



Issue 32
May 2002

Issues in Emerging Health Technologies

Continuous Glucose Monitoring in the Management of Diabetes Mellitus

Summary

- ✓ **Continuous glucose monitors (CGMs) measure interstitial fluid (ISF) glucose, and provide information about continuous glucose fluctuations that is not otherwise captured by intermittent blood glucose testing.**
- ✓ **CGMs may benefit patients having difficulty controlling their blood sugar or during initiation or monitoring of insulin pump use.**
- ✓ **CGMs require calibration with finger-stick tests and supplement, but do not replace conventional blood glucose testing.**
- ✓ **CGM values correspond to blood glucose values taken approximately 13-18 minutes earlier and may differ from metered readings.**

The Technology

Continuous glucose monitors (CGMs) measure glucose levels in the interstitial fluid surrounding skin cells, providing continuous information about glucose fluctuations that is not otherwise captured by intermittent testing. These devices require calibration with blood glucose levels as determined by finger-stick tests. Errors of 20% or more have been noted in blood glucose metered readings.¹ This error could be transferred to CGMs during calibration and thereby affect their overall accuracy. CGMs can record when meals, insulin injections, hypoglycaemic episodes and exercise occur.²

The Continuous Glucose Monitoring System (CGMS) (MiniMed Inc; Sylmar, CA, USA) supplements finger-stick glucose measurements by monitoring glucose fluctuations over a 72-hour period.³ A needle sensor is inserted under the patient's abdominal skin and is wired to an externally worn monitor. Glucose in the interstitial fluid reacts with glucose oxidase on the needle, producing hydrogen peroxide. This chemical reaction generates measurable current. Glucose is

measured over a range of 2.2 - 22.2 mmol/L. Readings, taken every 10 seconds, are averaged every five minutes and stored in the monitor's memory. Averaged readings are transferred to a computer for therapeutic planning by a physician; no real-time measurements are provided directly to the patient.

The GlucoWatch Biographer system (Cygnus Inc; Redwood City, CA, USA) is worn like a wristwatch for up to 12 hours at a time.⁴ An AutoSensor containing glucose oxidase-laden gel discs and electrodes snaps onto the back of the device. When a low electric current passes between the electrodes, glucose is extracted through the intact skin by electro-osmotic flow. ISF glucose collects in the discs and reacts with glucose oxidase producing hydrogen peroxide. The electrodes measure this reaction every 20 minutes.

Regulatory Status

Device	Country	Approval	Status
MiniMed CGMS	US ⁵	June 1999	Supplement conventional testing
	Canada ⁶	May 2000	Class III device licence
	Europe ⁷	June 2000	Available by prescription
GlucoWatch Biographer	Europe ⁷	Dec 1999	Approved
	US ⁴	March 2001	Supplement conventional testing
	Canada	Not approved as of 05/06/02	

Patient Group

Diabetes mellitus (DM) is a chronic condition wherein the body is unable to produce or use insulin. Without insulin regulation, cells cannot absorb sufficient glucose from the bloodstream or derive energy from food, resulting in high blood glucose levels. Long-term high blood glucose values are associated with damage to the eyes, kidneys, nerves and large blood vessels. Diabetes is the leading cause of blindness, kidney failure, and lower leg amputation and is also a major cause of premature heart disease and other vascular diseases.⁸

There are two types of DM, type 1 and type 2. Accounting for 10% of cases, type 1 occurs when islet cells of the pancreas do not produce insulin. With its onset, typically in the teen or young adult years, type 1 DM requires daily insulin injections. Approximately 90% of cases are type 2, resulting from insulin resistance and partial deficiency. Typically affecting people over 40 years of age, type 2 DM can sometimes be controlled by diet alone, however, medications may be required.⁸ Over two million people have DM and it is the seventh leading cause of death in Canada.⁹

CGMs provide information about glucose fluctuations that may be of particular benefit to patients with type 1 DM that is difficult to control. This includes patients with asymptomatic hypoglycemia, nocturnal hypoglycemia, unpredictable blood glucose levels regardless of therapeutic adjustments, and patients starting or changing insulin regimens.

Current Practice

Maintaining blood glucose at near-normal levels reduces the risk of long-term complications.⁸ However, tight control of glucose levels increases the risk of low blood glucose levels that are associated with significant consequences. Periodic testing for glycosylated hemoglobin (HbA1c) is recommended; this assesses the average blood glucose levels over the preceding three months.¹⁰

Self-monitoring allows persons with diabetes to measure their blood glucose levels at home and adjust therapy appropriately.¹¹ Self-monitoring requires a finger-prick to draw blood several times a day.¹¹ Alternative site testing on an arm or leg may reduce callus formation and loss of sensation from frequent testing. Many patients are reluctant to perform finger-stick tests frequently due to inconvenience, pain, and expense, making it difficult to adjust therapy appropriately.¹¹ Glucose meter types differ by: the amount of blood required, testing time, size of the meter and presentation of the memory data.

Administration and Cost

Neither the CGMS device, the sensors, nor the procedure for insertion are covered by Canadian provincial health insurance plans (Mark Mailloux, MiniMed, Ile des Soeurs, PQ: personal communication, 2002 May 7).

Device	Cost	Component	Considerations
CGMS ⁷	US\$1,995	Monitor	5-yr device life expectancy Finger-sticks required
	US\$ 395	Com-station	
	US\$ 99	CGMS software	
	US\$ 19	ShowerPak (30/box)	
	US\$ 49	IV 3000 (100/box)	
	US\$ 49	SenSertter	
	US\$ 299	Sensor (10/box)	
GlucoWatch ¹²	UK£ 350	GlucoWatch Biographer	2-3 yr device life expectancy Finger-sticks required
	UK£ 50	Auto Sensor (16pads/box)	

Rate of Technology Diffusion

Available by prescription only, the CGMS supplements standard glucose measurement in specific situations. Glucose fluctuations identified with the CGMS can determine more precisely when finger-stick tests should be done.¹³ Therapy can then be adjusted to compensate for glucose fluctuations. Current studies are investigating CGMS use in paediatric and non-Caucasian patients, and patients with type 2 DM, concomitant disease states, or gestational diabetes.¹³

The GlucoWatch is used as an adjunct to standard testing by patients at home and in health care facilities. Cygnus received supplemental pre-market approval from the FDA for the GlucoWatch G2 Biographer. This technology has a shorter warm-up time, and displays and stores more readings than the first-generation GlucoWatch.¹⁴

Concurrent Developments

Several biosensors are under development; from a wireless system by TheraSense, to a transdermal patch that draws ISF glucose for reading by a hand-held meter (Technical Chemicals and Products Inc.).¹⁵ Bioject Medical Technologies is designing a combined patch and sensor that produces a continuous reading.¹² The Diasensor 2000 monitor (Biocontrol Technology Inc, Pittsburgh, USA), based on infrared technology, is used in Europe but is not yet available in North America.

The Evidence

CGMS:

Evidence of CGMS use, primarily in type 1 DM, includes a randomized controlled trial (n=11),¹⁶ several prospective comparative studies (n_T≈250),¹⁷⁻²³ and a post market surveillance trial (n=238).²⁴ CGMS measurements correlate closely

(correlation coefficient >0.85) with glucose levels measured by patients using home blood glucose meters, according to comparative studies.^{18,19,24} Both hypo- and hyperglycaemic episodes, that would have remained unrecognized by traditional testing, were identified in patients using CGMS.^{16,17,20-22} Therapeutic changes made based on CGMS measurements, not identified by intermittent tests, were effective in improving glucose control according to HbA1c measures.^{19,23} Since patients were aware the CGMS provided continuous recordings to their physicians, it is possible that patient compliance contributed to improved control in the trials.⁷

GlucoWatch:

In comparative studies, GlucoWatch readings correlate closely (correlation coefficient >0.80) with blood glucose measurements but lagged behind by a mean of 18 minutes.^{4,25-27} Set at a low glucose alert level of 5.6 mmol/L, the device correctly identified hypoglycaemic levels of ≤ 4.0 mmol/L 75% of the time, with 10% false alerts (sensitivity 75%, specificity 90%). Set at a high glucose alert level of 13.3 mmol/L, the device correctly identified hyperglycaemic levels of ≥ 15.0 mmol/L 79% of the time, with 8% false alerts (sensitivity 79%, specificity 92%).²⁵ Users can adapt the sensitivity or specificity balance to meet their own clinical needs.²⁸

Adverse Effects

Redness, bleeding, bruising and/or discomfort at the sensor insertion site was reported in 15% of patients participating in CGMS phase II trials.¹⁸

Skin irritation was observed in 50% of patients in clinical trials of the GlucoWatch.⁴

Implementation Issues

CGMs supplement, but do not replace, conventional blood glucose testing and are intended for occasional monitoring. Abrupt temperature changes, excessive sweat, and strong electromagnetic sources may affect operation.¹³

Addendum:

Following external review of this bulletin, a literature update identified a multicentre study. Measurements using a new subcutaneous glucose sensor (Glucoday; A. Menarini Diagnostics) showed close correlation with blood glucose measurements.²⁹ The Committee for Evaluation and

Diffusion of Innovative Technologies (CEDIT), France also plans to evaluate the CGMS.³⁰

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ISSN 1488-6324 (online)

ISSN 1488-6316 (printed)

Publications Agreement Number 40026386