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ORIGINAL ARTICLES

Pilot Studies of Transdermal Continuous Glucose Measurement in Outpatient Diabetic Patients and in Patients during and after Cardiac Surgery

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Abstract

Background:

We tested the hypothesis that glucose can be measured continuously and reliably in patients in diverse settings using a transdermal biosensor coupled to a permeated skin site. In addition, we compared a novel, abrasion-based skin permeation method to an ultrasound-based method for transdermal continuous glucose monitoring.

Method:

Transdermal continuous glucose monitors were applied to patients with diabetes (study I), patients undergoing cardiac surgery (study II), and healthy volunteers (study III). Reference blood glucose measurements were performed with glucometers or standard blood glucose analyzers. At the conclusion of the 24-hour study, data were postprocessed for comparison with the reference blood glucose values collected during the study period.

Results:

Data were validated for 10 subjects for 12 hours in study I, 8 subjects for 24 hours in study II, and 6 subjects in study III. The transdermal continuous glucose monitors usually required 1 hour of warm up. Depending on the study setting, single or multiple calibrations were applied to the datasets. Comparing predicted glucose versus reference blood glucose values, we found that study I yielded 89.6% in zone A and 9.0% in zone B in the Clarke error grid (222 data points), study II yielded 86.4% in zone A and 13.6% in zone B (147 data points), and study III yielded 89.9% in zone A and 10.1% in zone B (378 data points).

Conclusions:

Continuous transdermal glucose monitoring was demonstrated successfully in diverse clinical settings. The performance of abrasion was equivalent to ultrasound skin permeation methodology for transdermal glucose monitoring.

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Abbreviations: (BG) blood glucose, (CTU) cardiothoracic intensive care unit, (CEG) Clarke error grid, (IRB) institutional review board, (ICU) intensive care unit, (intra-op) intraoperation, (MARD) mean absolute relative difference, (PEGDA) polyethylene glycol diacrylate, (post-op) postoperation, (tCGM) transdermal continuous glucose monitor

Keywords: biosensor, continuous glucose, diabetes, intensive care, tight glycemic, transdermal

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Introduction

Diabetes mellitus is a serious, life-threatening metabolic disorder. There is an obvious value with monitoring blood glucose levels on a regular basis in patients with diabetes.[1] Of significant benefit is a device that allows accurate glucose monitoring in real time without the use of frequent finger sticks. A reliable, less invasive method providing for continuous glucose monitoring could facilitate strict blood glucose control, potentially rendering safer self-management and improved long-term health benefits through improved maintenance of normoglycemia.[2]

Tight glycemic control for critically ill patients has been shown to significantly improve outcomes by reducing mortality and complications, thereby decreasing hospital length of stay and costs.[3–5] Glycemic control is commonly achieved in the critically ill through intensive insulin continuously infused based on frequent blood glucose (BG) measurements. However, intensive insulin interventions have been shown to increase the risk of hypoglycemia, which is now known to be an independent determinant of death in the seriously ill patient.[6–8] A continuous noninvasive glucose monitor would provide both real-time BG measurements and trends potentially decreasing nursing labor and helping bedside practitioners achieve euglycemia while avoiding severe hypoglycemic events in their patients.

The performance of continuous glucose monitors of the invasive, subcutaneous type have been evaluated in various clinical studies. Wentholt and colleagues[9] compared two types of continuous glucose monitors on patients with type 1 diabetes and found that the microdialysis system was more accurate than the needle-type system. Deiss and associates[10] showed evidence of improved glycemic control using a real-time continuous glucose monitor on patients with diabetes. Vriesendorp *et al.*[11] examined two types of commercialized continuous glucose monitors in surgical intensive care and reported issues of technical failure. In a medical intensive care unit (ICU), Goldberg *et al.*[12] investigated the accuracy of a continuous glucose monitor that had been previously approved for outpatient applications. Although acceptable device performance was observed, the study was not designed to evaluate patients during or after surgical procedures. Minor bleeding due to needle insertion and a significant rate of device malfunctioning (17%, 7/41) were reported.[12]

This article describes the first minimally invasive glucose monitor that can provide reliable, continuous glucose information for patients during and after cardiac surgery. Safe and effective glucose measurements can be achieved by a miniaturized device—the transdermal continuous glucose monitor (tCGM), developed from the glucose biosensor, which measures glucose flux through ultrasonically permeated skin on patients with diabetes.[13] The performance characteristics are described comparing BG data obtained from the tCGM system with that of standard-of-care methods.

Materials and Methods

Device

SonoPrep®, Skin Permeation System (Echo Therapeutics, Inc., Franklin, MA). This Food and Drug Administration-approved device relies on software and a circuit between the reference electrode and the skin site to monitor real-time conductance and achieve optimal permeation without damage to the skin. A brief focal ultrasound can be used to transiently reduce the normally robust lipid barrier of normal intact skin.[14] Ultrasound application has been shown to increase glucose flux 25 times greater than the flux reported for the reverse iontophoresis technique.[15] Details of the SonoPrep system have been described elsewhere.[16,17]

Prelude™ SkinPrep System (Echo Therapeutics). Prelude is a new skin preparation device under development that provides a cost-effective and easy-to-use means for skin permeation. The system consists of a disposable abrasive end driven by an electrical motor in a stand-alone hand piece. Instead of ultrasound, Prelude utilizes a mechanical means to remove stratum corneum, with the process controlled by the same conductance-based feedback mechanism used in SonoPrep. As a result, the skin permeation procedure is safe, effective, and painless.

tCGM. The Symphony™ tCGM System (Echo Therapeutics) is a fully functional prototype biosensor instrument designed to measure glucose through permeated skin. tCGM consists of a biosensor/transmitter communicating wirelessly with a glucose monitor **(Figure 1)**.

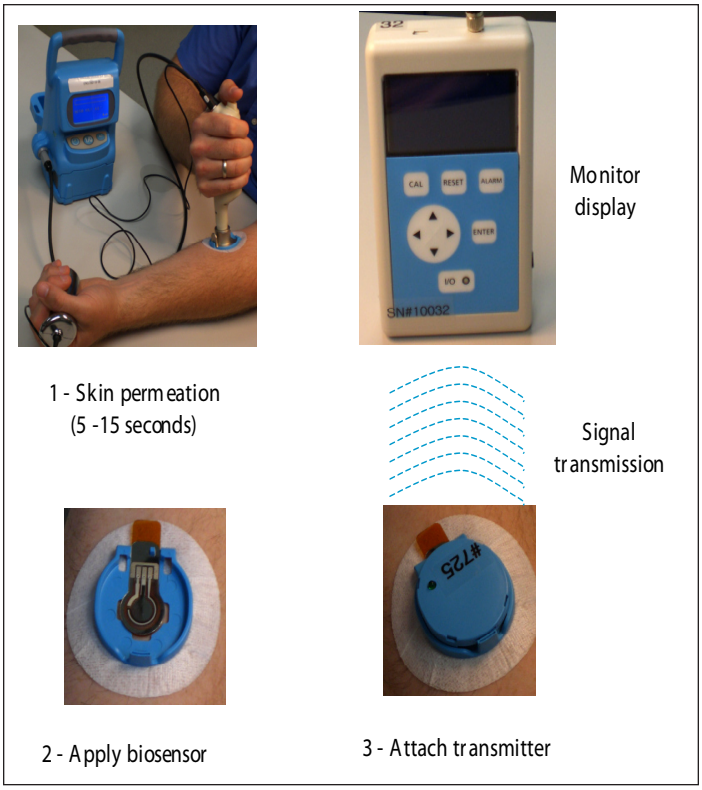

Figure 1. Symphony™ tCGM system and operation.

A sensitive biosensor has been developed to measure transdermal glucose flux, which is proportional to the BG concentration.[13] The biosensor is able to maintain reliable fluid contact with the skin through a proprietary biocompatible hydrogel utilizing glucose oxidase as the sensing chemistry.[18] When the biosensor is placed over permeated skin, glucose oxidase converts incoming glucose flux into hydrogen peroxide, which is in turn broken down to electrons through an electrochemical process. The resulting electrical signal is then converted into continuous measurements of the patient's glucose level. The biosensor is housed in a wireless transmitter, which acquires, stores, and transmits coded data to the receiver/monitor to display a reading every minute. Although all tCGM data were uploaded to computers for poststudy processing, the monitor has a basic function to display real-time BG readings in addition to trends and alarms for excessively high and low BG levels.[19]

Reference BG measurement device. Study I and study III: Bayer's Ascensia Contour BG meter (Bayer HealthCare, Tarrytown, NY). Study II: During surgery: Nova Stat Profile Ultra C (Nova Biomedical, Waltham, MA), cardiothoracic intensive care unit (CTU): Accu-Check Inform® system (Indianapolis, IN) as the glucometer, Bayer Rapidlab 865 blood gas analyzer (Siemens HealthCare Diagnostics, Tarrytown, NY) for whole blood glucose, and Unicel® DXC 800 (Beckman Coulter, Fullerton, CA) for serum glucose.

Study Design

Study I: Patients with diabetes. In this study, two types of biosensor configurations **(Table 1)** were investigated and applied to each of the subjects for up to 24 hours. In configuration A, polyethylene glycol diacrylate (PEGDA)-based hydrogel was used as the polymer framework of the sensing chemistry.[18] In configuration B, a porous membrane was added to the PEGDA hydrogel to mitigate potential biofouling as our first attempt to prolong the longevity of the biosensor. The two biosensors were applied to the subject's left and right upper chest areas at the same time.

Patients with diabetes (type 1 or type 2) were enrolled in a clinical facility (MassResearch, Waltham, MA). Institutional review board (IRB) approval of the study protocol was obtained from the Western Institutional Review Board. Subjects were 18 years of age or older. Excluded from the study were subjects who were pregnant or likely to become pregnant, subjects participating in concurrent clinical studies, subjects with known sensitivity to rubber-based medical grade adhesives or glucose oxidase, and subjects with a skin rash or inflammation.

Table 1.
Biosensor Configurations

Configuration	A	B	C
PEGDA hydrogel	√	√	√
Porous membrane		√	
Composite porous membrane			√
Hermetic seals			√

The subjects remained ambulatory at the clinic for the entire period of the study and were free to eat, move, or sleep at the clinic, mimicking a home care environment. Prior to the application of tCGM, the subjects were instructed on how to perform glucose testing with the BG meter and how to enter the information onto a diary/log form with the aid of the study coordinator. The procedures of SonoPrep skin permeation and installation of tCGM were both performed at the clinic. BG measurements were taken at least hourly during the waking period. Data on the tCGM monitor were blinded to ensure that there were no changes in the subjects' routine medication. Presumed relatedness of any adverse event to the treatment was assessed. Skin reactions, if any, were monitored. At the conclusion of the study period, the transmitter, monitor, and BG meter were disinfected with 70% isopropanol. The study subjects were compensated for their participation.

Study II: Patients in surgical critical care. The study was performed by the Division of Cardiothoracic Anesthesia at Tufts Medical Center (Boston, MA). After IRB approval, adult patients scheduled for cardiac surgery were enrolled in the study. Exclusion criteria were the same as study I, except that patients with a life expectancy of less than 48 hours were excluded. The period of the study included intraoperation (intra-op) and postoperation (post-op). Consented subjects were assigned a study number for blinded data collection purposes.

Biosensor configuration C was used in this study **(Table 1)**. This configuration integrated the PEGDA hydrogel with a composite porous membrane designed to prolong biosensor longevity, and hermatic seals were introduced to protect the biosensor electronics from fluid invasion. Two separate biosensors were applied to the subject in serial, one at the shoulder area prior to surgery (intra-op unit) and the other at the deltoid area (post-op unit) after the subject was tranferred to the CTU.

The subjects remained hospitalized for the entire study period. The procedures of SonoPrep skin permeation and installation of tCGM were both performed at the hospital. BG levels were monitored per standard-of-care protocols. Insulin, heparin, and vasoactive medications were administered, and blood was sampled either through the peripheral arterial catheter or from the bypass pump. Twenty-four-hour tCGM data could not be collected from some participating subjects because of their shorter lengths of stay in CTU. Data collected by the tCGM monitor were blinded to the participating subjects and the medical staff. At conclusion of the study period, the transmitter and monitor were retrieved by the study coordinators and disinfected with commercial disinfectant wipes. No compensation was provided for the subject's participation.

Study III: In-house study, abrasion vs ultrasound skin permeation. In this study, healthy volunteers without diabetes were enrolled. IRB approval of the study protocol was obained from the Western Institutional Review Board. After two skin sites at the subject's upper chest area were treated separately with SonoPrep and Prelude, two biosensors (configuration C) were applied. Prelude represented the newest skin permeation method, and study III became the first opportunity to test this approach clinically. This study used the same protocol as in study I, except that the subjects were free to continue their routine activities at work and at home. The participating subjects were compensated for their participation.

Data Analysis

Data were computed and analyzed with a personal computer-based algorithm after retrieval from each of the tCGM monitors. The algorithm contained functions for temperature compensation, noise filtration, and a calibration function based on linear regression. One point calibration (first reference BG reading after 1 hour of warm-up period) was applied to data collected from study I. For study II, the number of calibrations depended on the availability of reference BG readings and the patient's length of stay. Two or three point calibrations (first BG after warm-up, bypass pump off, 12 hours after pump off) were applied to data collected from the intraoperative period. One or two point calibration (first, 12 hours after the first) was applied to data obtained during the postoperative CTU stay. In study III, a three point calibration (first, at midpoint before a meal, right after wake up) was applied to tCGM data. Except for lag time difference, the same algorithm was used for all studies.

These tests were small-scale, pilot feasibility studies to determine the device performance in three distinct clinical settings. Although they were not powered to demonstrate statistical significance, hundreds of BG–biosensor data points from each study were collected for analysis. Results of the comparison were evaluated based on the performance of the tCGM in accuracy, correlation, and clinical relevance relative to the reference BG measurements.

Results

Demographic information from all studies can be found in **Table 2**.

Study I: Patients with Diabetes

Ten of the 11 consented subjects completed the enrollment. Data from one subject were not useful because of excessive noise caused by moisture-induced device

Table 2.
Demographics of Study Subjects

	Study I	Study II	Study III
Male	5 (50%)	7 (87.5%)	4 (66.7%)
Female	5 (50%)	1 (12.5%)	2 (33.3%)
Type 1 diabetes mellitus (DM)	1 (10%)	1 (12.5%)	0
Type 2 DM	9 (10%)	4 (50%)	0
Non-DM	0	3 (37.5%)	6 (100%)
Age average/standard deviation	63.4 /8.8	66.4 /6.8	41.1/8.9

malfunction. Because of significant downward signal drift and lack of response to BG excursion, data between 12 and 24 hours were excluded from the analysis. As a result, only data in the first 12 hours were reported.

A total of 222 BG–biosensor data points from this study were processed. For each dataset the calibration point was chosen as the first reference BG measurement taken 1 hour after the tCGM was turned on, and a lag time of 22 minutes was applied to BG data, based on the best correlation between reference BG and biosensor data as computed by the algorithm. When using biosensor configuration A with reference to BG measurements, the 12-hour mean absolute relative difference (MARD) was 12.4%. Of the data points, 89.6% fell in the clinically accurate A zone of the Clarke error grid (CEG) plot with 98.7% in the clinically relevant A+B zones **(Figure 2)**. tCGM reading also showed strong correlation to the reference BG measurements—the median R^2 (square of correlation coefficient) was 0.77 between these two methods. **Figure 3** illustrates two sample datasets, where the continuous trace of tCGM measurements closely tracks the discrete reference BG values for 12 hours.

For biosensor configuration B, the 12-hour MARD was 20.4% and the medium R^2 was 0.64 when compared to reference BG measurements. Error grid analysis revealed

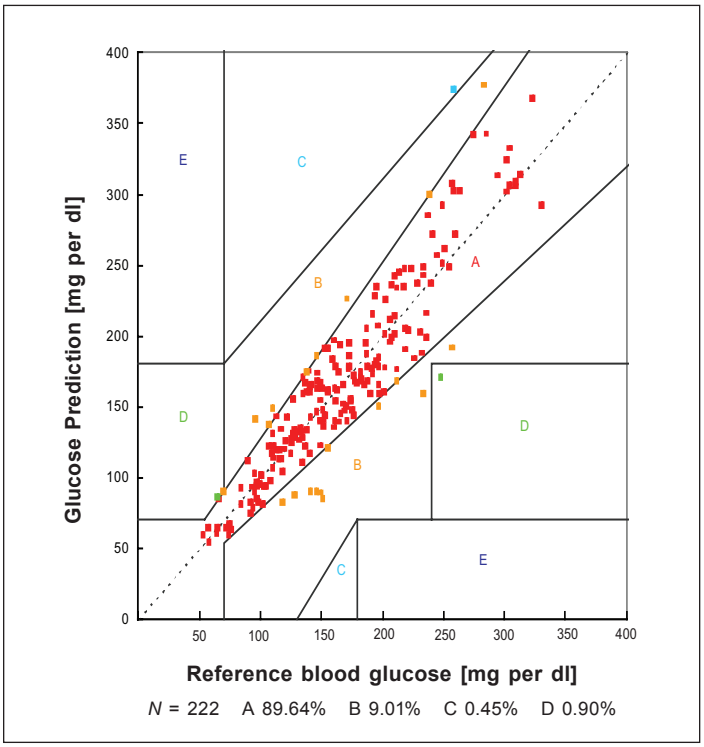

Figure 2. CEG analysis using biosensor configuration A on 10 patients with diabetes in a home care-mimicking clinical setting for 12 hours.

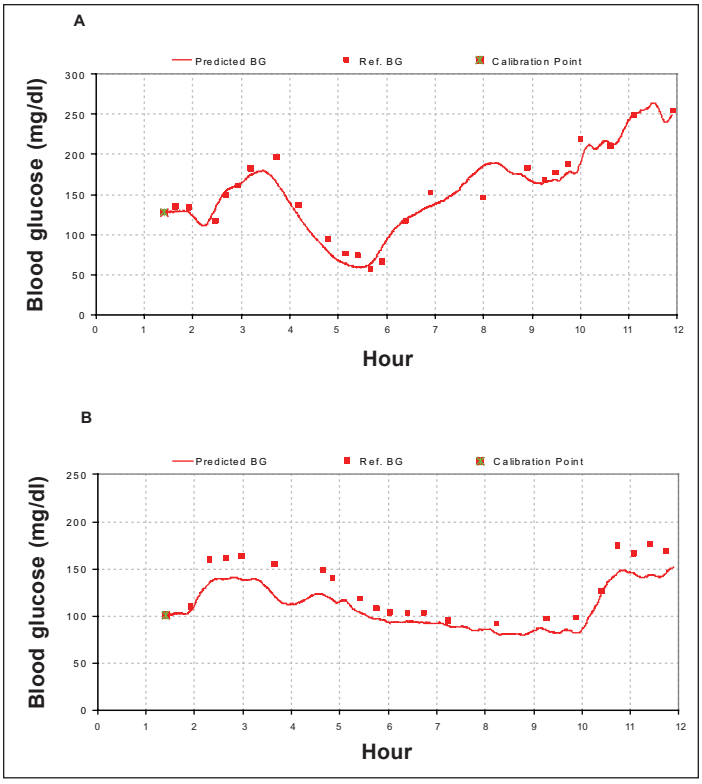

Figure 3. BG–biosensor profiles of patients with diabetes with higher **(a)** and lower **(b)** glucose levels. The continuous biosensor measurements follow the reference BG values closely in both cases.

that 70.7% of the data points fell in the A zone with 96.9% in the A+B zones. Introduction of the protective membrane appeared to deteriorate the biosensor performance. With additional development to the membrane and device configurations, however, the tCGM system showed significant improvement in subsequent studies.

Study II: Patients in Surgical Critical Care

A total of 37 subjects were enrolled in this two-phase feasibility study. Twenty-six subjects were enrolled in the initial phase to evaluate the device and make proper adjustments to the biosensor configurations for the challenging operative and surgical environments. Results were not reported from this phase of the study. In the second phase of the study, data were collected from 8 out of the 11 patients enrolled, of which 1 patient did not complete the study, and data from 2 patients were excluded because of a low biosensor signal, which, in our experience, suggested low glucose flux and insufficient skin permeation.

Collecting from the eight evaluable subjects, 12 datasets and 147 BG–biosensor data points were analyzed. Seven datasets were collected from the intraoperative period

and five from the postoperative period. A 30-minute lag time was applied to BG data, based on the best correlation between reference BG and biosensor data. Comparing the tCGM and reference BG measurements, the 24-hour MARD was 11.6%; 86.4% of the data points fell in the A zone of the CEG with 100% in the A+B zones, and the median R^2 was 0.83 **(Figure 4)**. **Figures 5a** and **5b** show datasets collected from the intraoperative and postoperative periods, respectively, where the continuous trace of tCGM measurements closely tracked the discrete reference BG values. There was no marked difference of sensor performance between intraoperative and postoperative study periods and no observable interferences from the surgical procedure and the use of routinely administered concomitant medications. The study demonstrated that the tCGM system accurately predicted BG readings in a cardiac surgical ICU setting every minute for up to 24 hours.

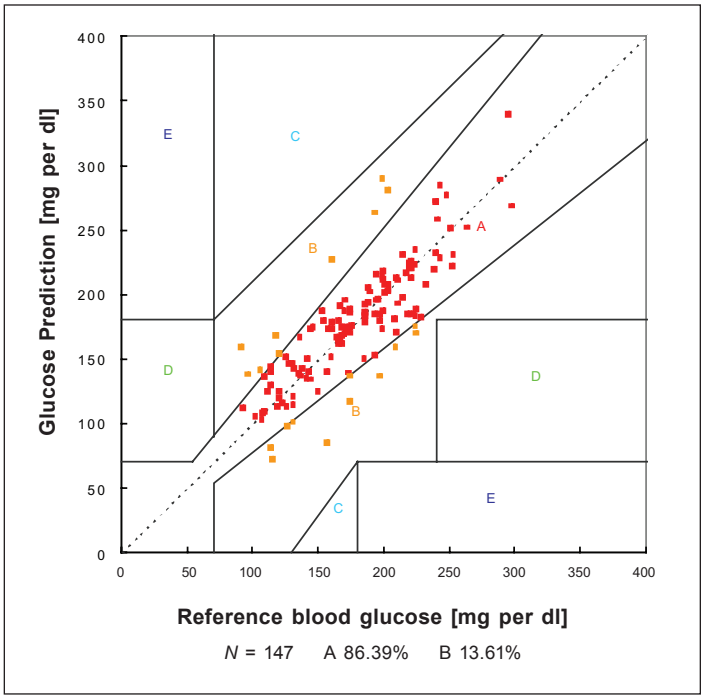

Figure 4. CEG analysis using biosensor configuration C on eight subjects in a surgical critical care setting for up to 24 hours.

Study III: Abrasion vs Ultrasound Skin Permeation

This study was designed to compare two skin permeation methods, SonoPrep and Prelude, for transdermal glucose monitoring. Six healthy in-house subjects completed the enrollment. A total of 12 datasets (6 for each method) were analyzed with an applied 14-minute lag time. One hundred eighty-three and 195 BG–biosensor data points were collected from the Prelude and the SonoPrep methods, respectively.

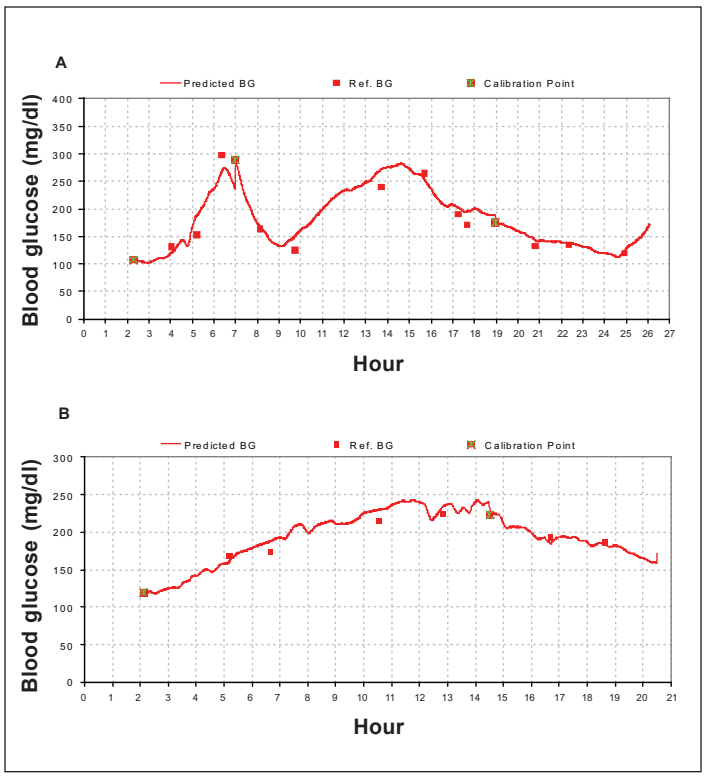

Figure 5. BG–biosensor profiles of one patient undergoing cardiac surgery **(a)** and another patient in CTU **(b)**. The continuous biosensor measurements follow the reference BG values closely in both cases.

With a three point calibration, the 24-hour MARD was 9.0% using Prelude and 10.8% using SonoPrep. One hundred percent of the data points from both methods fell in the A+B zones of the CEG. The median R^2 was 0.70 and 0.79 for Prelude and SonoPrep, respectively. **Figure 6** displays one sample dataset by overlapping two calibrated continuous glucose measurements, where close proximity of the two traces can be clearly seen throughout the study period. Overall, Prelude exhibited equivalent performance to SonoPrep for use of the tCGM system.

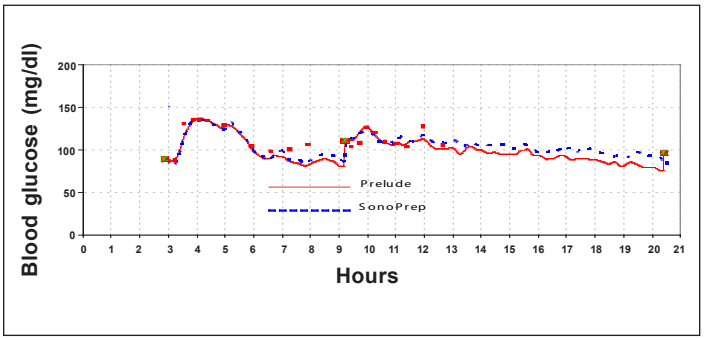

Figure 6. Comparison of SonoPrep and Prelude skin permeation methods for tCGM application. These data were collected from the same subject showing equivalent performance of the two skin permeation methods.

Discussion

Accuracy is an important performance indicator of any continuous glucose monitor because interventions may then be made by the end users based solely on the device readout. In both outpatient diabetes and surgical/CTU settings the prototype tCGM demonstrated comparable accuracy to other commercialized subcutaneous-based continuous glucose monitoring devices referenced in this article. To better assess the accuracy of tCGM in a clinical setting, a controlled study incorporating a single standard reference BG method and more frequent BG sampling will be required. While MARD and Clarke error grid analysis are used in this study, other statistical tools such as time series and glycemic range analysis can be used to further evaluate tCGM accuracy. It will be interesting to study the effect of lag time and calibration protocol to the accuracy and whether tCGM exhibits different performance in the intraoperative period as compared to the postoperative period. Future studies with this technology will require a larger sample size, entailing many more data sets, resulting in greater statistical power.

The long lag time of 15–30 minutes associated with tCGM data is not desirable, but can be improved by further refinement in biosensor design and data algorithm. A low biosensor signal from 2 out the 11 subjects in study II suggests that SonoPrep with tCGM may not be applicable to 100% of the patient population. However, rejection criteria can be set based on the initial magnitude of the biosensor current, and further improvement to the skin permeation technology may increase the applicability of tCGM. For outpatient diabetes the 12-hour biosensor use life will limit its applications. However, better biosensor longevity can be expected if an improved biosensor design, such as configuration C, is implemented.

A continuous glucose monitor will find its widest application only when its reading is available to the users in real time. In this regard, our data processing algorithm is designed for real-time use, although data are currently processed retrospectively. We envision that further work will be needed to utilize the live information provided by the tCGM, such as the direction and rate of change of BG levels and the designs for hypoglycemic and hyperglycemic alarms. In an earlier study, our device provided a better biosensor–BG correlation in the hypoglycemic region when compared with two other commercialized CGM devices.[20] Hypoglycemia performance will remain an important topic for our future clinical study.

We have observed from some study subjects that tCGM exhibits a use life of longer than 24 hours and such potential requires further investigation. These studies reported herein were feasibility/pilot studies of limited sample sizes: further studies testing longer biosensor duration will be needed in the near future.

A reliable method for continuous glucose monitoring represents an unmet need for both home care and critical care settings; when developed and refined successfully, the tCGM product can address this need. A cost-effective and easy-to-use Prelude SkinPrep exhibits equivalent performance to SonoPrep for tCGM application. With the advantages of a 1-hour warm-up period and minimally invasive nature, the tCGM system may become a preferred medical device in facilitating diabetes management. A combination of our new skin permeation and needle-free sensing technologies may provide a low-cost, convenient, safe, and effective solution for continuous glucose monitoring in diverse populations.

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Disclosure:

Stanley A. Nasraway, Jr., Han Chuang, My-Quyen Trieu, and James Hurley are employees of Echo Therapeutics.

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