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Bayesian Calibration Algorithm for Next Generation Dexcom Sensor: 8.4% MARD with One Calibration Every 4 Days

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Objective:
In most continuous glucose monitoring (CGM) devices, the electrical signal measured by the sensor is transformed to glucose concentration by a calibration procedure, which is periodically updated by self-monitoring of blood glucose (SMBG) measurements, usually twice a day. Recently, we developed and validated an online Bayesian calibration algorithm that is able to reduce the frequency of calibrations to one every four days without worsening the accuracy of the Dexcom G4 Platinum sensor. Here, we assess the performance of our algorithm when applied to a next-generation Dexcom CGM sensor prototype.

Method:
The data set consisted of 48 subjects with diabetes monitored for 10 days with a next-generation Dexcom CGM sensor prototype. We applied the new Bayesian calibration algorithm on raw signals by simulating an online setting where we test progressively fewer calibration scenarios (i.e., one-per-day, one-every-two-days, and one-every-four-days, respectively). Accuracy of the calibrated glycemic profiles was assessed by comparison to blood glucose reference values using: (1) mean absolute relative difference (MARD), (2) percentage of readings within 20mg/dL or 20% of the reference glucose value, and (3) percentage of data within the A-zone of the Clarke Error Grid (CEG-A).

Result:
The median MARD for one calibration per day and one calibration every two days calibration scenarios is 8.2%. The median MARD for one calibration every four days is 8.4%. All three scenarios had median values of 100% of data within 20mg/dL or 20% of the reference glucose value and >95% of data within CEG-A.

Conclusion:
The new Bayesian calibration algorithm performs well on CGM data acquired by a next-generation Dexcom sensor prototype independent of the frequency of calibrations. The performance of only three calibrations over the 10 days of sensor's functional life (8.4% MARD) is better than that of Dexcom G5 Mobile sensor (9.0% MARD), which is calibrated twice a day.

Acetaminophen Interference on ISF Based Glucose Monitoring Systems

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Objective:
The objective of this study was to evaluate the interference from acetaminophen on interstitial fluid (ISF)-based sensor technology under simulated use conditions.

Method:
Acetaminophen is electrochemically active and oxidizes at around 400mV under physiological conditions. Three sensor based glucose monitoring systems were evaluated under simulated use conditions for interference from acetaminophen. Two sensors of each type were placed in a flow system containing glucose in a phosphate-buffered saline (PBS) solution at pH 7.4. The concentration of glucose was adjusted to obtain a glucose reading of about 90mg/dL on the FreeStyle Libre. The Dexcom G5, and Medtronic Enlite sensors were calibrated to the glucose result from the FreeStyle Libre system to match the baseline glucose. Acetaminophen was added to the glucose solution in increments of 5mg/dL concentration to a maximum of 20mg/dL – the concentration recommended by Clinical & Laboratory Standards Institute guidance EP7-A2.

Result:
The sensor signal of FreeStyle Libre did not increase with successive addition of acetaminophen. Both Dexcom G5 and Medtronic Enlite sensors showed an increase of about 125mg/dL glucose upon the first addition of 5mg/dL acetaminophen. When the acetaminophen concentration reached 15mg/dL, the G5 sensors reported 'HI' while the Enlite sensors reporting glucose results well above 300mg/dL. These observations are consistent with published clinical data for these systems.

Conclusion:
Comparing to wired enzyme technology-based FreeStyle Libre system, the Dexcom G5 and Medtronic Elite systems use higher voltages required for the oxidation of hydrogen peroxide which makes them susceptible to interference from common electroactive compounds such as acetaminophen. These sensors could show erroneously elevated results even at therapeutic levels of acetaminophen resulting in incorrect treatment decisions.

Evaluation of Patient Acceptability of the Gocap Insulin Pen Smart Cap Dose Tracking Device

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Objective:
To evaluate patient acceptability of an insulin pen smart cap used alongside a connected blood glucose meter.

Method:
Eligible patients recruited from a diabetes specialty clinic had either type 1 (T1D) or type 2 (T2D) diabetes, were 18 years or older, used Lantus SoloStar insulin, and were English speaking. Participants received a Gocap insulin pen smart cap and an AgaMatrix Wavesense Jazz 2 glucose meter. Subjects were asked to transfer insulin dose and self-monitoring of blood glucose (SMBG) data using a smartphone application via Bluetooth for longitudinal tracking. After 1+ month, focus groups and semi-structured phone interviews were conducted and transcribed verbatim. Resulting transcripts were qualitatively analyzed by two investigators using an *a priori* code list generated from the Technology Acceptance Model. Survey data were collected to assess demographics, history of technology use, and perceptions of ease of use and usefulness of the devices.

Result:
Patients with T1D (n=2) and T2D (n=18) participated in the study. The majority of participants agreed the Gocap was easy to use (n=16) and useful in the management of their diabetes (n=15). Several participants reported appreciating the automatic data uploading, the convenience of not manually tracking their insulin doses and SMBG recordings, and the easy access they and their providers had to the longitudinal data. Identified areas of improvement included greater battery life of the Gocap and additional compatibility with iOS smartphones.

Conclusion:
The majority of participants in this study reported high acceptability of the Gocap device. Identifying patients who would benefit most from innovative connected health devices, and incorporating this information into patient care management plans, is necessary to improve diabetes-related health outcomes.

Optimal Injection Time of Insulin to Regulate Postprandial Glucose in Type I Diabetes *In Silico* with Pramlintide at Meals

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Objective:
The objective is to maintain plasma glucose in type 1 diabetes within normal glycemic ranges using a combination therapy: pramlintide administered prior to a meal and insulin administered at optimal time after a meal. The secondary objective is to demonstrate that plasma glucose is poorly controlled when following the FDA's recommendation of administering 50% of the insulin dosage either 15 minutes before, or during, the meal when using pramlintide.

Method:
A pramlintide pharmacokinetic/pharmacodynamics (PKPD) *in silico* model was used to test for optimization (Ramkissoon *et al,* 2014). Mismatches in meal size, glycemic index, and patient pramlintide sensitivity were investigated. Model results were compared to simulated FDA recommendations. In cases where plasma glucose was easily maintained within normal glycemic range, insulin amounts were reduced.

Result:
The results are outstanding only for patients with low pramlintide sensitivity at 30 mcg of pramlintide with glucose slightly exceeding the normal glycemic range. All other dosages of pramlintide (including 60 and 90 mcg) were associated with glucose within the normal glycemic range for an 82.5g meal. Pramlintide sensitivities at 90 mcg allow for a reduction of insulin dose. In addition, a high correlation was found between meal dynamics, patient sensitivity, and pramlintide dosage as well as an optimal time for the postprandial insulin bolus.

Conclusion:
The FDA's recommendation does reduce the incidence of hypoglycemia but it is a poor choice for blood glucose regulation and is worse than using insulin by itself. Simulations using the optimal insulin injection times with pramlintide at the meal illustrate better control by maintaining normal glycemic ranges in all but one case. Higher pramlintide doses/sensitivities allow for reduced insulin dosages.

Facilitators and Barriers for Uptake of Intra-Peritoneal Automated Insulin Delivery Systems

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Objective:
To explore the facilitators and barriers for uptake of intraperitoneal (IP) automated insulin delivery systems by conducting focus groups and a large-scale survey to determine the potential effect of this new technology on the lives of people with type 1 diabetes.

Method:
Focus group and large-scale survey data were collected from participants with type 1 diabetes. Questions focused on acceptability, usability, trust, influence of past experience, benefits and barriers, cost/benefit, financing the system, and physical experience expectations.

Result:
Thirty-six participants completed the pre-focus group questionnaires, of which twenty-one took part in focus groups and twenty-four completed post-focus group questionnaires. Knowledge of the ThinPump was initially low however this improved considerably in post-focus group questionnaire data. There was enthusiasm for the potential of the device in terms of improved glycemic control and reduced burden of living with type 1 diabetes. Specific benefits were: reduced visibility of disease state, the closed loop facility and ability to switch between closed and open loop modes, and reduced intrusion of diabetes in daily life. Predicted downsides were availability of healthcare professionals to support, scarring from surgery, and potential connectivity issues. A total of 581 participants completed the survey: 91% of whom would try the ThinPump, 90.9% stating it would improve quality of life, reduce the amount of effort required for diabetes (90.9%), would help manage diabetes (87.9%), prevent hypoglycemia (94.9%), and prevent hyperglycemia (95.2%).

Conclusion:
There was overall enthusiasm for the ThinPump device with high expectations. Most participants expressed a desire to use the device if it were available. Whether that translates into uptake remains to be seen.

Considering Blood Dilution Improves the Precision of Continuous Whole Blood Glucose (BG) Measurements

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Objective:
Continuous measurement of blood glucose (BG) concentrations is essential for automated glucose clamps; however, the measurement result might be affected by changes in blood dilution. Dilution may vary due to small, random variations at the mixing spot (e.g. caused by hand movements or pump pulsations) or due to changes in the tubing over time. ClampArt, a modern automated clamp device, measures both BG and blood dilution simultaneously. We compared the quality of ClampArt's continuous BG measurements with and without correction of blood dilution.

Method:
Retrospective analysis of BG measurements during a glucose clamp study (two-way cross-over study with single doses of 0.4 or 0.6 U/kg of insulin glargine U300 or insulin degludec in 48 patients with type 1 diabetes - in total 2,542 hours of operation). The BG-values during the clamp (corrected for the actual blood dilution) were compared with re-calculated values using a fixed blood dilution factor obtained at the start of each clamp. Clamp quality parameters precision (coefficient of variation), accuracy (mean absolute relative difference, MARD, from reference BG, calculated from 7,736 paired data-points) and control deviation (mean difference from target level) for both settings were calculated.

Result:
Clamp quality parameters substantially deteriorated when blood dilution was not considered: Mean precision when considering blood dilution was 3.7 ± 1.3 mg/dl versus 9.6 ± 3.6 mg/dl using a fixed dilution. Likewise, control deviation increased from 0.2 ± 0.2 mg/dl to -2.6 ± 4.2 mg/dl and accuracy from 4.1 ± 0.8% to 8.1 ± 2.9%.

Conclusion:
Correcting the continuous blood glucose measurements of ClampArt for blood dilution significantly increases measurement (and therefore clamp) quality.

Coordinated Insulin and Carbohydrates Delivery to Deal with Announced and Unannounced Exercise

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Objective:
The objective is the development of a specific carbohydrate controller that can help minimize the risk of hypoglycemia, specifically during and after exercising. This controller works alongside a uni-hormonal insulin based controller.

Method:
Based on a previously developed uni-hormonal insulin controller at our research laboratory, we developed a second feedback control loop for suggesting carbohydrates. Using a Matlab simulator that includes circadian variability, exercise, variability in meals, and noise in the sensor and actuator, we performed '*in silico*' simulations to challenge the new controller.

Result:
The preliminary results against a virtual cohort of ten type 1 diabetic patients show that, by using the carbohydrates controller, hypoglycemia events are reduced. Especially, the risk of hypoglycemia during and after exercise is minimized, provided the patient eats the carbohydrates suggested by the controller. The approach was compared to the uni-hormonal controller against announced and unannounced exercise sessions. Mean continuous glucose monitor (CGM) glucose was (131.23 mg/dl, 126.42 mg/dl) for the uni-hormonal with announced/unannounced exercise vs. (130.66 mg/dl, 129.94 mg/dl) for the carbohydrates controller with announced/unannounced exercise, percent time in range (70-180 mg/dl) was (92.02%, 90.50%) vs. (93.66%, 92.52%), percent time above 180 mg/dl was (6.11%, 5.68%) vs. (6.02%, 6.51%), percent time under 70 mg/dl was (1.87%, 3.72%) vs. (0.32%, 0.97%) and the number of hypoglycemic events were reduced (63, 116) vs. (18, 42).

Conclusion:
The use of the newly developed carbohydrates controller widens the operational range of the insulin controller, ensuring that glucose control is optimized without increasing the risk of hypoglycemia or hyperglycemia - even when the system is challenged against postprandial periods or exercise sessions.

In Silico Framework for Testing and Comparing Bolus Calculator Optimization Techniques Based on CGM Sensors

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Objective:
Bolus calculators (BC) are software tools that help type 1 diabetes (T1D) patients compute insulin bolus doses. BC are based on patient-specific parameters, like the carb-ratio (CR), usually tuned by physicians. Methods that exploit continuous glucose monitoring (CGM) data to optimize these parameters have been developed, but a framework to assess and compare their performance is still missing. The aim of this study is to develop a simulation tool for the assessment and design of BC parameter optimization techniques.

Method:
The proposed framework is based on the simulator of Vettoretti et al (2ndrev. IEEE TBME, 2017) which expands the UVa/Padova T1D model by including models of sensors error and patient behavior. Here, we introduced a module using CGM data to calculate indices of post-prandial glycemic control, which are used to implement CR-optimization techniques. As a case study, we implemented the run-to-run technique of Herrero et al. (IEEE JBHI, 2015) in which CR is adjusted according to the postprandial blood glucose (BG) area-under-the-curve, and tested possible modifications to the CR-optimization rule based on postprandial max/min/mean glucose, glucose variability, and time spent in hypo/hyperglycemia. The original technique and its modifications were simulated in 100 virtual patients over a four-month scenario and compared to standard performance metrics (e.g. time in hypo/hyperglycemia and risk indices).

Result:
The new framework allowed for testing the effectiveness of the original and modified CR-optimization rules, using the same individuals and scenarios, highlighting the pros and cons of their use, and providing evidence where/when one outperforms the others.

Conclusion:
We built a new simulation tool to test techniques for BC parameter optimization. In a case study, we showed that the tool can be used to design new algorithms and can provide evidence of effectiveness *in silico*.

Extended Operational Stability in a Combined Subcutaneous Insulin Cannula & Glucose Sensor

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Objective:
To determine (A) if subcutaneous glucose sensing is possible at the site of insulin delivery, and (B) if operational stability can be extended by increasing electrostatic attraction between layers.

Method:
For GEN1 devices, we compared glucose oxidase (GOX) sensors on rigid sensing cannulas made with and without an osmium-based redox mediator (RM). For GEN2, we fabricated sensors on flexible cannulas and increased the use of electrostatic attraction in order to immobilize the sensing layers. Devices were studied repeatedly *in vitro* and *in vivo* for 1-7 day periods in six pigs during administration of aspart insulin or saline.

Result:
During *in vivo* studies, immediately following insulin boluses at euglycemia, we saw large positive spikes that suggested marked hyperglycemia in the sensors without RM. Additional work demonstrated the cause to be oxidation of insulin excipients. No RM device showed such artifacts. GEN1 and GEN2 devices were tested *in vitro* before and after immersion in saline. For GEN1 devices, the loss of sensitivity to glucose averaged 40% after 7 days and 53% after 14 days. GEN2 devices, with a moderate level of electrostatic attraction, lost 10% after 7 days and 12% after 14 days. The best stability was seen in the GEN2 devices with a high level of electrostatic attraction. Such devices lost no sensitivity after being immersed for 7 days or 14 days. GEN2 sensing cannulas were also studied at two glucose levels in pigs over 7 days, during which time there was no loss of sensitivity.

Conclusion:
The use of a specialized RM-based chemistry avoids the positive-going sensing artifacts typical of standard peroxide-measuring GOX chemistry. GEN2 sensors with increased electrostatic attractive forces were stable *in vitro* and *in vivo*.

Real World Assessment of Healthcare Provider Experience with the MiniMed™ 670G Hybrid Closed-Loop System

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Objective:
This study evaluated real world healthcare provider (HCP) experience with the MiniMed 670G System, the world's first hybrid closed-loop system. The goal of the study was to quantitatively assess the system during a Customer Training Phase (CTP), wherein a limited number of patients were exposed to the product before commercial launch.

Method:
Prescribing HCPs were asked to complete an online survey (5-point scale) after their patients completed an 8-week use of the MiniMed 670G system, to quantitatively measure their experience. A total of 64 HCPs evaluated their experience based on: satisfaction, meeting expectations, onboarding, training, and clinical benefits of the system. Results were based on data from 74% of physicians and 26% of nurse practitioners, representing 237 of the 670 patients, respectively, in the CTP.

Result:
After 8 weeks, 100% of respondents rated the MiniMed 670G system as better than any other therapy that they have prescribed for their patients. There were 88% who expressed satisfaction with the MiniMed 670G System and 87% who were satisfied with the Guardian Sensor 3 sensor. Nearly all HCPs (96%) saw a noticeable improvement in patient outcomes when compared to their previous therapy, making it easier for them to manage their patients (91%). A majority of HCPs (92%) agreed that the onboarding experience and training effort were easy and reasonable and 96% thought the CareLink™ diabetes management software reports included sufficient data needed to make therapy adjustments.

Conclusion:
Most prescribing HCPs reported a high level of satisfaction with the MiniMed 670G system and the Guardian Sensor 3 sensor and most believed that the device improved patient outcomes and was the best available therapy for their patients.

Real World Assessment of Patient Experience with the MiniMed™ 670G Hybrid Closed-Loop System

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Objective:
This study evaluated patients' real-world experience with the MiniMed 670G system, the world's first hybrid closed-loop system. The goal was to quantitatively assess the system during a Customer Training Phase (CTP), wherein a limited number of patients were exposed to the product before commercial launch.

Method:
Patients were asked to complete a series of Medtronic-developed surveys online — before using the system and at 1, 2, 3 and 8 weeks after starting to use the system - in order to quantitatively measure their experience. A total of 411 patients, out of 670 invited, evaluated their experience based on: product and therapy satisfaction, training, user burden, and perceived benefits of the system.

Result:
After 8 weeks, patients reported significant reduction in concerns with variability in glucose levels (75% reduction), frequent lows (75% reduction), long-term complications due to diabetes (71% reduction), and inability to consistently control high blood sugar (67% reduction). All changes were statistically significant at $p<0.05$. Patients reported a reduction in burden of managing lows and highs ($p<0.05$), in addition to a reduced burden with carb counting. Overall, 81% expressed satisfaction with the MiniMed 670G system, while 75% were satisfied with the Guardian Sensor 3 sensor, and 94% reported satisfaction with system training. Key benefits highlighted by patients included: managing lows at night (82%), time within range (75%), decisions related to diabetes management (72%), reducing daytime lows (71%) and reducing overnight highs (67%).

Conclusion:
The survey demonstrated that patients in a CTP had high satisfaction with training and system performance. This was in large part due to the ability of the MiniMed 670G system to improve glycemic control and reduce the burden of managing diabetes.

Does Body Mass Index Affect Performance of a Long-term Implantable Continuous Glucose Monitoring System?

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Introduction:
A new, long-term continuous glucose monitoring (CGM) system, Eversense®, consisting of a fluorescence-based glucose sensor implanted in the upper arm, wearable smart transmitter, and smartphone app has been developed. A blinded, prospective, single-arm PRECISE II study was performed to investigate the CGM system's performance over a 90-day period. YSI measurements were taken as reference glucose during four in-clinic accuracy sessions. The analysis presented here investigates whether body mass index (BMI) had an impact on the CGM performance.

Method:
Eighty-two subjects in the primary effectiveness analysis population were included in this analysis. Subjects were divided into three groups based on their BMI values: normal or underweight (BMI < 25 kg/m^2), overweight (25 $kg/m^2 \leq$ BMI < 30 kg/m^2), and obese (BMI $\geq$ 30 kg/m^2). Mean absolute relative difference (MARD), percent within 20 mg/dL/20% of the reference glucose, and percent of points within the Clarke Error Grid A Zone were calculated as CGM performance metrics.

Result:
Among the 82 subjects, 22 (27%) were normal or underweight, 26 (32%) were overweight, and 34 (41%) were obese. The MARD ranged from 9.8% to 8.1%, percent within 20 mg/dL/20% of the reference glucose ranged from 92.4% to 94.2%, and percent of points in Clarke Error Grid A Zone ranged from 91.5% to 93.7%, respectively, among the three BMI categories. The difference in MARD between groups was not statistically significant (p = 0.10, repeated measures GEE model). Results are presented in the table below.

BMI (kg/m^2)	Number of Subjects	MARD (95% CI)	Percent within 20/20% Reference*	Clarke Error Grid A Zone
< 25	22	9.8% (8.5% - 10.7%)	92.4%	91.5%
[25, 30)	26	8.7% (7.5% - 9.9%)	93.1%	92.8%
>= 30	34	8.1% (7.3% - 8.9%)	94.2%	93.7%

*For YSI less than or equal to 80 mg/dL, the absolute difference in mg/dL was calculated; for YSI more than 80 mg/dL, the absolute relative difference in % was calculated

Conclusion:
The Eversense CGM system was accurate across the range of BMI categories studied, and no statistically significant differences in CGM performance were observed.

Open Artificial Pancreas System Improved Glycemic Control and Quality of Life in Patients with Type 1 Diabetes

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Objective:
Artificial pancreas combines continuous glucose monitoring (CGM) with insulin pump by using a control algorithm to direct insulin delivery. Although several control algorithms have been developed, control algorithms are beyond the reach of most of diabetes patients in need. The Open Artificial Pancreas System project (openAPS) is an open control algorithm for artificial pancreas, which is widely available to worldwide to patients with type 1 diabetes. Here, we present several interesting clinical experiences using openAPS.

Method:
Ten type 1 diabetes patients using the openAPS, a CGM (Dexcom), and an insulin pump (Dana R) were studied. Normal glycemic range was set to 80~180 mg/dl.

Result:
Median age was 9.5 years and 5 patients were male. Median openAPS duration of use was 30 days. By using openAPS, CGM analysis showed a significant decrease in A1C (6.8 ± 1.1 to 6.2 ± 0.7, p= 0.007), a significant increase in percent time in normal glycemic range (65.1 ± 25.1% to 82.8 ± 8.5%, p= 0.019), a significant decrease in percent time in high glycemic range (24.5 ± 16.8% to 12.3 ± 8.6%, p=0.002) and no change in percent time in low glycemic range (5.4 ± 3.2% to 4.9 ± 4.1%, p= 0.702). OpenAPS offered patients much greater flexibility with food choices and meal timing without compromising blood glucose control. Before openAPS, the guardians of the patients had to stay up all night to measure blood glucose frequently and give food in case of low glucose. However, after openAPS, there was no need for the night watch. There was no significant side effects due to openAPS.

Conclusion:
Open source artificial pancreas system improved the glycemic control and the quality of life of patients with type 1 diabetes.

Use of Remote Monitoring to Retain Highly Qualified US Army Soldiers with Type 1 Diabetes Mellitus

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Objective:
Retention of highly trained soldiers with type 1 diabetes would be beneficial to the military. The purpose of this study is to analyze the outcomes of active duty soldiers newly diagnosed with type 1 diabetes treated with remote monitoring technologies.

Method:
This retrospective study involved the last 50 consecutive soldiers with newly diagnosed type 1 diabetes seen in the diabetes clinic at Womack Army Medical Center, Fort Bragg, NC. All soldiers were immediately introduced to advanced technologies and were placed on an insulin pump and/or sensor. Expert technical training was provided by a certified diabetes educator/pump trainer. Telehealth was used immediately upon diagnosis and almost exclusively after Medical Evaluation Board (MEB) or a fitness for duty evaluation was initiated. A1C was obtained at diagnosis, MEB referral, and every three months until separation from the military and/or relocation.

Result:
The average age was 29.3 years; all but two were men. Mean A1C at diagnosis, initiation of MEB, and most recent visit was 11.1, 6.7, and 6.6, respectively. The mean A1C after diagnosis was 6.6. The mean time between diagnosis and MEB, and MEB to last follow-up was 8.5 and 20.2 months, respectively. All 18 soldiers who desired to stay on active duty were retained. The only adverse events were hypoglycemia requiring assistance (n=1) and DKA (n=2, one related to drug abuse).

Conclusion:
Through advanced technology and remote monitoring, soldiers with type 1 diabetes have excellent glucose control and reasonable safety profiles. These data support retention of highly motivated soldiers with type 1 diabetes.

Performance of the Guardian™ Sensor 3 Sensor at Abdomen and Buttock Locations, in Youth Aged 2-18 Years

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Objective: Excellent Guardian Sensor 3 sensor performance has been demonstrated in adults with diabetes (Christiansen et al., *Diabetes Technol. Ther.*, in Press). Sensor performance in children and adolescents with T1D, when sensors were inserted in the abdomen or buttock, was evaluated.

Method: Participants aged 2-18yrs (n=145) with T1D for ≥1yr were enrolled at 11 U.S. sites and underwent 6-hour frequent sample testing on day 1, 3 or 7 post-sensor insertion, where sensor glucose values were compared to YSI plasma reference or fingerstick blood glucose reference. Participants wore two sensors in the abdomen and/or buttock. Sensors were connected to a transmitter paired with a Guardian Connect (GC) system application on a mobile device or a glucose sensor recorder (GSR) for sensor-integrated pump systems. Accuracy (overall absolute relative difference, ARD) between sensor and reference values, based on minimum system-required calibrations; within ±20% or ±20mg/dL; and sensor life hours (hrs) for abdomen and buttock sites, were evaluated.

Result: Overall mean ARD±SD (number of paired points, median ARD) for GC abdomen and buttock sensors was 11.2±11.1% (1811, 8.6%) and 10.4±9.9% (1291, 7.6%), respectively; and accuracy for GSR sensors was 11.7±11.7% (1028, 8.6%) and 10.7±9.8% (1596,8.1%), respectively. Overall GC %20/20mg/dL agreement for sensors was 87.2% and 88.7%, respectively; and that for GSR sensors was 84.8% and 87.9%, respectively. The GC abdomen and buttock median of sensor life hours (number of sensors) were 138.9hrs (95) and 159.2hrs (66), respectively; and those for GSR sensors were 115.0hrs (56) and 160.2hrs (74), respectively.

Conclusion: The Guardian Sensor 3 sensor performed well at buttock and abdomen sites in youth with T1D, suggesting that it can be used in automated insulin pump and standalone systems.

Project ECHO: Expanding Access to Diabetes Care in Medically Underserved Communities through Telementoring

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Objective:
Nationwide and worldwide increases in diabetes prevalence in the setting of limited medical resources have prompted international interest in innovative healthcare delivery models. The ECHO model is a "telementoring" program which utilizes widely available videoconferencing technology to disseminate scarce specialized disease management knowledge to healthcare teams in underserved communities. We recently applied the ECHO model to improve health outcomes of patients with complex diabetes living in rural New Mexico.

Method:
We developed the "Endo ECHO" program which utilizes the hub-and-spoke ECHO model to partner with primary care providers (PCPs) and diabetes focused community health workers (CHWs) at 10 federally-qualified health centers across New Mexico. The rural teams participate in the Endocrinology TeleECHO Clinic consisting of a multidisciplinary team that includes a certified diabetes educator (CDE). The Endo ECHO CHWs also receive additional intensive telementoring from the CDE and a CHW Trainer independent of PCPs. Using guided practice and case based learning, videoconferencing "knowledge networks" have developed expertise in diabetes self-management support. CHWs are trained extensively in motivating behavior change, the AADE 7 self-care behaviors, health coaching, and providing social support. This 3-year, prospective case-control cohort design will evaluate health outcomes as well as cost-effectiveness associated with the Endo ECHO intervention.

Result:
Endo ECHO is an implementation of an innovative healthcare delivery model which builds capacity for diabetes self-management education in medically underserved communities through force multiplication.

Conclusion:
The current study design will demonstrate whether, and to what extent, Endo ECHO improves health outcomes for patients with complex diabetes living in rural New Mexico, and will serve as proof-of-concept for academic medical centers wishing to replicate the model.

A Non-Invasive Fingertip-mounted Device to Measure Multiple Physiological Bio-Parameters for Disease Management Improvement

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Background:
The MTX device (Cnoga Medical Ltd., Cesarea, Israel) is a novel, non-invasive, fingertip-mounted device, designed to measure a wide range of physiological bio-parameters without the need to take painful capillary or venous invasive blood samples. The technology is based on tissue photography analysis of the fingertip capillaries by means of complex mathematical algorithms. The MTX device can analyze more than 14 different bio-parameters within seconds without requiring a prior calibration.

Method:
In a standardized meal-study, 36 participants (15 healthy subjects, 6 type 1 diabetes and 15 type 2 diabetes patients, 18 female, age: 49±18 yrs.) ingested a standardized meal and non-invasive measurements of blood pressure, pulse, hemoglobin, hematocrit, and pO2 were performed by means of the MTX device at time-points 0, 60, 120, and 180 min. Reference values were obtained from a standard intensive care unit patient monitor (EDAN iM8) and by means of standard laboratory tests of venous blood samples, if applicable. The results were compared by common standardized statistical methods.

Result:
The use of the MTX device for hypertension assessment required the selection of a specific operational algorithm, which considered the physical anatomical condition of the patient ("virtual arm-cuff"). When properly selected, there was good agreement between the MTX results and the reference results (mean values: MTX: 119±19/75±11 mmHg vs. reference: 124±16/72±10 mmHg, n.s.; median: 115/75 mmHg vs. 123/72 mmHg). Mean heart rates were comparable (71±11 beats/min vs. 72±11beats/min). Acceptable agreement was also seen for pO2 (97±3 % vs. 96±3%, median: 97% vs. 97%), Hb (13.6±2.1 g/L vs. 13.6±1.2 g/L, median: 13.5 g/L vs. 13.6 g/L), and hematocrit (40.2±5.9 % vs. 41.8±3.5 %, median: 39.5 % vs. 41.5 %)

Conclusion:
In our experimental study, the MTX device showed acceptable agreement with the respective reference methods for six analyzed parameters. Combining the device with mobile application and cloud-based services can provide health care professionals and organizations with reliable access to medical data for better disease management thus enabling ongoing remote monitoring.

Leveraging Modeling and Simulation in the Development of the Bigfoot Biomedical Automated Insulin Delivery System

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Objective:
To compare anticipated performance of the Bigfoot automated insulin delivery system from modeling and simulation (MS) completed prior to trial conduct with performance of the system in ten adults and ten children (≥7 to <18) with type 1 diabetes over 48 hours of use.

In this trial, the Bigfoot system employed a model predictive control algorithm residing on a pump connected to a Dexcom G5® sensor to adjust basal insulin delivery and to retrospectively individualize insulin delivery parameters including basal rates, carbohydrate ratios, insulin sensitivity factors, and glucose targets.

Method:
Prior to clinical trial conduct, Bigfoot used simulations to evaluate algorithm candidates, tune parameters, and predict performance across a range of conditions. Simulations on the final algorithm assessed anticipated performance in a trial that included omission of a meal insulin dose, an increased meal insulin dose, and exercise challenges. The system was subsequently evaluated in a safety and feasibility trial conducted in a clinical research center in participants 10 to 57 years of age.

Result:
During the trial, automation was on ≥99% of the time for all participants; 20/20 participants completed both meal challenges and 19/20 participants completed the exercise challenge. CGM glucose value results: overall arithmetic mean/standard deviation was 164±51 mg/dL (MS predicted 164±57 mg/dL), 65% were [70-180] mg/dL (MS predicted 68%), 0.9% were <70 mg/dL (MS predicted 1%) and 34% were >180 mg/dL (MS predicted 31%).

Conclusion:
Results of the prospective modeling and simulations very closely matched performance during the trial providing validation of the Bigfoot simulation approach. Further, the results support use of modeling and simulation to complement clinical trial development and provide insights into anticipated trial and real world outcomes.

Acknowledgments:
The team at Bigfoot Biomedical, Inc. wishes to acknowledge and thank the clinical trial participants, Bruce Buckingham, MD and the research team at Stanford University, Department of Pediatric Endocrinology, Paul Wadwa, MD and the research team at The Barbara Davis Center for Childhood Diabetes, and Jordan Pinsker, MD and the research team at The William Sansum Diabetes Center, Roy Beck, MD, PhD and The Jaeb Center for Health Research, ProSciento, Inc. (formerly Profil Institute for Clinical Research, Inc.), AgaMatrix, Inc. , Dexcom, Inc. and Unomedical A/S.

Histology of Subcutaneous Tissue Surrounding Commercial Stainless Steel and Teflon Continuous Subcutaneous Insulin Infusion (CSII) Sets in Ambulatory Swine

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Objective:
Patients managing their type 1 diabetes with an insulin pump are required to insert a new continuous subcutaneous insulin infusion (CSII) set every 2-3 days to ensure safe and effective glycemic control. A pilot study was performed to better understand the tissue response of commercial CSII sets with Teflon catheters (Inset, Unomedical) versus sets with stainless steel needles (Contact Detach, Unomedical) when implanted in soft adipose tissue of ambulatory swine for up to 7 days.

Method:
CSII sets with Teflon catheters or stainless-steel needles were implanted within abdominal subcutaneous tissue of swine for up to 7 days. CSII sets were inserted 7 days, 5 days, 3 days, 8 hours, and 10 minutes prior to surgical excision. Insulin lispro (U-10) was continuously infused through the catheters (5uL/hr) using insulin pumps during wear time. CSII sets and the surrounding tissue were excised and immediately frozen. Tissue histology surrounding each Teflon catheter or steel needle was analyzed using hematoxylin and eosin (H&E) and Trichrome stains.

Result:
Catheter insertions initiated an acute inflammatory response and a layer of inflammatory tissue formed around the cannula, becoming thicker, denser, and more continuous over time. Tissue damage and local inflammation were more extensive in specimens with stainless-steel needles compared to Teflon catheters.

Conclusion:
Though stainless-steel needles were less susceptible to kinking and occlusions, they elicited a more severe tissue response surrounding the insertion site, which may interfere with insulin diffusion and absorption into the circulation. Results from this study provide information pertaining to biocompatibility and the acute inflammatory response that may cause insulin absorption variability and help guide the development of more effective insulin infusion catheters.

STAR-GRYPHON in the Neonatal ICU: 5 Years of Safe, Successful Glycemic Control

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Objective:
Hyperglycemia is a common complication of stress and prematurity in very/extremely premature infants in the neonatal ICU (NICU) and is associated with increased morbidity and mortality. This study evaluates 5 years of STAR-GRYPHON, a model-based insulin-only glycemic control protocol for the NICU, as a standard of care in Christchurch Women's Hospital.

Method:
STAR-GRYPHON uses a physiological model to estimate patient-specific, time-varying insulin sensitivity (SI). Stochastic models forecast likely future changes in SI, and thus a distribution of likely blood glucose (BG) outcomes for any insulin treatment. STAR-GRYPHON optimizes insulin dose so BG outcomes overlap the 80-145mg/dL target range with 5% (pre-specified) maximum risk of BG<80mg/dL STAR-GRYPHON has been utilized in Christchurch Women's Hospital NICU on a tablet-computer interface since January 2013. Results were analyzed as patient episodes of at least 12 hours of insulin, initiated by 2 consecutive BG>180 mg/dL. Results were re-sampled hourly due to differing measurement intervals, and compared to retrospective results (n=25; 3098 hours). Safety (i.e., %BG<72mg/dL and the number of patients with BG<40mg/dL), performance (%BG in 80-144mg/dL and %BG>180mg/dL), and clinical workload and burden on the neonate (measurement interval) were assessed.

Result:
From January 2013 to June 2017 there were 51 episodes (3198hours). Compared to retrospective results: 71% vs. 52% BG in 80-144mg/dL; 7.4% vs. 16.4% BG>180mg/dL; 0.64% vs. 2.1% BG<72mg/dL with 1 infant with BG<40mg/dL in both groups; and median [IQR] BG: 126 [110-148]mg/dL vs. 141 [119-164]mg/dL. Average measurement interval is longer with STAR-GRYPHON: 4.0 [range:3.9–4.2] hours vs. 3.2 [range:2.7–3.8] hours.

Conclusion:
STAR-GRYPHON, used as a standard of care in Christchurch Women's Hospital, provides tighter control for lower clinical workload compared to retrospective data, with improved safety from hypoglycemia.

Usability of a Predictive Low Glucose Suspend Feature on a Touchscreen Insulin Pump

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Objective:
Hypoglycemia is a debilitating adverse effect of insulin therapy. Systems are being developed that suspend insulin delivery to prevent hypoglycemia based on predicted glucose trends derived from continuous glucose monitoring (CGM) systems. Usability is a critically important characteristic of safe and effective automated insulin delivery (AID) systems. This abstract describes the results of a Human Factors study conducted to validate the safety of a predictive low glucose suspend (PLGS) feature, as part of the Tandem t:slim X2 Insulin Delivery System with Dexcom G5 Mobile CGM (the t:slim X2 System), in the hands of users (ages 6+), with and without previous insulin pump or CGM experience.

Method:
The study was conducted at independent research organizations in four different US cities. After a two-part training period (one live one hour session on the t:slim X2 System, followed by a break, and then a 45-minute e-learning module on the PLGS feature), participants (N=57) were asked to complete 10 critical tasks on the device in a simulated environment in order to uncover and identify errors and difficulties (parents could help children). Interactions were observed by a researcher seated in a separate observation room. Successful performance required completion of the task without any observed errors or assistance from the study moderator. Pass/fail scoring was completed according to pre-set criteria.

Result:
Out of a total of 570 task completions, there were 7 task failures (none related to safety), resulting in a 99% success rate.

Conclusion:
Usability is an important consideration for AID systems. These findings demonstrate that the t:slim X2 System requires minimal training and is easy for participants to use (including those who are pump and/or CGM naïve).

The Customer Training Phase Data Analysis of the MiniMed™ 670G System: Performance of the Guardian™ Sensor 3 sensor

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Objective:
The performance of the Guardian Sensor 3 continuous glucose monitoring (CGM) sensor, one of the key components of the MiniMed 670G system, was analyzed based on the real-world data obtained from the Customer Training Phase (CTP) launch and compared to that from the sensor accuracy pivotal study.

Method:
Data from 845 unique CareLink™ Personal accounts were downloaded to analyze sensor accuracy. Self-Monitoring Blood Glucose (SMBG) reference values received by the pump were used as reference SMBG values. Comparison between the sensor glucose (SG) and reference values included the pairing of the reference value to the SG reading within five minutes after the reference measurement. The SG values following a calibration were re-simulated in order to remove the effect of a calibration on the SG value. A survey was also distributed to the CTP participants to evaluate customer satisfaction with sensor performance.

Result:
Pivotal trial Guardian Sensor 3 sensor accuracy, for minimum system-required calibrations, demonstrated a mean absolute relative difference (MARD) of 10.6%, compared to YSI. When comparing sensor accuracy against SMBG readings in the same study, MARD was 11.7%. For the CTP, a total of 5,027 sensors with 37,490 sensor days over a four-month period were analyzed. The overall MARD, compared to SMBG, was 10.5%. In addition, 183 participants in the CTP reported an overall sensor satisfaction score of 75%.

Conclusion:
The analysis of commercial Guardian Sensor 3 sensor data demonstrate high accuracy in the field, which is consistent with performance in the pivotal trial. This level of performance, as well as user satisfaction, is critical in automated insulin administration based on sensor CGM measurement.

Using T1DMS Simulation for the Conceptualization and Design of Clinical Clamp Studies in the Development of Modified Insulin Therapeutic Agents. Part 1 – Regular Human Insulin (RHI)

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Objective:
The objective was to establish the utility of the UVA/Padova T1DM metabolic simulation platform (T1DMS) for designing clinical clamp studies in support of a glucose-responsive insulin (GRI) program. In this investigation, *in silico* simulations were performed to explore the glucose dynamics of regular human insulin (RHI) under multi-glycemic clamp conditions in order to understand the operational feasibility of the protocol and to establish a benchmark for *in silico* comparison of a novel insulin candidate, based on implementation of the candidate's pharmacology.

Method:
A T1DMS-based in-silico clamp study was designed to characterize glucose disposal rate, and insulin-dependent uptake as *in-silico* subjects switch between euglycemic, hypoglycemic, and hyperglycemic target levels. Multiple variations of clamp durations and glycemic levels were explored, before finalization of the final clinical protocol for RHI, which aimed to test the operational feasibility of a multi-glycemic clamp study. The subject glucose dynamics were used to quantify key pharmacological properties both at steady-state and transient stages between glycemic targets for prospective predictions of the clinical trial outcome.

Result:
The simulation predicted both the summary statistics and the time-to-steady state of glucose dynamics measured in the RHI multi-glycemic clinical clamp study. Subsequently, these results set the stage for a similar examination of a GRI, relative to RHI, both *in-silico* and clinical trials.

	Insulin concentration (pM)	Total Insulin Clearance (mL/min/kg)	Insulin infusion rate# (pmol/kg/min)	$GIR_{[GLU]=75}$ § (mg/kg/min)	$GIR_{[GLU]=300}$ § (mg/kg/min)
Predictions using T1DM simulator	203 (109-529)	16	3.3 (1.1-7.4)	2.1 (0-5.6)	6.6 (2.6-8.8)
Predictions from literature	193 (170-220)	15	2.9 (2.6-3.3)	2.6 (2.2-3.0)	6.4 (5.5-7.4)
Observed in pilot study	220 ± 89	15 ± 4	3.4 ± 1.3	3.1 ± 1.3	7.4 ± 1.9

Table: Predictions and observations for RHI in T1DM patients
#Insulin infusion rate to maintain a 200 mg/dL clamp target while GIR is fixed at 5 mg/kg/min
§Glucose infusion rate required to clamp plasma glucose at 75 or 300 mg/dL with a given insulin infusion rate

Conclusion:
In-silico studies provide an arena to conceptualize and design clinical studies related RHI properties. Understanding of the predictive performance of RHI simulations increases the confidence that the T1DMS can be used (in a modified version) for the explorations of glucose dynamics of GRI. Moreover, this approach lays the foundation for model-informed clinical testing of modified insulin or insulin mimetic therapeutic agents, and a better understanding of their clinical effects.

In Vivo Study of a 3rd Generation Enzyme Presenting an Alternative to Glucose Oxidase

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Objective:
Glucose sensing devices transformed from burdensome lab-based measurements to CGMS, which strive to become a central part of treatment. Interestingly, while the shape of the devices has evolved, the core technology has not. Most of the systems rely on the sensing principle conceived in the 1970's using the glucose oxidase (GOX) enzyme and measurement of a reaction product or its co-substrate oxygen. The enzyme is highly recognized for its well understood behavior and availability, but it dictates a sensor design with major limitations.

Method:
The distinguishing feature of a 3rd generation enzyme is the capability of direct electron transfer. No co-substrate or mediator is needed. The enzyme itself generates an electrical signal, that can be measured with simple carbon electrodes run at extremely low working potential (-0.1 V vs. Ag|AgCl). This allows for the construction of a highly selective glucose sensor, unaffected by typical interferents like acetaminophen, without the need for a selective membrane.

Result:
For this study, a sensor prototype for subcutaneous glucose measurement was constructed and evaluated. A carbon electrode, prepared by standard screen-printing technique was modified with the 3rd generation enzyme. Evaluation in a porcine model revealed excellent *in vivo* signal strength and relation to a reference method. Derived performance parameters and interference data will be presented.

Conclusion:
This prototype study highlights the benefits of a 3rd generation glucose sensing enzyme. While the enzyme is similar to GOX in terms of stability, cost of goods, and safety, it allows for the construction of simpler, more sensitive, and highly specific sensors, adding value to CGMS and, eventually, patient therapy.

Device-Supported vs. Routine Titration of Insulin Glargine 300 U/mL (Gla-300) in Type 2 Diabetes (T2DM): Efficacy and Treatment Satisfaction

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Objective:
The objective is to evaluate the efficacy and treatment satisfaction of device-supported versus routine (investigator-recommended) titration of Gla-300 using MyStar DoseCoach™ (MSDC), a combined titration device/blood glucose meter.

Method:
AUTOMATIX was a randomized, parallel-group, multicenter, treat-to-target trial in insulin-pretreated or -naïve people with T2DM. Participants were titrated to a fasting self-monitored plasma glucose (FSMPG) target of 90–130 mg/dL (5.0–7.2 mmol/L). The primary endpoint was the percentage of participants achieving target FSMPG at week 16 without severe hypoglycemia. Secondary endpoints included the time to first achieve the FSMPG target and participant-reported outcomes (PROs) including ease-of use (1=difficult to 7=easy), and diabetes treatment satisfaction questionnaire (DTSQ; 0=low to 36=high).

Result:
Participants were randomized to device-supported (n=75) or routine titration (n=76). Although not significant (p=0.262), a higher proportion of participants achieved the primary endpoint using device-supported versus routine titration (45.9% vs 36.8%) and the median time to first achieve FSMPG target was shorter (device-supported: 10.0 [95% CI: 8.0, 10.0] weeks; routine titration: 13.0 [6.0, 16.0] weeks). Cumulative incidence of FSMPG target achievement at week 16 was 0.8 (95% CI: 0.67, 0.87) versus 0.6 (0.54, 0.75), respectively. LS mean change in DTSQ score was 4.46 (SE: 0.60) and 2.90 (0.61) for routine and device-supported titration, respectively (LS mean difference −1.57 [95% CI: −3.28, 0.15]). MSDC use had high scores for ease of titration (mean [SD]: 6.23 [1.36]), dose selection (6.11 [1.36]), calculating doses (6.07 [1.40]), and dose adjustment (6.24 [1.30]). Healthcare Professionals considered MSDC the most convenient titration method for 80.3% of participants who used it.

Conclusion:
Device-supported self-titration enabled participants to achieve the FSMPG target (primary endpoint) in a shorter median time without adversely affecting PROs.

Capillary Recruitment Predicts the Increase in Subcutaneous Insulin Absorption Rate during Exercise

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Objective:
An insulin pump infusion into subcutaneous tissue has been shown to absorb more quickly during exercise, potentially causing hypoglycemia. We developed a predictive model that directly relates exercise-induced physiological changes in the subcutaneous tissue to the rate of insulin absorption (k).

Method:
Drawing on concepts of fluid dynamics and the microcirculation, we revealed the relationship between k and two physiological parameters that characterize the subcutaneous tissue: the tissue perfusion rate (Q, i.e. blood flow rate) and the capillary insulin permeability surface area (PS). Independently measured values of Q and PS found in the literature were used in the derived relationship to make predictions. We compared the predictions to experimental observations from two pump-wearing T1D cohorts; (1) Resting subjects (n=17) given a mixed meal tolerance test (MMTT) and (2) exercising (50% $V0_2$ max for 75 minutes) subjects (n=14) given a MMTT.

Result:
Experimental observations show that plasma insulin concentration increases by an average of 30% during exercise. We make predictions of plasma insulin concentration using literature values of Q and PS measured at rest and during exercise. Without curve fitting, the predictions match the observations – during exercise a similar 30% increase in plasma insulin concentration is caused by a 35% increase in k.

Conclusion:
The derived relationship shows that, because the capillary walls have a low permeability to insulin, PS limits k with Q having almost no effect. This implies that the physiological mechanism for enhanced k during exercise is capillary recruitment, which increases the number of perfused capillaries and thus the capillary surface area. This mechanistic understanding provides a physical basis for handling exercise in model predictive control algorithms for the artificial pancreas.

Accuracy Assessment of Two Tissue Glucose Monitoring Devices

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Objective:
In diabetes management, frequent self-monitoring of glucose is a fundamental factor. Two devices for tissue glucose monitoring (TGM) are intended for non-adjunctive use in the European Union, i.e., TGM measurements may replace blood glucose (BG) measurements for therapeutic decisions except in few situations. The performance of these systems, Dexcom G5® (DG5) and FreeStyle Libre (FSL), was evaluated using ISO 15197:2013 accuracy limits, the standard applicable for BG meters.

Method:
Each of 20 patients wore 2 sensors per system in parallel for 14 days. DG5 sensors were routinely replaced after 7 days. Patients stayed at the study site 3× 48 hours. Each time BG was measured with a BG meter (FreeStyle Freedom Lite; FSFL), FSL was scanned for a current glucose value (FSLscan). FSL additionally recorded continuous data (FSLcont); DG5 provided exclusively continuous real-time TGM data. The BG meter test strip lots were characterized based on ISO 15197:2013: 100% of results were within ±15 mg/dL or ±15% (for BG < or ≥100 mg/dL) of laboratory analyzer results. According to ISO 15197:2013, BG meters have to show ≥95% of results within these limits. Differences between TGM values and corresponding BG meter values and percentages of results within the accuracy limits of ISO 15197:2013 were calculated.

Result:
The results showed that 77.0% (DG5, n = 9453), 75.4% (FSLcont, n = 8856) and 72.4% (FSLscan, n = 8641) of TGM values were within the applied ISO 15197:2013 limits (±15 mg/dL or ±15% for BG < or ≥100 mg/dL) of the corresponding BG measurements (30 mg/dL - 424 mg/dL).

Conclusion:
High accuracy of TGM systems is important for adequate diabetes therapy, especially in the hypoglycemic range. Accuracy should be considered in devices intended for non-adjunctive use.

Clinical and Psychological Characteristics of Patients with Type 1 Diabetes and a High Risk of Hypoglycemic Events: Comparison of the HypoDE study with other studies

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Objective:
The HypoDE study is a randomized controlled CGM trial with a reduction of CGM-tracked hypoglycemic events (glucose ≤55 mg/dL) as the primary outcome. We compared the hypoglycemic profiles of HypoDE-participants with data from other studies.

Method:
Patients with type 1 diabetes on a multiple daily injection (MDI) insulin regimen and with an increased risk for hypoglycemic events (severe hypoglycemic episode [SH] in the past 12 months or hypoglycemia unawareness) were eligible for the HypoDE study. During the baseline phase, participants wore blinded CGM for 28 days (Dexcom G4/505). Baseline data of 149 participants were analyzed (age 46.5±11.9 yrs, 40.3% female, A1c 7.5±1.0%, diabetes duration 21.3±11.9 yrs).

Result:
HypoDE-participants reported 2.3±5.0 episodes of SH and 0.6±1.2 episodes of hypoglycemic episodes with coma/seizure per year prior to study participation. This corresponds to 359% and 375% of the hypoglycemic episodes reported in the DCCT (0.64, respectively 0.16 episodes per year). HypoDE-participants had 12.5±11.3 hypoglycemic events per 28 days (glucose reading ≤55 mg/dl for at least 20 min). They spent 108 min/day at glucose levels ≤70 mg/dl and 33 min/day ≤50 mg/dl. This corresponds to 32.5% and 55% more time in the respective range than reported for the adult participants in the JDRF CGM-trial. In the Hypoglycemia Fear Survey, HypoDE-participants achieved a score of 32.4±14.9 and a Diabetes Distress Scale mean-item score of 2.5±0.8. Both scores were significantly higher than those of the respective normative sample that was not specifically selected for hypoglycemia problems.

Conclusion:
These data suggest that HypoDE-participants represent patients with a high risk of clinical as well as biochemical hypoglycemic events. Compared to the “typical” patient with type 1 diabetes, these patients reported a high amount of hypoglycemic-related worries and diabetes-related distress.

Comparison of Methods for Measuring Basal Rate Delivery Accuracy of Patch Pumps

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Objective:
Insulin pump therapy requires an accurate and reproducible delivery of bolus doses and basal rates. However, different methods exist for measuring the accuracy of insulin delivery. The standard IEC 60601-2-24 describes test settings that are applicable to infusion systems in general, but are not specific to insulin pumps. We evaluated the suitability of different setups for measuring the accuracy of basal rate delivery of patch pumps.

Method:
Four different test settings, modified based on the descriptions in IEC 60601-2-24, were investigated. For all methods, insulin aspart was infused into a water-filled, oil-covered vessel on a balance. However, the particular installation of the pump differed between the methods. For methods A and B, the pump was placed inside the balance chamber closely above a Petri dish; method B used a smaller dish than method A. For methods C and D, the pump was placed outside the chamber using a plastic (C) or a steel (D) tube for transferring the insulin into a beaker. Each method was tested for 72 h at a basal rate of 0.05 U/h or 1 U/h and the overall error for each repetition was calculated.

Result:
Methods A, B, and D showed consistent and reproducible results, whereas C showed inconsistent values. In methods A and B, the oil layer, which rises due to the infusion, might come into contact with the pump and impair the results, especially when larger basal rates are used.

Conclusion:
Method D with the pump placed outside the balance chamber and connected to a steel tube was considered to be the most suitable test setting for the assessment of accuracy of different basal rates delivered with patch pumps.

In-Vivo Performance of Optimized Second-Generation Materials for Light Controlled Minimally Invasive Insulin Delivery

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Objective:
We have previously demonstrated the *in-vivo* efficacy of light-controlled insulin depot materials. These are materials that are injectable, like insulin, but remain at the injection site until we irradiate them, transcutaneously, with a light source. The purpose of these materials is to allow for continuously variable insulin release without the physical connections associated with insulin pumps. First generation materials, while effective at releasing insulin and reducing blood sugar, released amounts of insulin that was lower than is optimal for human use. The objective of this study is to develop second generation of materials that are able to deliver higher levels of insulin.

Method:
We have synthesized multiple second-generation materials to address the above-described issue. Specifically, we have increased the density of insulin on the material by ten to twenty-fold, and increased the wavelength of light used to release the insulin. The expectation of these combined methods is that it will significantly increase the amount of insulin released *in-vivo*.

Result:
We have tested second generation materials, both *in-vitro* and *in-vivo*, and, in both settings, they display markedly improved performance over prior generations. Specifically, we have observed a twenty-fold increase in insulin release and a complete reduction in blood glucose in diabetic rats to normal levels using light-activated materials.

Conclusion:
High density second generation photo-activated depot materials show significantly improved properties including insulin release. This further strengthens their potential as a minimally invasive and continuously variable insulin delivery method.

Continuous Subcutaneous Insulin Delivery - Infusion Sets: Patient Perspectives from Social Media

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Objective:
In a consumer driven industry, social media can play an important role in the understanding of patient needs. The focus of this study was searching and analyzing social media content for diabetes-related discussions to understand patient perspectives and provide a basis for product improvement and innovation.

Method:
Multiple social media domains and sources of conversations were reviewed for the 28 months' period from October 2014 to January 2017. The database search terms included different types of infusion sets, and common adverse events such as adhesive falling off, adhesive loose, air bubbles, cannula kink/bending, cannula pull out, high blood glucose (BG), site bruising/pain, site irritation/infection, site leaking, site occlusion, site/cannula bleeding, skin irritation, and infusion set inserter malfunction. Sentences containing insight-rich text were found for these types of criteria and an analysis was performed to rank patients' top concerns.

Result:
Based on the searched criteria, the most frequently mentioned topics were high BG, blood at site, cannula bending, scar tissue, and site occlusion. Data analysis also revealed varying durations of infusion set usage, sometimes beyond recommended labeled usage life. In some instances, if a patient found a viable site for infusion, they used the site until insulin was no longer being absorbed. This usage of a site/infusion set beyond labeled usage life potentially contributed to the occurrences of adverse events.

Conclusion:
Though social media data may be anecdotal and therefore unsubstantiated/uncontrolled, when the data are used in combination with internal databases it can provide insightful data for design and development of infusion sets leading to a better user experience.

Personalized Plasma Insulin Concentration Estimator for Use in an Artificial Pancreas System

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Objective:
The artificial pancreas (AP) necessitates estimates of active insulin already present in the body to avoid overdosing. Our objective is real-time estimation of plasma insulin concentration (PIC) under inter- and intra-subject variabilities. The proposed PIC estimator uses CGM and subcutaneous insulin delivery data to provide an accurate estimate of PIC without using other information such as meal time and amount.

Method:
An adaptive and personalized PIC estimator was designed in this work to accurately quantify the insulin present in the bloodstream. The developed PIC estimation approach incorporates the Hovorka's model, a glucose-insulin dynamics model, with the unscented Kalman filtering algorithm. Methods using patient's demographic information, for the personalized initialization of the time-varying model parameters to individual patients for improved estimator convergence, were developed. A total of 20 datasets from closed-loop (CL) clinical experiments conducted over three days at University of Chicago Medical Center and 13 datasets from five-hour euglycemic clamps, performed with and without an insulin infusion site warming device (IISWD), at Yale Children's Diabetes Clinic involved subjects with T1DM to evaluate the proposed PIC estimation approach.

Result:
The proposed methods are tested with clinical data containing significant disturbances, such as unannounced meals, exercise and with and without IISWD, and the results demonstrate the accurate, real-time estimation of the PIC. The root mean squared error (RMSE) mean absolute error (MAE) value is 7.15 (4.77) mU/L for the CL experiments. The RMSE (MAE) values are 13.38 (10.18) and 13.83 (11.12) mU/L for the clamp with and without IISWD, respectively.

Conclusion:
The accurate real-time estimation of PIC will benefit AP systems by preventing over-delivery of insulin when significant insulin is present in the bloodstream.

Filling the Void in Diabetes Management: Designing Apps to Capture and Sustain User Attention

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Objective:
Though various diabetes management apps aim to assist users in their diabetes management, few published data are available regarding sustained use. The evidence suggests existing apps generally have failed to capture and engage user attention in sustained use. We employed a survey to gain an understanding of user attitudes and barriers regarding diabetes management apps.

Method:
An Upper Midwest children's hospital collected survey data from their type 1 diabetes population—279 adolescents ≥12 years and 131 parents/guardians of children <12 years. Survey responses included data on sentiment towards current testing regimens and attitudes towards mobile health.

Result:
Results are reported separately for patients ≥12 years and parents/guardians of children <12 years, respectively. A majority of respondents (81.2% and 45%) indicated a diagnosis duration of ≥3 years. Results reveal that 51.8% and 60.8% of respondents felt discouraged about managing diabetes over the past month. A majority, 54% and 57.7%, also acknowledged struggles with accommodating life changes necessary to manage diabetes. Regarding glucose testing, 45.3% and 57.4% reported that distractions and forgetfulness resulted in missed testing. Only 22.7% and 26.48% reported regularly using a phone app to manage their diabetes, but 89.1% and 74.7% reported willingness. Finally, 88.1% and 70.1% reported a belief that an app would help them to manage diabetes more effectively.

Conclusion:
Though our data show very low app use for diabetes management, they also reveal a strong opportunity for engaging patients through app technology. Data from other health-related areas (e.g., electronic medical records) indicate that cognitive design fosters sustained success. Successful outcomes may also be achievable in diabetes management. Future diabetes app design should take these findings into account.

Steel versus Teflon - Systematic Evaluation of Inflammatory Tissue Response to CSII Catheters over 7 Days

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Objective:
Continuous subcutaneous insulin infusion (CSII) catheters are considered the weak link of insulin pump therapy. Catheters are manufactured in both steel and Teflon and the choice of material is largely based on personal preference or experience rather than on empirical data. We therefore systematically evaluated the inflammatory response to commercially available CSII over a wear-time of 7 days in farm swine.

Method:
Steel (Medtronic Sure-T) and Teflon (Medtronic Quick-set) CSII catheters (6 mm) were inserted into the subcutaneous adipose tissue of 10 swine for 1 day, 4 days and 7 days of wear-time. The tissue surrounding the catheters was analyzed using histopathological methods and quantitative real-time PCR. The areas (mm2) of inflamed tissue, fibrin deposition, and fat necrosis were measured and mononuclear cell infiltrate was categorized from “none” to “severe”. Gene expression analysis was carried out for pro- and anti-inflammatory cytokines and macrophage marker CD68.

Result:
Fibrin deposition ($p < 0.05$) and mononuclear cell infiltrate ($p < 0.0001$) were significantly elevated around steel catheters on day 4. Pro-inflammatory cytokines were upregulated within 24 hours independent of material but there was a trend towards higher levels around steel over 7 days. CD68 expression increased significantly over wear-time while IL-10 was consistently high indicating unresolved wound healing. The sharp tip and stiffness of the steel catheter continuously ruptured connective tissue and blood vessels.

Conclusion:
Softer, more flexible Teflon elicits a less severe inflammatory tissue response over the first 4 days of wear-time and are the superior choice for future CSII catheter development.

Rapid Code Generation for Hardware-in-the-Loop (HIL) Testing of a Medical Internet-of-Things (IoT)-Enabled, Wearable Artificial Pancreas

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Objective:
Next-generation decision-making platforms in embedded artificial pancreas (AP) systems require sophisticated control algorithms to be deployed from medical Internet of Things (IoT)-enabled low-power wearable platforms and a systematic method to evaluate these algorithms in a hardware in the loop (HIL) setting. Code translation to specific target platforms requires significant technical, temporal, and fiscal resources. To expedite this process, we developed a rapid code generator to deploy state-of-the-art controllers for wearable technology.

Method:
We used Matrix Laboratory (MATLAB) programming language to create a code generator that rapidly generates ready-to-upload code for embedded systems. We offered a wide range of customization for the end-user, including: patient personalization (basal insulin, carbohydrate ratio, total daily dosage of insulin, correction factor), prediction/control horizons and zone boundaries for model predictive control (MPC) variants, low-complexity optimization solvers, and communication protocols [Bluetooth Low Energy (BLE), USB serial)] capable of reliably exchanging information with edge devices (glucose sensors, insulin pumps). Additionally, we exploited matrix sparsity to save memory and simplify the mathematical operations to lower latency.

Result:
Our code generator implemented a zone MPC on an Arduino Feather-M0 and evaluated HIL on ten patients' data obtained from the UVA/Padova simulator. The mean-squared error between the insulin trajectories, when implemented in the HIL simulation using wired/wireless communication, was $3.92 \pm 2.07 \times 10^{-4}$U, compared to the software implementation. Code optimization decreased code size from 56KB to 42KB and led to a reduction of controller update time from 11.80s to 3.75s. The wearable AP ran continuously for 105hr on a 2000mAh battery with 5min measurement intervals.

Conclusion:
The automatic code generator serves as a rapid, reliable way to evaluate next-generation controllers and perform HIL testing and verification for wearable AP systems informed by the medical IoT, without wasting time and effort in writing code for various target hardware platforms. This tool generates pre-optimized code and offers plug-and-play modules for testing new control designs and demonstrates excellent performance in preliminary tests.

Can CGM Discriminate between Patients with Type 1 Diabetes with and without Severe Hypoglycemia? Assessment of the Baseline Data of the HypoDE Study

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Objective:
Patients with type 1 diabetes on a multiple-daily injection (MDI) insulin regimen and at an increased risk for hypoglycemic events (severe hypoglycemic episode [SH] in the past 12 months or hypoglycemia unawareness) were eligible for the HypoDE study. We analyzed whether continuous glucose monitoring (CGM) can discriminate between patients with and without SH.

Method:
Blinded CGM recordings (Dexcom G4/505; 28 days) of 149 patients (age 46.5±11.9 yrs, 40.3% female, A1c 7.5±1.0%, diabetes duration 21.3±11.9 yrs) were analyzed. All participants completed the Hypoglycemia Awareness Questionnaire (HAQ). Ninety (90) patients reported at least one episode of SH and 59 patients reported reduced hypoglycemia awareness without SH.

Result:
Patients with SH spent a longer time in low glucose ranges in comparison to those without SH (≤70 mg/dl: 130.5±98.9 min/day vs. 72.4±56.1 min/day; ≤55 mg/dl: 59.4±60.0 min/day vs. 27.3±26.5 min/day; all p<.001) and had more hypoglycemic events (i.e., glucose ≤55 mg/dl: 14.5±11.8 vs. 8.1±7.8, p<.001). The area under the Receiver Operating Characteristics curves for different low glucose ranges and the number of hypoglycemic events differed significantly from chance (≤70 mg/dl: AUC 0.68; ≤55 mg/dl: AUC 0.68; number of events ≤55 mg/dl: AUC 0.67; all p<.001). Time-in-range (71-180 mg/dl) did not allow identification of patients with SH in the past (AUC 0.59, p=.062).

Conclusion:
Time spent in low glucose ranges and the number of hypoglycemic events enables discrimination of patients with type 1 diabetes with previous SH from patients without SH. The potential of CGM to identify patients with and without SH is not fully exhausted. In patients with SH, prevention of the re-occurrence of SH should be the primary therapeutic aim (secondary prevention). In patients without SH but with hypoglycemia unawareness, the primary prevention of SH should be the primary objective.

Psychological Impact of Severe Hypoglycemia on Fear of Hypoglycemia and Diabetes-related Distress: Baseline Assessment in Participants of the HypoDE Study

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Objective:
Patients with type 1 diabetes on a multiple-daily injection (MDI) insulin regimen and at an increased risk for hypoglycemic events (severe hypoglycemic episode [SH] in the past 12 months or hypoglycemia unawareness) were eligible for the HypoDE study. We compared the psychological profile of patients with SH to that of patients with hypoglycemia unawareness, but without SH.

Method:
Baseline data of 149 participants (Dexcom G4/505; age 46.5±11.9 yrs, 40.3% female, A1c 7.5±1.0%, diabetes duration 21.3±11.9 yrs) who completed the Hypoglycemia Awareness Questionnaire (HAQ), the Hypoglycemia Fear Survey (HFS), and the Diabetes Distress Scale (T1-DDS) were analyzed.

Result:
Patients with SH had a lower HAQ-score compared to those without SH (4.6±0.6 vs. 5.0±1.4, p=.018). They reported more worries about hypoglycemia (34.6±14.4 vs. 29.2±15.2), more avoidance behavior towards low glucose values (22.2±9.1 vs. 18.7±8.3), and more overall diabetes-related distress (2.7±0.8 vs. 2.3±0.7) than patients without SH (all $p<.05$). The following specific areas of distress were higher in patients with SH (all $p<.05$): powerlessness (3.3±1.2 vs. 2.8±1.1), hypoglycemia-related (3.9±1.2 vs. 3.3±1.2), social problems (2.2±1.1 vs. 1.8±0.9), family arguments (2.7±1.1 vs. 2.1±1.1), physician-relating (1.4 ±0.7 vs. 1.2±0.4), and eating-relating (2.7±1.2 vs. 2.3±1.1). Overall distress (r=.19, p=.022) and family arguments (r=.20, p=.012) showed significant correlations with the duration of hypoglycemic episodes.

Conclusion:
SH affects many areas of living of patients with diabetes with the strongest impact on family arguments and overall distress levels. Avoidance of hypoglycemia was more prominent in patients with SH. Diabetes-related distress and family arguments were associated with occurrence of SH and with the duration of low glucose values. Besides aiming to reduce biochemical and clinical hypoglycemia by optimizing diabetes therapy, hypoglycemic-related distress should be addressed in such patients by patient-physician/nurse interaction.

Type 1 Diabetes Experience Simulator App

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Objective:
One challenge clinicians face when treating people living with type 1 diabetes (T1D) is the difficulty to understand the burden associated with self-management. The aim of the Type 1 Diabetes Experience Simulator (T1DES) is to simulate the experience of living with T1D for people with normal glucose tolerance and, in particular, for healthcare professionals. The application has been developed in collaboration with INPUT Patient Advocacy (London, UK), the UK diabetes technology advocacy charity.

Method:
The Type 1 Diabetes Experience Simulator (T1DES) consists of a smartphone application developed in Android which includes a validated T1D simulator incorporating realistic intra-day variability of insulin pharmacokinetic, insulin sensitivity, and meal estimation. T1DES provides a set of graphical user interfaces (GUI) that allow the user to visualize glucose levels emulating continuous glucose monitoring (CGM) or self-monitoring blood glucose (SMBG). In CGM mode, the App alerts the user about low and high glucose events. The GUI also allows the user to manually input information about meals consumed and exercise taken. Then, the user has to estimate the insulin doses needed to control glucose levels. Finally, T1DES incorporates a bolus calculator to assist to the calculation of insulin doses.

Result:
Software specifications were gathered through focus groups organized by INPUT with people with T1D. The App went through several iterations before achieving a satisfactory result.

Conclusion:
A functional user-friendly smartphone application aiming to emulate the experience of living with type 1 diabetes has been developed. T1DES will be evaluated by a group of people with normal glucose tolerance over a prolonged period of time (e.g. 1 month). Semi-structured usability and quality of life questionnaires will be employed for this purpose.

A Global Overview of Smartphone Apps for People with Diabetes

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Objective:
The objective of this study is to assess the number and proportion of diabetes self-management apps in major languages of the top 10 countries with the most number of people with diabetes.

Method:
Diabetes-related terms in English, Chinese, Arabic, Spanish, Portuguese, Russian, Japanese, Urdu, and Bahasa Indonesian were searched on the Android and iOS platforms in January 2017. Extracted app titles and description were checked for language relevance on google translate and duplications on each platform before being screened for relevance to diabetes self-management by calibrated reviewers.

Result:
The screening identified 1019 Android and 1303 iOS apps for diabetes self-management. Apps in English (56.6%) and Chinese (31.7%) language constitute the majority (88.3%) of all relevant apps, followed by apps in Spanish (3.7%), Portuguese (3.0%) and Japanese (1.4%). Apps in Urdu and Hindi were mainly identified from English descriptions. Despite the high number of apps returned by the English search terms, only a quarter of the apps were screened to be relevant for diabetes self-management. Chinese Android apps have the highest proportion (55.6%) of apps relevant for diabetes self-management from the search terms, possibly due to additional searches conducted on third-party platforms.

Conclusion:
Diabetes self-management apps are not distributed proportionately across app operating platforms and assessed languages. English and Chinese language apps have the highest potential for advancements in mDiabetes but are faced with challenges in identifying and regulating apps for diabetes self-management. Under-developed markets can focus on translating or creating a few good apps by partnerships. App functionalities and content should be assessed to identify potential ‘useful’ attributes for diabetes self-management apps.

A Systematic Approach using Data Mining of Central Laboratory and Point of Care Glucoses to Evaluate the Analytical Accuracy of Two Blood Gas Analyzers' Glucose Methods

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Objective:
To evaluate the performance of two point of care (POC) blood gas analyzers' glucose by comparing intensive care unit (ICU) patients' POC blood gas glucoses to central laboratory (CL) glucoses run on almost simultaneously drawn blood specimens.

Method:
We obtained 5 years of blood gas glucoses from two adult ICUs, Calgary's Foothills University Hospital ICU [glucose measured by tandem Instrumentation Laboratory GEM 4000s] and Edmonton's University of Alberta Hospital ICU [glucose measured by tandem Radiometer 800 ABLs]. We identified CL glucoses obtained within $\pm$30 minutes of the POC specimen procurement. As blood glucose depends on glucose-modifying therapy and glycolysis, we calculated the mean absolute deviations between the POC and CL glucoses to determine the maximum time interval that the two samples provided stable differences. We then determined the glucose bias and % outliers in accordance with the FDA 2016 guidance.

Result:
The differences between POC and CL glucoses were stable for 15 minutes and 10 minutes for the Radiometer and GEM, respectively. A total of 7,920 Radiometer-CL (22 samples < 54 mg/dL) and 33,827 GEM –CL differences (164 < 54 mg/dL) were reviewed. We compared the magnitude of the differences against the FDA guidance for three periods: 1) 24h period, 97.1% and 92.4% of data pairs were within 12% of CL glucose ≥ 75mg/dL; 2) for 3:30am-7:30am 96.9% and 91.4% of data pairs were within 12% of CL glucose ≥ 75mg/dL, respectively, and for 3) 7:30am-3:30am 97.5% and 94.9% of data pairs were within 12% of the CL glucose ≥ 75mg/dl, for the Radiometer and GEM, respectively.

Conclusion:
The GEM glucoses did not meet the FDA guidance requirements. Our work suggests new, unconventional guidelines for future evaluations.

BMI and Diabetes Duration Affect Baseline Pulmonary Function in Adults with Type 1 and 2 Diabetes Versus Non-Diabetic Controls and Responses to 24 Months Treatment with Prandial Inhaled (Afrezza) or Subcutaneous Insulin

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Objective:
The contributions of disease duration (DUR) and body mass index (BMI) to declines in pulmonary function (PF) in diabetes require further elucidation.

Method:
The effects of diabetes, baseline (b) BMI, and DUR on bFEV1 and bFVC and changes in FEV1 over 24 months treatment with either TI or C were compared to normal controls (NC) in certified PF laboratories. Study Intent-To-Treat population: nonsmoking (> 6 months) adults without malignancy with T1D (total=446, n=246 comparator), T2D (total=1108, n=578 comparator) or NC (n=145). Data were analyzed by a mixed-effect repeat measurement (MMRM) model with model components: disease, region, visit, treatment.

Result:
Subjects with T2D, but not T1D, had lower bFEV1 than NC (median NC 3.45L, T1D 3.51L, T2D 3.06L). DUR significantly affected bFEV1 (-0.02L/yr, $p<0.0001$) in T1D and T2D. Increasing bBMI negatively impacted bFEV1 in T2D but not T1D (each +1 kg/M2 BMI decreased bFEV1 by 0.025L, $p<0.0001$). Overall, bFEV1 was 8.9% less in obese than overweight diabetics. bBMI was also associated with decreased bFVC in T2D, but not T1D. bFEV1 was similar in TI and C treatment groups (T1D TI 3.55±0.720L v C 3.65±0.84L; T2D TI 3.09±0.66 v C 3.15±0.74; control 3.67±0.91). With bBMI in the MMRM model, the LS mean TI vs. C treatment difference (T1D and T2D) was -0.03675L [95%CI -0.06115, -0.01235], $p=0.0032$ (LS mean difference without BMI -0.03609 (95% CI -0.0605, -0.01169). This represents a 1.3% treatment difference after 24 months. bBMI was itself associated with a -0.0403L change/+1 kg/M^2 over this time period ($p=0.0361$). Treatment differences remained significant in diabetic subjects with BMI > 30 kg/M2, but not in normal or overweight subjects. Differences developed over a period of weeks, were non-progressive after 3 months, and were reversible after TI discontinuation.

Conclusion:
Factors intrinsic to diabetes (DUR) and associated demographic characteristics (BMI) that affect baseline lung function and response to treatment (BMI) in diabetes must be taken into account when determining the relative contribution of TI treatment to the PF declines in diabetes.

Impact of Insulin and Diluent Induced Tissue Reaction to Continuous Subcutaneous Insulin Infusion (CSII) Longevity

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Objective:
To date, minimal effort has been directed towards evaluating or optimizing the continuous subcutaneous insulin infusion (CSII) biological interface at insulin infusion sites. Progress has been hampered by the lack of pertinent cellular and animal models that would provide a rational foundation for enhancing insulin infusion performance. Thus, we modified the classical murine air pouch model (APM) in order to investigate both the tissue toxicity of insulin and insulin diluents *in vivo*, as well as the impact of local inflammation on blood glucose (BG) levels in diabetic mice.

Method:
Tissue toxicity and inflammation were determined using APM lavage and fluorescence-activated cell sorting (FACS) analysis. The impact of local (air-pouch) inflammation on insulin-induced BG levels was also evaluated utilizing the APM. Using APM, we assessed the effects of the various inflammatory cell populations induced by insulin, and/or its excipients, at 3 and 7 days of air-pouch infusion.

Result:
APM data demonstrated that both commercial insulin and insulin diluents were tissue toxic. Extensive air-pouch inflammation was characterized by a significant influx of both polymorphonuclear leukocytes (PMN) and macrophages (MQ) in both wild type and diabetic mice. Furthermore, we demonstrated that induction of inflammation at insulin infusion sites significantly diminished the ability of insulin to control BG levels in diabetic mice.

Conclusion:
Insulin infusion remains one of the least studied, but most critical elements of an integrated artificial pancreas system. However, little is known about the impact of insulin excipients/diluents and continuous subcutaneous insulin infusion (CSII) malfunctions that lead to the failure of blood glucose regulation. The application of the APM and associated CSII analysis will likely provide new insights into BG levels in patients with diabetes.

Role of Leukocytes & Leukocyte Proteases in Limiting Insulin Regulation of Blood Glucose Levels During Continuous Subcutaneous Insulin Infusion (CSII)

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Objective:
To date, little effort has been dedicated to evaluating or optimizing the continuous subcutaneous insulin infusion (CSII) biological interface. In fact, most pump set users are taught the maxim "when in doubt, pull it out…" and replace the set, which circumvents the issues but incurs added healthcare costs, patient inconvenience, lower quality of life, and a predisposition to suboptimal control and more severe complications such as ketosis. Recent studies in our laboratories have indicated that: 1) insulin and preservatives trigger inflammation when infused into murine models of diabetes/CSII, and 2) that this inflammation is associated with the failure of insulin to control blood glucose levels in these mice. We hypothesize that this failure of insulin regulation during CSII was this result of insulin-leukocyte interactions at CSII infusion sites.

Method:
To test this hypothesis we developed an *in vitro* model of insulin – human peripheral blood leukocyte (hPBL) interactions. Specifically, we evaluated insulin / preservative toxicity and activation (cytokine expression) of hPBL *in vitro*. We further investigated the impact of leukocytes and leukocyte proteases on insulin integrity (degradation) *in vitro*.

Result:
We demonstrated that insulin and its preservatives are toxic to *hPBL*, and trigger expression of pro-inflammatory cytokine *in vitro*. We also demonstrated that *hPBL* (i.e., polymorphonuclear neutrophils and monocytes, but not lymphocytes) as well as leukocyte proteases can degrade insulin *in vitro*. Finally, protease inhibitors were able to inhibit this protease-based insulin degradation.

Conclusion:
Our results support the hypothesis that leukocytes play a major role in limiting insulin efficacy *in vivo* by taking up and degrading insulin at sites of insulin infusion. Uses of protease inhibitors maybe useful for improving insulin receptivity and infusion set lifespan *in vivo*.

Influence of Technical Down Time on the Outcome of Automated Glucose Clamps

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Objective:
Automated glucose clamps are the gold standard for assessing pharmacodynamic (PD) properties of blood glucose (BG) lowering agents. However, clamp quality may be influenced by the technical down-times of the clamp device. We therefore investigated the impact of the clamp quality parameter 'utility' (operational time in percent of total clamp duration) on key ClampArt outcome parameters.

Method:
Numerical simulations were performed to calculate the glucose infusion rates (GIR) needed to keep BG levels close to a pre-defined target during PD-assessments of a short-acting insulin. To induce down-time and lower utility, GIR and BG data were carried forward (simulating a HOLD-mode) over different clamp periods with varying duration and the impact on outcome parameters such as 'total area under the curve' (AUC), 'time of maximum GIR' (tGIRmax), and 'maximum GIR' (GIRmax) were evaluated.

Result:
Compared to clamps with 100% utility, a utility of 90% had almost no impact on AUC and only changed GIRmax and tGIRmax by 1-2%. When clamp utility declined to 80%, the impact on AUC and GIRmax was still small (1-3%), but more pronounced (3-6%) for tGIRmax. With a further decline in utility to 70%, the impact on AUC was still below 1% whereas a relevant impact was observed for GIRmax and tGIRmax with changes in a range of 1-9% compared to corresponding values of clamps with 100% utility.

Conclusion:
Technical down-time in automated clamps leading to a decrease in the clamp quality parameter "utility" of up to 70% had little impact on the AUC. In contrast, more relevant changes were seen for other clamp parameters, in particular tGIRmax, for utility-values below 90%.

An Intraperitoneal Continuous Glucose Monitoring System

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Objective:
The objective of this work was to develop and perform feasibility on a continuous glucose monitoring (CGM) system capable of integration into a fully implantable, intraperitoneal (IP) artificial pancreas. The IP CGM system is comprised of three glucose sensing elements outfitted on an insulin catheter: custom microelectronics that can be housed inside an insulin pump, a sensor control, and a communication algorithm.

Method:
The electrochemical glucose biosensor under development at Biorasis/UConn was used as a starting point. Insulin catheter material (provided by PhysioLogic Devices, Inc.) was equipped with glucose sensing elements. The sensing elements included 3x redundancy and were placed near the insulin-dispensing tip of the catheter. The sensing elements were coated with dexamethasone-eluting biocompatible coatings that prevent a foreign body response. A Biorasis' custom embedded chip was integrated on a custom PCB board that can be housed inside an insulin pump. The PCB board was used to collect and report glucose data. First generation prototypes were tested *in vitro* for their response to glucose as well as for their ability to periodically alternate between the three glucose sensing elements.

Result:
The IP CGM system showed a linear response to glucose *in vitro* throughout the physiologic glucose range (2.5 – 20 mM). The custom PCB was optimized to be able to selectively interrogate each sensing element, alter the sampling frequency, and perform first-stage calibration against manually-provided blood glucose values.

Conclusion:
An IP CGM system integrated on an insulin catheter was developed and successfully tested *in vitro*. The data collected so far proves the feasibility of this approach. Future studies will focus on further *in vitro* testing using bio-relevant intraperitoneal liquid and testing in large animals.

Accuracy and Precision of a Non-invasive Glucose Monitoring Device

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Objective:
To evaluate the accuracy and precision of GlucoTrack, a non-invasive glucose monitoring device that tracks glucose-related physiological changes by measuring the ultrasonic, electromagnetic and thermal parameters of earlobe tissue.

Method:
Device accuracy was assessed on 132 people with type 2 diabetes mellitus (T2DM) from which up to 48 paired invasive-GlucoTrack measurements were obtained. The accuracy of the device was clinically evaluated using consensus error grid analysis and numerically evaluated using absolute relative difference (ARD) values. Sensor to sensor precision was evaluated on 15 people with T2DM using simultaneous measurements from two devices placed on each earlobe. The precision of the two devices worn by the same subject was assessed using precision absolute relative difference (PARD). Additionally, measurement precision was evaluated on 14 people with T2DM by obtaining 3-6 sequences of four invasive-GlucoTrack measurements every 10 minutes under stable glycemic conditions achieved at ~3 hours postprandial. The coefficient of variation (CV) of sequential measurements was calculated.

Result:
Overall, 98.2% of 5,920 measurements were in the clinically acceptable A and B zones of the consensus error grid, with 75.6% of the measurements in zone A. Mean and median ARD were 23.2% and 18.4%, respectively. Mean PARD for 806 pairs of measurements obtained from two devices worn in parallel was 8.2 ± 6.9%, which was comparable across postprandial periods and glucose concentrations. Mean CV of 54 sequences was 9.5 ± 11.0%

Conclusion:
GlucoTrack measurements are highly accurate and consistent. Specifically, sensor-to-sensor precision is comparable to that of continuous glucose monitoring systems and does not depend on glucose concentrations or postprandial time. Moreover, the performance of a specific device is constant under stable glycemic values.

Support Vector Machine Fed by CGM-based Glycemic Variability Indices Can Distinguish Between IGT and T2D Subjects

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Objective:
Glycemic Variability (GV) indices are compact metrics useful for characterizing the dynamic properties of CGM-acquired glucose concentration profiles. Although multiple GV indices have been proposed, there is still no consensus on how to use them. With the aim of investigating whether or not a suitable set of literature CGM-based GV indexes can be used for classification of subjects, in this work we consider the problem of automatically identifying subjects affected by IGT and T2D on the basis of their often similar CGM profiles and some basic clinical information by means of a machine learning approach.

Method:
The dataset included 62 subjects, 37 affected by IGT and 25 affected by T2D. Subjects were monitored using the iPro CGM system (Medtronic MiniMed, Inc., Northridge, CA) for six days (Botnia study in Finland, data acquired within the EU FP7 Mosaic project), resulting in CGM-profiles from which we extracted 37 GV indices. A linear Support Vector Machine model was used to classify subjects affected by IGT and T2D on the basis of a subset of GV indices and four clinical parameters (sex, age, BMI, waist circumference), after feature selection by an expert diabetologist to confirm the clinical interpretability of the indices.

Result:
Subjects affected by IGT/T2D are distinguished with 85.5% accuracy by means of an easily interpretable technique and a clinically sound set of indices. Expert-knowledge-driven feature selection increases classification performance by 33%.

Conclusion:
CGM-based GV indices and basic clinical parameters can be used to quite accurately distinguish the subtle differences between IGT and T2D glucose recordings by relying only on the metrics trusted by an expert clinician.

Using Video-Based Telemedicine to Reduce Hypoglycemia Fear in Parents of Young Children with Type 1 Diabetes: It's Feasible and Acceptable

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Objective:
Sixty percent of parents of young children (<7 years old) with type 1 diabetes (T1D) report moderate levels of hypoglycemia fear (FH), which is often associated with poor child glycemic control (Patton et al., 2011; Barnard et al., 2010). We describe the feasibility and acceptability of video-based telemedicine to deliver a group intervention targeting reduced FH in parents of young children with T1D.

Method:
Twenty-six parents (Parent age=34.80±5.36yrs; Child age=4.48±1.25yrs; Child sex=52.4% male; Race/ethnicity=91% Non-Hispanic White) enrolled in the Reducing Emotional Distress for Childhood Hypoglycemia in Parents intervention (REDCHiP). All sessions were conducted via Zoom, a HIPAA-compliant video-based telemedicine platform. Zoom accommodates group discussion and media presentations. It can digitally record sessions for reliability checks. Parents can connect to Zoom from their home or office, reducing the burden of travel. We interviewed 10 parents regarding the feasibility and acceptability of REDCHiP and our telemedicine format.

Result:
There were no differences in mean parent age (p=.37), child age (p=.88), child sex (p=.23), or race/ethnicity (p=.22) for this subset of the larger sample. Our results showed 92.3% parent attendance for sessions. Reliability checks revealed 85.7% researcher adherence to the treatment manual. These both support the feasibility and acceptability of delivering REDCHiP via video-based telemedicine. Qualitative interviews queried parents about their experience using Zoom (e.g., connectivity, system limitations, user feeling), barriers/facilitators of participation, and overall satisfaction. We will present common themes and illustrative quotes from parents' interviews.

Conclusion:
Group telemedicine delivery of behavioral interventions is potentially more scalable than traditional in-person treatment delivery, but is understudied in T1D. We show preliminary support for the feasibility and acceptability of using video-based telemedicine to deliver the REDCHiP intervention.

In Silico Assessment of Literature Methods to Adjust Insulin Bolus Dose according to CGM Trend

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Objective:
Continuous Glucose Monitoring (CGM) devices have been recently approved, by the FDA, for use in type 1 diabetes (T1D) treatment non-adjunctively, i.e. without confirmatory fingerstick (SMBG) measurements (Edelman, JDST, 2017). Consequently, setting the amount of insulin bolus by relying on the glucose rate of change (ROC) has become a topic of particular interest. Our aim is to evaluate extensively *in silico* the empirical literature methods proposed for such a task.

Method:
The UVa/Padova T1D Simulator was expanded using the decision-making model (reported by Vettoretti, 2ndrev. IEEETBE, 2017) to simulate 100 virtual patients in single-meal, noise-free scenarios with different preprandial BG and glucose ROC. Standard performance metrics, i.e. percentage of time spent in hypoglycemia (T_{HYPO}), hyperglycemia (T_{HYPER}) and euglycemia (T_{EU}), were used to compare a reference situation, i.e. bolus dose calculated using SMBG only using three literature methods (i.e. Scheiner, ADA, 2015, Pettus, JDST, 2017, Buckingham, PD, 2008).

Result:
When ROC is negative, the Pettus and the Buckingham methods obtained better results in terms of T_{EU} and T_{HYPO}. When ROC is positive, the Pettus and the Buckingham methods obtained better T_{HYPER}, while the best T_{EU} and T_{HYPO} values were obtained using the reference and the Scheiner method. Furthermore, we found that, for positive glucose ROC and high preprandial BG values, the scenario is very challenging. In this case, the reference and the Scheiner methods outperform the other methods by keeping T_{HYPO} almost to zero.

Conclusion:
A preliminary assessment of literature methods for insulin bolus dose adjustment using ROC has been made. Results strongly depend on BG and glucose ROC at mealtime. None of the methods clearly outperform the others. Still, further investigations are needed to optimize insulin therapy using CGM trends.

Feasibility of Full Automated Closed Loop Artificial Pancreas

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Objective:
The objective of this study is to evaluate the feasibility of a fully automated closed loop artificial pancreas (FACL-AP)

Method:
Data from two different clinical studies were combined to make a 24-hour day. The endpoints of average blood glucose, %time within the 70-180mg/dL range, and %time <70 mg/dL were used. We have combined data from two separate studies, a 22-hour exercise and overnight study and a 9-hour ad lib living study during the daytime.

Result:
Data for the 9-hour ad lib living study for 8am-5pm showed average glucose results were 208mg/dL, 35% time 70-180mg/dL, 0.6% time <70mg/dL. The carbohydrate intake during that period averaged 113 grams (range 33-190 grams) and the exercise averaged 24.8 minutes (range 0-84 minutes). The average glucose of the 5pm-8am 15-hour period of the exercise studies was 143mg/dL, 80% time within 70-180mg/dL, and 0% time <70mg/dL. Using a combination of the results from these two studies, we estimate the 24-hour endpoints. Average glucose was 167mg/dL, 63.1% time within 70-180mg/dL, and 0.2% time <70mg/dL. This would correlate to an A1c of 7.5%.

Conclusion:
A FACL-AP is potentially possible and would decrease diabetes burden and may be beneficial for many subgroups who have difficulty managing their diabetes (e.g., adolescents, those with difficulty carbohydrate counting, etc.) This study is limited because of the limitations inherent in combining data from two studies. New 72-hour studies are planned for the near future.

New Hybrid Closed Loop (HCL) Fuzzy Logic Investigational Device

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Objective:
The objective of this study is to assess the safety and effectiveness of a revised (v2.3) Dose Safety fuzzy logic controller (FLC) when used in hybrid closed loop (HCL) mode on a new iPhone ambulatory investigational device.

Method:
The CRC study ran from 0830-1530; a 75g CHO meal was given at 1100. The study included testing the robustness of the device by injecting CGM and pump wireless communication failures into it. The new investigational device uses an iPhone, Dexcom G4 CGM and an Insulet OmniPod pump. At this time, 5 subjects are enrolled and 3 studies have been completed. Two studies were cancelled due to wireless communication issues caused by high electromagnetic interference (EMI) in the clinical research center. Revising the system startup procedure corrected the problem. The FLC dosing algorithm is designed to run 24-hours per day as a fully automated closed loop (FACL) dosing algorithm. It doesn't have a meal CHO input or meal notification. To prevent over-insulinization after the manual bolus, the device suspends FLC dosing when a manual insulin bolus is detected, and then resumes FLC dosing after 105 minutes.

Result:
Clinical endpoints: 0.0% time < 70mg/dL; 96.3% (SD 0.06) time within 70-180 mg/dL; 3.7% (SD 0.06) time > 180 mg/dL. Mean glucose was 124.1 (SD 22.8). The system uptime was 100%. The mean time to peak postprandial blood glucose was 83.0 minutes (SD 7.2). Blood glucose was falling when the FLC resumed dosing after the 105-minute suspension so, by design, very little insulin was delivered after the mode transition.

Conclusion:
Initial HCL performance, although from a very small number of subjects, is excellent. The new Dose Safety investigational device shows promise for use in upcoming hotel studies.

A Proof-of Concept Study to Evaluate a Weekly Physician-Driven Insulin Titration Algorithm in Patients Prescribed V-Go® Wearable Insulin Delivery Device

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Objective:
Therapeutic inertia is prevalent with insulin intensification. To support development of dosing guidance, this retrospective proof-of-concept study evaluated the use of a weekly physician-driven insulin titration algorithm in patients prescribed V-Go in order to formulate the design of a prospective patient-driven insulin titration study. Improvement in glycemic control with V-Go is well documented yet no data exist evaluating efficacy and safety outcomes when a specific dosing algorithm is applied for titration. Primary endpoints of this evaluation were achievement of A1C targets (<7.5%) and prevalence of hypoglycemia based on self-monitored blood glucose logs.

Method:
Electronic medical records were used for the evaluation. Patients' bolus doses were up-titrated weekly/meal when two hour postprandial averages exceeded 170 mg/dl and down-titrated when below 100 mg/dl. Basal rates were adjusted if needed following bolus dose optimization. Four-point daily glucose profiles were used for titration decisions.

Result:
Fifteen patients with T2DM (mean age 60 y; A1C 8.7%; weight 116 kg) are evaluated after four months of which thirteen administered insulin (mean total daily dose (TDD): 144 U/day) at baseline. After one week, bolus up-titration occurred in 73% of patients (18 to 33 bolus U/day) and active bolus titration continued for two additional weeks. Basal rates increased in five patients and decreased in one patient during the first month. A1C target was achieved in 67% of patients. Hypoglycemia prevalence decreased from 23% at baseline to 7% of patients by four months despite significant A1C reduction (8.7 to 7.1%; $p<0.001$). TDD of insulin decreased to 60 U/day; $p=0.002$.

Conclusion:
The adoption of a physician-driven titration algorithm to optimize insulin dosing for V-Go proved safe and resulted in clinically relevant glycemic improvement. Applying these findings to a patient-directed approach needs further investigation.

Determining Glucose Ingestion and Appearance from Frequently Measured Glucose Concentrations

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Objective:
The two objectives were: 1) to back-determine glucose ingested from the evaluation of a 75-g oral glucose tolerance (OGT) challenge curve and, 2) to determine the amount of glucose from that challenge appearing in the extracellular space for disposition.

Method: OGT curves from untreated subjects with varying degrees of glucose tolerance were studied. The extracellular space (ES) was estimated using Kg body weight and hematocrit. The peak (Pk) and baseline (BL) glucose concentrations multiplied by "*e*" and divided by "*e*", respectively provide the basis for calculating the value of the extracellular glucose concentration change. The product provides the amount of glucose appearing in the extracellular space. (BL – BL/e)*ES added to the amount of glucose in the ES approximates the amount of glucose ingested.

Result:
Total glucose appearance in the ES was calculated for normal glucose tolerance, impaired fasting glucose, impaired glucose tolerance, and impaired fasting and post-prandial glucose. The back-calculation to the amount of glucose ingested showed a close correspondence with the known amount.

Conclusion:
Hepatic glucose uptake first pass closely corresponds to the decrease in hepatic glucose production and is insulin dependent in varying degrees of glucose intolerance. All glucose ingested appears in the extracellular space in impaired fasting with postprandial glucose intolerance. Knowing the amount of glucose ingested by back calculation and the amount of appearance in the extracellular space should contribute to better diabetes management and the interpretation of responses to treatment of subjects with varying degrees of glucose intolerance. Additional calculations must be made to account for protein, fat, and the effect of activity and medication on changes in glucose appearance and will require further study. Can this methodology be a substitute for "carb counting?"

Evaluation of a Highly Accurate BGMS based on Innovative Optical Transmission Absorbance System

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Objective:
Because blood glucose monitoring (BGM) is essential to diabetes care and management, further improvement in the accuracy of BGM is mandatory to achieve better glycemic control of diabetics. At last year's Diabetes Technology Meeting (DTM), we proposed the principle and the evaluation results of BGMS based on an innovative optical transmission absorbance system. In this paper, we report the evaluation results of our newly developed super highly accurate BGMS.

Method:
To realize the high-accuracy measurement of the blood glucose level, we have developed a highly sensitive reagent, with a brand-new enzyme, an original absorption dye, and accurate hematocrit detection technology, with multi-wavelength detection (reported in DTM2016). In order to realize highly accurate and convenient blood glucose measurements, we developed a novel BGMS, with a small meter, based on an original optical system, and a test strip with a simple structure.

Result:
Accuracy of our new BGMS was evaluated with blood samples. We have achieved an accuracy of ±5%.

Conclusion:
We have developed a novel BGMS with a highly sensitive reagent and an innovative optical transmission absorbance system. Our new BGMS achieved an accuracy of ± 5%.

Clinical Feasibility and Home-Use Study of a Percutaneous Optical Fiber Glucose Sensor

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Objective:
Current continuous glucose monitoring systems (CGM) exhibit a rather short lifetime of up to 7 days. We present data of a novel CGM (FiberSense) with improved duration of action and accuracy based on a fluorescent biosensor placed on the tip of an optical fiber.

Method:
FiberSense was inserted in the subcutaneous upper arm tissue of six patients and worn under home-use conditions for 29 days. Patients were blinded to FiberSense readings. During 6 in-clinic measurement sessions of 4-6 h each, FiberSense readings were compared to capillary blood glucose measured by a laboratory method and a commercial CGM system placed at the abdomen. The commercial system was replaced every week. Blood glucose was altered by administration of insulin and carbohydrates. During home-use, patients took at least 4 to 5 SMBG readings daily. Fluorescence was measured using a miniaturized photometer. Two-point calibration, as well as one-point calibration, was applied.

Result:
FiberSense was clinically well tolerated for up to 29 days without complications or signs of inflammation. The pooled data exhibit a MARD of 10.3% (two-point calibration) compared to 12.3% for the commercial CGM system used at the same measurement times. MARD changed only marginally over the course of the trial.

Conclusion:
The present clinical feasibility study proves the capability of FiberSense to replace current CGM systems with the possibility to extend the duration of action to up to 29 days.

The "Catch 22" of Sleep: Effects on Fear of Hypoglycemia and Parenting Stress

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Objective:
Parents work 'around the clock' to care for their young child (<7yrs) with type 1 diabetes (T1D) and encounter unique challenges in daytime and nighttime management. We examined the parental factors associated with child sleep duration and efficiency in a sample of families of young children with T1D.

Method:
Nineteen parents and children (parent mean age= 35.21±5.53yrs; child mean age= 4.63±1.38yrs; child sex= 50% male; race/ethnicity = 88.9% Caucasian) participated. Children's average A1c was 8.4±1.14 and 72.2% used insulin pumps. Parents completed the Hypoglycemia Fear Survey-Parents of Young Children (Patton et al., 2008), Pediatric Inventory for Parents (Streisand et al., 2001), and provided a medical history of their child. Children wore an accelerometer on their non-dominant wrist for five consecutive days. We calculated sleep duration and efficiency from accelerometer data and examined Pearson correlations between parent's hypoglycemia fear (FH), parenting stress, and children's sleep.

Result:
Children had a mean sleep duration of 8.8 hours and mean sleep efficiency of 88.5%. Sleep duration was positively associated with FH (r=0.61, p=0.003). Sleep efficiency was positively associated with FH (r=0.47, p=0.020) and negatively associated with the frequency (r=-0.65, p=0.011) and intensity (r=-0.57, p=0.005) of parenting stress.

Conclusion:
Young children with T1D in this sample did not meet the recommended 10-13 hours of sleep/night. In addition, parents' FH and parenting stress are related to children's sleep duration and efficiency. Specifically, our findings suggest a "Catch 22;" children's poor sleep patterns were negatively associated with parent's perceived stress around daytime T1D management, but children's better sleep patterns were related to greater parental FH, which may be related to nighttime lows. These findings highlight an understudied way T1D can negatively impact family functioning.

Insulin Phenolic Excipients Induce Local Subcutaneous Inflammation and Alter Insulin Pharmacokinetics *In Vivo*

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Objective:
Continuous subcutaneous insulin infusion (CSII) therapy has clinical benefits for diabetes management yet is impacted by an abbreviated 3-day infusion set usage life. As set wear times increase, patients experience altered pharmacokinetic (PK) and pharmacodynamic (PD) profiles, adverse tissue reactions, and loss of glycemic control. Previous research has shown that insulin phenolic excipients, *m*-cresol and phenol, induce acute inflammatory cytokine release *in vitro*, implicating them as a culprit for limited set lifetime. However, these physiological and pharmacological effects of excipient exposure have not been reliably demonstrated *in vivo*. Using a preclinical swine model, this abstract shows for the first time that phenolic excipients both induce an acute inflammatory response and alter insulin PK.

Method:
Female Yorkshire swine (n=5) received subcutaneous bolus injections of *m*-cresol and phenol at various physiologically relevant doses (0.5 - 5 mg in 250 µL of phosphate buffered saline) to assess the inflammatory effect. Saline was used as a negative control. Six hours following dose treatment, biopsies were taken, homogenized, and processed with Tissue Protein Extraction Reagent. Contents were then analyzed via ELISA for pro-inflammatory IL-6 content. To assess excipient-related PK effects, female Sinclair swine (n≥5, full crossover design) were given one of three treatments: (1) a 5-mg subcutaneous injection of *m*-cresol (250 µL volume), (2) a 100 µL subcutaneous injection of lipopolysaccharide (LPS) at a dose of 10 EU/kg (positive control), or (3) a 100 µL subcutaneous saline injection (negative control). As an initiator of inflammation, LPS was used to mimic local CSII-induced tissue effects. Twenty-four hours following dose treatment, an insulin PK study was performed by injecting 4 U of U100 insulin lispro into the treated site. Glucose levels were maintained via catheter fluid therapy of 5% dextrose at a rate of 300 mL/hr. Blood samples were taken at specific time points for 6 hours following injection, serum separated and analyzed for lispro content via a lispro-specific radioimmunoassay. PK metrics (C_{max}, t_{max}, AUC and AUC_{60}) were statistically compared across treatments using either a one-way ANOVA with associated post-hoc tests for normally distributed data or a Kruskal-Wallis test for non-parametric data ($p \leq 0.05$).

Result:
Both excipients induced elevated IL-6 release that was statistically different ($p<0.05$) from saline controls at doses ≥ 2 mg for *m*-cresol and ≥ 3 mg for phenol. Moreover, increased IL-6 levels were linearly correlated with increasing *m*-cresol and phenol presence at doses ≥ 2 mg. Cresol treatment also altered insulin PK, significantly decreasing C_{max}, AUC and AUC_{60} relative to the saline control, suggesting that phenolic excipient exposure alters insulin PK/PD by reducing the amount absorbed from a local subcutaneous dose.

Conclusion:
Here we present for the first time *in vivo* data demonstrating the effect of insulin phenolic excipients on both local subcutaneous physiology and downstream insulin absorption. Results establish that excipients induce local inflammation that could contribute to adverse changes in insulin PK metrics. As shifts in PK/PD and loss of glycemic control are correlated to limited infusion set lifetime, these findings suggest that local inflammation should be further studied as a factor affecting clinical device performance.

Preclinical stability results of Glucowizzard™

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Objective:
Biorasis, Inc. and the University of Connecticut are developing a highly miniaturized (0.5 ´ 0.5 ´ 5 mm), totally implantable device (Glucowizzard™) for long-term (3-6 months) continuous glucose monitoring (CGM). In order to afford such miniaturization, our team is leveraging the integration of multiple technologies packaged within a light-based powering and communication platform. The objective of this work is to demonstrate long-term stability of Glucowizzard™ in a rabbit model.

Method:
Glucowizzard™ is composed of: *(a)* a miniaturized implant that is implanted subcutaneously at the upper part of the wrist; *(b)* a watch-like proximity communicator that powers and communicates with the implant through the skin; and *(c)* a smart phone app that communicates via Bluetooth with the proximity communicator and assists with data storage and plotting as well as with other higher functions. Glucowizzard™ employs a first-generation Clark-type enzymatic amperometric sensor for detecting glucose levels, along with an active suppression of tissue reaction through a drug-eluting biocompatible coating. The current, fully-integrated Glucowizzard™ implant with size of 1.2 ´ 1.2 ´ 7 mm was tested *in vitro* and *in vivo* (using a rabbit model).

Result:
A fully integrated Glucowizzard™ was shown to exhibit a linear and stable *in vitro* response to glucose throughout the physiologic glucose range (2.5 – 20 mM). The stability of the entire platform was also tested *in vivo* (using a rabbit model) for a period of 3 months.

Conclusion:
The first fully integrated Glucowizzard™ platform was developed and successfully tested both *in vitro* and *in vivo* (using a rabbit model). The data collected so far prove the feasibility of this approach. Future studies will focus on further *in vivo* testing in large animals.

Hypoglycemic Exposure Among Children Using the Dexcom Share Cloud

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Objective:
Delayed recognition of hypoglycemia poses a risk for children with type 1 diabetes and is a concern for their caregivers. We hypothesized that real-time access to children's continuous glucose monitoring (CGM) data would result in earlier recognition and treatment of presymptomatic hypoglycemia in a population of children whose CGM data were shared and monitored remotely.

Method:
Share/Follow is part of the Dexcom G5 Mobile CGM system which allows for remote monitoring of data from one "sharer" by up to 5 "followers." It relies on data transfer from the sharer's Dexcom G5 Mobile App to the Dexcom Share Cloud, and then to the linked Follow app on the follower's smart device via Wi-Fi or cellular networks. We identified 8,805 children ages 2-14, who had uploaded data during May 2017 and categorized them according to the presence or absence of followers on 2 June 2017. Hypoglycemia was measured as the percentage of sensor glucose (SG) values <70 mg/dL ("%<70"). Between-category differences were calculated using t-tests.

Result:
Children in the "no followers" (n=197) and "≥1 follower" (n=8,608) categories had mean (±SD) ages of 9.3±3.3 and 10.4±3.1 years, respectively ($p<0.0001$); SG values of 156.3±60.7 and 165.9±35.3 mg/dL, respectively ($p<0.03$); sensor usage of 12.9±10.1 and 24.9±8.2 days/month, respectively ($p<0.0001$); and %<70 of 19.0±27.6 and 10.9±12.7, respectively ($p<0.0001$).

Conclusion:
Over 97% of children using the Dexcom Share Cloud had at least one associated follower. Compared to children with no followers, these children had increased sensor usage and 43% fewer SG readings indicative of hypoglycemia, consistent with appropriate and timely involvement of follower(s). Children with ≥1 follower also had slightly higher mean glucose levels, but less glycemic variability, than children with no followers.

Hypoglycemic Exposure Among Older Adults Using the Dexcom Share Cloud

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Objective:
Delayed recognition of hypoglycemia poses a risk for older adults with type 1 diabetes and is a concern for their friends and family members. We hypothesized that real-time access to continuous glucose monitoring (CGM) data would result in earlier recognition and treatment of presymptomatic hypoglycemia in a population of adults whose CGM data were shared and monitored.

Method:
Share/Follow is part of the Dexcom G5 Mobile CGM system which allows for remote monitoring of data from one "sharer" by up to 5 "followers." It relies on data transfer from the sharer's Dexcom G5 Mobile App to the Dexcom Share Cloud, and then to the linked Follow app on the follower's smart device using either Wi-Fi or cellular networks. We identified 1,653 adults, ages 65 and older, who had uploaded data during May 2017 and categorized them according to the presence or absence of followers on 2 June 2017. The summary statistic associated with hypoglycemia is the percentage of sensor glucose values <70 mg/dL ("%<70"). Between-category differences were calculated with t-tests.

Result:
Adults in the "no followers" (n=934) and "≥1 follower" (n=719) categories had mean (±SD) ages of 69.9±4.7 and 73.0±8.1 years, respectively ($p<0.0001$); sensor glucose values of 145.8±36.2 and 151.6±35.1 mg/dL ($p<0.002$); sensor usage of 24.3±8.8 and 26.0±7.6 days/month ($p<0.0001$); %<70 of 10.3±15.4 and 8.9±12.6 ($p<0.04$).

Conclusion:
Over 43% of older adults using the Dexcom Share Cloud had at least one associated follower. Compared to those with no followers, these adults had higher mean SG values, used the sensors more frequently, and had 14% fewer SG readings <70 mg/dL. Older adults may benefit from technologies that facilitate involvement of others in diabetes-related treatment decisions.

Technology-Enabled Diabetes Self-Management Education & Support

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Objective:
This study will present findings of the American Association of Diabetes Educators (AADE) Technology Workgroup assessment of the technology landscape in diabetes self-management education and support.

Method:
In 2016, AADE convened a group of technology-aware diabetes educators, people with diabetes, and technology providers to explore the current technology landscape and make recommendations for future strategic advancement. The committee evaluated the current diabetes landscape from the perspective of educators, people with diabetes, and the association. These findings guided further discussion and the development of a Technology Framework & Strategic Plan for the association. Because the technology environment is rapidly evolving, a literature review was conducted to determine the state of evidence. The robust literature published since 2011 warranted a systematic review.

Result:
Two major deliverables emerged from the work group: 1) The AADE Technology Framework was developed to lead the association efforts to define the domains of interest. The framework is based on the Architecture for Integrated Mobility (AIM) which integrates the technology user ecosystem. 2) The Technology-Enabled Self-management (TES) feedback loop is a new model supported by the outcomes of the systematic review. The key elements required for improved A1C in digital diabetes self-management include: 2-way communication, analysis of patient generated health data, tailored education, and individualized feedback.

Conclusion:
Technology areas of interest include more than diabetes devices e.g., pumps and continuous glucose monitors. Digital diabetes self-management that incorporates the TES feedback loop improves A1C and may increase access to diabetes self-management education and support in real-time when the person with diabetes is ready to engage. Convening broad stakeholder groups is necessary to ensure a valid assessment of the state of the science.

Evaluation of a New Non-Invasive Glucose Monitoring Device by Means of Standardized Meal Experiments

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Background: Frequent blood glucose readings are the most cumbersome aspect of diabetes treatment for many patients. Therefore, devices are under development that assess glucose by means of non-invasive (NI) technologies. TensorTip CoG (CoG, CNOGA Medical Ltd, Caesarea, Israel) employs optical measurements from reflection and transmission of visible and near-infrared light at the tip of any finger. The light is absorbed by a color image sensor in which a change in the tissue pattern tint is identified by a dedicated mathematical algorithm as a change in a tissue glucose or other physiological body tissue signals. The mathematical algorithm is derived from chaos theory in order to deal with the disorder of the raw data collected by the color image sensor. In preparation of regular operations, the device needs a comprehensive calibration procedure with frequent comparator measurements between the NI readings and an add-on, built-in, regular invasive glucose oxidase-based blood glucose meter.

Method: After successful calibration, 36 participants (15 healthy subjects, 6 type 1 diabetes and 15 type 2 diabetes patients, 18 female, age: 49±18 yrs.) ingested a standardized meal and blood glucose was assessed from capillary blood samples by means of the invasive CoG-meter, YSI Stat 2300 plus, Ascensia Contour Next, and the NI-CoG Method, at time-points -30, 0, 15, 30, 45, 60, 75, 90, 120, 150, and 180 min. Statistical analysis was performed by consensus-error-grid (CGA) and calculation of mean absolute relative differences (MARD) in comparison to YSI.

Result: For the NI-CoG technology, 100 % of the data pairs were found to be in CGA zones A (96.6 %) and B (3.4 %), while all data pairs were seen in zone A only for the Invasive CoG meter results and Contour Next. MARD over the entire measurement range (59 – 317 mg/dL) was calculated to be 4.2 % for Contour Next, 9.2 % for the invasive CoG meter, and 14.4 % for the NI CoG Technology. No significant differences were seen between the results derived from the tested sub-populations (healthy subjects or patients with type 1 or type 2 diabetes).

Conclusion: After appropriate individual calibration of the non-invasive technology, both the non-invasive component and the invasive component of the TensorTip CoG device were shown to reliably track tissue and blood glucose values, respectively, during standardized meal experiments with high accuracy in comparison to the YSI standard reference method. This enables patients with diabetes to monitor their glucose levels frequently, reliably, and, most important of all, pain-free.

How to Miniaturize an Osmotic-Pressure-based Implantable Glucose Sensor?

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Background:
Competitive and reversible binding of glucose, or the polysaccharide dextran to the glucose-specific lectin concavalin A (ConA), is the technical basis for a novel implantable glucose affinity biosensor (Sencell, Lifecare, Norway).

Method:
The Sencell technology uses osmotic pressure differences arising between a reagent chamber (containing active fluid with ConA and dextran) and a diffusion chamber (in direct contact with interstitial fluid) to determine interstitial glucose concentrations. Both compartments are separated by a nanoporous membrane permeable to glucose and water, but not to ConA or dextran. Proof of concept studies have been successfully performed in pigs with wired working prototypes (2 x 1.5 x. 0.6 cm^3). The next development steps include substantial miniaturization in combination with wireless data and energy transfer.

Result:
Miniaturization of the current osmotic pressure Sencell sensor to the planned size of 2 x 3 x 6 mm^3 requires access to small and very sensitive pressure transducers. A suitable solution is nano strain sensors based on nanogranular metals with a size of 20 x 50 nm^2. The sensors are printed on the bottom of the measurement chamber by means of a proprietary 3D printing technology. The augmented bottom then functions as a pressure transducer. The nano strain sensors can be printed on any type of material and do not pose any restriction regarding the geometrical configuration of the substrate. Thus, the bottom of the measurement chamber can be freely adjusted towards a sensitive (e.g. thin) pressure sensor membrane with very small diameter. Such a device is an ultra-miniaturized pressure sensor offering a higher sensitivity compared to common piezo-resistive pressure sensors. Osmotic pressure formation in a closed volume is dependent on the concentration of osmotically active particles. Since the current ConA/dextran system becomes more viscous upon up-concentration, a new binding partner for ConA has to be identified which maintains similar fluidic properties even at high concentrations. Wireless power induction and data transfer requirements can be established by commercially available microelectronic components already in use in other medical devices (e.g. in implantable temperature sensors). The potential energy consumption of nanogranular strain sensors lies in the µW regime. Additionally, the nano strain sensors can be driven with very low voltages below 1 V.

Conclusion:
Combining these technologies offers an attractive approach to achieve miniaturization of a glucose affinity biosensor to the desired small size. The Sencell device is expected to provide higher convenience than needle sensors, while having the advantage of pronounced longevity by measuring interstitial glucose with a reversible physical method that does not consume any chemistry during the measurement process.

Nano-Immuno-Assay (NIA) – Use of Cantilever-based Nanosensors Functionalized with Specific Antibodies for Measurement of Proteins in Biological Samples

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Background:
Nanosensors for direct protein determination by means of a nano-immunoassay (NIA) are composed of a cantilever structure with a surface that has been functionalized by the binding of specific antibodies directed against the desired target protein. Binding of the antigen results in a change of the surface tension and leads to bending of the cantilever. A metallo-carbonated nanosensor element 3D-printed on the basis of this cantilever transfers this micromechanical bending into an electrical signal. The timing of the binding process to completion in a defined sample volume is directly related to the concentration of the analyte in the sample.

Method:
A proof of concept study was performed to specifically measure human IgG contaminations in an artificially produced solution containing human and chicken IgG. The NIA-sensors were functionalized with protein A to enable human IgG antibody binding. The artificially produced samples (50 % human IgG and 50 % chicken IgG) were tested for IgG presence by means of NIA and also by common anti-human IgG ELISA as laboratory reference method. Each experiment was carried out in triplicate.

Result:
The ELISA reference method was shown to have 100 % specificity within an observed linear detection range from 10 ng/mL to 1000 ng/mL. With similar specificity, the linear detection range of the NIA was shown to be between 0.01 ng/mL to 1 ng/mL (i.e., the NIA was 1000-fold more sensitive than the reference ELISA). Minor unspecific binding of IgG was observed with the NIA technology at chicken IgG concentrations > 1000 ng/mL

Conclusion:
In our proof-of-concept experiment, the NIA in comparison to the classic ELISA was shown to be substantially more sensitive and was less time and resource consuming. With the NIA, it is possible to determine the analyte-binding directly within minutes and without any further labeling requirement. In addition, the small size of the NIA sensors allows for integration into Lab-on-a-Chip technologies, which will enable point-of-care testing with a laboratory quality level.

Targeting the ß-Cell – Successful Intensive Temporary Pharmacological Intervention DET (De-escalation Treatment) to Stop Disease Progression in Patients with Type 2 Diabetes

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Background:
Type 2 diabetes is considered to be a chronic progressive disease, naturally requiring a continuous treatment intensification, and resulting in secondary microvascular and macrovascular complications after sufficiently long disease duration. The underlying pathophysiological disorders (ß-cell dysfunction (ßCD), insulin resistance (IR), and chronic systemic inflammation (CSI)) are present in the individual patient with different degrees of severity. Instead of following common treatment guidelines, we have alternatively employed intensive temporary multi-pharmacotherapy interventions, de-escalation treatment (DET), to achieve sustained improvement in ß-Cell function and glucose control.

Method:
Personalized treatment selection was based on the results of a biomarker panel consisting of classic biomarkers (glucose, lipids, A1c) and additional pathophysiology-oriented biomarkers (hsCRP, intact proinsulin, adiponectin). Here we report on the results (with up to 12 years of follow-up) of 22 patients (8 women, 14 men, age: 62±8 yrs., disease duration: 12±7 yrs., A1c: 7.8 %, BMI: 33.2±2.4 kg/m²). The temporary intensive treatment approach lasted 3 months and consisted in general of low doses each of basal insulin to address ßCD, treatment of IR (exercise and/or pioglitazone), a component to reduce CSI (diet, GLP-1 and/or SGLT-II), and an additional hypoglycemic intervention (metformin, DPP-IV), if applicable.

Result:
The DET approach was well tolerated (nausea: 4 cases, edema: 1 case). All patients experienced either a normalization or pronounced improvement of their glycemic control without any report of hypoglycemia. Mean A1c after 3 months improved to 5.9±0.4 %. Intact proinsulin decreased from 9.3±2.1 pmol/L to 2.3±0.6 pmol/L, adiponectin improved from 3.4±1.2 to 8.6±2.4 mg/dL, and mean body weight decreased by 2.4±1.1 kg (all: $p<0.01$). After the DET, the majority of the patients were continued with measures of lifestyle only or a drug monotherapy targeting the major component of their individual diabetes phenotype. The DET effect lasted on average for about 2 years (range until next DET: 6 months to >11 years). Maintenance of the DET effect was associated with adherence to recommended lifestyle measures. Lack of compliance with the complex treatment requirements were the reasons for treatment failure in two patients resulting in chronic disease progression.

Conclusion:
Regeneration of ß-cell function by means of DET resulting in repeatable consecutive “type 2 honeymoon periods” may help to achieve a temporary (or in some cases even permanent) stop of chronic disease progression. We currently investigate the long-term effects of repetitive DET interventions. We are afraid, however, that we will not live long enough to see this personalized treatment approach become an evidence-based alternative way to treat type 2 diabetes.

Performance Evaluation of the ADAMS™ A_{1c} HA-8180V System

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Objective:
Glycosylated Hemoglobin (A_{1c}) measurements are used to monitor long-term glycemic control in diabetic patients. Uncontrolled blood glucose levels can lead to serious microvascular and macrovascular complications. ARKRAY's ADAMS™ A_{1c} HA-8180V, a robust fully automated A_{1c} measurement device based on ion-exchange HPLC technology, was recently determined by the FDA to be substantially equivalent to a legally marketed predicate device. The purpose of this study was to evaluate the ADAMS™ A_{1c} HA-8180V accuracy and precision against the TOSOH G8 (TOSOH Bioscience, Inc., CA, USA).

Method:
An IRB approved method comparison study was conducted using the ARKRAY ADAMS™ A_{1c} HA-8180V system and the TOSOH G8 system. A total of 143 venous samples ranging from 4.1% to 17.6% A_{1c} were tested in singlet as both whole blood and hemolysate samples on both systems. The resulting data sets were analyzed using a weighted Deming regression. A precision study was also conducted using three HA-8180V devices, three reagent lots per device, and seven samples over 60 days (20 days per lot/device combination).

Result:
The whole blood weighted Deming regression equation was: $y = 0.99x + 0.10$ with an $r = 0.998$. The hemolysate weighted Deming regression was: $y = 0.99x + 0.08$ with an $r = 0.998$. Additionally, 99.3% (CI range: 96.15% to 99.98%) of all HA-8180V results were within 6% of the TOSOH G8 results. The HA-8180V system also demonstrated average repeatability imprecisions of 0.3% & 0.3% and average reproducibility imprecisions of 0.8% & 0.9% for whole blood and hemolysate samples, respectively.

Conclusion:
The ARKRAY ADAMS™ A_{1c} HA-8180V system demonstrated high analytical performance equivalent to the TOSOH G8 system.

Long Term Implantable Continuous Glucose Monitoring (CGM) System Demonstrates Benefits in Glycemic Control over a 90-Day Period

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Background: CGM use over prolonged periods can be linked to improvements in time within target, average glucose, A1c reduction, and hypoglycemia prevention. The Eversense® CGM System (Senseonics Inc. MD, USA) consists of an implantable fluorescence-based glucose sensor that lasts up to 90 days, a wearable smart transmitter, and a mobile app to display real-time glucose readings every 5 minutes. The sensor glucose reading is calculated on the wearable smart transmitter and sent to the smartphone via Bluetooth low energy. This first generation Eversense CGM system is commercially available in Europe.

Method: A group of 56 people with diabetes who initiated use of the Eversense CGM system in May 2017 were followed over the 90-day sensor life period to evaluate the group's glycemic status. The status indicators utilized were time within target between 80-180 mg/dL, percentage of time in low glucose below 80 mg/dL, percentage of time in high glucose above 180 mg/dL, and average glucose reading. The data were calculated cumulatively over 30-day intervals. The Eversense Data management system (DMS), a cloud based platform, was utilized to analyze and calculate statistics of the data collected over the 90-day period.

Result: The results show that users observed an improvement in glycemic control. Over 90 days, users intensified their diabetes management to achieve target glucose levels while progressively reducing hypoglycemia. Results also show reduction in average glucose values during the same period as displayed below:

	MAY	JUNE	JULY
LOW (<80 mg/dL)	9%	8%	7%
WITH-IN (80-180 mg/dL)	58%	60%	62%
HIGH (>180 mg/dL)	33%	32%	31%
AVERAGE GLUCOSE VALUE	159 mg/dL	154 mg/dL	152 mg/dL

Conclusion: Long term use of CGM can help with optimization of diabetes control and a reduction in time spent in hypoglycemia. Real-time glucose trend data helps patients anticipate highs and lows and take action to mitigate glycemic variability.

Strategies for Blood Glucose Control during Unannounced Meals

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Objective:
The objective of this study is to use a previously presented meal detection algorithm to employ strategies to reduce postprandial hyperglycemia and improve outcomes caused by unannounced meals in the artificial pancreas.

Method:
Postprandial hyperglycemia minimization strategies were employed in a proportional-integral-derivative (PID) controller with sliding mode reference conditioning and the performance was compared to the same closed-loop setting without pre-meal boluses. The meal detection algorithm calculates the cross-correlation between the difference of a disturbance parameter, estimated using an Unscented Kalman filter, and continuous glucose monitor (CGM) levels. Two thresholds were employed: one for high sensitivity, which allowed for a predefined fixed bolus to be given at an earlier time and another for high specificity, which allowed for a correction bolus to be given later. This methodology was tested *in silico* using the UVa-Padova simulator with 10 adult patients over a period of 14 days (42 meals per subject) with additional variability on insulin sensitivity, meal estimation, and insulin pharmacokinetics.

Result:
Mean CGM was 149 mg/dl vs. 156 mg/dl (p=0.002), time within range (70-140mg/dl) was 52% vs. 47% (p=0.0001), time within range (70-180mg/dl) was 79% vs. 74% (p=0.009), time greater than 300 mg/dl was 0% vs. 0.4% (p=0.2), time greater than 250 mg/dl was 1% vs. 4% (p=0.04), time greater than 180 mg/dl was 21% vs. 26% (p=0.009), and time less than 70, 60, and 50 mg/dl was 0% for both.

Conclusion:
Significant improvement in glucose control is observed when incorporating a meal detection algorithm in a PID control strategy. However, a large gap remains when compared to announced meals and further work is required to improve these outcomes.

Assessment of the Performance of the WaveForm CGM System

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Background:
WaveForm is now in the final stages of commercially launching a new CGM system. A critical step in that process is to finalize the algorithm and confirm the clinical performance of the device.

Method:
The Pilot 8 Clinical Evaluation of the System included 15 subjects with type 1 and 2 diabetes. On day 1, 4, and 7, 12-hour in-clinic CGM accuracy studies were performed. Each subject wore two CGM devices. YSI glucose measurements were performed on the plasma for venous blood that was sampled every 15 minutes. Calibrations were performed at the beginning of each in-clinic day and a prospective analysis was performed using an algorithm that had been developed with part of the data set. Sensor performance was retrospectively assessed by analysis of mean absolute relative difference (MARD), mean absolute difference (MAD), and the Clarke error grid.

Result:
Twenty eight out of 30 sensors performed for the full 7 days of testing. The MARD of 28 sensors was 14.9% and MAD was 19.8 mg/dL. Clarke error grid analysis showed that 96% of data points were in zone A and B, with the remaining 4% in C and D-zones.

Conclusion:
The overall performance of the CGM device meet the goals that were set for the system. The data is now being used to optimize the sensor and to improve the algorithm.

Results of First 10-day use Study for WaveForm CGM

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Background: WaveForm is now in the final stages of commercially launching a new CGM system. It is intended that the CGM will provide blood glucose equivalent information to the user over a period of 10 days.

Method: The evaluation of the system included 15 subjects who have either type 1 or type 2 diabetes. On day 1, 4, 7, and 10, 12-hour in-clinic CGM accuracy studies were performed. Each subject wore two CGM devices. YSI glucose measurements were performed on the plasma from venous blood every 15 minutes. Calibrations were performed at the beginning of each in-clinic day. On day 10, half the sensor transmitters were replaced by transmitters that had been specifically designed to more accurately track motion. On day 10, the subjects participated in a one-hour exercise routine to evaluate the impact of motion on sensor performance.

Result: Twenty six out of 30 sensors performed for the full 10 days of testing. Two sensors did not remain attached due to adhesive failure issues. An initial analysis has been completed on the first six subjects. The overall mean absolute relative difference (MARD) for all 4 in-clinic days was 15.1%, Day 7 MARD = 13.6%, and Day 10 MARD 13.2%.

Conclusion: The study results confirmed that the WaveForm CGM can be used effectively for 10 days.

Adaptive Learning Postprandial Hypoglycemia Prevention Algorithm for the Artificial Pancreas

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Objective:
The objective of this study is to mitigate postprandial hypoglycemia by adaptively changing the postprandial insulin administration for an artificial pancreas (AP).

Method:
An adaptive learning postprandial hypoglycemia-prevention algorithm (ALPHA) was introduced to adjust postprandial insulin rates based on the prior postprandial glucose. ALPHA uses a post-prandial insulin delivery aggressiveness factor which updates when the sensed glucose, after the prior meal, deviates from the target range. ALPHA updates the aggressiveness factor in proportion to the excursion of the glucose beyond the target range. ALPHA was tuned to select the optimal window of time during which the postprandial aggressiveness factor was applied (from 30 minutes to 3 hours). ALPHA was evaluated within an AP (AP-ALPHA) on an *in-silico* virtual patient population across two days with 100 g meals and compared with an AP without ALPHA (AP). Percent time in hypoglycemia was the primary outcome measure for the second day.

Result:
AP-ALPHA yielded substantially reduced percent time in hypoglycemia, 0.2% [CI: 0.1-0.3] compared with AP, 4.1% [CI: 3.3-4.8] (Wilcoxon rank-sum: $p<0.001$). AP-ALPHA reduced the low blood glucose index (LBGI) to 0.7% [CI: 0.5 - 0.9] compared with AP, 3.2% [CI: 2.9 – 3.6], and the number of rescue carbs is reduced by 95% to 0.2/day per patient for AP-ALPHA compared with 3.5/day for AP ($p < 0.001$). The percent time in euglycemia was 87.0% for AP and 84.6% for AP-ALPHA ($p= 0.09$). The percent time in hyperglycemia was 9.0% for AP and 15.2% for AP-ALPHA ($p<0.001$). AP-ALPHA demonstrated better performance on day 2 compared with AP-ALPHA on day 1, 1.6% [CI: 1.3-1.9], demonstrating the benefit of providing a day to adapt.

Conclusion:
Incorporating an adaptive meal aggressiveness dosing factor into an AP can help reduce post-prandial hypoglycemia.

Non-Contact Wireless Electric Field Therapy to Enhance Diabetic Wound Healing

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Objective:
Electric field (EF) stimulation of tissue repair is promising for the treatment of chronic ulcers. Progress in developing EF-based therapies is impeded due to a poor mechanistic understanding of EF-cell interactions and EF effects on tissue repair. The overall goal of this research is to develop a nonpharmacological, non-contact, EF-based therapy for chronic diabetic wounds focused on correcting diabetes-induced deficiency in angiogenesis. The hypothesis is that a newly established EF modality can stimulate wound repair via activation of cells in the wound, enhance vascularization, and improve granulation tissue formation.

Method:
A custom set-up allowed non-thermal, non-contact, high frequency EF application to full-thickness wounds created in db/db mouse and porcine wound healing models *in vivo*. Theoretical simulations were performed using ANSYS software to quantitatively describe EF-cell interactions, the role of the EF frequency, and the extracellular substrate on cell activation; the results were then used to choose the optimal EF stimulation parameters. Therapy was applied 1 hr/day, 5 days/week for 1 week (mouse) or 2 weeks (porcine). Wound tissue was harvested and analyzed for wound morphology (hematoxylin and eosin – H&E) and vascularization (lectin).

Result:
Theoretical predictions demonstrated the frequency-dependent EF penetration into the cell cytoplasm can be varied by tuning the physical properties of the cell environment. *In vivo* wound treatment with high-frequency EF resulted in significantly improved wound healing at day7 (mouse) and day14 (porcine), including reduced epithelial gap, increased granulation tissue area, and capillary counts compared to control wounds that received no EF treatment.

Conclusion:
These findings demonstrate significant therapeutic potential of the proposed EF modality that may contribute to the development of new non-invasive treatments for impaired wound healing.

Fluoroscopic Assessment of Percutaneous Cannula Penetration Depth

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Objective:
Self-administered injection is a common practice for diabetes therapy and continues to increase in prevalence with subcutaneous (SC) tissue as the preferred site for syringes, pen injectors, and insulin pump systems. Ideally, devices should enable consistent and reproducible SC delivery regardless of variation in tissue morphology, injection location, and delivery technique. Therefore, a pre-clinical fluoroscopic imaging method was developed to accurately visualize and measure post-injection cannula penetration depth (CPD).

Method:
Currently no *in vitro* model exists to simulate the complexities of an intact *in vivo* integumentary system and animal models provide the best surrogate for evaluating injection dynamics/biomechanics. The skin and SC structures on the flank of 30-40 kg Yorkshire swine provide an effective facsimile of human abdominal tissue. Testing of 20µl injections (350 mg/ml Iohexol), using 5 different 6mm patient end length (PEL) syringes (n=50/group), were made on swine flanks and imaged using fluoroscopy. The radiopaque injectate effectively indicated the cannula tip location allowing for CPD measurements from the skin surface.

Result:
Mean CPD±SEM varied slightly across syringe types: A-7.32±0.15mm, B–8.38±0.13mm, C–7.24±0.12mm, D–7.21±0.12mm, E–7.45±0.13mm. All syringes demonstrated CPD greater than the nominal 6mm cannula PEL ($p<0.0001$). Mean CPD of device B was statistically greater than any other device ($p<0.001$); no other statistical differences were observed between devices.

Conclusion:
CPD greater than cannula PEL may be due to differences in localized tissue compression created by device design or to the technique used during the injection procedure. Devices with identical PEL produced different CPD, demonstrating that PEL alone may not be a reliable predictor of injection depth. Factors influencing CPD should be further examined to increase the consistency and reproducibility of injections. Fluoroscopic imaging provides a reliable method for evaluating these effects.

A New Powerful Model-Based Artificial Pancreas Predictive Control Approach

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Objective:
The objective of this study is the development of a novel artificial pancreas (AP) control approach that overcomes critical limitations of current model-based predictive control approaches to significantly tighten blood glucose concentration (BGC) for around-the-clock use.

Method:
This approach uses a novel modeling method to predict BGC very accurately a distance into the future (i.e., 30 to 60 minutes) when changes in the insulin infusion rate (IFR) begins to affect BGC. This future virtual BGC sensor is used in the place of measured BGC in the feedback error (set point – BGC), and a classical proportional integral derivative (PID) controller changes IFR in the present to minimize this difference the future. This approach does not require a model for the relationship of IFR on BGC. High accuracy is achieved for one week of test data per each of 11 subjects. The superiority of our feedback predictive control (FBPC) method over model predictive control (MPC) is demonstrated in two studies – a continuous flow stirred-tank reactor (CSTR) simulator with unmeasured disturbances and a diabetes simulator for 30 subjects.

Result:
For 30 and 60 minutes-ahead-predictions (MAP) on the 11 subjects, model bias was nearly negligible for all cases and correlations between the measured and fitted BGC (r_{fit}) were 0.93 and 0.83, with highs of 0.96 and 0.88, for 30 and 60 MAP, respectively. In both studies, FBPC greatly outperformed MPC as measured by the standard deviation (SD) about the target. In the CSTR study, the SD of FBPC was 38% lower than MPC and in the diabetes simulator study, the SD of FBPC was 21% lower than MPC on the average.

Conclusion:
Thus, the FBPC approach using our modeling methodology, has the potential to significantly advance AP research by overcoming current limitations in modeling and control.

The Customer Training Phase Data Analysis of the MiniMed™ 670G System: Performance of the Hybrid Closed-loop System

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Objective:
The performance of the Minimed 670G system was analyzed based on the real-world data obtained from the 'Customer Training Phase' (CTP) launch (United States only). In Auto Mode, the system is designed to automatically adjust basal insulin delivery every 5 minutes, based on sensor glucose (SG) values, by using the state-of-the-art SmartGuard™ hybrid closed-loop (HCL) technology

Method:
Data ranging from Feb-2017 until Jun-2017, from 817 unique CareLink™ Personal accounts linked to the Minimed 670G CTP program were downloaded to analyze the performance of the SmartGuard technology. The system included the MiniMed 670G pump, with the Medtronic proprietary HCL algorithm, and the Guardian™ Sensor 3 sensor.

Result:
A total of 29,051 patient days were analyzed from which the sensor was available a mean of 93% of the time and the Auto Mode feature was used a mean of 86% of the time. The mean percentage of time SG was in-target (70–180 mg/dL) was 74%; in hypoglycemia (<70 mg/dL) was 2%; and in hyperglycemia (>180 mg/dL) was 24%. During the overnight hours (2300 – 0700), time within-target, in hypoglycemia and in hyperglycemia, were 81%, 2%, and 17%, respectively. The average mean SG value during the 24-hour period and overnight hours was 151 mg/dL and 144 mg/dL, respectively.

Conclusion:
The analysis of the CTP data shows that the MiniMed 670G system with SmartGuard technology is effective for patients with T1D patients under real-world conditions. Essentially, these results mirror those derived from the pivotal trial of the MiniMed 670G system, that concluded in mid-2016 and the data from which has subsequently been published.

Using a Data Collection Tool in the Electronic Medical Record (EMR) to Lower Rates of Hypoglycemia by Determining Root Causes

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Objective:
The primary objective is to identify root causes of hypoglycemia in medicine unit patients using an electronic tool in the EMR. The secondary objective is to develop a targeted educational intervention to implement strategies to decrease the rate of hypoglycemia on these units.

Method:
An RN survey identified key risk factors for hypoglycemia. The survey data informed the creation of a hypoglycemia root cause survey tool in the EMR. The RN completed the tool whenever a patient had a glucose value below 70 mg/dL. A targeted educational intervention for safe and effective use of insulin was launched for RNs and prescribers. This strategy was designed to empower the team to adjust the appropriate insulin dose to prevent future hypoglycemia episodes.

Result:
Blood Glucose (BG) data was compared from March & April in 2016 and 2017 on two medicine units. Rates of hypoglycemia (BG <70mg/dL) decreased from 2.3% to 1.5%; BG values within the target range (70-180mg/dL) increased from 59.4% to 65.7%; and hyperglycemia (BG >180mg/dL) decreased from 38.3% to 32.8%. In addition, the number of patients with recurrent hypoglycemia (3 or more episodes during the hospital stay) decreased from 5.7% to 2.2%.

Conclusion:
The top two modifiable causes of hypoglycemia (i.e., nutrition and insulin) were identified by the RN survey and confirmed by chart review. A targeted educational intervention addressing safe and effective insulin dosing resulted in a significant decrease in hypoglycemia and recurrent hypoglycemia. Of note, the decrease in hypoglycemia was associated with an improvement in overall glycemic control. Ongoing nurse and prescriber education, accompanied with discussions between RNs and prescribers to address each hypoglycemic event in real-time, could continue to lower the rate of occurrence.

Detection and Discrimination of Exercise and Stress from Wearable Device Data

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Objective:
Multivariable artificial pancreas (AP) systems leverage additional information collected by wearable devices to complement information from continuous glucose monitoring (CGM) in order to improve insulin management in response to major factors that affect glucose homeostasis, such as meals, exercise, stress and sleep (MESS). The objective of this study is to detect the presence of exercise (acute physiological stress) alone, or concurrent with acute psychological stress, in real time and well before their occurrence affects CGM values.

Method:
Signals from a wearable device were collected and interpreted to detect the real-time presence of: (1) exercise without psychological stress, (2) exercise with psychological stress, (3) sedentary state without psychological stress, and (4) sedentary state with psychological stress. Streaming data from the device was processed by machine learning and a fuzzy logic algorithm to detect and discriminate these four states.

Result:
The developed fuzzy logic classifier algorithm was successful in generating indicator variables that had different patterns over time for the four states, and to detect and discriminate their occurrence with very little delay in diagnosis, before significant changes occurred in CGM values.

Conclusion:
Streaming data from wearable devices can assist AP systems by providing information in advance about occurrences of MESS factors to enable feedforward control of glucose concentrations that complement model-based control-based CGM values.

Mobile Health Tool for Long-Acting Insulin Dose Adjustment Improves Glycemia in People with Type 2 Diabetes

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Objective:
Insulin management can be an arduous process for a person with diabetes (PWD). While mobile health technologies (mHealth) have emerged to help PWDs track blood glucose (BG), it remains unclear whether or not these tools can be effective for insulin management and dose titration. In this feasibility study, we evaluate the extent to which an mHealth tool for long-acting insulin (LAI) dose adjustment can assist people with type 2 diabetes make appropriate titration adjustments and improve glycemia.

Method:
Fourteen participants with type 2 diabetes were prescribed a personalized LAI dosage treatment plan by a clinician. The treatment plans were implemented via a smartphone mobile app. During the study period (lasting 7-23 days), the mobile app delivered fasting BG and insulin reminders, as well as LAI dose change recommendations based on each participants' fasting BG and treatment plan.

Result:
On average, the recommended LAI dosage increased by 18.7% by the end of the study period ($p = .013$). Compared to BG levels from the 14 days prior to the study period, BG levels during the study period decreased by 18.2 mg/dL ($p = .046$), and the proportion of within-range BG readings (80 – 180 mg/dL) increased by 9% ($p = .048$). The proportion of within-range BG readings was positively correlated with titration adherence (i.e., the proportion of prescribed titrations completed; $r=0.65$, $p=0.017$).

Conclusion:
We observed promising evidence that a mHealth LAI dose-adjustment tool can help PWDs better manage their insulin and glycemic control. Positive outcomes were linked to treatment adherence, which remains a challenge in diabetes management. Overall, PWDs and care teams have reason for optimism as mHealth tools continue to evolve to better augment diabetes self-management.

Digital Health for Diabetes – A Good Idea Whose Time Has Come

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Background:
Individuals with T2 diabetes are burdened by potentially complex medication regimens and are challenged by the need for lifestyle and behavioral change. Health care providers are charged with delivering high quality care to a greater number of patients with less face-to-face time with them.

Method:
Digital health tools for diabetes hold the promise of both coaching users into optimizing diabetes self-management and supporting clinicians with decision support and efficient patient communication. Recent data suggest that self-monitored blood glucose (SMBG) may have little or no benefit for most patients with T2 diabetes. This is likely due to: (1) the data not being collected and used optimally to support self-management and behavior change and, (2) the data not being available in a digestible format to support health care teams. In 2014, WellDoc launched the first FDA-cleared platform, BlueStar, for diabetes coaching and provider clinical decision support.

Result:
BlueStar provides resources and intelligent messaging to users that support diabetes self-management and problem-solving in an automated fashion. SMBG data as well as behavioral and lifestyle information is collected in a non-burdensome manner. These patient-generated data are used to deliver tailored, individualized, and contextual insights to users more effectively than what can be provided by SMBG alone. These data are also distilled into a summary report that is sent to health care providers to enhance the face-to-face visit or to support a virtual visit and aid in decision-making that goes beyond what an A1C value can give.

Conclusion:
The question now is not whether the healthcare system should use digital tools or not, but rather which tools and how should they be implemented to best enhance the interaction between patients and providers to improve health outcomes.

Measures Beyond A1C Provide Insights on Glycemic Control for People with Type 2 Diabetes

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Objective:
Measures beyond A1C are needed for T2 diabetes to identify clinical glycemic control issues such as wide BG variations and very high and very low blood glucose (BG). For people with T1 diabetes using continuous glucose monitors, parameters that reflect glycemic variability and percent time within range have been proposed and may correlate with health outcomes.

Method:
We constructed the following measures that are more suitable for people with T2 diabetes who generally have sparse data: standard deviation fasting (SDF) and non-fasting (SDNF), # days per month that a hypoglycemia is recorded (NLD), # days per month that a very high is recorded (NHD), #days per month that a hypoglycemia or a very high is recorded (NLHD), % of days per month in which all BGs are in the target range (PDIR), % of days per month without BG extremes (PDNE). We evaluated how useful these metrics would be for real de-identified patient data.

Result:
Measures were calculated from a patient who was checking 3 BGs per day. The average BG and projected A1C appear constant. The average fasting BG and SDF did not change monthly, but changes occurred in the SDNF, suggesting issues with the consistency of breakfast and lunch meals. Despite stability of A1C and average BG, the PDIR worsened from 52% in month 1 to 33, 39, and 23% in months 2, 3, and 4, respectively. This reflects changes that can be appreciated via visual inspection of the logbook.

Conclusion:
These proposed metrics provide insight to BG data that go beyond measures of average. These metrics may be useful for clinical decision support and can be embedded into digital health tools.

Feeding Hyperglycemic Patients Better than 158 ICUs: Clinical Nutrition Delivery of STAR

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Objective:
Critically ill patients often experience stress-induced hyperglycemia, with increased morbidity and mortality. STAR is a proven, tablet-based, glycemic control (GC) protocol, that varies insulin *and* nutrition to control glycaemia. However, varying nutrition rates can be contentious and may appear to underfeed patients. This study evaluates the performance of the STAR variable nutrition protocol versus other ICUs, based on a clinical review of 158 ICUs by Cahill et al (2011).

Method:
The STAR nutrition protocol maximizes the nutrients given to patients while maintaining euglycemia, resulting in a variable and very patient specific feed rate. Thus, inter- patient feeding variation and the mean nutrition rates achieved per day in the ICU for the STAR Christchurch (2011-2015) cohort (n=267 patients) were investigated and compared to the mean and best units reviewed in the Cahill et al. study.

Result:
Per-patient results showed that, on the STAR variable nutrition protocol, some patients did not achieve the ideal 100% caloric ACCP guideline goal feed (25kcal/kg/day). However, over 74% of patients attained over 85% of the caloric guideline goal after day 3. Mean nutrition rates for STAR were significantly higher than the mean and best ICU of those reviewed for the first 3 days of ICU stay.

Conclusion:
The ability to deliver and take up nutrition varies significantly between GC patients but generally increases with ICU stay. STAR's current patient-specific variable nutrition protocol achieves clinical results for hyperglycemic patients that are better than the best of those reported in the Cahill et al. survey for all patients in 158 ICUs in 20 countries.

Design of a Unique Medical Mobile Application for Insulin Dosing in Patients with Type 2 Diabetes

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Objective:
Managing patients with type 2 diabetes typically requires therapy intensification that eventually leads to adding exogenous insulin. Initiating and titrating basal and bolus insulin therapy is complex and challenging for both health care providers and patients (Go Dose 510k Section13.pdf pg.1,8). This abstract describes how user inputs were incorporated into the design of an insulin dosing software application using a rapid iterative approach.

Method:
The Go Dose System application (class 2 mobile-medical application [app]; i.e., the Go Dose and Go Dose Pro apps) was developed to fulfill an unmet clinical need to simplify initiating and titrating prandial insulin using a prescribed mobile iPhone or iPad app. The app's unique design recommends a prandial insulin lispro dosage using daily pre-meal blood glucose inputs (IOQC clinical study; NCT01215955). It is recommended that patients using this app are first optimized on insulin glargine and oral anti-diabetes medications and require treatment intensification with insulin lispro 100 U/mL.

Result:
The Go Dose System user interfaces were optimized for safety and effectiveness through an iterative, human-centered process that involved health care providers, caregivers, and patients throughout all phases of design, development, and evaluation. The software was developed using multiple rapid, iterative design sprint cycles (i.e., agile) incorporating human factor results. This approach affords the opportunity to write code, test, iterate, and make incremental design changes focused on risk mitigations.

Conclusion:
The Go Dose System app, approved by the FDA (510K# K160949) on December 22, 2016, is intended to simplify prandial insulin therapy initiation and titration for health care providers and for managing patients with type 2 diabetes.

Suppression of Foreign Body Reaction to Drug Coated Subcutaneous Implants for Continuous Glucose Monitoring in Rabbits

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Objective:
To demonstrate the suppression of the foreign body reaction (FBR) to drug coated subcutaneous implants for continuous glucose monitoring in rabbits and confirm dependence of suppression of FBR on the continuous release of dexamethasone.

Method:
The drug/polymer co-precipitation method was used to prepare sustained release dexamethasone microspheres. The drug coatings composed of dexamethasone microspheres, dispersed in a polyvinyl alcohol (PVA) hydrogel matrix, were then prepared using a grooved mold. *In vitro* release testing was performed on these drug coatings. *In vivo* drug coating efficacy studies were conducted on normal rabbits. Briefly, dummy sensors coated with drug coatings were implanted into the subcutaneous tissue of rabbits. The implants and tissue surrounding the implants were harvested, processed, subjected to hematoxylin and eosin (H&E) staining, and microscopic analysis was performed.

Result:
The *in vitro* release profile demonstrated a burst release of approximately 40% during the first 24 h, which was a result of the free crystalline dexamethasone added to the drug coatings to counteract the acute inflammation. Approximately 100% of the dexamethasone was released by day 60 from the drug coatings. The *in vitro* release correlated well with the *in vivo* observations, since the FBR was suppressed *in vivo* for the initial 2 months until the dexamethasone release was complete. Following the initial 2 months, a thin, fibrous capsule was observed surrounding the implants indicating progression of FBR and signifying that suppression of FBR was dependent on continuous release of dexamethasone.

Conclusion:
The FBR to subcutaneous implants was completely suppressed in rabbits for 2 months. The recurrence of the fibrous capsule after 2 months confirmed the necessity for continuous release of dexamethasone to suppress the FBR.

Utilization of Electronic Glycemic Management Systems for Hospital Discharge Insulin Dosing

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Background:
This prospective Quality Improvement project evaluated the effectiveness of an electronic Glycemic Management System (eGMS) utilizing Glucommander™ and admission hemoglobin A1c (A1c) to transition patients to insulin therapy upon discharge using a Hospital-to-Home (H2H) function.

Method:
After inpatient insulin titration by eGMS, providers used the H2H algorithm to determine insulin dosing prescribed at discharge. Upon discharge, patients checked their blood glucose (BG) before each meal, at bedtime, and with perceived episodes of hypoglycemia. After discharge, we conducted four consecutive telephone interviews every 7 days. The primary endpoint was the safety of patients discharged using H2H to calculate basal, or basal/bolus, doses of insulin on the day of discharge for patients with a A1c >6.5%. The aim was to reduce hypoglycemic events measured as mild (40-69mg/dL) or severe (<40mg/dL) as the primary safety measure. The secondary endpoint included the change in fasting and mean daily blood glucose concentrations, number of ER visits, and 30-day hospital readmissions.

Result:
A total of 28 patients were enrolled. Average admission A1c was 9.5%, admission BG was 223 mg/dL, average daily BG was 152 mg/dL, and average discharge BG was 157 mg/dL. Telephone interviews revealed the following incidence; % of patients <40 mg/dL 3.6%; 40-69 mg/dL 46%, >300 mg/dL 25%, and average outpatient fasting BG was 119 mg/dL. After discharge, 3.6% of patients visited Urgent Care, 7.1% had ER visits, and 14.2% were readmitted for reasons other than diabetes.

Conclusion:
The eGMS is a useful tool for providers to use at the time of discharge to determine home insulin dosing and titration. There was reasonable BG control post- discharge. The incidence of severe hypoglycemia was minimal and there were no ER visits or readmissions due to glucose-related causes.

Glycaemic Control in ICU: Stable Patients Tend to Remain Stable

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Objective:
STAR is a glycaemic control (GC) protocol with proven safety and performance. It uses a cohort-based 2D stochastic model of model-based, patient-specific, insulin sensitivity (SI). Given current SI, it predicts a range of future SI values to dose insulin based on the specified risk of hypoglycaemia. This study examines whether considering the prior change in SI (%SI) as an input into a 3D stochastic model can reduce the conservatism and provide more accurate estimates.

Method:
Metabolic data from 3 clinical ICU cohorts (819 episodes and 68,629 hours) in Christchurch (SPRINT and STAR) and Hungary (STAR) were used. Triplets ($\%\Delta SI_n$, SI_n, SI_{n+1}) were created for every hour to create a 3D stochastic model with inputs ($\%\Delta SI_n$, SI_n) and output SI_{n+1}. The 5-95th percentile prediction width of the 3D model was compared at every $\%\Delta SI_n$ value to the 2D model 5-95th width. A narrower band for the 3D model indicated that the 2D model was overly-conservative (i.e., GC could be more aggressive) while a wider bound indicated increased risks.

Result:
The 2D model is over-conservative for 77% of hours, mainly where $\%\Delta SI$ is within an absolute 25% change, with 25-40% narrower prediction ranges. Predictive power is similar for both models, but much closer to the ideal value of 90% for the 3D model, indicating greater patient-specificity. Cross-validations show these results generalise well to different ICU populations.

Conclusion:
By reducing the prediction range for 77% of hours across 3 ICU cohorts, predominantly where SI is stable, the new 3D model shows that stable patients tend to remain stable in terms of $\%\Delta SI$. The new model better characterizes patient-specific response to insulin allowing for more optimal dosing while increasing performance and safety.

Impact of Use Frequency of Mobile Diabetes Management Application on Blood Glucose Control

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Objective:
To analyze the effect of the frequency of use of a diabetes management application (app) on glycemic control.

Method:
A randomly selected group of 211 of users of Social Diabetes (144 type 1 and 67 type 2) were included. Inclusion criteria: engagement (logging on ≥5 days/month for ≥6 months) and a mean blood glucose at baseline ≥183 mg/dl (representing eA1c ≥8%). The cohort was split into two groups according to the intensity of app engagement: Group A: high engagement group (logging on ≥15 times/month for ≥6 months); group B: low engagement group (between 5 and 10 times logging on per month for ≥6 months). BG at baseline, month 3, and month 6 were calculated using an intercept of regression model based on data from months 1, 4 and 7 respectively.

Result:
Baseline BG-results for the type 1 groups A and B were 213.61±31.57 mg/dl and 206.43±18.65 mg/dl, decreasing at month 6 to 175.15 ±37.88 mg/dl and 180.6 ±40.47 mg/dl respectively. This decrease represents a percent reduction in mean glucose of 18% ($p<0.0001$) and 13% ($p<0.0001$), respectively. For the type 2 groups, baseline BG were 218.77±40.18 mg/dl and 232.55±46.78 mg/dl, decreasing at 6 months to 160.51±39.32 mg/dl and 173.14±52.81 mg/dl for groups A and B, respectively. This decrease represents a percent reduction in mean glucose of 27% ($p<0.00001$) and 26% ($p<0.0002$). Based on the reduction blood glucose, this would correspond to a reduction of eA1c of approximately 1.3% and 0.9% for diabetes type 1 groups A and B and 2% for both A and B diabetes type 2 groups.

Conclusion:
Significant reductions of BG has been found in all groups independent of the frequency of app use. Larger improvements were observed for the type 2 diabetic patients.

In Silico Assessment of State-of-Art and New Algorithms for Real-Time Basal Insulin Modulation in Sensor-Augmented Pumps

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Objective:
In type 1 diabetes (T1D) sensor-augmented pump therapy, continuous glucose monitoring (CGM) data can be exploited in real-time to assess hypoglycemic risk and, accordingly, attenuate basal insulin to prevent hypoglycemia. In the literature, three algorithms have been proposed for this purpose [i.e., brakes (B), power brakes (PB) and insulin-on-board PB (IOB-PB)], which assess hypoglycemic risk using CGM, predicted CGM, and predicted CGM corrected for IOB, respectively. Here, we compare *in silico* the original version of these methods and a modified version in which the use of the static risk (SR) function is substituted with the dynamic risk (DR) function, which takes into account both the glucose value and its derivative.

Method:
Simulations were performed by the T1D patient decision simulator, a simulation framework including the UVA/Padova T1D physiology model and models of CGM sensor, self-monitoring of blood glucose, insulin pump, and patient's behavior in making treatment decisions. In particular, 100 virtual adults were simulated for 14 days with basal insulin either constant or automatically modulated by B, PB, IOB-PB algorithms with SR or DR. Time in eu/hypo/hyper-glycemia were compared between algorithms.

Result:
B, PB and IOB-PB reduce median time in hypoglycemia from 2.84% with constant basal insulin to 1.99%, 1.92% and 1.61%, respectively, with a slight increase of hyperglycemia (from 35.23% to 36.72%, 36.90% and 38.46%, respectively). The introduction of DR allows for a further reduction of time in hypoglycemia in B and PB (1.88% and 1.85%, respectively), while no difference between SR and DR use is observed for IOB-PB.

Conclusion:
CGM-based algorithms for basal insulin attenuation are effective in reducing hypoglycemia, despite slightly increasing hyperglycemia. The use of DR allows further reduces hypoglycemia in methods not using IOB.

Validation of the One-Week Type 1 Diabetes Patient Decision Simulator vs. REPLACE-BG Study

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Objective:
We recently developed the type 1 diabetes (T1D) patient decision simulator (Vettoretti et al., 2nd rev. IEEE TBME, 2017) which models T1D patient's physiology (UVA/Padova T1D model) and behavior in making treatment decisions as well as the accuracy of self-monitoring of blood glucose and continuous glucose monitoring (CGM) devices. In addition, the model accounts for CGM performance variability over one week of sensor wear. Here, the aim is to validate the simulator vs. data acquired in the REPLACE-BG study; a recent 26-week trial where both adjunctive and non-adjunctive CGM use were compared.

Method:
Adjunctive and non-adjunctive CGM-based treatments were implemented in the T1D patient decision simulator mimicking the REPLACE-BG trial protocol. Glucose profiles were simulated for one week in 100 virtual adults for both adjunctive and non-adjunctive scenarios. Percent time in eu/hyper/hypo-glycemia were then calculated for both simulated data and each week of real data. A non-parametric statistical test was performed between metrics of simulated data and those of a subset of real data, obtained randomly by extracting one week per subject. This comparison was repeated for 100 different random selections of study weeks.

Result:
With adjunctive CGM, treatment time in eu/hyper/hypo-glycemia were 63.93% vs. 63.87%, 32.36% vs. 31.96%, and 3.03% vs. 3.38%, and no statistically significant difference was obtained in 100%, 100%, and 93% of data random selections, respectively. In both simulated and real data, CGM non-adjunctive use reduced time in hypoglycemia (1.63% in simulation, 2.91% in real data) with a slight increase of time in hyperglycemia (33.35% in simulation, 34.28% in real data).

Conclusion:
Results suggest the T1D patient decision simulator is able to reproduce realistic treatment scenarios based on both adjunctive and non-adjunctive CGM use.

Evaluation of the GLUCOCARD Shine XL Blood Glucose Monitoring System's Ease of Use

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Objective:
It is important that a Blood Glucose Monitoring System (BGMS) is easy to use, since it is a critical tool used in the self-management of diabetes mellitus, including the prevention of micro and macrovascular complications. The "Ease of Use" consumer study is typically evaluated as part of the FDA 510(k) approval process for BGMS. The objective of this study was to evaluate the Ease of Use of the GLUCOCARD Shine XL BGMS.

Method:
A total of 30 subjects, aged 19 to 88, participated in the study by performing a fingerstick self-test and answering a questionnaire directed at the ease of use of the device and test strip. All of the subjects responded to the topics in the questionnaire which included, "Removing Test Strip from Bottle", "Inserting a Test Strip into Meter", "Removing Test Strip from Meter", "Performing a Blood Glucose Test from your Fingertip" and "Reading Meter Display". The subjects were asked to rate the topics as Very Easy, Easy, OK, Difficult, or Very Difficult. For evaluation purposes, these topics were grouped as Positive [Very Easy/Easy/OK] or Negative [Difficult/Very Difficult].

Result:
From the questionnaire, "Performing a Blood Glucose Test from your Fingertip" received a 96.7% positive rating while all of the remaining topics received a 100.0% positive rating, including "Removing Test Strip from Bottle", "Inserting Test Strip into Meter", "Removing a Test from the Meter" and "Reading Meter Display".

Conclusion:
The GLUCOCARD Shine XL BGMS scored an overall average 99.3% positive "Ease of Use" rating by the subjects.

Performance Comparison of the GLUCOCARD Shine and OneTouch Verio Flex Blood Glucose Monitoring Systems Compared to FDA 2016 Guidance Accuracy Criteria

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Objective:
Blood Glucose Monitoring Systems (BGMS) are used in the management of diabetes mellitus. In order to prevent potential micro and macrovascular complications due to uncontrolled blood glucose levels, the systems must provide accurate readings. The FDA's 2016 Guidance, "Self-Monitoring Blood Glucose Test Systems for Over-the-Counter (OTC) Use", is FDA's recommendation for measuring the accuracy of OTC BGMS. The accuracy boundaries of the guidance require that 95% of all results be within ±15% of reference and 99% be within ±20% of reference. This study evaluated the performance of the GLUCOCARD Shine and OneTouch Verio Flex BGMS compared to the accuracy boundaries of the 2016 FDA Guidance for Self-Monitoring Blood Glucose Test Systems for OTC Use.

Method:
Two lots of GLUCOCARD Shine and OneTouch Verio Flex test strips were evaluated in a side-by-side study at the ARKRAY Factory in Minneapolis, MN. Blood samples were drawn from the fingertip of people with diabetes (n0) by laboratory professionals. Reference values were obtained using the YSI Model 2300 Analyzer. Data were evaluated against the accuracy boundaries of the FDA's 2016 Guidance for Self-Monitoring Blood Glucose Systems for OTC Use.

Result:
For GLUCOCARD Shine, 97.5% of the combined two lots (117/120) fell within the ±15% of the reference and 100% (120/120) were within ±20% of the reference. Overall bias was 2.6 % and correlation coefficient (r) = 0.99. For OneTouch Verio Flex, 97.5% of the two lots (117/120) fell within ±15% of the reference and 99.2% (119/120) were within ±20% of the reference. Overall bias was -0.7% and correlation coefficient (r) = 0.99.

Conclusion:
In our side-by-side testing, the GLUCOCARD Shine performed slightly better with 100% of results within ±20% of the reference while the OneTouch Verio Flex had one result outside of ±20%. Overall, both BGMS performed within the accuracy boundaries of the FDA's 2016 Guidance for Self-Monitoring Blood Glucose Test Systems for OTC Use.

Performance of the Assure® Platinum Blood Glucose Monitoring System throughout Shelf-Life

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Objective:
Blood Glucose Monitoring Systems (BGMS) need to provide accurate results throughout their product life-cycle. ARKRAY employs a rigorous quality testing program for the release of new test strip lots, and evaluates a sampling of lots over its entire product life-cycle, including expiration. ISO 15197:2015 is an accepted global standard for assessing the accuracy of BGMS. The accuracy boundaries of this standard require 95% of BGMS results to be within ±15 mg/dL of the reference analyzer at glucose concentrations <100 mg/dL and within ±15% of the reference analyzer at glucose concentrations ≥100 mg/dL. Furthermore, 99% of all results are required to be within the A and B zones of the Consensus Error Grid.

Method:
Six lots of test strips were evaluated at the ARKRAY Factory. Blood samples were drawn at time points throughout the product shelf-life and post-expiration from the fingertip of confirmed diabetics (n=30 at each time point) by laboratory professionals for a total n=750. Reference values were obtained using the YSI Model 2300 Analyzer. Data were analyzed against accuracy boundaries of the ISO 15197:2015 Standard and Consensus Error Grid. Average bias throughout shelf-life with 95% Confidence Intervals (CI) was also calculated.

Result:
The data show that 99% (71/72) of results <100 mg/dL were within ±15 mg/dL of reference, and 96.9% (657/678) of results ≥100 mg/dL were within ±15% of reference. Average bias throughout shelf-life and post-expiration for all lots combined was -2.3% [95% CI of -2.8% to -1.8%] and the correlation coefficient (r) = 0.98.

Conclusion:
Data collected on the Assure® Platinum BGMS performed within the accuracy boundaries of the ISO 15197:2015 Standard and demonstrated consistent performance throughout its product life-cycle.

Performance of the GLUCOCARD® Shine Blood Glucose Monitoring System throughout Shelf-Life

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Objective:
Blood Glucose Monitoring Systems (BGMS) need to provide accurate results throughout their product life-cycle. ARKRAY employs a rigorous quality testing program for the release of new test strip lots and evaluates a sampling of lots over its entire product life-cycle, including expiration. The FDA's 2016 Guidance, "Self-Monitoring Blood Glucose Test Systems for Over-the-Counter (OTC) Use", is FDA's recommendation for measuring the accuracy of OTC BGMS. The accuracy boundaries of the guidance require that 95% of all results be within ±15% of reference and 99% be within ±20% of reference.

Method:
Two lots of test strips were evaluated at the ARKRAY Factory. Blood samples were drawn at time points throughout the product shelf-life including post-expiration from the fingertip of confirmed diabetics (n=30 at each time point) by laboratory professionals for a total n=450. Reference values were obtained using the YSI Model 2300 Analyzer. Data were analyzed against the accuracy boundaries of the FDA's 2016 Guidance for Self-Monitoring Blood Glucose Test Systems for OTC Use. Average bias throughout shelf-life with 95% Confidence Intervals (CI) was also calculated.

Result:
The data show that 97.1% (437/450) of results were within ±15% of reference and 99.6% (448/450) were within ±20% of reference. Average bias throughout shelf-life and post-expiration for all lots combined was -0.3% [95% CI of -0.8% to 0.3%] and the correlation coefficient (r) = 0.98.

Conclusion:
Data collected on the GLUCOCARD® Shine BGMS performed within the accuracy boundaries of the FDA's 2016 Guidance, Self-Monitoring Blood Glucose Test Systems for OTC Use, and demonstrated consistent performance throughout its product life-cycle.

Nitric Oxide-Releasing Subcutaneous Insulin Infusion Cannula

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Objective:
This study investigates the effect of *in-vivo* nitric oxide (NO) release on the subcutaneous insulin adsorption into the bloodstream and the decrease of bacterial infections – both of which enhance the overall performance of insulin infusion cannula for diabetes management.

Method:
Nitric oxide release rates from cannula tubing impregnated with an NO release agent were analyzed by using a chemiluminescence-based NO gas analyzer. Intravenous glucose tolerance tests in a sheep model were used to evaluate the rates of insulin adsorption during 1 week for control and NO release cannula. Hematoxylin and eosin (H&E) staining was used to evaluate the tissue reaction to the cannula implants. Microbial biofilm growth on cannulas was examined using a CDC biofilm reactor.

Result:
Nitric oxide release of 3 days to > 1 month at physiological temperatures was obtained from various biomedical tubing impregnated with a *S*-nitrosothiol type NO donor. When implanted into the subcutaneous tissue of the back of adult sheep, the NO-releasing cannula improved insulin adsorption rates (vs. control cannula in same animals) as determined by an intravenous glucose tolerance test. Histopathology analysis showed that NO release is able to suppress the inflammatory response at the insulin infusion site. *In vitro* biofilm experiments demonstrated that growth of bacteria typically involved in insulin infusion device infections is significantly suppressed for NO-releasing cannula compared to control cannula.

Conclusion:
Preliminary experiments demonstrate that release of NO from subcutaneous cannula may enhance insulin adsorption rates via mitigating inflammatory response, and also can potentially reduce infusion site infection rates by preventing microbial biofilm formation.

Modeling Glucose Regulation in Postprandial Intermittent High Intensity Exercise with T2DM Patients

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Objective:
Based on existing studies of the acute effects of exercise, we strove to create a representative mathematical model of these in type 2 diabetic subjects, in a way that supports integration into the metabolic model defined by Dalla Man. This effort was limited to modeling effects during, and within a few hours following, a single postprandial, intermittent, high intensity exercise session.

Method:
We examined publications on the effects of exercise on glucose regulation, primarily relying on data from those that involved high intensity exercise in type 2 subjects. We attempted to reproduce observed glucose responses by modeling the underlying causes, shown in the literature to be changes in endogenous glucose production (EGP) and glucose utilization. Interpreting the data in the context of the Dalla Man's model allowed us to distinguish portions of glucose utilization due to insulin dependent vs. independent effects. Using analytical techniques and optimization methods within the Diabetes Mellitus Metabolic Simulator (DMMS.R, The Epsilon Group), we established time profiles for each effect (changes of EGP and of both utilization types) spanning several hours from exercise initiation.

Result:
Using DMMS.R, we showed that when exercise begins 45 minutes after a meal, addressing the two utilization effects was sufficient to reproduce the glucose concentration impact seen in the literature. With other exercise timing, or when addressing longer term responses, the EGP effect would need to be considered.

Conclusion:
An exercise model, spanning a few hours, of the glucose response to postprandial intermittent high intensity exercise, has been defined and incorporated into a simulator based on the Dalla Man's metabolic model. More investigation involving EGP effects would be useful in defining a more general, longer term model.

Mid-Infrared Laser Spectroscopy for *In Vivo* Glucose Sensing in Interstitial Fluid

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Objective:
Quantum cascade (QC) lasers are powerful tools for sensing biomarkers, including glucose, due to their high-power emission in the mid-infrared (MIR). Glucose has absorption features between 8-10μm that differentiate it from other molecules. We utilize the MIR light emitted by a QC laser source to detect glucose in the interstitial fluid (ISF) of skin.

Method:
The sensor consists of three primary components: the QC laser, a miniature integrating sphere, and an MCT detector. The subject places their hand on sample port of the integrating sphere where the light penetrates into the dermis layer of the skin. The dermis layer of the skin contains interstitial fluid (ISF). The glucose concentration in ISF is highly correlated (~95%) to the glucose concentration of blood and thus is an ideal location to detect glucose. The laser light is absorbed by the glucose molecules and scattered back out of the skin. The backscattered spectrum is collected by an integrating sphere and analyzed using principal component analysis (PCA).

Result:
The PCA of the backscattered spectra, which shows the wavelengths of most variance across many spectra (~50 per subject), was closely correlated to the absorption spectra of glucose. For three subjects, the average error in peak alignment between the PCs and absorption spectrum of glucose was 3.7%.

Conclusion:
We are developing a sensor using MIR spectroscopy to non-invasively detect glucose in skin. We believe incorporating a pressure sensor into the system will help eliminate fluctuations in signal strength due to arm movement. We use PCA and other multivariate algorithms to predict glucose concentrations in human subjects.

Automated Regulation of Plasma Glucose in Type I Diabetes Mellitus with Insulin and Pramlintide: *In Silico* Study

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Objective:
The objective is to obtain optimal proportional integral derivative (PID) tuning for a) insulin only, b) combination therapy of 90 mcg pramlintide bolus at the meal with insulin automated, and c) co-infusion therapy using fixed ratios of 1.5, 2.0 and 2.5 units insulin to mcg pramlintide with PID control. The three optimal controllers were evaluated to see which is best.

Method:
Traditional PID feedback control is implemented to achieve optimal tuning for each case using a pharmacokinetics and pharmacodynamics (PKPD) model (Ramkissoon *et al,* 2014) *in silico* tests with brute force optimization. Pramlintide sensitivities from the literature were investigated to provide patient population data. Model mismatches in patient sensitivity, glycemic index, and meal size were investigated. Different ratios of pramlintide to insulin for co-infusion control were also tested.

Result:
The 2.5 ratio for co-infusion therapy provided the best results and is used for all mismatch cases. There are no hypoglycemic incidences in the standard cases however, all went hyperglycemic due to limitations in pure feedback control. Hypoglycemic incidence occurs when the meal has a lower glycemic index than for what the controllers is tuned. The co-infused fixed ratio insulin and pramlintide perform better at glycemic index mismatches of the meal; in all other cases, a pramlintide bolus at meal with controlled insulin shows better results.

Conclusion:
Simulation results show pure feedback control even with the combination therapy is not enough to maintain the patient in normal glycemic ranges for a meal of 82.5 g carbohydrates. Therefore, it is important to use a model based strategy so there is some feed forward control, where insulin /pramlintide are given prior to large changes in plasma glucose from the meal. Lower total insulin is required to maintain plasma glucose when pramlintide is given.

A New Method to Measure Blood Glucose

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Objective:
Extremely weak absorption bands, strong water absorption, incontrollable and time variant scattering, and interference noises have, to-date, prevented the possibility of a workable non-invasive blood glucose monitor utilizing NIR absorption bands. Using a new NDIR measurement technique, the present work aims at overcoming these problems in order to achieve this long-awaited goal.

Method:
By experimentally selecting the best available glucose absorption bands in the NIR [U.S. Pat. No. 9,678,000 (2017)] and taking full advantage of available ultra-high performance NIR semiconductor lasers, InGaAs photodetector, and clever electronics, the signal-to-noise (S/N) problems, caused by weak glucose absorption bands and strong water absorption in the NIR, were overcome. A new NDIR measurement technique for determining the concentration of glucose in blood or interstitial fluid, while suppressing the scattering noise, has been advanced [U.S. Pat. No. 9,606,053 (2017)]. Another NDIR measurement technique using multiple laser sources to account for absorption interference noise caused by other molecules coexisting with glucose has also been developed (U.S. patent allowed).

Result:
NIR glucose absorption bands in the critical "optical tissue window" were identified and confirmed. Design and construction of custom laser and driver system for narrow band, stable, and low noise NDIR operation have been completed. The NDIR measurement technique suppresses scattering noise and accounts for absorption interference. Detection of increasing glucose levels in water, milk types, and 2% Intralipid with assembled optical bench and analysis software was validated. Relationships with key vendors to support future custom software and hardware requirements have been established.

Conclusion:
With adequate financial resources for the acquisition of custom software and hardware and continued R&D efforts, a non-invasive glucose monitor for blood or interstitial fluid could soon become a reality.

Preparation of Low Invasive Biosensor for Continuous Glucose Monitoring

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Background:
Recently, several continuous glucose monitoring systems (CGMS) have been released into the market and they are gaining popularity as effective devices for measuring the glucose of diabetic patients. However, the requirement of the sensor probes to be implanted into the skin tissue is still problematic. Therefore, the development of minimally-invasive CGMS is expected to greatly improve the quality of life of all diabetic patients.

Method:
In this study, a minimally-invasive type of amperometric glucose sensor, which has a sensing region at the tip of a finely-tapered electrode, is proposed. Glucose oxidase was immobilized onto a platinum-iridium alloy electrode by the electrodeposition of the enzyme in the presence of surfactant, following the electro-polymerization of o-phenylenediamine in order to generate a polymer film from the electrode surface, which functions not only as an enzyme entrapping film, but also as a permeably-selective film.

Result:
Glucose sensor properties of the fabricated electrode were evaluated *in vitro* using a pH 7.4 phosphate buffer solution at 40˚C, and also *in vivo* through measurements using a rabbit. The sensor showed a stable and linear response current at various glucose concentrations. It also exhibited good stability and the influences of electroactive compounds existing in biological fluids were not significant. Changes of the blood glucose level, induced by oral administration of glucose, was measured using the proposed biosensor and was comparable with that of a conventional needle type biosensor, when both were implanted in a rabbit. Both sensors provided similar response behavior and correlated with the trend of blood glucose levels.

Conclusion:
The data suggest that the proposed sensor holds good promise for practical use as a minimally-invasive type biosensor – one that requires no more than 1 mm of length to be inserted into the skin.

Insulin Occlusion in the Cannulas of Infusion Sets: *In-vivo*/*In-vitro* Studies

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Objective:
Patients undergoing continuous subcutaneous insulin infusion (CSII) as a means of insulin delivery are currently advised to replace their infusion set every 2 to 3 days, as the probability of adverse events increases after 72 hours. One such adverse event is the formation of cannula occlusions, likely caused by insulin precipitation, which prevent effective insulin delivery and can result in hyperglycemic episodes. Cannula occlusion has been one of the top 10 patient complaints with infusion sets for many years. Up to now, little is known about the chemical composition of these occlusions and the factors that cause their formation. The objective of this study was to characterize the chemical composition of residues in the occluded cannulas and investigate the fundamental nature of the occlusion mechanism.

Method:
Residues in the occluded cannulas explanted from CSII studies in diabetic animals were characterized by various analytical techniques: wet chemistry, pH measurement, dithizone staining, ELISA, ICP-MS, etc. Experiments were also conducted to re-create cannula occlusions *in-vitro*.

Result:
Experimental data indicated that the occluded cannulas/catheters were filled by aggregated/precipitated insulin gel with elevated levels of metal ions, as well as high concentrations of an extracellular protein which is significant in the early innate immune response. Furthermore, attempts to induce these occlusions in a simulated *in-vitro* environment, in absence of the extracellular protein, were unsuccessful even after several days. This suggests that biological elements involved in the inflammatory immune response and clotting pathways may be responsible for precipitate formation.

Conclusion:
Cannula occlusion is a complicated process which involves various factors: insulin aggregates, metal ions, tissue immune responses, as well as cannula structural characteristics (material, surface morphology, dimension, etc.) which may impact insulin aggregation/precipitation.

Game-Based Non-Weight Bearing Exercise to Improve Daily Physical Activity in Diabetic Patients Undergoing Hemodialysis: A Pilot Randomized Controlled Trial

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Objective:
Hemodialysis (HD) treatment often leaves diabetic patients with end stage renal disease (ESRD) too fatigued to engage in any physical activity or daily exercise, deteriorating their motor-abilities. In this study, we examined the feasibility and effectiveness of an innovative game-based, non-weight bearing, exercise (Exergame) to improve daily physical activity in diabetic patients undergoing HD.

Method:
ESRD subjects (n=33) receiving HD were recruited. They were randomized into an intervention group (IG: n=15, age=62.2±7.6, BMI=29.1±6.1) and a control group (CG: n=18, age=66.6±8.7, BMI=32.5±9.0). Both groups underwent a 4-week ankle exercise program (for 30 minutes, twice a week) during HD sessions. The IG received exercise via the Exergame program, which integrates data from wearable sensors attached to subject's feet into a human-machine interface designed for game-based motor adaptation training. The CG received traditional exercise without technology. Daily physical activity data were recorded using a wearable sensor for a continuous 24-hours after the program.

Result:
All IG subjects completed all exercise sessions during HD process indicating the feasibility of the Exergame program. During the 24 hours post HD, the IG performed 53% more posture transitions to walking compared to the CG (*Cohen's d*=0.5). In addition, the IG performed 39% more posture transitions between sitting and walking compared to the CG (*Cohen's d*=0.5). For posture durations, the IG spent 10% less time sitting and lying (*Cohen's d*=0.6), and 46% more time standing and walking (*Cohen's d*=0.8).

Conclusion:
This pilot study provides the proof of concept for an innovative Exergame program to improve daily physical activity in diabetic patients undergoing HD, which could open new avenues to implement game-based ankle exercises in clinic. Further studies should be addressed to confirm the observation with larger sample sizes.

Auto-Regressive Modelling of Drift and Random Error to Characterize the GlySure CGM

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Objective:
Continuous glucose monitoring (CGM) devices offer potential benefits for glycemic control in the intensive care unit (ICU). However, CGM errors, including drift and random errors, mean that higher accuracy, intermittent, blood glucose (BG) measures are still the most common method. CGM sensor glucose (SG) models are lacking, but would enable better protocol design to utilize these devices. This study presents an auto-regressive (AR) modelling method that separately characterizes the drift and random noise of the GlySure CGM sensor (GlySure LLC, UK).

Method:
Clinical SG data (n=33 patients; 21-51 hours/patient; SG every 15 seconds) and reference BG measurements (YSI or blood-gas; every 2.5 hours) from cardiac ICU patients were used to generate 2 AR models describing sensor drift and random noise. Reference BG model inputs were used to generate 100 Monte-Carlo simulations to compare model output to original SG data using mean absolute relative difference (MARD), Trend Compass, and the Clarke Error Grid.

Result:
Point accuracy MARD was very similar between simulated SG and clinical SG (9.6% vs 9.9%). Trend Compass assessment of trend accuracy show similar simulated and clinical SG profiles (trend index 11.4° vs. clinical trend index 10.9°). The model-simulated Clarke Error Grid had 99.9% of points in Zones A-B versus 99.8% for clinical SG.

Conclusion:
The model and method accurately represents cohort sensor behavior by providing a generalizable modelling approach to any such sensor by separately characterising each type of error. It can thus enable better protocol designs based on accurate, expected CGM behaviour, as well as the analysis of what level of each type of sensor error would be necessary to obtain the desired glycaemic control, safety, and performance with a given protocol.

CGM-Enabled STAR: A Virtual Trial Analysis

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Objective:
Continuing improvements to continuous glucose monitoring (CGM) devices have improved point accuracy and thus offer the potential benefit of workload reduction for glycemic control (GC) in ICU. However, limited point accuracy and the risk of (unseen) sensor drift have inhibited uptake in the ICU and GC protocols still generally rely on intermittent BG. This study uses a validated CGM sensor model, in clinically validated virtual trials, to optimize the clinically proven STAR GC protocol in order to evaluate the trade-off between GC workload, performance, and safety for the CGM-enabled STAR.

Method:
Virtual patients generated from clinical data (n=236 patients; 62,500 hours) were used in CGM-enabled STAR virtual trials changing interventions hourly using CGM measurements. Guardrail limits of 80mg/dL, 144mg/dL, and rapid changes over 20-30min bands in this range were assessed in triggering calibration checks and new interventions to minimize the impact of CGM drift and error. Monte-Carlo virtual trials (N=3/case) assessed workload (measurements), GC performance (percentage time within the 80-144mg/dL band), and safety (%Patients with BG<40mg/dL).

Result:
BG measures/day was reduced from 12.7 for clinical STAR, to 3.4 for CGM-enabled STAR (3/day minimum for calibration) - a 73% reduction in workload. GC performance (86.4% clinical; 86.2-87.8% CGM-STAR) and safety (0.85% patients clinical; 0.85-1.13% patients CGM-STAR) were similar in all cases. Safety from light hypoglycemia (%BG<72mg/dL) was also clinically similar (0.51% clinical; 1.1-1.4% CGM-STAR)

Conclusion:
CGM-enabled STAR successfully demonstrated the potential of using CGM sensor measurements to guide glycemic control in clinically validated virtual trials. The results clearly delineated trade-offs in safety, performance and workload using guardrails to offset the impact of CGM errors in guiding control, and thus justify pilot clinical trials.

Occlusion Detection Time of Different Insulin Pumps

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Objective:
An important safety feature of all insulin pumps is the detection of occlusions in the insulin infusion set (IIS) and the release of an alarm to notify the user. In this study, the time required by different insulin pumps to detect an occlusion was measured with two different basal rates under experimental conditions.

Method:
In addition to four previously tested insulin pumps with different IIS, two further pumps with soft cannula were evaluated (Animas® Vibe® [AV] and MiniMed® 640G [640G]). Occlusion of the infusion sets was induced manually and the time until an alarm was triggered was measured. Each insulin pump was tested nine times with two different basal rates (1.0 U/h and 0.1 U/h) under controlled conditions. The AV was tested with both programmable sensitivity levels for occlusion detection.

Result:
Median occlusion detection time at the 1.0 U/h basal rate was 2:40 [hh:mm] (1.-3. quartile: 2:37-3:04) for the AV with low sensitivity and 3:01 (2:57-3:10) with high sensitivity. For the 640G, median time was 3:49 (3:44-3:50). At 0.1 U/h, occlusion detection times were 34:57 [hh:mm] (31:58-36:01) for AV with low sensitivity, 29:04 (26:29-32:15) for AV with high sensitivity, and 41:21 (38:08-45:10) for 640G.

Conclusion:
At the higher basal rate, both tested pumps alerted early enough after IIS occlusions to allow patients to react in time. However, at a low basal rate of 0.1 U/h, (as used e.g. in children), alarms were activated much too late from a clinical point of view, raising the possible risk of harmful complications. Especially when low basal rates are used in insulin pump therapy, regular glucose monitoring is important to detect catheter occlusions and thus avoid hyperglycemia and diabetic ketoacidosis.