

The MiniMed Continuous Glucose Monitoring System

JOHN J. MASTROTOTARO, Ph.D.

DIABETES is a major source of morbidity, mortality, and economic expense. All patients with type 1 diabetes and an estimated 3–4 million patients in the United States with type 2 diabetes must take insulin to control their glucose levels. The majority of these patients self-monitor their blood glucose one or more times each day, using fingerstick blood sampling and analysis with a portable glucose meter device. Approximately 200,000 type 1 diabetes patients in the United States practice intensive insulin therapy, requiring four or more blood glucose measurements each day coupled with either multiple daily injections of insulin or an insulin pump.

The Diabetes Control and Complications Trial (DCCT) clearly demonstrated the importance of frequent self-monitoring of blood glucose (SMBG) in attaining tight glycemic control.¹ Patients undergoing intensive therapy had a 39–76% reduced occurrence of long-term complications as compared to patients treated with conventional therapy. The primary drawback of intensive therapy was a threefold increase in the occurrence of severe hypoglycemia, despite performing four or more SMBG tests per day. Consequently, methods to improve the ability to achieve intensive control without hypoglycemia are being explored.

There is a tremendous need to develop and commercialize a truly simple, accurate method of measuring glucose that can provide a basis for more accurate and directed disease self-management. Generally, it is not practical to perform SMBG frequently enough throughout the day to accurately identify every blood glucose excursion. MiniMed® has taken a first step

in advancing the practice of glucose self-monitoring by developing a short-term, continuous glucose sensor. The sensor is inserted subcutaneously and is capable of reliable operation for up to 3 days, followed by replacement with a new sensor at a different location, if necessary. The assay method is based on electrochemical detection of glucose through its reaction with glucose oxidase. Data are collected once every 5 min by a pager-sized monitor device and can be periodically downloaded into a computer for analysis and interpretation.

In future product iterations, the sensor will function as a hypoglycemia and hyperglycemia alarm, by notifying the user when blood glucose levels reach preselected thresholds (such as 60 mg/dL and 200 mg/dL), and will provide real-time glucose readouts. The alarm feature will be especially important in patients with hypoglycemic unawareness, which is believed to occur in anywhere from 25% to 50% of patients with type 1 diabetes,² especially those who have neuropathy or those without complications who are following intensive glycemic control regimens.³ Fanelli et al.⁴ have shown that meticulous control to prevent low glucose excursions can result in a significant recovery of hypoglycemic awareness.

DESCRIPTION OF THE DEVICE

The MiniMed Continuous Glucose Monitoring System (CGMS; MiniMed Inc., Northridge, CA; www.minimed.com) is a Holter-style (hardwired) sensor system comprised of four components: (1) a pager-sized glucose monitor,

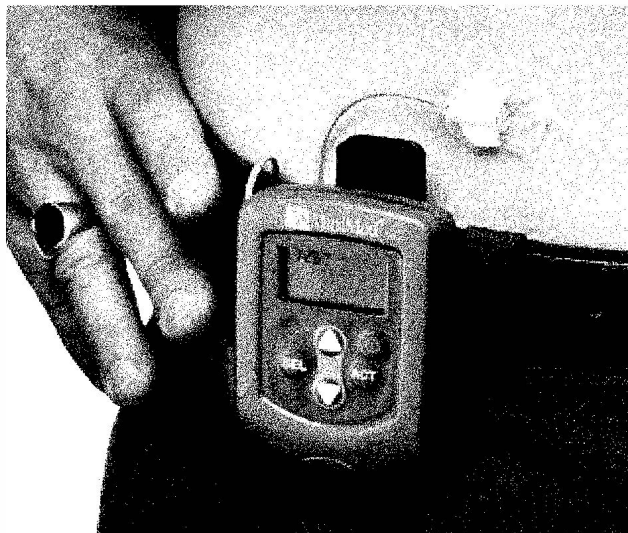


FIG. 1. Continuous glucose monitoring system.

(2) a sterile, disposable subcutaneous glucose sensing device with an external electrical connector, (3) a connecting cable, and (4) a communication device (Com-Station) enabling data stored in the monitor to be downloaded to a personal computer.

The CGMS (Fig. 1) uses a subcutaneous sensor to continuously monitor interstitial glucose levels in the range of 40–400 mg/dL. The function of the glucose monitor is to acquire, display, and store signals from the subcutaneous glucose sensor. The glucose sensor signal is acquired every 10 sec, with an average of the signals saved in memory every 5 min. The CGMS monitor, which is powered by two standard AAA alkaline batteries, can acquire and store up to 2 weeks of information.

The Com-Station is designed to retrieve glucose data from the glucose monitor and download it via infrared pulses to a personal computer (PC) through a serial port (Fig. 2). Once glucose data from the monitor have been downloaded, the CGMS Com-Station software can be used to analyze and display the data. The data can be viewed as graphical data and summary statistics, or as numerical data.

The CGMS is used primarily by the health-care professional (HCP) to gather continuous glucose data on patients already diagnosed with diabetes mellitus. The data collected by the system, when downloaded to a PC, can be useful to the HCP in managing a patient's di-

abetes, by identifying patterns of high or low glucose concentrations. This information may be used to adjust insulin administration patterns, change the patient's diet, or improve patient education efforts. This information is particularly beneficial for patients whose diabetes is difficult to manage due to rapidly fluctuating glucose levels. The device is also quickly gaining acceptance among clinical researchers as a primary endpoint reflecting glycemic control.

SET-UP AND USE OF THE CGMS

The first CGMS product does not provide glucose values to the patient in real time. Instead, the CGMS is used by the HCP as a tool to provide retrospective information on daily glucose excursions during the period of use. The HCP inserts the sensor and programs the monitor at the office and then sends the patient home wearing the device. Patients continue to self-monitor their blood glucose as instructed by their HCP and enter these blood glucose values into the CGMS. Event markers for meals,



FIG. 2. Monitor placement in the Com-Station.

insulin administration, and exercise can also be entered. After wearing a sensor for up to 3 days, patients return to the medical office where the data from the CGMS is downloaded to a PC for review. Data are presented in the form of daily glucose trend plots and a summary table of average glucose levels, glucose ranges, and standard deviations. The HCP then can make adjustments to the therapeutic regimens based on continuous, accurate measurements.

SENSOR CALIBRATION

The CGMS sensor, when inserted subcutaneously, measures an electrical current in nanoamperes (nA) that is related to the interstitial glucose concentration. Although the exact relationship between interstitial and capillary blood glucose remains to be uncovered, clinical studies have shown that subcutaneous sensor measurements generally follow finger-stick meter measurements and venous blood laboratory values.⁵⁻⁹ These studies have shown that the concentrations of glucose in the interstitial fluid are typically lower than those in blood, and changes in interstitial glucose may be detected either earlier or later than those occurring in the blood.

Nevertheless, numerous studies in humans have demonstrated the value of measuring glucose in the interstitial fluid.¹⁰⁻¹³ Rebrin et al.¹⁴ found that subcutaneous sensor measurements of interstitial glucose consistently predicted plasma glucose independent of increases in endogenous or exogenous insulin and without correction for delays in interstitial glucose equilibration.

The CGMS instructions recommend that at least four SMBG meter readings be entered into the monitor each day that the CGMS is used. These blood glucose readings are used to calibrate the sensor's nA readings at the time the data are downloaded to a PC and the graphing utility is run. The retrospective calibration approach uses a modified form of linear regression to determine calibration factors (slope and offset). A separate calibration is performed for each calendar day of CGMS data. The calibration is based upon a linear regression of all of

the meter entries with corresponding valid sensor readings (nA).

FORMAT OF DATA DISPLAY FOR THE HEALTHCARE PROFESSIONAL

Once the CGMS data are downloaded to a PC using the Com-Station, the HCP has the ability to review summary statistics, daily trend plots, and a "Modal" day plot of the sensor and meter data.

Evaluation of optimal accuracy criteria

Based on clinical research of the CGMS, two criteria for optimal accuracy have been established: (1) a correlation between the sensor and meter readings of at least 0.79, and (2) a mean absolute difference of no more than 28%. For each calendar day, the correlation coefficient between the meter readings and the calculated sensor glucose values is automatically calculated. The mean absolute difference is calculated by taking, for each pair of data, the absolute difference between the meter glucose reading and the sensor glucose measurement, dividing by the meter value, and then averaging across pairs within a day. The optimal accuracy criteria are then applied independently to each day of sensor data. If the sensor fails to meet these criteria, a warning message appears on the sensor profile and as a note to the summary statistics for that day. This message also appears if there are fewer than three meter-sensor data pairs for that day, because the correlation coefficient in such a case cannot be meaningfully calculated. Any statistic that fails to meet the criteria is identified in three ways: (1) the statistic is shaded in the summary table for easy identification, (2) an "x" will appear next to the date in the summary table and in the worksheet tab of the daily graph, and (3) the "optimal accuracy" message will appear as a footnote to the summary table and on the daily graph.

Creation of data summary

Summary statistics are calculated for each calendar day and for all dates combined. The sum-

Data Summary											
Optimal Accuracy Criteria				Sensor				Meter			
Date	Number of Paired Sensor/Meter Readings	Correlation Coefficient [r]	Mean Absolute Error (%)	Number of Readings	Average (mg/dL)	SD (mg/dL)	Sensor Range (mg/dL)	Number of Readings	Average (mg/dL)	SD (mg/dL)	Meter Range (mg/dL)
12-20-99	4	1.00	2	171	149	49	81-268	4	138	39	82-180
12-21-99	4	0.96	19	288	105	34	44-193	4	100	49	58-183
12-22-99	4	0.95	7	221	132	32	57-193	5	120	32	69-163
12-23-99 x	1	n/a	0	28	171	41	98-236	2	109	5	104-114
All Days	13	0.97	9	708	127	43	44-268	15	118	40	58-183

x: This day does not satisfy the criteria for optimal accuracy as indicated by the shaded entries in the summary table. Please use your clinical judgement in evaluating the graph.

c: The calibration slope for this day is outside the allowable range of 2 to 10 or no paired sensor/meter data are available. As a result, no sensor plot is provided.

FIG. 3. Example of data summary table.

mary table includes three sections: Optimal Accuracy Criteria, Sensor, and Meter. The Optimal Accuracy Criteria includes the number of paired meter readings, correlation coefficient

(r), and mean absolute difference (%). The sensor and meter sections each include the number of readings, average value, standard deviation, and range of glucose values. These

Glucose Sensor Profile: 12-21-99

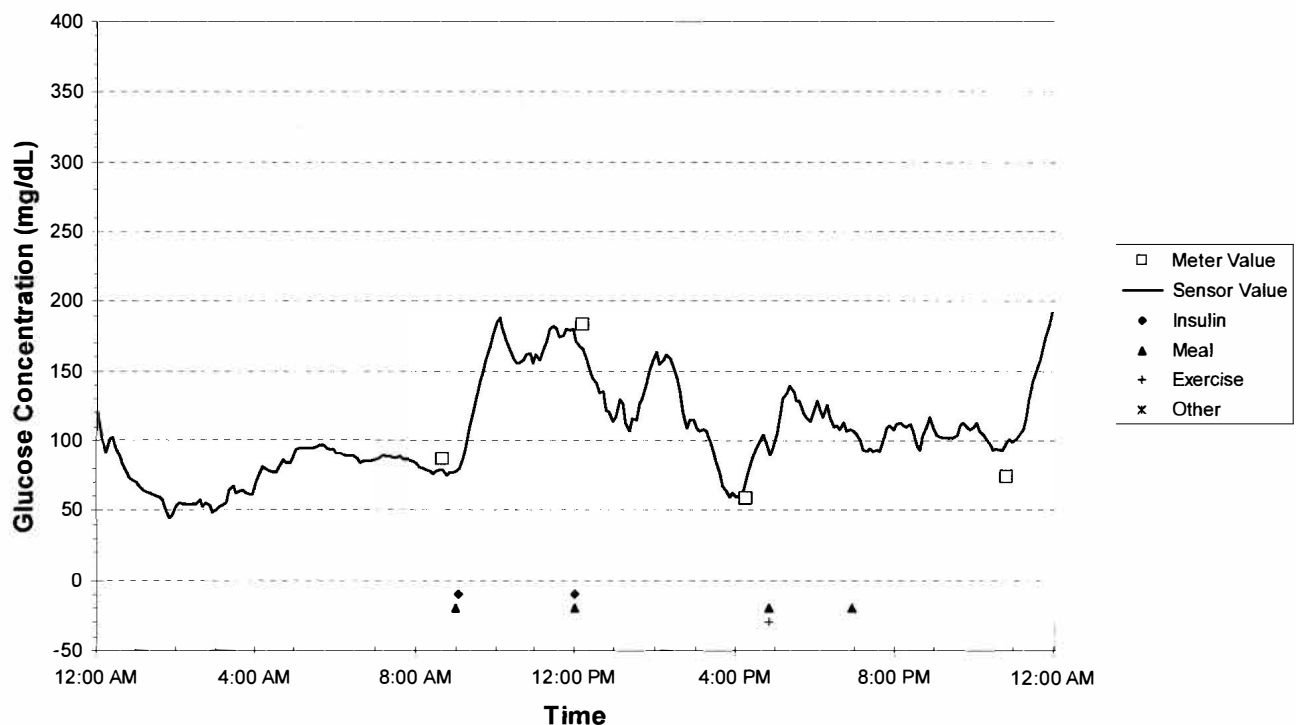


FIG. 4. Example of daily graph.

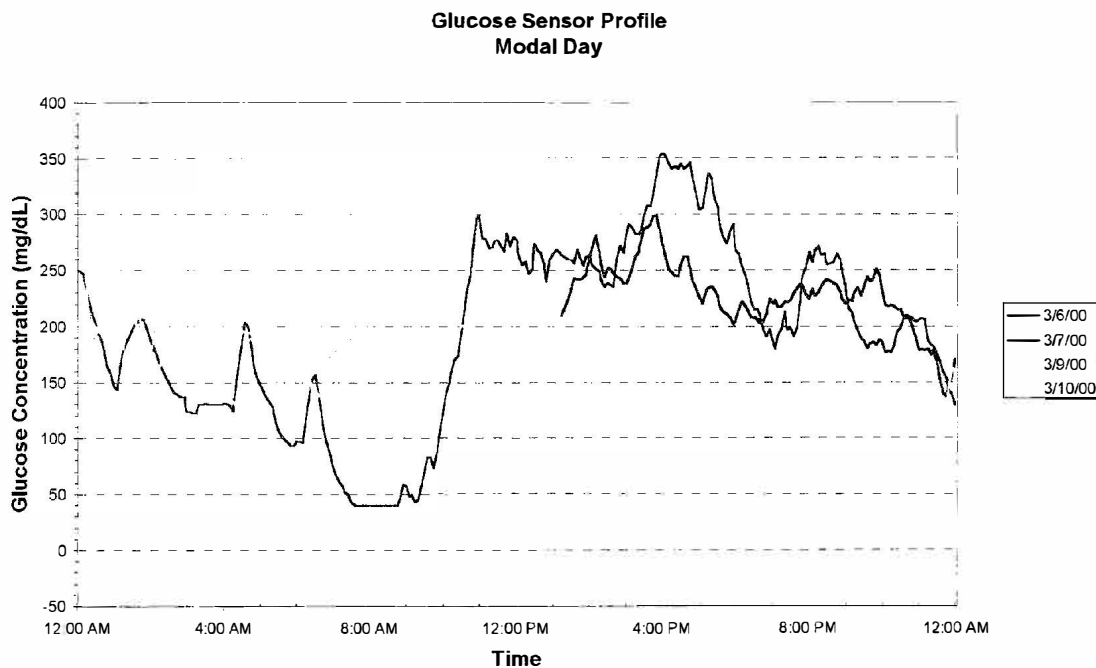


FIG. 5. Example of modal day graph.

summary statistics are placed in a "Data Summary" worksheet within the patient file (Fig. 3).

Creation of daily graphs

A scatter plot is created for each available calendar day in the data set (Fig. 4). Each graph plots real time on the horizontal axis (with a fixed 24-h range from midnight to midnight) and blood glucose from both the CGMS and the meter on the vertical axis, with a fixed range of 40–400 mg/dL. User-entered events (meals, insulin, exercise, and other) are also plotted and are positioned on the graph outside the range of blood glucose values, so that the data markers for these events do not interfere with the profiles.

Creation of modal day graph

A composite graph is generated that superimposes all daily sensor profiles from a data download on a single graph. Each day of sensor data appears in a different color, and the graph legend lists the dates being plotted. This graph, known as a "Modal Day" plot, may be used to identify consistent patterns of glucose excursion across days of sensor use (Fig. 5).

CONCLUSION

The MiniMed CGMS is the first ambulatory continuous glucose monitoring system with FDA approval. For the first time, healthcare professionals can evaluate glucose trends and the effects of various intensive treatment modalities during normal activities of daily living. Its effect on the treatment of diabetes could have a similar impact as the advent of self-monitoring of blood glucose.

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Address reprint requests to:

John Mastrototaro, Ph.D.

MiniMed Inc.

18000 Devonshire Street

Northridge, CA 91325

E-mail: johnm@minimed.com