunosuppression and the limited supply of donor tissue. Recently, glucose-responsive mature β -cells derived from human embryonic stem cells, called SC β , have been developed as an essentially unlimited human cell source for replacement therapy. The immunoisolation of insulin-producing cells with porous biomaterials to provide an immune barrier is one strategy to overcome the need for immunosuppression however, clinical implementation has been challenging due to host immune responses to implant materials.

Results:

Here we report the first long-term glycemic correction of a diabetic, immunocompetent animal model with human SC β cells. SC β cells were encapsulated with novel alginate derivatives capable of mitigating foreign body responses *in vivo*. Our results show glycemic correction in streptozotocin-treated C57BL/6J mice for over 170 days with encapsulated human SC β cells implanted in the intraperitoneal space without any immunosuppression.

Conclusions:

Human C-peptide and *in vivo* glucose responsiveness demonstrate therapeutically relevant glycemic control. Retrieved implants revealed viable insulin-producing cells even after 170 days in immunocompetent mice.

Simulation of Patient Decision Making to Test Safety and Effectiveness of Continuous Glucose Monitoring Sensors for Nonadjunctive Use in Type 1 Diabetes: A Patient Modular System Model

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Objective:

Continuous glucose monitoring (CGM) sensors are used to support self-monitoring of blood glucose (SMBG) in type 1 diabetes (T1D) management, e.g., by providing real-time hypo-/hyperglycemic alarms and glucose trends. Recent improvements of CGM accuracy suggest that CGM should be safe enough for nonadjunctive use. However, CGM is still not approved to substitute SMBG by regulatory agencies. To test safety of CGM nonadjunctive use, realistic *in silico* clinical trials can be of great help. Here we design a patient modular system model that can be used to simulate decision making in a broad class of T1D patients.

Method:

The T1D patient decision-making simulator is built by four modules: 1) model of T1D patient glucose-insulin dynamics based on the University of Virginia/Padova simulator now including inter- and intraday variability of insulin sensitivity (which allows simulating multiple days); 2) models of glucose monitoring devices, i.e., SMBG and CGM; 3) model of T1D therapy that emulates patient decisions, including insulin dosing, hypo treatments, and patients' common errors, e.g., carbohydrate counting and early/delayed/missed delivery of insulin boluses; and 4) model of subcutaneous insulin pump delivery.

Result:

The simulator allows creating realistic glucose dynamics of T1D patients and scenarios, as demonstrated by the ability of reproducing the statistics observed on real data sets (e.g., time in target, number of hypo events). Several-days simulations can be run in virtual patients by using models of SMBG and CGM devices having different accuracies.

Conclusion:

The presented decision-making model is a versatile tool usable for *in silico* designing and testing SMBG- and CGM-based therapies. Its most straightforward development is the *in silico* comparison of CGM-driven with SMBG-driven insulin therapies to determine if CGM is accurate enough for nonadjunctive use.

Simulation of Patient Decision Making to Test Safety and Effectiveness of Continuous Glucose Monitoring Sensors for Nonadjunctive Use in Type 1 Diabetes: Self-Monitoring of Blood Glucose–Based versus Continuous Glucose Monitoring–Based Therapies

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Objective:

Nonadjunctive use of continuous glucose monitoring (CGM) sensors in the management of type 1 diabetes (T1D) has not been approved yet by regulatory agencies. Indeed, assessing safety and effectiveness of CGM-driven versus self-monitoring of blood glucose (SMBG)-driven insulin therapies is a delicate task that, in the present work, is investigated in an in silico environment by exploiting a patient modular system model.

Method:

A simulator of T1D patient decision making is used to conduct a 14-day in silico experiment in 100 virtual patients. In each of them, four different insulin therapy scenarios are compared: premeal boluses calculated using SMBG (#1), premeal boluses calculated using CGM (#2), premeal boluses calculated using CGM plus postmeal correction boluses in response to CGM hyperglycemic alarms or hypo treatments in response to CGM hypoglycemic alarms (#3), and #3 plus use of literature guidelines to correct insulin boluses according to CGM trend (#4).

Result:

The median values of time in target (within 70–180 mg/dL), time in hyper (over 180 mg/dL), and time in hypo (under 70 mg/dL) are respectively 62.53, 36.62, and 0.29% in therapy #1; 62.23, 37.54, and 0.32% in #2; 70.21, 29.46, and 0.19% in #3; and 70.74, 28.75, and 0.16% in #4. Compared with #1, therapy #4 drives to a statistically significant improvement for all the metrics considered (paired sign test, P value < 0.05).

Conclusion:

Simulations show that replacing SMBG simply with CGM samples does not improve nor deteriorate therapy safety and effectiveness (#1 vs. #2). Use of CGM plus trends for triggering alarms and corrections (#4) significantly improves glycemic control over SMBG-driven therapy.

Modeling the Effect of Liraglutide in Type 2 Diabetes Mellitus with the Type 2 Diabetes Mellitus Simulator: A Paradigm for In Silico Trials

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Objective:

Liraglutide is a once-daily glucagon-like peptide-1 receptor agonist for the treatment of type 2 diabetes mellitus (T2DM). Several clinical studies have been conducted to evaluate its pharmacological effects. However, the use of in silico computer simulation would allow the evaluation of drug effects with relevant time-/cost-savings. Recently, we presented a T2DM simulator for in silico testing of new drug candidates. Here we aim to model liraglutide's pharmacological effects on fasting and postprandial glucose in T2DM subjects using the T2DM simulator.

Method:

The database comes from a randomized, open-label, two-arm, parallel-group, multicenter pharmacodynamics study aimed to evaluate the effect of 4 weeks of treatment with liraglutide on postprandial and fasting glucose. Seventy-one T2DM subjects underwent a breakfast meal test pretreatment (i.e., baseline) and posttreatment (i.e., 4 weeks after treatment). Time courses of C-peptide, glucose, and insulin were used to identify the model included into the T2DM simulator. C-peptide model identification provided insulin secretion β -cell responsiveness and glucose model identification provided parameters of glucose absorption and insulin action on glucose disposal and production. Liraglutide effects were evaluated by comparing the parameter estimates pre- versus posttreatment.

Result:

Model fits were satisfactory for both C-peptide and glucose models. After 4 weeks of treatment, liraglutide significantly increased β -cell responsiveness and insulin sensitivity. On the other hand, liraglutide didn't substantially change glucose absorption and gastric emptying, in agreement with previously reported clinical data.

Conclusion:

The incorporation of these clinical results into the T2DM simulator allows in silico testing of liraglutide to predict its effect on postprandial glucose control under various conditions. This work also provides a case study for the application of T2DM simulator as a translational modeling tool for other antidiabetic-drug in silico trials.

Usage and Perceptions of Type 1 Diabetes Devices

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Objective:

Type 1 diabetes (T1D) accounts for 5 to 10% of cases in the United States and is characterized by significant hyper- and hypoglycemia on an everyday basis. Despite significant advances in technologies to manage the disorder, glucose control continues to be suboptimal. Arizona State University and the Mayo Clinic Diabetes Technology Center developed the Diabetes Technology Survey (DTS) to measure usage and perceptions of T1D devices and thus understand human factors that can be addressed to improve device use and glucose control.

Method:

The DTS was distributed electronically to T1D patients after receiving informed consent. The survey gathers basic demographics, diabetes history, and information about usage and perceptions of devices.

Result:

Twenty-six individuals (8 male, 18 female) have completed the survey so far. All report using glucose meters and insulin pumps. The most frequently used pump features include entering carbohydrates and bolus calculator and least frequently are changing insulin sensitivity and uploading data at home. Overall, patients find the pump satisfying and convenient to use. Only five report using a continuous glucose monitor (CGM). CGMs were rated as most useful for low blood glucose alarms, swimming, and sleeping and least useful for cost and displaying data on smartphones.

Conclusion:

Overall, the individuals surveyed frequently use glucose meters, insulin pumps, and CGMs. These devices are perceived well, with many high ratings for device usefulness, convenience, and satisfaction. Features that received low ratings of usefulness and convenience need to be addressed in future studies.

Feasibility of Use of Novel Stable Soluble Glucagon Analog ZP-GA-1 in Artificial Pancreas Systems

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Objective:

Unavailability of a stable liquid form of glucagon has limited its use in automated diabetes management devices. Zealand Pharma A/S developed a stable soluble glucagon analog ZP-GA-1, which demonstrated in preclinical models glycaemic effects similar to currently marketed glucagon. To evaluate the feasibility of ZP-GA-1 for artificial pancreas (AP) systems, we compared glycaemic profiles during dual-hormonal (DH) and mono-hormonal (MH) closed-loop (CL) control in diabetic dogs using Medtronic's portable research AP platform.

Method:

A proportional-integral-derivative algorithm controlled insulin delivery. The glucagon delivery algorithm was based on the rate of blood glucose decline below a set point of 100 mg/dL. Boluses of ZP-GA-1 (0.035 mg) were delivered when hypoglycemia was predicted. If hypoglycemia persisted 30 min after the initial ZP-GA-1 bolus, a follow-up bolus was delivered. Six dogs underwent 12-h both DH and MH CL studies performed in random order. In both CL settings, high insulin gains were used to promote hypoglycemia in order to test the ability of ZP-GA-1 to prevent/correct hypoglycemia.

Result:

During 72 h of DH studies, 21 ZP-GA-1 boluses were delivered; the daily dose of ZP-GA-1 boluses per dog varied (0.035–0.245 mg/day). In nine instances, follow-up boluses of ZP-GA-1 were required. The area under the curve below 80 mg/dL was not significantly lower during DH control (1.7 vs. 5.2 mg/dL×h for DH and MH, respectively; $P = 0.4$). Insulin use was comparable (24 vs. 21 units during DH and MH, respectively; $P = 0.6$).

Conclusion:

The stable soluble glucagon analog ZP-GA-1 could successfully be used in AP systems, although the DH compared with the MH system did not show significant differences in reducing hypoglycemia in this limited study.

Telehealth System: Smartphone-Based Self-Management for Diabetes Patients

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Objective:

Singapore must reduce the alarming rate at which diabetes is developing. We therefore evaluated the clinical effects of Telehealth System, which offers information-and-communications-technology-based diabetes self-management.

Methods:

Telehealth System comprises three modules. In data transmission, patients' data measured at home—blood glucose, blood pressure, and daily activity/exercise—are automatically sent by smartphone to the server. In diet input, patients send photos of their meals, which the server returns with readings to show how each meal affects the patient's blood glucose. In communication, all data can be shared by whichever family members and friends patients designate so they can encourage patient measurements and input. However, Telehealth System does not evaluate input or return lifestyle modification advice. A pilot study was conducted to assess Telehealth System effectiveness.

Results:

Thirty-five patients enrolled (male 62.9%, ethnic Chinese 68.6%, mean age 36.6 ± 6.9 years, body mass index [BMI] 24.5 ± 5.4 kg/m², HbA_{1c} $5.6 \pm 0.9\%$). Of these, 10 had elevated HbA_{1c}, 25 controls were nonelevated (respectively, age 39.4 ± 8.2 vs. 34.8 ± 5.9 years; BMI 25.9 ± 5.5 vs. 24.1 ± 4.6 kg/m²; HbA_{1c} 6.5 ± 1.1 vs. $5.3 \pm 0.3\%$). At 1-month follow-up, the elevated group's HbA_{1c} was significantly reduced versus that of the controls (-0.3 ± 0.2 vs. $+0.1 \pm 0.4\%$; $P = 0.01$). And the elevated HbA_{1c} group's total energy intake ($-327.0 \pm 1,140.9$ kcal), protein (-12.9 ± 41.9 g), and fat (-28.9 ± 61.9 g) tended to decrease, though not with statistical significance. When interviewed, most participants stated that reviewing their measured data helped them understand their health situation, but they needed some feedback to let them know how they should modify their lifestyle.

Conclusion: Telehealth System seems to improve HbA_{1c} in diabetic and prediabetic patients. We plan to develop feedback functions for the system.

Accuracy of a Blood Glucose Monitoring System as It Relates to the ISO 15197:2013 Requirements in the Management of Diabetes Mellitus

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Objective:

The purpose of this study was to demonstrate that GLUCOCARD Shine meets the ISO 15197:2013 blood glucose monitoring system (BGMS) accuracy performance requirements.

Method:

Three lots of GLUCOCARD Shine test strips were analyzed for performance and bias comparison ($n = 104$ data points). Samples were collected from the fingertip of confirmed diabetic subjects by trained personnel at the ARKRAY Factory Inc. in Minneapolis, MN. Reference values were obtained using the YSI 2300 analyzer. Data were analyzed using the system accuracy performance criteria published in the ISO 15197:2013.

Result:

Results revealed that 100% of <100 mg/dL samples ($n = 6/6$) were within ± 15 mg/dL, meeting the 95% accuracy criteria, and 99.0% of the ≥ 100 mg/dL samples ($n = 97/98$) fell within the predetermined 15% meeting the 95% performance criteria. All data were within the A and B zones of the consensus error grid. Overall bias was -1.3% , demonstrating strong agreement between the GLUCOCARD Shine and YSI reference analyzer results. Correlation coefficient (r) = 0.99 demonstrated a strong linear relationship between the YSI reference method and BGMS results.

Conclusion:

Data acquired on the GLUCOCARD Shine meet the ISO 15197:2013 system accuracy performance criteria.

Evaluation of a Blood Glucose Monitoring System in Comparison with Global Accuracy Performance Requirements

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Objective:

The purpose of this study was to demonstrate that the GLUCOCARD Vital meets the global blood glucose monitoring system (BGMS) accuracy performance requirements of 95% of results within ± 15 mg/dL for glucose samples < 100 mg/dL and 95% of results within 15% for glucose samples ≥ 100 mg/dL.

Method:

Three lots of GLUCOCARD Vital test strips were analyzed for performance and bias comparison ($n = 104$ data points). Samples were collected from the fingertip of confirmed diabetic subjects by trained personnel at the ARKRAY Factory Inc. in Minneapolis, MN. Reference values were obtained using the YSI 2300 analyzer. Data were analyzed using the accuracy performance criteria of 95% of results within ± 15 mg/dL for glucose samples < 100 mg/dL and 95% of results within 15% for glucose samples ≥ 100 mg/dL.

Result:

Results revealed that 100% of < 100 mg/dL samples ($n = 6/6$) were within ± 15 mg/dL, meeting the 95% accuracy criteria, and 99.0% of the ≥ 100 mg/dL samples ($n = 97/98$) fell within the predetermined 15%, meeting the 95% performance criteria. All data were within the A and B zones of the consensus error grid. Overall bias was 0.5%, demonstrating strong agreement between the GLUCOCARD Vital and YSI reference analyzer results. Correlation coefficient (r) = 0.98 demonstrated a strong linear relationship between the YSI reference method and BGMS results.

Conclusion:

Data collected and analyzed on the GLUCOCARD Vital meet the global accuracy performance criteria of 95% of results within ± 15 mg/dL for glucose samples < 100 mg/dL and 95% of results within 15% for glucose samples ≥ 100 mg/dL.

Autonomous Shape-Memory-Alloy-Based Actuator Reaching Subcutaneous Blood Capillaries: Results from In Vitro Characterization and Two Pilot Human Studies

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Objective:

Despite numerous claims for less invasive solutions, reliable glucose monitoring is still based on blood samples drawn by finger pricking, which can be tedious and painful and affect patients' adherence to disease management. A novel shape-memory alloy (SMA)-based actuator has been developed to provide a reliable, autonomous, wearable solution for skin lancing, blood sample collection, and in situ blood glucose analysis. This study offers in vitro characterization and in vivo human testing of this realistic approach for glucose maintenance.

Method:

Eight SMA-based actuator prototypes were successfully fabricated using compression molding. Two of them were prepared on a mechanical test station to characterize the output force and penetration depth, which are the major factors facilitating skin penetration. The other six prototypes were integrated on watch straps that were worn on the forearms of two volunteers to examine the blood extraction capability.

Result:

In vitro tests demonstrated that the actuator can produce a maximum penetration force of 160 gf and a maximum depth of 2.45 mm, which both exceeded the minimum requirements for blood-capillary-reaching skin penetration in humans. In subsequent human studies, visual observation of the testing site was performed after the actuation. In three tests, a blood drop autonomously emerged at the skin surface within 1 min. In the other three tests, a blood drop was formed by mildly squeezing the skin around the testing site.

Conclusion:

The designed SMA actuator successfully reached capillaries in all six human tests. However, the width and the depth of skin penetration should be expanded in order to reliably extract a sufficient amount of whole blood for further analysis. The method has the potential to become a core technology for reliable autonomous blood glucose monitoring.

Development of a Primary Isotope Dilution Mass Spectrometry Traceable Reference Procedure in China for Blood Glucose Testing Is a Key Step for Evaluating Point-of-Care Glucose Methodologies

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Background:

There is considerable discussion about the accuracy of hospital blood glucose monitoring systems (BGMS) and self-monitoring of blood glucose (SMBG) meters. Studies undertaken with the same point-of-care (POC) glucose meters have shown different results, and this is often related to the different comparative methods used. With new Food and Drug Administration, International Organization for Standardization, and Clinical and Laboratory Standards Institute guidelines emerging, it is important that evaluations are standardized to a true and traceable definitive reference method. We advocate the use of an isotope dilution liquid-chromatography mass spectrometry (ID-LCMS) aligned hexokinase (HK) method on a central laboratory analyzer (Roche Modular) for undertaking evaluations combined with pretreatment of samples with perchloric acid (PCA) to hemolyze and deproteinate specimens, and we describe our validation method for achieving this traceability.

Methods:

The definitive ID-LCMS reference method was calibrated using a bracketing technique using varying concentrations of glucose in water (primary standards, National Institute of Standards and Technology [NIST] 917a). NIST 965b secondary protein-based standards were then evaluated to demonstrate the performance of the ID-LCMS definitive method and its agreement with the NIST-assigned target values as compared with the primary standards. The alignment of the laboratory HK and PCA (PCA-HK) methods to the ID-LCMS method was undertaken with NIST primary (aqueous) and secondary (serum albumin based) standards and plasma samples. The correlation of the ID-LCMS aligned PCA-HK to the routine HK method was further assessed with patient whole blood specimens and subsequent plasma samples.

Results:

Excellent linearity was obtained and correlation was obtained between all three methods: plasma HK, PCA-HK, and ID-LCMS. For example the R^2 for NIST 917a and 965b on the HK laboratory reference analyzer method were 0.999 with 95% confidence level 1.015 to 1.048, standard error = 7.7143 E-03, and a P value < 0.0001. PCA-HK and ID-LCMS demonstrated comparable results.

Conclusion:

In China, SMBG meters are routinely used in hospitals, and POC with BGMS is now beginning to be used more frequently. Consequently, the missing element for proper assessment of these devices to glucose performance standards is defining an acceptable primary reference method. In our facility, we have chosen a PCA-HK method that is closely aligned to ID-LCMS method for plasma glucose measurements, and in turn, the routine plasma HK method is closely aligned to the PCA-HK method. This type of method traceability approach is essential in evaluations of POC glucose methods.

Comparison of Point-of-Care Blood Glucose Monitoring System Performance Isotope Dilution Mass Spectrometry Aligned Reference Methods: An Extensive Evaluation

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Background:

Hospital glycemic management protocols help reduce hyperglycemia and subsequent mortality in critically ill patients. Handheld blood glucose monitoring systems (BGMSs) are ideal for guiding intensive insulin therapy and maintaining safe and effective glycemic control. However, while many of these BGMSs are used in hospitals, these have not been fully validated for use in critical care patient settings in China. Complicating matters, BGMSs are validated against various methods. Our approach was to evaluate BGMS devices with several comparative methods. This includes plasma glucose measurements via hospital chemistry analyzers serving as a comparative/reference method or hexokinase (HK)-based definitive reference method calibrated using National Institute of Standards and Technology isotope dilution mass spectrometry (IDMS) traceable standards and further verified with perchloric acid (PCA) deproteinated samples on both the HK laboratory reference laboratory method and isotope dilution liquid-chromatography mass spectrometry definitive method. The objective our study was to evaluate the performance of existing BGMSs against IDMS, PCA, and plasma glucose methods.

Methods:

One hundred remnant venous whole blood specimens were collected and tested on four BGMSs, two from manufacturer A (StatStrip, Nova Biomedical, Waltham, MA) and two from manufacturer B (AccuChek Inform II, Roche Diagnostics, Indianapolis, IN). BGMS performance was compared against IDMS (LC-MS/MS, Thermo Fisher TSQ Quantum Access Max, Waltham, MA), hospital laboratory reference analyzer HK method (Roche Diagnostics, HK generation 3, Mannheim, Germany), and the subsequently aligned PCA/HK (Roche Diagnostics, Modular P module, Mannheim, Germany). We used several statistical methods to evaluate the concordance of the methods evaluated.

Results:

Data on method precision, effect of interferences, and comparison of BGMS to central laboratory reference HK and PCA/HK aligned definitive methods too numerous to include in this abstract will be presented in the poster.

Conclusions:

BGMSs from both manufacturers showed differences when compared with the reference methods. These data illustrate differences among BGMSs and reference methods. To this end, there is a critical need in China to standardize performance measurements for BGMSs and hospital laboratory analyzers.

Glucosense: A Low-Cost Glucose Meter System for Resource-Poor Settings

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Objective:

In low-resource settings that rely on donated medical supplies, glucose monitoring supplies are not always available to patients, and even when they are, standard supplies can be prohibitively expensive. Our objective is to design a low-cost glucose meter system that can be used in resource-poor settings.

Method:

Our system utilizes test strips made using a desktop inkjet printer. Empty printer cartridges are filled with enzyme and dye solutions. Precise amounts of the solutions are printed onto filter paper using a word processor template document. Glucose in the blood induces a color change on the printed strips. To read the strips, we designed a low-cost glucose meter, which determines the glucose concentration based on a preprogrammed standard curve. However, the strips can double as a visual indicator if a meter is not available.

Result:

Both pipetted and printed test strips have shown accuracy in processing glucose standards and bovine blood with added glucose in the range of 0–350 mg/dL. The design incorporates an internal calibration to account for varying patient blood color and oxygen concentration that may affect results.

Conclusion:

The research thus far confirms that a printable test strip is feasible as a means for monitoring glucose levels. While these strips are not as fast as current commercially available strips (readings take ~30 s), they meet the standard for accuracy in a glucose meter. The desktop printing of test strips is easy to implement in clinics in resource-poor settings.

Cytotoxic Effect of Three Commercial Rapid-Acting Insulin Analogs on Four Human Immune Cell Types

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Objective:

Local tissue inflammation from continuous subcutaneous insulin infusion is well documented, but causation and overall cellular effects are poorly characterized. The present study characterizes the in vitro cytotoxic effects of insulin analog formulations (lispro, glulisine, and aspart) on four human immune inflammatory cell types active in the subcutaneous (SC) tissue: peripheral blood mononuclear cells (PBMC), polymorphonuclear leukocytes (PMN), human macrophages (THP-1), and human mast cells (HMC-1).

Method:

THP-1 and HMC-1 cells were cultured in vitro; primary PBMC and PMN were freshly isolated from human blood. Each cell type was incubated with serial dilutions of each insulin analog in culture media (0.26–33 U/mL concentration range). Cell viability was evaluated at 24 h via CyQUANT Direct Cell Proliferation Assay (Life Technologies).

Result:

Regardless of analog, insulin dilutions exhibited a dose-responsive direct cytotoxic effect on each cell type tested. Cytotoxicity curves for individual cell types were nearly superimposable between insulin formulations, except for HMC-1 at 16.7 U/mL, where glulisine reduced viability >50% but aspart and lispro did not. PMN exhibited the overall cytotoxicity with viability of 70% (glulisine and lispro) to 90% (aspart) at 33 U/mL and recovery to 100% at 16.7 U/mL for all analogs. Fifty percent reduction in cell viability, EC₅₀, across the three insulin formulations occurred at 13 U/mL (lispro and glulisine) and 15 U/mL (aspart) in PBMC, 7–8 U/mL (all formulations) in THP-1 and 28 U/mL (aspart and lispro) and 16 U/mL (glulisine) in HMC-1.

Conclusion:

All three insulin analogs demonstrated direct cytotoxicity against SC immunoreactive cells at exposures at or below expected therapeutic concentrations. Additional exploration of specific insulin formulation components and in vivo confirmation is warranted to obtain a better mechanistic understanding and develop inflammation prevention methods.

Characterization of the Information Technology Utilization and Experiences of Diabetes Patients Insured Under the Affordable Care Act

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Objective:

In 2014, the Affordable Care Act (ACA) was implemented extending insurance coverage to nine million previously uninsured patients. These patients represent a population with unique demographics, lifestyles, and socioeconomic status. In this study, we sought to characterize how differential access to technology and information sources correlate with the health outcomes of diabetes patients covered by the ACA compared with those with other insurance types.

Method:

Using dual data collection methods, involving telephone-based interviews and Internet-based questionnaires, a total of 2,282 diabetes patients in the United States were sampled. Questions focused on demographic, lifestyle, treatment, access to information, technology/device ownership, and socioeconomic status and were stratified by insurance coverage (ACA, Medicare, Medicaid, and private insurance).

Result:

ACA patients have high rate of Internet access at home (98.3%); however, when asked about utilized information sources, ACA patients most frequently listed no regularly used source of diabetes education, whereas Medicare and private insurance patients listed the Internet as their most common source. ACA patients showed poor control over their diabetes, with 20.9% claiming “little or no control” (Medicare 6.56%, Medicaid 6.49%, private 5.67%). Additionally, ACA patients are not adhering to personal monitoring, with 42.61% complying with the frequency of blood glucose testing recommended by their physician (Medicare 73.93%, Medicaid 65.51%, private 63.37%)

Conclusion:

Our findings show that despite having access to Internet-capable devices, ACA patients insured are not using the available education sources that allow them to properly self-manage their diabetes. Additionally, these patients are not taking the required precautions to make sure their diabetes is properly controlled. It is necessary that programs targeting these patients understand these behaviors in order to develop future intervention strategies.

Human Kinetic Approach to Improving Conformability in PaQ, a 3-day Wearable Insulin Delivery Device

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Objective:

Adhesive tape conformability can depend on tape-to-device fixation and material stretch properties for body-worn devices such as PaQ (CeQur SA), an insulin delivery device adhered to the abdomen for 3 days, providing continuous subcutaneous insulin infusion. The purpose of this work was to identify an adhesive tape fixation and orientation that improves conformability, emphasizing freedom of movement and security while optimizing adherence around the cannula to maintain insulin delivery.

Method:

Ten people of varying height, weight, and gender were recruited to evaluate the natural stresses imposed on the abdomen during physical activity. Four dots were drawn in a rectangular pattern on the abdomen at a specified distance from the navel. Participants then performed a series of rotational and elongating movements in which dot displacement was measured. Based on these results, a test system was designed to assess conformability by mimicking the shear and stretch experienced by the adhesive tape during normal daily activities. PaQ devices were tested in a crossed design consisting of four fixation methods and two stretch orientations for 1 h, approximating 1,000 cycles of movement. Conformability was assessed by quantifying the nonadhered surface area.

Result:

An optimal combination of fixation method and orientation was determined and compared with a control. The optimal test group exhibited an average adherence loss of only 8%, outperforming the control group, which had an average loss around 25% of total surface area.

Conclusion:

The data from the test system demonstrated that improved conformability can be achieved by optimizing the combination of adhesive tape fixation method and material stretch orientation. Additional studies will be conducted to assess these improvements on human subjects.

Simulation Study on Insulin Sensitivity Factor Changes for Patients with Illness/Stress

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Objective:

The hybrid closed-loop (HCL) system is an integrated system that calculates the insulin dose based on continuous glucose monitor sensor data to achieve glycemic control throughout the day. The HCL system simulation was composed of the HCL algorithm, the NGP pump model, physiology model, blood glucose meter model, and a glucose sensor. The closed-loop algorithm used proportional-integral-derivative controller with insulin feedback, where this algorithm is designed with additional safeguards that includes maximum insulin delivery safeguards and moving window optimized patient-specific parameters so as to mitigate the potential risks of closed-loop control throughout the day and night. Our goal is to investigate the system performance under the circumstances when the patients are either sick or under stress with preprogrammed carbohydrate ratios (user provided carbohydrate ratios).

Method:

We first simulated the reference case, where the gains of insulin sensitivity factor (ISF) are static. Next we simulated the experiment case, where the gains of ISF are dynamic. Our goal is to explore the patients' glucose with various food boluses amounts. We consider the 30/70 case, where the ratios of basal delivery total and food boluses daily delivery total is 30:70, together with 50:50 ratio. In order to implement insulin sensitivity with alternate basal-bolus ratio, the system is required to feature two optimized patient parameters: total daily insulin dose (TDD) and carbohydrate ratio. We use preprogrammed carbohydrate ratios for all three meals for each patient. Next the meal profiles for various basal-bolus ratios can be set as follows. There are no unannounced meals. All the patients have three meals per day and the amounts of meals are identical. More specifically, for 30:70 ratio, breakfast occurred at 7:00 a.m. with an amount of 100 carbohydrates, lunch occurred at 12:00 p.m. with an amount of 120 carbohydrates, and supper occurred at 6:00 p.m. with an amount of 130 carbohydrates. For 50:50 ratio, breakfast occurred at 7:00 a.m. with an amount of 50 carbohydrates, lunch occurred at 12:00 p.m. with an amount of 100 carbohydrates, and supper occurred at 6:00 p.m. with an amount of 100 carbohydrates. $\text{SafeBasal} = \text{TDD}/48$ (2.1), $\text{SafeBasalLow} = \text{TDD}/166$ (2.2), $U_{\max} = \text{TDD}/33$ (2.3), and carbohydrate ratio = $500/\text{TDD}$ (2.4).

Result:

Sensor glucose is high and insulin delivery is insufficient due to U_{\max} limit when patients are sick or under stress.

Conclusion:

Insulin was delivered at the maximum allowable rate, and preprogrammed carbohydrate ratio prevented patients from hyperglycemia when they were recovered from stress/sickness. Future research will focus on discussing relaxing the maximum allowable insulin infusion rate constraints.

Accuracy of Select Wearable Technology for Varying Exercise Modalities and Intensities in Persons with and without Type 1 Diabetes

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Objective:

We examine the accuracy of two wearable devices that will be used in future studies involving the artificial pancreas. The BioHarness by Zephyr and the Metria Armband by Vancive were used during varying exercise intensity ranges plus modalities in persons with and without type 1 diabetes. The variables of interest included heart rate (HR), breathing frequency (BF), and caloric expenditure (EE).

Method:

The subjects (24.4 ± 6.1 years, four males and three females) were outfitted with a Metria, BioHarness, and Polar HR monitor. The subjects completed an incremental to maximal oxygen consumption (VO_2max) protocol twice and were randomly assigned to complete 40 min of continuous aerobic exercise and callisthenic-based circuit, once or twice. Oxygen consumption and BF were measured throughout each exercise session using the indirect calorimetry unit (Cosmed Fitmate or discrete system).

Result:

The results of the incremental to VO_2max protocol were categorized into the following exercise intensity ranges: light-to-moderate, moderate-to-vigorous, and vigorous-to-maximum. Paired *t* test and Bland-Altman analyses were performed. Within all exercise intensities, there were no differences in HR between the BioHarness and Polar monitor ($P = 0.713, 0.347, 0.785$, respectively). Significant differences in BF were observed in both moderate-to-vigorous ($P = 0.01$) and vigorous-to-maximum ($P = 0.000$) exercise intensity ranges between the BioHarness and indirect calorimetry unit. Significant differences were also observed in the derived EE between the indirect calorimetry unit and the Metria during the vigorous-to-maximum exercise intensity range ($P = 0.000$).

Conclusion:

The preliminary findings indicate that the 1) Bioharness HR is accurate at all exercise intensity ranges, 2) Bioharness BF is only valid during light-to-moderate exercise intensities, and 3) Metria provides an acceptable estimation of EE for light-to-moderate and moderate-to-vigorous but not vigorous-to-maximum exercise intensities.

Pilot Study of Oral Insulin Enteric-Coated Soft Capsules Research and Development in Chinese

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Objective:

We study the pharmacodynamics and pharmacokinetics of oral insulin enteric-coated soft capsules and then evaluate the clinical efficacy and safety of capsules in type 2 diabetes patients.

Method:

Twenty healthy volunteers received insulin enteric-coated soft capsules 50 IU or regular insulin 15 IU after a baseline period of 2 h, with hyperinsulinemia euglycemic clamp technique. Glucose infusion rates (GIRs) were determined to calculate pharmacodynamics and pharmacokinetic parameters. Two hundred sixty type 2 diabetes patients were enrolled in a multicenter, randomized, open, parallel-controlled clinical trial. Patients were orally administered with enteric-coated soft capsules ($n = 135$) or subcutaneously injected neutral protamine Hagedorn insulin ($n = 125$) 1 h before breakfast and dinner for 12 weeks. Prior to the trial, at the end of weeks 6 and 12, patients were served a standard test meal. Fasting blood glucose, 2 h postprandial blood glucose, and glycosylated hemoglobin A_{1c} (HbA_{1c}) were tested. Before the end of week 8, patients were followed up every 2 weeks. The dose of trial drugs was titrated to reach the goal of glycemic control based on the blood glucose monitoring results. At the end of week 12, physical and biochemistry examinations were performed the same as before.

Result:

The maximal concentration (C_{\max}) of insulin was 22.1 ± 8.0 and 118.6 ± 25.2 mIU/L (oral versus regular insulin); the time for reaching C_{\max} (T_{\max}) was 225.8 ± 142.2 vs. 115.5 ± 43.4 min. The maximal GIR (GIR_{\max}) was 3.56 ± 0.85 vs. 4.87 ± 1.26 mg·kg⁻¹·min⁻¹; the time for reaching GIR_{\max} ($TGIR_{\max}$) was 166.3 ± 75.9 vs. 148.0 ± 40.8 min. The relative bioavailability and bioefficacy of insulin capsules were 7.42 ± 3.25 and $24.78 \pm 0.08\%$. HbA_{1c} were significantly decreased in both groups ($P < 0.05$; in control group, from 8.42 ± 1.53 to $7.23 \pm 1.17\%$; in capsule group, from 8.39 ± 1.34 to $7.42 \pm 1.00\%$), and the decreasing amplitude of HbA_{1c} in capsule group (0.98 ± 0.94) was remarkably smaller than control group ($1.19 \pm 1.03\%$; $P < 0.05$). Decreasing of HbA_{1c} $\geq 0.5\%$ was considered clinically effective. The effective rate in capsule and control group was 72.22 and 77.87%, respectively ($P = 0.305$). In terms of the percentage of patients achieving HbA_{1c} target recommended by American Diabetes Association ($\leq 7.0\%$) was 38.9 and 45.1% in capsule and control groups, respectively ($P = 0.323$). The incidence of adverse effect was not different in two groups ($P = 0.618$). The satisfaction score was significantly higher in capsule group ($P = 0.000$).

Conclusion:

The action profile of the oral insulin enteric-coated soft capsules is similar to intermediate-acting insulin injection preparation. The difference between relative bioavailability and bioefficacy indicates the oral insulin capsules may mimic physiological procedure of insulin endosecretion. It has similar effectiveness and safety with insulin

Continuous Glucose Monitoring Accuracy Improvement Using the Autocalibration Feature of MiniMed Veo

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Objectives:

The autocalibration feature of the MiniMed Veo system (Medtronic MiniMed Inc., Northridge, CA), allows for the immediate calibration of continuous glucose monitoring sensors based on blood glucose (BG) measurements. The purpose of this analysis is to evaluate the impact of autocalibration on sensor accuracy.

Methods:

CareLink personal data from 6,435 patients worldwide from December 1, 2013, to February 25, 2015, were analyzed. Sensor accuracy was compared between patients who enabled the autocalibration feature 100% of the time (On) versus those who never enabled it (Off) using a Kruskal-Wallis nonparametric test. Sources of inaccuracy were further considered by comparing accuracy with calibration frequency and with the percentage of calibrations performed more than 2 min after a BG reading (delayed calibration).

Results:

Sensors of autocalibration On users ($n = 276$) had a mean absolute relative difference (MARD) value that was 1.52 percentage points less than sensors of autocalibration Off users ($n = 5,567$; $P < 0.001$). Sensor accuracy following delayed calibrations from autocalibration Off users had a 3 percentage point greater MARD as compared with timely calibrations ($P < 0.001$). The median calibration frequency for users with autocalibration On was 4.3/day compared with 3.4/day for autocalibration Off. Patients with any autocalibration use (20–80% of use) had a 0.85 percentage point MARD improvement as compared with patients with autocalibration Off ($P = 0.03$).

Conclusions:

The autocalibration feature, when enabled, significantly improves the sensor accuracy. Furthermore, the frequency of autocalibration use directly correlates to sensor accuracy. Accuracy improvement is primarily associated with immediate calibration and greater calibration frequency. The autocalibration feature allows for both benefits without the burden of additional finger sticks.

Real-World Performance of a Predictive Low-Glucose Management Algorithm

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Objectives:

The MiniMed 640G system includes the SmartGuard feature and the new-generation Enlite sensor. This system allows for the automatic suspension of insulin delivery using a predictive low-glucose management (PLGM) algorithm. We evaluated the real-world implications of routine use of SmartGuard by analyzing sensor data that were voluntarily uploaded to the CareLink personal database (Medtronic MiniMed Inc., Northridge, CA).

Methods:

The PLGM algorithm includes suspend before low, a feature that is triggered when the sensor glucose (SG) value is predicted to reach or fall below a preset low-glucose limit within 30 min. We evaluated biochemical hypo- and hyperglycemia at various thresholds for time intervals in which the feature was enabled versus intervals when it was not.

Results:

The feature was used by 597 people from January 13, 2015, to May 14, 2015 (a total of 12,012 patient-days of use), and resulted in 25,937 pump suspension events (2.2 per patient-day). With respect to hypoglycemia, SG values ≤ 50 mg/dL occurred 0.4% of the time when the feature was enabled versus 0.8% of the time when it was disabled. SG values ≤ 80 mg/dL occurred 5.3% of the time when the feature was enabled versus 7.0% of the time when it was disabled. With respect to hyperglycemia, SG values ≥ 180 mg/dL occurred 31.9% of the time when the feature was enabled versus 33.7% of the time when it was disabled. SG values ≥ 300 mg/dL occurred 3.4% of the time when the feature was enabled versus 3.5% of the time when it was disabled.

Conclusions:

Routine use of the PLGM algorithm and its suspend before low feature appears to lessen severe and moderate hypoglycemia with no detrimental effects on hyperglycemia.

Real-World Assessment of Undetected Glycemic Excursion Events in Type 2 Diabetes

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Objectives:

This study used continuous glucose monitoring (CGM) data from patients with type 2 diabetes to quantify the frequency and severity of glycemic excursions otherwise missed by finger sticks. We also compared excursion frequency between therapy regimens to gauge the potential utility of CGM studies in different populations.

Methods:

This study included noninterventional professional CGM iPro2 data from the CareLink database (Medtronic MiniMed Inc., Northridge, CA). Hypoglycemia (sensor glucose [SG] ≤ 55 mg/dL) and hyperglycemia (SG ≥ 240 mg/dL) event frequency and duration were calculated. Patient recognition of an event was determined by a meter blood glucose (BG) value within ± 15 min of a CGM-detected excursion.

Results:

Data from 99,102 patients and 367,080 patient-days from December 14, 2011, to May 27, 2015, were analyzed. A total of 70,024 hypoglycemic events lasting >20 min (69 events/patient-year) were detected, 74.4% of which were not accompanied by a BG reading. A total of 192,471 hyperglycemic events lasting >2 h (189 events/patient-year) were detected, 40% of which were not accompanied by a BG reading. Insulin users (either multiple daily injection or pump) had lower rates of hypoglycemia than patients treated with oral medications or lifestyle interventions (0.146 vs. 0.158 events/day) and lower rates of hyperglycemia (0.40/day) than either oral medication users (0.43 events/day) or those using lifestyle interventions (0.46 events/day).

Conclusions:

Over 70% of hypoglycemic and 40% of hyperglycemic events were missed by contemporaneous BG measurements in patients with type 2 diabetes. Notably, insulin users had lower rates of glycemic excursions than those treated with lifestyle modification therapy or oral medications. CGM studies provide important additional information for managing type 2 diabetes.

Particle Size Does Not Impact the Pharmacokinetic Response of a Novel Inhaled Human Insulin

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Objective:

Deep lung delivery of inhaled insulin maximizes its systemic absorption. This first-in-human trial investigated the optimal particle size for absorption of Dance 501, an aerosolized liquid human insulin for inhalation (INH).

Method:

Twelve subjects with type 1 diabetes received 50 IU INH using an inhaler on four visits and 6 U subcutaneous insulin lispro (LIS) on a separate visit to assess relative bioavailability (F_{REL}) of INH. The inhaler was configured to generate insulin aerosol particles sized 3.5–4.0 μm (Small), 4.3–4.8 μm (Medium), or 5.0–5.5 μm (Large) during low inspiratory flow. To assess within-subject variability, Medium was used twice. After dosing, subjects consumed a meal and insulin with glucose (pharmacokinetic [PK]/pharmacodynamic [PD]) concentrations measured for up to 8 h.

Result:

Stratified by particle size, the resulting PK/PD parameters (PK: AUC_{INS} , F_{REL} , C_{MAX} , T_{MAX} , onset of appearance and mean residence time [MRT]; PD: ΔAUC_{BG} , ΔBG_{MAX}) for INH were not statistically different from each other. Mean values for F_{REL} were in a range (10–12%) typical for published inhaled insulin data. Within-subject variability was 27.5% for AUC_{0-8h} which is similar to published results for subcutaneous soluble insulin. Compared to LIS, onset of appearance of INH was faster (1.1 ± 0.2 vs. 12.3 ± 6.4 min [mean \pm standard deviation, INH Medium vs. LIS]), C_{MAX} lower (16.7 ± 6.5 vs. 45.2 ± 15.2 $\mu\text{U/mL}$), and duration of exposure quantified by MRT longer (179 ± 17 vs. 103 ± 43 min). INH was well tolerated; no cough and no relevant changes in lung function were observed.

Conclusion:

Inhalation of Dance 501 insulin is safe and results in clear and reproducible PK responses. Small variations in aerosol particle size do not influence the PK/PD response.

Dance 501 Inhaled Human Insulin Has a Dose-Linear Response and Similar Within-Subject Variability as Rapid-Acting Insulin Lispro

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Objective:

This study investigated the pharmacokinetic (PK) and pharmacodynamic (PD) properties of Dance 501, a novel inhaled human insulin liquid formulation (INH) and inhalation device.

Method:

Twenty-four subjects with type 2 diabetes received five INH doses (low [70 IU] ×2, medium [140 IU] ×2, and high [210 IU]) and one equivalent medium dose (18 IU) of subcutaneous insulin lispro (LIS). To determine the response to different formulation strengths, 300 and 900 IU/mL formulations were used for two low-dose INH administrations, while the 900 IU/mL formulation was used for all other INH doses. The medium dose was repeated to determine within-subject variability. PD were investigated during a 12-h euglycemic clamp.

Result:

In comparison with LIS, the medium INH dose was absorbed faster (T_{MAX} 54 ± 31 vs. 89 ± 32 min [mean \pm standard deviation]), resulting in a faster initial effect ($T_{50\%-GIR_{max}}$ 49 ± 30 vs. 61 ± 20 min, where GIR is the glucose infusion rate). Relative bioavailability and biopotency were 12.2 ± 8.1 and $13.6 \pm 5.9\%$. A linear dose response was observed for the primary baseline-corrected PK parameters (AUC_{0-8h} , C_{MAX}) and a dose-dependent increase for the primary PD parameters ($AUC_{GIR0-12h}$, GIR_{MAX}). Within-subject variability was comparable between insulins for AUC_{0-8h} (15.5 vs. 12.0%), C_{MAX} (16.9 vs. 24.5%), and GIR_{MAX} (25.7 vs. 21.4%), but higher with INH for $AUC_{GIR0-12h}$ (29.9 vs. 17.0%). The PK/PD responses of the 300 IU/mL and 900 IU/mL formulation strengths were similar. No safety issues were identified; cough was observed only in 3 out of 462 inhalations.

Conclusion:

In conclusion, Dance 501 inhaled insulin shows promising PK/PD characteristics with rapid absorption and onset of action and may therefore become a clinically meaningful alternative to rapid-acting insulin injectables.

Faster-Acting Insulin Aspart Using Continuous Subcutaneous Insulin Infusion: Earlier Onset of Exposure and Greater Early Pharmacokinetic and Pharmacodynamic Effects than Insulin Aspart

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Objective:

We compare pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart (faster aspart) with insulin aspart (IAsp) in the continuous subcutaneous insulin infusion (CSII) setting. Faster aspart is IAsp in a new formulation with faster initial absorption after subcutaneous injection.

Method:

Patients with type 1 diabetes ($n = 48$, age 46 ± 9 years, HbA_{1c} $7.4 \pm 0.6\%$, diabetes duration 24 ± 12 years [mean \pm standard deviation]) received faster aspart or IAsp as a CSII bolus dose (0.15 U/kg) on top of basal CSII (0.02 U/kg/h) under glucose clamp conditions (ClampArt; target 5.5 mmol/L [100 mg/dL]); 13-h run-in with basal rate, 14-h postbolus dosing) in a randomized, double-blind, crossover trial.

Result:

Faster aspart had earlier onset of exposure compared with IAsp: $t_{50\%C_{max}}$ occurred 11.8 (95% confidence interval, $9.2;14.4$) and t_{max} 25.7 ($17.1;34.3$) min earlier. Early exposure was greater for faster aspart versus IAsp: first 15 min, sevenfold (ratio 7.05 [$3.73;136.57$]); first 30 min, threefold (ratio 2.95 [$2.32;3.73$]); and first hour, 1.5-fold (ratio 1.52 [$1.37;1.69$]). Pharmacodynamic end points (glucose-lowering action) likewise showed earlier onset of action ($t_{50\%GIR_{max}}$ occurred 11.1 [$6.9;15.4$] and $t_{GIR_{max}}$ 18.7 [$3.0;34.4$] min earlier, where GIR is the glucose infusion rate) and greater early action (first 30 min, ratio 2.18 [$1.33;5.04$]; first hour, ratio 1.52 [$1.29;1.83$]) for faster aspart versus IAsp. Total exposure and total glucose-lowering effect were similar for faster aspart and IAsp. Both treatments were well tolerated, with no infusion-site reactions reported.

Conclusion:

Faster aspart showed faster onset and greater early exposure and action versus IAsp in CSII. These improvements were more pronounced than those previously reported for subcutaneous injection of faster aspart.

Demonstration of Very High Compliance and HbA_{1c} Benefit of a Long-Term Implantable Glucose Sensor in the PRECISE Study

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Objective:

The objective of this analysis is to evaluate the HbA_{1c} benefit of long-term continuous utilization of an implantable, fluorescent-transducer-based continuous glucose monitoring (CGM) system.

Method:

An open-label, outpatient, multisite study with unblinded CGM is ongoing in 81 patients with type 1 or type 2 diabetes. An interim analysis was performed on a 44-subject cohort completing 90 days of CGM. The sensor was implanted in the upper arm and is in synchronous communication with a smartphone application via a body-worn smart transmitter and Bluetooth Low Energy. The application displays the current glucose value, the rate and direction of glucose change, and graphical trends, along with alerts for impending hypoglycemia or hyperglycemia. HbA_{1c} was measured at baseline and at day 90. The subject population's changes in HbA_{1c} were evaluated as well as their overall wear compliance with the CGM system.

Result:

Compliance with CGM system wear was high, with a median wear time of 23.5 h/day with 25th percentile also greater than 23 h/day. HbA_{1c} levels decreased on average from 7.8% (standard deviation [SD] = 1.0) at sensor insertion to 7.3% (SD = 0.8) at day 90. A total of 29 subjects of the 44 had a reduction in HbA_{1c}, and 8 subjects had a reduction of more than a 1%.

Conclusion:

Clinical data from a 90-day pivotal study of an implantable fluorescence-based CGM system has demonstrated a high level of compliance for the full 3-month duration and a cumulative benefit in HbA_{1c} levels in the preliminary study population.