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Vascular Glucose Sensor Symposium: Continuous Glucose Monitoring Systems (CGMS) for Hospitalized and Ambulatory Patients at Risk for Hyperglycemia, Hypoglycemia, and Glycemic Variability

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Abstract

Hyperglycemia, hypoglycemia, and glycemic variability have been associated with increased morbidity, mortality, length of stay, and cost in a variety of critical care and non–critical care patient populations in the hospital. The results from prospective randomized clinical trials designed to determine the risks and benefits of intensive insulin therapy and tight glycemic control have been confusing; and at times conflicting. The limitations of point-of-care blood glucose (BG) monitoring in the hospital highlight the great clinical need for an automated real-time continuous glucose monitoring system (CGMS) that can accurately measure the concentration of glucose every few minutes. Automation and standardization of the glucose measurement process have the potential to significantly improve BG control, clinical outcome, safety and cost.

Keywords

vascular glucose sensor, continuous glucose monitoring system, continuous glucose monitor, artificial pancreas, hyperglycemia, hypoglycemia, glycemic variability

This introduction to the Vascular Glucose Sensor Symposium describes the clinical and technical advantages/disadvantages of CGMS developed for hospitalized patients and ambulatory patients with diabetes. Early research has focused on the demonstration of safety and point accuracy in a variety of patient populations and environments. Current research is attempting to demonstrate whether the CGMS trend data can be used by the clinician and patient to improve overall BG control and eliminate the risk for hypoglycemia.

Although clinicians strongly believe CGMS has great potential to improve safety and clinical outcome, additional clinical trials are required before hospital administrators and insurance companies are willing to pay for a new technology to replace current methods of BG monitoring and control. A long-term goal of this research is an automated closed-loop artificial pancreas system capable of safely controlling the concentration of BG in a wide variety of hospital ized patients.

CGMSs are also being developed for long-term implantation within the subcutaneous tissue and bloodstream. A long-term implantable CGMS could be coupled with an external or implantable insulin pump to automatically control the concentration of BG in ambulatory patients with diabetes.

Clinical Need for Glucose Monitoring and Control in the Hospital

Hospitalized patients with diabetes mellitus (DM) commonly develop mild to moderate hyperglycemia (prevalence 90% in 1 survey) due to rapid enteral/parenteral infusions of dextrose plus beta cell dysfunction and mismatched insulin therapy.[1] An estimated 18-38% of DM patients have persistent hyperglycemia while in the hospital, defined as 3 consecutive days with a BG level >200 mg/dl.[1,2] In addition, many diabetic and nondiabetic patients develop "stress hyperglycemia" following major surgery or acute medical illness due to increased gluconeogenesis and insulin resistance.[3] Stress hyperglycemia may occur secondary to increased levels of corticosteroids, cat-

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echolamines, cytokines, growth hormone, general anesthetics, and/or hypothermia.[1-3]

Hyperglycemia, hypoglycemia, and glycemic variability have been independently associated with increased morbidity, mortality, length of stay, and cost in a variety of critical care and non–critical care patient populations in the hospital.[4-12] Observational trials have revealed a moderate to strong association between hyperglycemia, hypoglycemia, and glycemic variability with an increased risk for infection, deep vein thrombosis, pulmonary embolism, acute kidney injury, neuropathy, and worse clinical outcome after myocardial infarction, heart failure, stroke, burns, and trauma.[13-28]

The results from prospective randomized controlled trials (RCTs) designed to determine the risks and benefits of intensive insulin therapy and tight glycemic control have been confusing, and at times conflicting.[29-31] Some prospective RCTs demonstrated a significant decrease in morbidity and mortality when the BG concentration was targeted to the near-normal BG range with IV insulin; while other RCTs in medical and surgical ICU patients did not show a clinical benefit from IV insulin therapy and tight glycemic control.[29-37]

Results from the RCT highlighted the limitations of current clinical methods of glucose monitoring and insulin delivery. All of the RCTs were complicated by a high incidence of mild, moderate and severe hypoglycemia; and a low percentage of time spent in the target range.[29-37] Several of the major endocrinology and critical care societies subsequently changed their guidelines to a more conservative target BG range (140-180 mg/dl) to minimize the risk for hypoglycemia.[38-43]

Current Methods for Monitoring BG in the Hospital

Safe and effective insulin therapy in the hospital requires accurate BG measurements every 2 to 4 hours when a patient's physiology and BG concentration are stable and every 30 to 60 minutes when the BG is changing rapidly, especially in the hypoglycemia range.[43-49] Current methods of BG monitoring are labor intensive and prone to preanalytical and analytical error. Hourly BG monitoring for 1 patient requires more than 2 hours of a nurse's time per day to sample blood, measure the concentration of BG, and document the result in the medical record.[50] Intensive insulin therapy and tight glycemic control are therefore limited to a small number of patients in the hospital that are managed in the OR and ICU.[49]

The most accurate and precise BG measurements in the hospital are obtained using blood sampled from a radial artery catheter that is assayed with a central laboratory glucose analyzer or an ICU blood gas analyzer.[51-54] Whole blood samples obtained from a central venous catheter or a peripheral venous catheter may be contaminated or diluted by adjacent infusions.[55] The glucose concentration in peripheral arterial blood is typically 4 to 8 mg/dl higher than peripheral venous blood.[51-53] The BG concentration in the vena cava can be variable due to hepatic/renal glucose production, absorption of food from the intestines, analytical error due to variable oxygen and hematocrit levels, and contamination/dilution from adjacent infusions.[55-62]

The most timely but least accurate BG measurements are obtained using a fingerstick capillary blood sample and a point-of-care glucose meter/test strip. Fingerstick capillary blood may produce an erroneous BG measurement due to poor tissue perfusion, dilution with edema fluid, or contamination from glucose on the skin surface.[51-53,56-58,60-62] Accuracy of the point-of-care meters can be adversely affected by anemia, polycythemia, hypoxemia, acidosis, drugs (acetaminophen, dopamine, mannitol, and maltose), low sample volume, and human transcription error.[43,51-52,60-61,63]

In conclusion, hyperglycemia, hypoglycemia, and glycemic variability commonly occur in hospitalized patients with diabetes and stress hyperglycemia despite significant nursing time and hospital resources devoted to BG control.[1,2,29,30]

Additional prospective randomized trials are required in specific patient populations to determine whether intensive insulin therapy and tight BG control lead to improved clinical outcomes. Future RCTs will use real-time CGMS with a validated insulin dosing algorithm to maintain a hospitalized patient's BG level in the target range; while eliminating the risk for hypoglycemia.[43,64,65]

Continuous Glucose Monitoring Systems (CGMS) for Hospitalized Patients

The limitations of point-of-care BG monitoring in the hospital highlight the great clinical need for an automated real-time CGMS that can accurately measure the concentration of glucose every few minutes, especially when managing ICU patients with intensive insulin therapy.[57-60] Automation and standardization of the glucose measurement process have the potential to significantly improve BG control, clinical outcome, safety, and cost.[64-70] CGMS could become the standard of care for BG management if the systems are easy to use in the clinical setting, significantly increase time in the target BG range, and eliminate the risk for moderate/severe hypoglycemia (Tables 1, 2, and 3).[64-72]

Caregivers will observe the CGM data display during each patient encounter to assess the (1) glucose concentration (mg/dl or mmol/liter), (2) direction of glucose change (increasing, decreasing, or stable), and (3) rate of glucose change (slow, fast, or stable). The dose of intravenous (IV) and subcutaneous insulin will be adjusted frequently according to the glucose trend data using clinical protocols and computer algorithms.[64-70] A caregiver will typically assess the risk for hypoglycemia during each patient encounter by

Table 1. Vascular Catheter Blood-Sampling CGMS for Hospitalized Patients: Vascular CGMS Intermittently Transports Blood to an External Glucose Sensor.

Company name	Product name	Regulatory status/ hospital use	Sample location	Glucose source	Sensor location	Measurement method	Measurement frequency
Edwards Lifesciences	GlucoClear	CE Mark	Catheter in peripheral vein	Venous blood	Sensor in catheter lumen	Electrochemical/enzymatic	5 to 60 minutes
International Biomedical	GlucoScout	FDA-approved, no CE	Catheter in peripheral vein, central vein, or radial artery	Venous or arterial blood	External sensor with tubing	Electrochemical/enzymatic	5 to 60 minutes
B.Bruan	?	Pending	Catheter in peripheral vein, central vein, or radial artery	Venous or arterial blood	External sensor with tubing	NIR absorption spectroscopy, electrochemical/enzymatic	5 to 60 minutes
Cascade Metrix	CMI system	Pending	Catheter in peripheral vein, central vein, or radial artery	Venous blood	External sensor with tubing	Electrochemical/enzymatic/ NIR absorption spectroscopy	5 to 60 minutes
OptiScan	Optiscaner	CE Mark	Catheter in central vein	Venous blood transformed into plasma	External sensor with tubing	MIR absorption spectroscopy	15 minutes

Table 2. Indwelling Vascular CGMS for Hospitalized Patients: Vascular CGMS Use an Optical Fiber and Fluorescence or a Micro-Dialysis Catheter and External Electrochemical Sensor.

Company name	Product name	Regulatory status/ hospital use	Sample location	Glucose source	Sensor location	Measurement method	Measurement frequency
Medtronic (GluMetrics technology)	GluCath	Pending	Optical fiber in radial artery, peripheral vein, or central vein	Venous or arterial blood	Sensor in artery or vein lumen	Boronic acid quenched fluorescence	1 to 5 minutes
GlySure	GlySure CGMS	Pending	Optical fiber in central vein, peripheral vein, or radial artery	Venous or arterial blood	Sensor in artery or vein lumen	Diboronic acid quenched fluorescence	1 minute
GlucoSet	GlucoSet CGMS	Pending	Optical fiber in peripheral vein, central vein, or radial artery	Venous or arterial blood	Sensor in artery or vein lumen	Boronic acid, change in hydrogel volume	1 to 5 minutes
Flowsion	Diramo System	Pending	Micro-dialysis catheter in central vein, peripheral vein, or radial artery	Dialysate from venous or arterial blood	External sensor with tubing	Quenched fluorescence	5 to 10 minutes
Maquet Critical Care	Eirus System	CE Mark	Micro-dialysis catheter in central vein, peripheral vein, or radial artery	Dialysate from venous or arterial blood	External sensor with tubing	Electrochemical/ enzymatic	5 to 10 minutes
Probe Scientific	MicroEye	Pending	Micro-dialysis catheter in central vein, peripheral vein, or radial artery	Dialysate from venous or arterial blood	External sensor with tubing	Electrochemical/ enzymatic	5 to 10 minutes
A. Menarini Diagnostics	GlucoDay	Pending for blood	Micro-dialysis catheter in peripheral vein, central vein, or radial artery	Dialysate from venous/arterial blood	External sensor with tubing	Electrochemical/ enzymatic	5 to 10 minutes

Table 3. Subcutaneous Tissue and Transdermal CGMS for Hospitalized Patients: CGMS Measure the Tissue Fluid Glucose Concentration, Not the BG Concentration.

Company name	Product name	Regulatory status/ hospital use	Sample location	Glucose source	Sensor location	Measurement method	Measurement frequency
A. Menarini Diagnostics	GlucoDay	CE Mark for ISF	Micro-dialysis catheter in subcutaneous tissue	Dialysate from ISF	SC tissue	Electrochemical/ enzymatic	5 minutes
Roche Diagnostics	?	Pending	Electrochemical electrode in subcutaneous tissue	Interstitial fluid	SC tissue	Multiple electrodes electrochemical/ enzymatic/fluorescence	1-5 minutes
Medtronic MiniMed	Medtronic Hospital Glucose Management System HGMS	CE Mark	Electrochemical electrodes in subcutaneous tissue	Interstitial fluid	SC tissue	Multiple electrodes electrochemical/ enzymatic	1-5 minutes
DexCom	DexCom G4 Platinum	Pending	Electrochemical electrode in subcutaneous tissue	Interstitial fluid	SC tissue	Electrochemical/ enzymatic	1-5 minutes
Abbott Diabetes	Freestyle Navigator II	Pending	Electrochemical electrode in subcutaneous tissue	Interstitial fluid	SC tissue	Electrochemical/ enzymatic	1-5 minutes
Echo Therapeutics	Symphony tCGM System	Pending	Electrochemical electrode on skin surface; noninvasive	Transdermal interstitial fluid	Skin surface	Electrochemical/ enzymatic	1-5 minutes

glancing at the bedside display. A steep downward slope of glucose trend data will be easily recognized as a high-risk clinical situation requiring increased vigilance. Threshold and predictive alarms will also help to minimize the risk of mild/moderate hypoglycemia and eliminate the risk for severe and prolonged hypoglycemia.[71,72]

The use of real-time CGMS glucose measurements, trend data, and alarms has the potential to increase the safety of insulin administration and decrease cost due to a reduction in nursing time, decreased hospital length of stay, and improved patient outcomes.

Of interest, clinical use of current subcutaneous tissue CGMS during hospital trials actually increased the number of blood samples, point-of-care BG measurements, and nursing time required for glucose control.[70,71,73] Nurses are required to calibrate the CGMS, follow the upward/downward trends in the CGMS glucose measurements, respond to alarms for hyper/hypoglycemia, obtain a patient blood sample, and measure the BG concentration before making any change in the insulin dose.[39,41,43,73]

A hospital CGMS will be routinely used by clinicians if it (1) decreases the amount of caregiver time and effort required for glucose monitoring and BG control, (2) is easy to set-up, calibrate, and use in a variety of hospital environments, (3) produces real-time glucose measurements with accuracy and reliability sufficient for dosing insulin, (4) has a low incidence of false alarms for hyper and hypoglycemia, (5) has a low incidence of device-related adverse events and no risk for a serious adverse event, and (6) has a cost/benefit ratio that justifies adding a new point-of-care technology for the critical care and general floors of the hospital.[73-80]

Subcutaneous Tissue CGMS for Hospitalized Patients

A few studies have shown that subcutaneous tissue CGMS sensors can be used in the hospital to continuously monitor the concentration of glucose in critically ill ICU patients and ambulatory patients on the general floors. The glucose trend data and alarms have been used to improve glucose control and minimize the incidence, severity, and duration of hypoglycemia.[71,79-88] The CGMS sensors can be safely and easily inserted through the skin into the subcutaneous tissue of the abdomen, flank, thigh, and chest wall. It is important to insert the CGMS sensor using aseptic technique to minimize the risk for infection, especially in patients with decreased immunity due to cancer, HIV, corticosteroids and transplant medications. In addition, CGMS sensors should be monitored closed after insertion because significant bleeding can occur due to damaged blood vessels, especially in hospitalized patients with abnormal coagulation due to platelet inhibitors, anticoagulants, and liver failure.[64,65,82,89-95]

Several generations of the subcutaneous tissue enzyme-electrochemical CGMS developed by DexCom, Inc, Medtronic Diabetes, Inc, and Abbott Diabetes, Inc for outpatient DM management have been studied in a variety of hospital environments and patient populations.[89-101] Many of the CGMS sensors correlated closely with reference BG measurements when calibrated 4 to 6 times per day. Some sensors, however, had a noisy output signal or drifted significantly and needed to be recalibrated more frequently.[73,80,81,89,91-93,98-101]

Medtronic developed a subcutaneous tissue CGMS optimized for hospitalized patients called the Hospital Glucose Management System® (HCMS). The HCMS sensor has 2 electrodes, each containing multiple glucose-oxidase electrochemical sensors attached to a bedside monitor that displays the glucose measurement once every minute.[102] The HCMS recently received CE Mark approval for routine use in the ICU and general floors of the hospital. Sensor drift and variable time-lag forced regulatory authorities to label all of the subcutaneous tissue CGMS as adjunctive devices- limiting the clinical use of CGMS to tracking and trending with alarms. A nurse must obtain a blood sample and BG measurement prior to adjusting insulin therapy.[38-45] Clinical trials are under way to evaluate whether a clinical nurse can use the subcutaneous tissue CGMS trend data to maintain a hospitalized patient's BG concentration in the target range, eliminate hypoglycemia, and improve clinical outcomes.

Vascular Catheter Blood-Sampling CGMS for Hospitalized Patients

Vascular catheter CGMS have the potential to become a standard of care for the management of BG levels in the critical care units of the hospital. The near-continuous CGMS automatically transfer whole blood from a radial artery, peripheral vein, or central venous catheter to an external flow-through glucose sensor. A vascular catheter CGMS acquires a fresh blood sample every 5 to 15 minutes, measures the concentration of BG, and then flushes the sample back into the bloodstream using flush solution. Standardization of blood sample acquisition, analysis, and calibration will increase the accuracy and precision of the BG measurement, a major advantage of CGMS compared to routine clinical methods.[43,64,65]

Blood-sampling CGMSs attached to a peripheral IV catheter, however, are limited by the formation of thrombus within the vein and catheter lumens.[103] Thrombus tends to form at the site of vascular wall injury immediately after catheter insertion. Plasma proteins, platelets, and clotting factors adhere to the catheter and endothelial cell surface, especially in regions of low blood flow.[103-106] Platelets and clotting factors that adhere to the catheter surface and endothelial cells will break away in regions of high blood flow and shear forces, limiting the formation and propagation of thrombus. Aspiration of blood into the catheter lumen activates platelets and clotting factors.[104-107] Rapid infusion of the activated platelets and factors back into the vein with flush solution can cause inflammation of the endothelial

cells. Thrombus commonly forms on the injured endothelial cells, proximal to the catheter tip. Sample acquisition from a peripheral IV catheter commonly fails due to valves, lumen collapse, platelet plugs, and thrombus.[103-107]

When using a vascular catheter CGMS, it is important to avoid infusing a glucose-free or glucose-containing solution through an adjacent IV catheter to minimize contamination or dilution of the aspirated sample. A small amount of sample contamination with 5% dextrose solution (5000 mg/dl of glucose) can cause a large preanalytical error.[53,55] Thrombus within the vein lumen can cause flush solution to be trapped near the catheter orifice; leading to acquisition of a diluted sample and a large preanalytical error. The majority of clinicians do not add heparin to the flush solution (1-4 units/ml) to minimize the risk for heparin-induced thrombocytopenia.[43,64,65]

Blood-sampling CGMS attached to a radial artery catheter should have a lower incidence of thrombus formation due to high blood flow and shear forces within the artery lumen. However, the region between a 20 gauge catheter (outer diameter 1.0 mm) and the radial artery wall (inner diameter 1.8 to 2.2 mm) becomes a low flow, low shear force environment.[106,107] This leads to thrombus formation within the radial artery lumen, especially when sampling and flushing more frequently than once per hour. Flushing activated platelets and clotting factors back into the radial artery can cause capillary leakage and hand edema.

Blood-sampling CGMS attached to the proximal port of a central venous catheter (CVC) have the lowest incidence of thrombus formation due to the large diameter of the superior vena cava and high blood flow/shear forces.[108] Requiring a CVC for sample acquisition significantly limits CGMS use to a subpopulation of medical and surgical patients managed in the critical care environment. Furthermore, dedicating a CVC port for glucose monitoring or placing a custom CVC necessitates advance planning. Vigilance is required to avoid sample contamination or dilution from solutions infused into the distal port of the CVC or a peripheral IV catheter.[43,55,109]

The following blood-sampling vascular catheter CGMSs are either available for clinical use or being evaluated to obtain regulatory approval in the United States and Europe:

The GlucoScout® (International Biomedical, Inc, Austin, TX, USA) has Food and Drug Administration (FDA) clearance for monitoring the concentration of BG in blood sampled from a CVC, radial artery catheter, or a peripheral IV catheter as frequently as every 5 for 72 hours. The CGMS automatically transports a 1.6 ml sample of blood from the catheter into a sterile flow-through glucose oxidase electrochemical sensor. The concentration of BG is measured with sufficient accuracy to allow adjustments in insulin dose. Initial set-up requires a manual 2-point calibration using saline (0 mg/dl) and a salt-dextrose flush solution (82 mg/dl). The IV solution produces a 1-point calibration before every blood sample acquisition. Frequent sample acquisition can become unreliable and lead to volume overload because each sample is flushed back into the bloodstream using 6 ml of salt solution.[109-111]

The GlucoClear® CGMS (Edwards Lifesciences, Inc, Irvine, CA, USA) is CE Mark approved for monitoring the concentration of BG in blood sampled from a peripheral IV catheter every 5 minutes for 72 hours. The CGMS automatically transports a 0.3 ml sample of blood into a glucose-oxidase enzyme electrochemical sensor located within the IV catheter lumen. The concentration of glucose is accurately measured by monitoring the quality of the blood sample and by performing a 1-point sensor calibration prior to every blood sample acquisition. The flush/calibration solution is manufactured with a standard concentration of glucose to ensure sensor accuracy. Heparin can be added to the flush solution to improve reliability and accuracy. Obstruction of venous blood flow by thrombus may cause reaspiration of flush solution and a preanalytical dilution error.[112-115]

The OptiScanner® (OptiScan, Inc, Hayward, CA, USA) is CE Mark approved for monitoring the concentration of plasma glucose in blood sampled from the proximal port of a CVC every 15 minutes for 72 hours. The CGMS automatically transports a small sample of blood from the CVC to a bedside monitor that contains a centrifuge, spectrometer, and data display. The CGMS flushes the residual sample back into the bloodstream to minimize blood loss. Midinfrared spectroscopy is used to measure the concentration of plasma glucose. A robust calibration model was developed using absorption spectra from a wide variety of hospitalized patients.[116-119] A multicenter clinical trial is currently under way in the United States to obtain FDA approval for real-time BG monitoring in critically ill hospitalized patients.

The CMI System (Cascade Metrix, Inc) consists of an automated blood sampling and glucose monitoring system attached to a peripheral IV catheter. The CGMS automatically transports a small volume of venous blood into an external flow-through glucose-oxidase enzyme electrochemical sensor. Clinical trials are currently under way to obtain CE Mark approval. A prior embodiment of the vascular CGMS demonstrated feasibility of using near-infrared absorption spectroscopy to measure the concentration of glucose in whole blood with satisfactory sensitivity, specificity, and accuracy.[120]

Indwelling Vascular CGMS for Hospitalized Patients

In contrast to the near-continuous blood-sampling vascular catheter CGMS described above, the indwelling CGMS technologies can provide a continuous measurement; and therefore a higher resolution of glucose trends.

The EIRUS® (Maquet Critical Care, AB Rastatt, Germany) consists of a custom micro-dialysis CVC inserted into the superior vena cava, with an external fluidics system and a flow-through glucose-oxidase and lactate oxidase enzyme electrochemical sensor. The CGMS is CE Mark approved for

monitoring the concentration of dialysate glucose and lactate every minute for 48 hours. Rapid blood flow and shear forces minimize fouling of the semipermeable porous membrane. Glucose-free dialysate is perfused through the dialysis catheter at a slow and constant rate. Glucose molecules in the plasma diffuse through the porous membrane into the dialysate with near-complete equilibration. The external sensor is automatically calibrated using standard glucose and lactate solutions.[121-125]

The GlySure Continuous Glucose Monitoring System (GlySure, Ltd, Oxfordshire, United Kingdom) is a small optical fiber with a distal tip covered with diboronic acid and fluorescent chemistry surrounded by a semipermeable porous membrane coated with heparin. The optical fiber is inserted into the superior vena cava through the proximal port of a multilumen CVC. The luminescence chemistry has been optimized for glucose specificity and high sensitivity in the hypoglycemia range. Rapid blood flow and high shear forces minimize bio-fouling of the porous membrane. The CGMS has been submitted for CE Mark approval for monitoring the concentration of plasma glucose every minute for 48 to 72 hours.[126,127]

The GluCath® Intravascular CGMS (GluMetrics, Inc, Irvine, CA) is a small diameter optical fiber tipped with boronic acid fluorescent chemistry. The optical fiber CGMS sensor is inserted through a 20 gauge catheter into the lumen of a radial artery. The chemistry was optimized to produce a large and rapid change in fluorescence signal following a small change in the BG concentration, especially in the hypoglycemia range. Clinical performance has been limited by variable blood flow and thrombus formation around the radial artery catheter and optical fiber sensor. The GluMetrics, Inc technology was recently acquired by the diabetes division of Medtronic MiniMed Inc (Northridge, CA, USA).[128-132]

The GlucoSet Continuous Glucose Monitoring CGMS (GlucoSet, AS Trondheim, Norway) is a small-diameter optical fiber tipped with a hydrogel matrix incorporated with 3-phenylboronic acid. The optical fiber CGMS is inserted through a catheter into the radial artery lumen. The hydrogel volume contracts in direct response to an increase in the local glucose concentration, and expands following a decrease in the glucose concentration. An interferometer is used to accurately measure the diameter of the hydrogel. The optical fiber is covered with a heparinized semipermeable coating to facilitate the rapid diffusion of glucose and minimize the formation of thrombus. The CGMS is required to recognize a change in hydrogel volume due to glucose from a change in hydrogel volume due to arterial pulsations or body movement.[133-134]

Closed-Loop Artificial Pancreas Systems for the Hospitalized Patient

The Biostator® (Miles Laboratory, Elkhart, Indiana, USA) was commercialized in the 1970s as the first closed-loop system artificial pancreas (AP) system for the hospital; followed by the Nikkiso STG-22® (Nikkiso Company, Ltd, Tokyo, Japan) 30 years later. The 2 AP systems use real-time vascular CGMS and closed-loop algorithms to control the IV infusions of insulin and dextrose. Blood is continuously transported from a peripheral IV catheter to an external flow-through glucose-oxidase enzyme electrochemical sensor at 2 to 4 ml/hour. Heparin is infused into the IV catheter lumen to minimize thrombus formation within the tubing and sensor. Heparinized blood is continuously transported through the IV tubing into an external glucose sensor, then into a waste container.[135-145]

The closed-loop AP systems have been used to safely control the concentration of BG in a wide variety of medical and surgical patient populations in the hospital. The IV insulin/dextrose infusions are increased or decreased every 1 to 10 minutes based on the BG concentration and direction/rate of change.[135-138,143-145] Furthermore, the AP systems have been used to safely perform glucose clamp and insulin pharmacokinetic/pharmacodynamic experiments by automatically adjusting the IV glucose infusion rate. Unfortunately, the current AP systems are too large and complex for routine clinical use at the bedside. In addition, sample acquisition can become unreliable and the systems remove a large volume of blood (60 to 120 ml) per day.[135-145]

Long-Term Implantable Vascular CGMS for Ambulatory Patients With Diabetes

There is also great clinical need for a long-term implantable vascular CGMS that can accurately measure the concentration of BG in ambulatory patients with T1DM and severe T2DM. The real-time CGMS trend data can be used to determine the optimum dose and timing of insulin therapy in relation to meals, activity, illness, and the circadian rhythm of cellular metabolism.

Vascular catheter CGMS have been designed with an enzyme-based electrochemical or oxygen sensor on the distal end, covered by a multilayered porous membrane. Long-term performance requires the porous channels of the membrane to remain patent so glucose and oxygen can passively diffuse from the plasma into the enzyme layer adjacent to the working electrode. The membrane structure and biomaterials are designed to minimize the adhesion of plasma proteins, platelets, red blood cells, white blood cells, thrombus, and fibrous tissue.[146] Vascular CGMSs are typically implanted within the superior vena cava or aorta due to their large diameter, rapid velocity of blood flow and high shear-forces.[104-108] For example, the vascular CGMS developed by Data Science International, Inc for rodent research requires implantation within the abdominal aorta to ensure reliable sensor performance for >60 days. Vascular CGMS failure may occur after several months due membrane degradation, enzyme denaturation, and/or electrode fouling.[146-148]

Medical Research Group, Inc (acquired by Medtronic) developed a long-term implantable vascular catheter CGMS that utilized glucose-oxidase/catalase enzymes and differential oxygen electrodes to measure the concentration of plasma glucose. A novel mechanical design and multilayered porous membrane ensured an excess supply of oxygen, protected the enzymes from degradation, and compensated for dynamic changes in the ambient oxygen concentration.[149] Medtronic developed a long-term implantable AP system for human use that integrated this vascular CGMS with an implantable insulin pump. Feasibility trials demonstrated safe and effective AP system performance when using a PID closed-loop control algorithm (proportional-integral-derivative controller) in ambulatory patients with T1DM.[150,151] The closed-loop AP system was not commercialized; perhaps due to cost, CGMS performance issues, and regulatory hurdles.

Animas Corporation, Inc developed a long-term implantable optical CGMS that utilized near-infrared (NIR) absorption spectroscopy to measure the concentration of BG in flowing blood. The miniature optical sensor head was implanted around the outside wall of a small artery or vein, similar to a blood flow probe used for animal research. A flexible cable connected the optical sensor head to a hermetically sealed package that contained electronics, optics, and a battery. Locating the light source and sample detector external/internal to the vessel wall produced high quality NIR spectra. The optical CGMS used multiple wavelengths, signal averaging, and a universal calibration model to measure the concentration of glucose in blood with satisfactory accuracy and specificity.[152-155] The program was discontinued in 2005 following Animas's acquisition by Johnson & Johnson, Inc.

Conclusion

In conclusion, this review summarizes many of the promising vascular CGMS previously developed, and being developed to help manage hospitalized patients and ambulatory patients with diabetes. There is greatly clinical need for an automated CGMS that provides an accurate measurement of the glucose concentration in blood, plasma, or tissue fluid.

Industry is trying to commercialize real-time vascular CGMS for the hospital that are safe, user-friendly, accurate, reliable, and easy to calibrate. Several of these systems have CE Mark approval and are being used by clinicians to manage patients in a wide variety of critical care environments. Technical difficulties remain, especially at the sensor-blood and sensor-tissue interface.

Insulin dosing algorithms are being developed and validated that utilize the real-time CGMS data to optimize the time a patient's BG concentration is in the desired target BG zone, while eliminating the risk for moderate, severe, and prolonged hypoglycemia. Hospitalists and payers are waiting to review more clinical trial data that demonstrate an improvement in clinical outcome, prior to endorsing a new technology for glucose monitoring and control. A fully automated closed-loop AP system for hospitalized patients is an ultimate goal of this CGMS research.

Long-term implantable vascular and subcutaneous tissue CGMS continue to be developed in academia and industry with promising data. A safe, accurate, reliable, and easy-to-use long-term implantable CGMS would be a major breakthrough in the management of ambulatory patients with diabetes. A fully automated closed-loop AP system for ambulatory patients is an ultimate goal of this CGMS research.

Abbreviations

AP, artificial pancreas; BG, blood glucose; CE Mark, Conformité Européenne–Mark of Approval in Europe; CGM, continuous glucose monitor; CGMS, continuous glucose monitoring system; CVC, central venous catheter; DM, diabetes mellitus; FDA, Food and Drug Administration; HGMS, Hospital Glucose Management System; ICU, Intensive Care Unit; IV, intravenous; NIR, near-infrared; MIR, mid-infrared; RCT, randomized controlled trial; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: In the past 5 years, the following CGMS companies sponsored research at the Jefferson Artificial Pancreas Center, Department of Anesthesiology, Sidney Kimmel Medical College of Thomas Jefferson University, with JIJ as the principal investigator: Medtronic Diabetes, Edwards Lifesciences, DexCom, GluMetrics, Hospira, and Echo Therapeutics. JIJ was also a consultant to Medtronic Diabetes, Edwards Lifesciences, Becton Dickinson, Teleflex, and Echo Therapeutics. All funds were provided to the university. JIJ is currently a co-founder and equity owner of Capillary Biomedical, Inc. PJS is a co-founder, equity owner, and employee of Capillary Biomedical and formally an employee of GluMetrics. Capillary Biomedical Inc. is developing a long-term implantable CGMS and insulin delivery system. MCT had no potential conflicts to declare.

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