ABSTRACT

The goal of glucose monitoring in diabetes is to obtain useful information about the patient's overall glucose status to normalize glucose and prevent hypoglycemia and minimize hyperglycemia through meaningful and timely interventions. As glucose control is the foundation of diabetes care, self-monitoring of blood glucose (SMBG) is the foundation of glucose monitoring. Studies have shown a direct correlation between SMBG and improved glycosylated hemoglobin (HbA1c) levels. The American Diabetes Association recommends that most individuals with diabetes should attempt to achieve and maintain blood glucose levels as close to normal as possible, and patients with type 1 diabetes should self-test at least 3 times daily. The optimal frequency for those patients with type 2 diabetes is unknown, but the frequency should be sufficient to reach glucose goals. The accuracy of the results is instrument- and user-dependent, thus the clinician should evaluate each patient’s technique frequently, including use of alternate-site testing. There are several obstacles to optimal SMBG—denial, ignored results, clinician passivity, pain, expense, and inconvenience, any of which can severely compromise a treatment plan. Blood glucose measurement is actually intermittent monitoring of a continuous variable. Continuous glucose monitoring (CGM) is an emerging technology that will change the way healthcare practitioners and patients think about glycemia. This article reviews the currently available CGM meters, in addition to those meters under development and review by the US Food and Drug Administration. Measurement of HbA1c is the gold standard for assessing glucose control in persons with diabetes. This article also reviews the strengths and limitations of HbA1c measurement and the physiology behind its use as a diabetes marker. Maintaining good glycemic control is important. The therapeutic tools to achieve good blood glucose control are available and continue to evolve. It is now well established that glycemic control can significantly reduce the morbidity and mortality of diabetes.

One of the foundations of diabetes care is monitoring glucose control, whether it is performed by the patient or healthcare professional. Glucose measurements are used to evaluate the effectiveness of the overall treatment plan and guide specific changes in therapeutic modalities, whether it is medical nutrition therapy (ie, nutrition and lifestyle changes that are scientifically supported), an exercise activity plan, or pharmacotherapy. Methods of glucose monitoring include urine testing (glucose and ketones), blood glucose testing (by the patient or healthcare professional), and glycation testing (hemoglobin).

SELF-MONITORING OF BLOOD GLUCOSE

The goal of glucose monitoring in diabetes is to obtain useful information about the patient's overall glucose status, prevent hypoglycemia, and minimize hyperglycemia through meaningful and timely interventions with the ultimate goal of achieving near-normal glycemia. As glucose control is the foundation of diabetes care, self-monitoring of blood glucose (SMBG) is the foundation of glucose monitoring. The
responsibility for SMBG lies with the patient, but SMBG provides a wealth of information for the patient and healthcare team from which the best treatment plan can be devised and modified over the patient’s lifetime. Specifically, SMBG enables the healthcare team to do the following: set glycemic goals; recommend pharmacologic interventions; evaluate the efficacy of diet and drug therapy; instruct patients on the significance and response to blood glucose patterns; identify hypoglycemia unawareness; and modify therapy in response to exercise, illness, and other medications.

Studies have shown a direct correlation between SMBG frequency and lower glycosylated hemoglobin (HbA1c) levels. For example, in a study sample of 24,312 adult patients with diabetes (members of a large group model managed-care organization), more frequent SMBG was associated with clinically and statistically better glycemic control regardless of diabetes type or therapy (Figure 1) based on models adjusted for age, sex, race, education, occupation, income, duration of diabetes, medication refill adherence, clinic appointment “no-show” rate, annual eye examination attendance, use of nonpharmacologic (diet and exercise) diabetes therapy, smoking, alcohol consumption, hospitalization and emergency room visits, and the number of daily insulin injections. Although the study does not prove that more frequent SMBG results in lower HbA1c levels, it does show an important relationship between the 2 variables. This association likely occurs, in part, because patients who test more often may be more motivated to adhere to all aspects of their care plan. SMBG also can provide reinforcement and motivation to the patient, in addition to information to the healthcare team, making it a necessary tool for diabetes management. More recently, a study comparing insulin-treated patients to those patients not receiving insulin at Atlanta Diabetes Associates showed that more frequent SMBG correlated with lower HbA1c levels, especially in those patients receiving insulin (Figure 2). The American Diabetes Association (ADA) recommends that most individuals with diabetes should attempt to achieve and maintain blood glucose levels as close to normal as possible and monitor for and prevent asymptomatic hypoglycemia, as summarized in Table 1.

**Diabetic Ketoacidosis**

Diabetic ketoacidosis (DKA) is 1 of the 2 most

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**Figure 1. Relationship Between SMBG and HbA1c in a Large Cohort from a Managed Care Organization**

This figure compares the HbA1c values to SMBG frequency in 3 sets of patients with diabetes. The data for those patients treated with insulin were downloaded from patient glucose meters. The data indicate a strong correlation (r = 0.76) between HbA1c and SMBG frequency in insulin-treated patients. Thus, patients who monitor 4 or more times per day have a greater chance of achieving HbA1c less than 7%. We also analyzed the records of 552 noninsulin-treated patients. Patients were divided into quintiles based on their frequency of blood glucose monitoring. Those patients who tested more frequently had an average HbA1c of 6.7 compared to those who tested less frequently, with an HbA1c of 7.2 (P <.0007).

**Figure 2. Increased SMBG Testing Frequency Lowers HbA1c in Patients Using Insulin Pumps**

This figure compares the HbA1c values to SMBG frequency in 3 sets of patients with diabetes. The data for those patients treated with insulin were downloaded from patient glucose meters. The data indicate a strong correlation (r = 0.76) between HbA1c and SMBG frequency in insulin-treated patients. Thus, patients who monitor 4 or more times per day have a greater chance of achieving HbA1c less than 7%. We also analyzed the records of 552 noninsulin-treated patients. Patients were divided into quintiles based on their frequency of blood glucose monitoring. Those patients who tested more frequently had an average HbA1c of 6.7 compared to those who tested less frequently, with an HbA1c of 7.2 (P <.0007).

Table 1. Summary of ADA Recommendations on Tests of Glycemia

1. Most individuals with diabetes should attempt to achieve and maintain blood glucose levels as close to normal as is safely possible.
2. SMBG is recommended for all insulin-treated patients with diabetes.
3. Healthcare providers need to evaluate each patient’s monitoring technique, initially and at regular intervals thereafter.
4. Optimal use of SMBG requires proper interpretation of the data.

ADA = American Diabetes Association; SMBG = self-monitoring of blood glucose.
Data from American Diabetes Association.1

SIDEBAR 1
DIABETIC KETOACIDOSIS
Diabetic ketoacidosis (DKA; Table) results from a relative deficiency of insulin, which is the primary anabolic hormone. When insulin is absent, tissues that use glucose (ie, muscle, brain, fat, and the liver) are not able to take up glucose from the blood. The body perceives the lack of insulin as a hypoglycemic state and responds by increasing the counter-regulatory hormones, such as glucagon, catecholamines, and growth hormone. Because glucose is not entering the tissues, those that make glucose (ie, muscle, liver, and adipose tissue) begin making their own from other starting molecules (gluconeogenesis) or by breakdown of complex molecules (eg, triglycerides are broken down into free fatty acids and glucose), which elevates serum glucose further. The free fatty acids are oxidized to form ketone bodies. Overall, metabolism in DKA shifts from the normal fed state characterized by carbohydrate metabolism to a fasting state characterized by fat metabolism.1,2

Table. Symptoms, Signs, and Causes of Diabetic Ketoacidosis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic symptoms of hyperglycemia:</td>
<td>General signs:</td>
<td>• Infection (of which urinary tract infections are most common)</td>
</tr>
<tr>
<td>• Thirst</td>
<td>• Ill appearance</td>
<td>• Inadequate insulin or discontinuation of insulin treatments</td>
</tr>
<tr>
<td>• Polyuria, polydipsia</td>
<td>• Dry skin</td>
<td>• Newly diagnosed or previously unknown diabetes</td>
</tr>
<tr>
<td>• Nocturia</td>
<td>• Labored respirations</td>
<td>• Myocardial infarction</td>
</tr>
<tr>
<td>Other symptoms:</td>
<td>• Dry mucous membranes</td>
<td>• Cerebrovascular accident</td>
</tr>
<tr>
<td>• Generalized weakness</td>
<td>• Decreased skin turgor</td>
<td>• Complicated pregnancy</td>
</tr>
<tr>
<td>• Malaise/lethargy</td>
<td>• Decreased reflexes</td>
<td>• Trauma</td>
</tr>
<tr>
<td>• Nausea/vomiting</td>
<td></td>
<td>• Stress</td>
</tr>
<tr>
<td>• Decreased perspiration</td>
<td></td>
<td>• Surgery</td>
</tr>
<tr>
<td>• Fatigue</td>
<td></td>
<td>• Alcohol abuse</td>
</tr>
<tr>
<td>• Anorexia or increased appetite</td>
<td></td>
<td>• Pancreatitis</td>
</tr>
<tr>
<td>• Confusion</td>
<td></td>
<td>• Drugs that affect carbohydrate metabolism (eg, corticosteroids, thyroid, and sympathomimetic drugs [dobutamine, terbutaline])</td>
</tr>
</tbody>
</table>

Other metabolic consequences of DKA include metabolic acidoses and hyperglycemia-induced osmotic diuresis, which depletes sodium, potassium, phosphates, and water. Ketones and glucose also are excreted in the urine. The total body water deficit is common.

(Continued on page S1120)
A Primer on SMBG

**Sample Site**

Because blood sampling from the fingertip can be painful, some patients prefer to sample from their arm or thigh. However, such alternate-site testing can affect diabetes.

**SMBG Monitoring Systems**

The meters for SMBG typically use either of 2 technologies—photometric or electrochemical measurement of blood glucose (explained more fully in Sidebar 2). Photometric technology is older and requires more technique from the user for proper maintenance, such as the optics need to be cleaned periodically and potentially can be damaged with everyday handling. Some photometric devices require large blood samples (≥25 μL) and some take longer to perform a test (30 seconds). Electrochemical measurement (amperometric or coulometric), by contrast, typically requires small blood samples (as little as 0.3 μL), and some meters have short test times (as short as 5 seconds).

**REFERENCES**


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Table 2. Diagnostic Criteria for Diabetic Ketoacidosis

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose, mg/dL</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;250</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.25–7.30</td>
<td>7.00–7.24</td>
<td>&lt;7.00</td>
</tr>
<tr>
<td>Serum bicarbonate, mEq/L</td>
<td>15–18</td>
<td>10–&lt;15</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Urine ketones*</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Serum ketones*</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Effective serum osmolality, mOsm/kg</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Anion gap‡</td>
<td>&gt;10</td>
<td>&gt;12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Alteration in sensorial or mental obtundation</td>
<td>Alert</td>
<td>Alert/</td>
<td>coma</td>
</tr>
</tbody>
</table>

* Nitroprusside reaction method.
† Calculation: 2[measured Na (mEq/L) + glucose (mg/dL)/18].
‡ Calculation: (Na+) - (Cl- + HCO3-) (mEq/L).

DKA = diabetic ketoacidosis.

results. There are several physiologic influences on alternate-site testing. For example, there can be a lag time (up to 30 minutes) between arm/thigh and finger readings immediately after a meal, resulting in potential missing of hyperglycemia or erroneous treatment decisions. As shown in Figure 4, the fingertips contain highly concentrated networks of anastomosing arteries (2 arteries that are connected), whereas the anastomosing network of arteries in the proximal limbs is less concentrated, and the dermis is not as vascular as in the fingertips. Testing on the finger or palm at the base of the thumb is recommended when testing for hypoglycemia or for patients who suffer from hypoglycemia unawareness. Alternate-site testing is reliable if blood glucose levels are not changing rapidly (eg, premeal or fasting). When alternate-site testing is used for testing postmeal, the results should be considered cautiously.

**Timing**

It is important to remember that blood glucose measurement is actually intermittent monitoring of a continuous variable. What frequency and timing are optimal for overall good glucose control? The answer, in short, is it varies from 4 times per day to several times per week, depending on the lability of blood glucose levels, thus the patient’s circumstances, and if there is a treatment change, which would then require more frequent monitoring. The ADA recommends that patients with type 1 diabetes self-test at least 3 times daily. The optimal frequency for those patients with type 2 diabetes is unknown, but the frequency should be sufficient to reach glucose goals, as the risks for hypoglycemia and hyperglycemia are reduced with tight blood glucose control and SMBG. In fact, daily SMBG is recommended for all insulin-treated patients.

The accuracy of the results is instrument- and user-dependent, thus the clinician should evaluate each patient’s technique frequently. Patients should also use calibration and control solutions on a regular basis to check for accuracy of test results. Also, plasma glucose values are 10% to 15% higher than blood glucose values, thus patients should know whether their monitors are providing results for whole blood or plasma. Based on the results at each testing, patients should be taught how to use the data to adjust medical nutrition therapy, exercise, or pharmacotherapy.

Self-monitoring of blood glucose is typically done before each meal and at bedtime in patients with type 1 diabetes, in addition to periodically during the mid-

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**Sidebar 2**

**Technology for Measuring Blood Glucose Levels**

First-generation meters used a photometric measurement based on a dye-related reaction, which required wiping or blotting and exact timing. The second-generation meters use an electrical charge via a chemical reaction. These advances have allowed for the development of meters that are less technique-dependent, thus less prone to user error.

A drop of blood is placed on a test strip and the glucose contained within the drop is enzymatically oxidized. An electrode quantifies the electrical charge generated by this reaction and displays a numerical value representative of the concentration of glucose present in the drop of blood (Figure 1). Electrochemical meters are generally considered second-generation meters. They are a good example of technology influencing the way patients participate in self-monitoring of blood glucose.

![Figure 1. Electrochemistry](image)

**Coulometry** is an analytical method for measuring an unknown concentration of an analyte in solution by the production of a current when a potential is applied between 2 electrodes. The same interfering factors that affect electrochemical meters (ie, environmental temperature and variations in hematocrit) may change the shape of the electrochemical response curve generated during amperometry and interfere with the accuracy of glucose measurement. Also, only a portion of the glucose is used to generate the electrochemical signal, thus the signal will be weak with small blood samples. Therefore, the principle of amperometry requires a sufficient drop of blood to produce an accurate reading.

Coulometry is an analytical method for measuring an unknown concentration of an analyte in solution by the production of a current when a potential is applied between 2 electrodes. The same interfering factors that affect electrochemical meters (ie, environmental temperature and variations in hematocrit) may change the shape of the electrochemical response curve generated during amperometry and interfere with the accuracy of glucose measurement. Also, only a portion of the glucose is used to generate the electrochemical signal, thus the signal will be weak with small blood samples. Therefore, the principle of amperometry requires a sufficient drop of blood to produce an accurate reading.

(Checked on page S1122)
completely converting the analyte from one oxidation state to another. Coulometry is an absolute measurement similar to gravimetry or titration and requires no chemical standards or calibration. Therefore, it is valuable for making absolute concentration determinations of standards. Coulometric meters, the newest technology available, use an electrochemical reaction whereby the total accumulated charge of the reaction is in proportion to the glucose concentration. In this system, all glucose is consumed and measured. In other words, coulometric meters convert a blood sample’s entire glucose content into an electric charge (Figure 2). Coulometric meters also produce a response curve, but the total charge or area under the curve is used to calculate the glucose concentration. Factors, such as environmental temperature and hematocrit, may alter the shape of the response curve but do not alter the area under the curve. Therefore, glucose measurements are unaffected by these factors.

Figure 2. Relative Glucose Consumption in Amperometry and Coulometry

![Figure 2. Relative Glucose Consumption in Amperometry and Coulometry](image)

(Continued from page S1121)

dle of the night. If glycemic control is not obtained with premeal monitoring or there is a discrepancy between HbA1c and SMBG results, postprandial monitoring should be done with appropriate adjustment in the insulin regimen, carbohydrate-to-insulin ratio, and meal plan. In patients with type 2 diabetes who are not on insulin, periodic premeal and postmeal monitoring can be done with appropriate adjustment in treatment plan, including diet, exercise, and pharmacotherapy. For those patients with gestational diabetes, fasting and postprandial monitoring is recommended with the glycemic goal being lower than 90 mg/dL fasting and lower than 120 mg/dL 1 hour after the start of a meal. Premeal and postmeal monitoring should be done in pregnant women with type 1 diabetes.

As discussed by Dr Rodriguez in this monograph, hypoglycemia is a serious event and many patients are often not aware of their hypoglycemic episodes, particularly those that occur nocturnally. Nocturnal hypoglycemia, particularly in those patients with brittle type 1 diabetes, can be lethal.9

If the HbA1c values do not match the reported SMBG results, more frequent SMBG is required to uncover previously undetected highs and lows. Table 3 lists the correlating HbA1c values for different mean plasma glucose concentrations.10,11

OBSTACLES TO MONITORING

It has been our experience that there are several obstacles to optimal SMBG—denial, ignored results, clinician passivity, pain, expense, and inconvenience, any of which can severely compromise a treatment plan. A frequently cited obstacle to daily SMBG by patients is denial—the patient does not want to know the test results because they do not want to alter their eating or exercise patterns or they are not sure of how to do so. Addressing patient denial is a matter of diabetes education to get patients interested and confident in their test results and invested in improving glycemic control. Patients must know how to interpret their results, when to report them to the healthcare professional, and how to modify self-care. Patients need to understand that their fate is in their own
hands. Clinicians also drive the use of SMBG and sometimes do not recommend or promote it sufficiently. Clinicians must show an interest in SMBG and interpret results for patients. In fact, clinicians can sometimes be too casual in recommending SMBG out of concern that the patient will not like it. In reality, most patients take to SMBG very well; they like knowing "where they are" and the results that show good glucose control act as positive reinforcement on the other components of the care plan (ie, medical nutrition therapy, exercise, and medication). As discussed later in this article, most glucose meters offer the ability to download results onto a computer for easier interpretation. Although frequently cited by physicians as an obstacle to SMBG, pain is a surprisingly infrequent complaint of people who self-monitor regularly.* Some patients do not test as frequently as they should because of the expense—health insurance providers (private or government) may not cover all aspects of diabetes care. However, the healthcare team must educate the government and payers, in addition to the patients, that the cost of diabetes is in its complications, not in its clinical management. Intensive diabetes management with frequent SMBG, multidose insulin administration, and support services is highly cost effective. Frequent SMBG is sometimes inconvenient and takes time to perform. However, current meters are faster, smaller, and more convenient than first-generation meters.

*This statement is based on Dr Bode’s 21-year clinical practice experience (as opposed to a formal study).

**EMERGING TECHNOLOGIES:**

**CONTINUOUS GLUCOSE MONITORING**

One of the major limitations with traditional glucose monitoring is the snapshot of glycemia it provides; each result, no matter how frequently obtained, represents only one point in time. It provides no information on what the patient’s glucose levels have been or what they will be. Figures 5A and 5B illustrate the implications of periodic glucose monitoring for diabetes care. Even with 5 tests per day, hyper- and hypoglycemia can be missed.

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**Table 3. Correlation Between HbA1c Level and Mean Plasma Glucose Levels**

<table>
<thead>
<tr>
<th>A1c (%)</th>
<th>Mean Plasma Glucose (mg/dL)</th>
<th>Mean Plasma Glucose (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>135</td>
<td>7.5</td>
</tr>
<tr>
<td>7</td>
<td>170</td>
<td>9.5</td>
</tr>
<tr>
<td>8</td>
<td>205</td>
<td>11.5</td>
</tr>
<tr>
<td>9</td>
<td>240</td>
<td>13.5</td>
</tr>
<tr>
<td>10</td>
<td>275</td>
<td>15.5</td>
</tr>
<tr>
<td>11</td>
<td>310</td>
<td>17.5</td>
</tr>
<tr>
<td>12</td>
<td>345</td>
<td>19.5</td>
</tr>
</tbody>
</table>

HbA1c = glycosylated hemoglobin.
Reprinted with permission from American Diabetes Association10; Rohlfing et al.11

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**Figure 5. Continuous Glucose Monitoring Versus Point-in-Time Testing**

If a patient presented the readout in Figure 5A, most healthcare practitioners would be pleased for several reasons—the patient is highly compliant and motivated to perform SMBG frequently, the glucose levels are documented, and they appear to be within normal range. However, even with careful SMBG, the true story is not told. Figure 5B shows the true levels over a 24-hour period, revealing wide variations in blood glucose levels. Thus, CGM provides much more information that the healthcare team and patient can use to avoid hyper- and hypoglycemia and its complications. CGM = continuous glucose monitoring; SMBG = self-monitoring of blood glucose.
Continuous glucose monitoring (CGM) is an emerging technology that will change the way healthcare practitioners and patients think about glycemia. CGM involves a sensor, a storage device for the data, and a monitor. The sensor measures and reports a glucose reading every 1 to 10 minutes and stores the data in the storage device. The results can be downloaded by the physician (retrospective data) or displayed in real-time. CGM provides information on glucose levels, patterns, and trends, thus showing the effects of meals, stress, exercise, and other factors that influence glycemic levels. Importantly, CGM detects events of hypoglycemia and hyperglycemia more frequently than periodic SMBG. For example, we performed a small study in our practice (n = 102) comparing CGM to SMBG 10 times per day for 21 days. With CGM, we observed a 69% increase in detected hypoglycemic events and a 20% increase in detected hyperglycemic events compared to periodic SMBG. The clinical accuracy was also high, with a 92.4% hypoglycemic detection rate (false-negative 7.1%; false-positive alarms 11.5%) and a 100% hyperglycemic detection rate (false-negative alarms 0%; false-positive alarms 1.2%).

Available Systems

Currently, 2 CGM systems are available in the United States—the CGM systems Gold and Guardian RT (Medtronic MiniMed, Northridge, Calif; Figure 6). The GlucoWatch (Cygnus, Inc., San Francisco, Calif) was available in the United States, but it has been removed from the US market. The GlucoDay (A. Menarini, Florence, Italy) is available in Europe. Several more CGM devices are under development and some are under review by the US Food and Drug Administration (FDA; Figure 7). A summary of their features and abilities is provided in Table 4.

The CGM system Gold is about the size of a pager (Figure 6). The sensor system provides an average blood sugar measurement every 5 minutes for up to 3 days. The data are retrospective, to be reviewed with the healthcare team member at the end of the 3-day period. The user can mark events, including meals, exercise, hypoglycemic reactions, and insulin injections.

Table 4. CGMS Devices: A Comparison

<table>
<thead>
<tr>
<th>Device</th>
<th>CGMS Gold</th>
<th>Guardian RT</th>
<th>Dexcom STS*</th>
<th>FreeStyle Navigator*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive?</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Real-time OR retrospective data</td>
<td>Retrospective</td>
<td>Real-time</td>
<td>Real-time</td>
<td>Every minute</td>
</tr>
<tr>
<td>Frequency of data</td>
<td>Every 5 minutes</td>
<td>Every 5 minutes</td>
<td>Every 5 minutes</td>
<td>Low, high, pending low/ high</td>
</tr>
<tr>
<td>Alarms?</td>
<td>No</td>
<td>Low, high</td>
<td>Low, high</td>
<td>Low, high, pending low/ high</td>
</tr>
</tbody>
</table>

*CGMS under development/review by the US Food and Drug Administration. For investigational use only.

CGMS = continuous glucose monitoring system; LTS = long-term sensor; STS = short-term sensor.

For more information:
Dexcom STS/LTS: www.dexcom.com
FreeStyle Navigator: www.abbottdiabetescare.com/freestylenavigator/qa.aspx
The Guardian RT (Figure 6) provides real-time information on glucose levels, and the data can be stored for up to 21 days. The sensor can be worn for up to 3 days in normal activities. The user can set target ranges with an auditory or vibratory alarm. Both Medtronic MiniMed CGM systems are downloadable for further review of the data by the patient and healthcare provider.

**PRODUCTS UNDER INVESTIGATION/FDA REVIEW**

The DexCom STS (short-term sensor; DexCom, Inc., San Diego, Calif) CGM system is a patient-insertable sensor that wirelessly transmits blood glucose readings to a hand-held receiver (Figure 7). The user can wear the sensor for up to 3 days before needing replacement. A long-term sensor (LTS) is also available. The LTS is implanted under the skin in the abdomen through a short outpatient procedure by a physician, which requires local anesthetic, and is designed to function for up to 1 year. At the end of its life, the sensor is removed. The STS and LTS provide continuous glucose values; 1-, 3-, and 9-hour glucose trend information; high and low glucose alerts; and a low-glucose alarm.

The Freestyle Navigator (Abbott Laboratories, Abbott Park, Ill) is currently under review by the FDA (Figure 7). It has a sensor, transmitter, and receiver about the size of a pager. It records real-time glucose levels every minute, has alarms for actual and projected high/low glucose levels, and reports trends and statistics. The user can enter events (eg, meal, insulin, medications, and exercise). The device also has a traditional glucose meter built in for system calibration, in addition to a backup glucose meter.

**PRACTICAL APPLICATIONS AND LIMITATIONS**

To reiterate, the goal of glucose monitoring, in general, is to obtain useful information about overall glucose status, so that hypoglycemia can be prevented and hyperglycemia minimized. Knowing the trend of a patient's glucose levels over time and how quickly they may reach a dangerous level (high or low) allows for meaningful and timely action that can avoid acute and chronic complications. CGM addresses this goal by providing a more complete picture of glucose status (ie, glucose levels, patterns, and trends).

Currently, those who would benefit most from CGM include patients with hypoglycemic unawareness, patients not at glycemic goal (whether taking insulin or not taking insulin), and certain patient populations (ie, children/adolescents, insulin-pump users, all insulin-using patients who strive for tight glycemic control, and pregnant women). The technology also can be applied to patients with type 2 diabetes to determine the major contributing factor or factors to elevated glucose levels, such as whether the problem is primarily postmeal or fasting hyperglycemia. Appropriate changes can then be made to the medical treatment plan. CGM also could be used as an educational and assessment tool in promoting patients' understanding of their disease and the behavior modifications that affect glycemic control. It also can be used to help determine why a patient may not be reaching their glycemic goal.

In the future, CGM can be used as part of the “artificial pancreas” to close the loop on glycemic control. If the CGM device is connected to an insulin pump, one can program the device to adjust the insulin dose based on glucose results. These closed loop systems are currently under investigation.

Despite the insight CGM offers, there remain several limitations to optimal use of this technology—use of real-time data, convenience and ease of use, limited availability of experienced clinicians, potential for “data overload,” and cost reimbursement. The diabetes educator will play a key role in addressing and overcoming each of these challenges (Sidebar 3).

**THE ROLE OF HbA1c IN MONITORING DIABETES MANAGEMENT**

Measurement of HbA1c is the gold standard for assessing glycemic control in individuals with diabetes, thus it is important to understand how HbA1c blood levels relate to glycemia. Sidebar 4 discusses the history of HbA1c in diabetes.

Hemoglobin A (HbA) comprises approximately 90% of hemoglobin in normal human erythrocytes, which are completely permeable to glucose. HbA becomes glycosylated nonenzymatically from glucose in the blood. This occurs post-translationally (ie, after formation of the protein in the cell). Circulating erythrocytes are incapable of initiating protein synthesis after 3 days in circulation, thus the glycosylation of hemoglobin is all post-translational.

Glycosylated hemoglobin measures are not “real-time” representations of blood glucose levels. Rather, they represent average blood glucose levels over the
REVIEW

SIDEBAR 3

IMPLEMENTING CONTINUOUS GLUCOSE MONITORING: THE ROLE OF THE DIABETES EDUCATOR

There remain several limitations to optimal use of continuous glucose monitoring (CGM)—use of real-time data, convenience and ease of use, limited availability of experienced clinicians, potential for “data overload,” and cost.

- Some of the currently available devices do not provide real-time data (ie, rate of change and trending information). Real-time data would prove useful not only for patients to immediately identify and rectify changes in blood glucose levels but also in the intensive care unit to decrease nursing workload or provide alarms for impending glycemic changes.
- Some of the devices offer alarms, but the key is to identify patterns that precipitate hypo- and hyperglycemia. Also, most of the devices are not waterproof and some can cause skin irritation.
- Some clinicians are averse to learning new technology (required to download the data). Also, data review and patient education take time.
- Analyzing the data requires specific software to identify and assess patterns and determine appropriate interventions. Many of the current and future devices offer their own software.
- Because data analysis will involve the clinician and possibly other members of the healthcare team to educate the patient, reimbursement systems may not yet be in place for this technology, thus the patient will bear the brunt of the cost.

Clearly, there are several intersections at which the diabetes educator will play a critical role to educate patients and healthcare providers. Patients need to understand what CGM is and what the information it provides can do to improve their health, and they need encouragement to incorporate CGM into their daily lives. Educators also can work with physicians and other providers to integrate the CGM system into the office computer system, train office healthcare providers on using CGM, and provide diabetes education in general.

As Valentine notes, educators must consider several key issues in deciding their role in using CGM technology:

- The effect on time allotment for patients
- The time to evaluate, learn, and implement each CGM device and how it affects the educator’s current fee structure

(Sidebar 3 continued)

- Integrating CGM into current practice regarding physician referral (ie, which physicians use CGM) and collaboration
- Effectively integrating this technology into the patient’s self-care regimen.

REFERENCE


previous 3 months. Erythrocytes circulate for approximately 120 days. This time in circulation provides an opportunity for the nonenzymatic glycation to occur. Glycation occurs on several different types of proteins, which become advanced glycation end products (AGEs). AGEs in tissues that are longer lived than erythrocytes become important markers of diabetes pathology and normal aging because the extent of glycation reflects the amount of glucose to which the tissue has been exposed. Because erythrocytes live for only approximately 120 days, HbA1c levels represent mean glycemic levels over the past 3 months. In fact, HbA1c is a weighted measure of average blood glucose over the past 3 months. A large change in mean blood glucose is accompanied by a large change in HbA1c 1 to 2 weeks later. The mean blood glucose level in the 30 days before sampling comprises approximately 50% of the final HbA1c result, whereas the HbA1c levels during days 90 to 120 before sampling comprise only approximately 10% of the final result.1

HbA1c: STRENGTHS AND LIMITATIONS

Glycosylated hemoglobin measurement should be considered a complement to SMBG. Every person with diabetes should be followed up using HbA1c measures every 3 to 6 months, in addition to a baseline measurement when initiating care. HbA1c measures also are used to confirm the results of self-monitoring. A target HbA1c level is as close to normal as feasible without hypoglycemia, with the ADA target being lower than 7% and the American Association of Clinical Endocrinologists, European Association for the Study of Diabetes, and the World Health Organization target being lower than 6.5%. Dr
Rodriguez discusses in this monograph the current recommended HbA1c levels, in addition to the correlation between HbA1c values and glucose levels. In general, each 1% increase in HbA1c corresponds to a 35-mg/dL (1.95-mmol/L) increase in mean plasma glucose.

There are many assays for measuring HbA1c, but each uses 1 of 2 general methods for identification and quantification of HbA1c—based on the charge difference between glycosylated and nonglycosylated Hb or based on the structural characteristics of the glycogroups on Hb (via immunoassay or affinity chromatography). There is no evidence to show that one method is better than the other.16

Certain situations or conditions can affect the results. For example, vitamins C and E can falsely lower HbA1c levels, whereas iron-deficiency anemia can increase them. Also, hypertriglyceridemia, hyperbilirubinemia, uremia, chronic alcoholism, chronic ingestion of salicylates, opiate addiction, chemically modified derivatives of Hb, and hemoglobinopathies can interfere with some assay methods.17-20

Hemoglobin variants can affect HbA1c measurements, depending on the specific hemoglobinopathy and the method used for measurement. A review of preanalytical and analytical variables affecting assays has been published in the literature and on the National Glycohemoglobin Standardization Program (NGSP) Web site (www.ngsp.org).21,22 An example of the clinical implications of such an erroneous HbA1c result is the following: the immunoassay method has been found to overestimate HbA1c in patients with hemoglobin C trait.23 A possible result of this overestimation is overly rigorous glycemic control with a concomitant increase in risk of hypoglycemia. This may be especially important in certain ethnic populations, such as African Americans, who have a relatively high prevalence of the HbC trait. Another assay method (cation exchange chromatography) has been found to falsely lower HbA1c levels in patients with hemoglobinopathies C and S.24 Reference values for certain hemoglobinopathies have been published.25 The clinician should consider hemoglobinopathy when the HbA1c value does not correlate with clinical expectations.

Each laboratory should determine its own reference interval (ie, the standard mean value for normal glucose levels ± 2 standard deviations for that particular laboratory’s assay method) following the Clinical and Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards) guide-

SIDEBAR 4

THE HISTORY OF HBA1C IN DIABETES

Glycosylated hemoglobin (HbA1c) was first discovered in the 1950s as 1 of at least 3 minor components of hemoglobin A (ie, hemoglobin A was actually a mixture of hemoglobin molecules). These 3 minor components were more negatively charged than hemoglobin A and were termed HbA1a, HbA1b, and HbA1c, based on their order of elution during cation-exchange chromatography.11-16 In the 1960s, Rahbar et al discovered that HbA1c was elevated in patients with diabetes (Figure).3,4 However, it was not until the 1970s that investigators realized the relationship between HbA1c and fasting plasma glucose, glucose peak during the oral glucose tolerance test (OGTT), the area under the curve of the OGTT, and mean glucose levels over the preceding weeks.5-10 By the early 1980s, HbA1c was established as a measure of long-term glycemia, distinct from urine or blood glucose measures.

Figure. First Sign of “Abnormal” Hemoglobin in Patients with Diabetes

In 1962, Rahbar, an Iranian blood-bank hematologist, described “abnormal” hemoglobin in red blood cells of diabetics. HbA1c = glycosylated hemoglobin.


REFERENCES


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lines, and laboratory directors should provide clinicians with information about the assay method for HbA1c—type, nondiabetic reference interval, potential assay interferences, and assay performance. All commercially available HbA1c methods and tests done in the United States should be standardized to the Diabetes Control and Complications Trial assay range (4.0%-6.0%) and verified by the NGSP.

CONCLUSIONS

Maintaining good glycemic control is critical to avoid the long-term complications of diabetes. The monitoring tools needed to achieve good blood glucose control continue to evolve, including more convenient SMBG meters, continuous glucose meters, and better understanding of the strengths and limitations of HbA1c measurement. Although the responsibility of SMBG lies with our patients, the responsibility of educating and encouraging our patients to take a more active role in their disease management lies with the healthcare team. It is now well established that glycemic control can significantly reduce the morbidity and mortality associated with diabetes.

REFERENCES


