Blood glucose self-monitoring in management of diabetes mellitus

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Last literature review version 19.1: January 2011  |  This topic last updated: February 9, 2011

INTRODUCTION — All patients with diabetes mellitus who use insulin and some patients who take other glucose lowering medications that can cause hypoglycemia should measure their blood glucose concentrations to help maintain good glucose control. The effectiveness of self-monitoring in patients with type 2 diabetes who do not use hypoglycemic agents is less certain.

Self-monitoring of blood glucose (SMBG) usually requires intermittent capillary blood sampling and the use of a glucose meter, with different frequencies of testing indicated for type 1 and type 2 diabetes. Devices to sample the glucose continuously from subcutaneous fluid are now available, with ongoing development in progress.

In addition to self-monitoring of blood glucose, periodic measurement of glycosylated hemoglobin (A1C) permits estimation of chronic glycemic control. Several practical points about blood glucose monitoring will be reviewed here, including the accuracy of glucose meters and glucose sticks, the accuracy of the operator, and how to use the glucose information that is obtained. The use of A1C measurements to estimate mean blood glucose is reviewed elsewhere. (See "Estimation of blood glucose control in diabetes mellitus".)

INDICATIONS

Type 1 diabetes — Results of the Diabetes Control and Complications Trial (DCCT) [1] and a follow-up study to that trial [2] demonstrate that intensive insulin therapy is appropriate for most patients with type 1 diabetes, to decrease the risk of both micro- and macrovascular disease. (See "Insulin therapy in adults with type 1 diabetes mellitus".) SMBG is an important component of a regimen for intensive insulin therapy. Self-monitoring allows adjustments of insulin and diet content to be made based on immediate feedback of glucose results, and allows timely intervention for low glucose readings to avert serious hypoglycemic events. Self-monitoring of blood glucose is also important for patients with type 1 diabetes who are not managed with intensive insulin, although they may require somewhat less frequent testing.

The American Diabetes Association (ADA) recommends that patients with type 1 diabetes monitor blood glucose at least three times daily [3,4]. For most patients with type 1 diabetes, testing blood sugar levels before and at intervals after meals; before, during, and after exercise; and occasionally during the night will provide useful information for adjusting insulin and carbohydrate intake.
**Type 2 diabetes** — The fasting blood glucose concentration is often used to monitor control in type 2 diabetes since it correlates well with A1C values [5,6]. Fasting blood glucose concentrations are fairly stable in patients with type 2 diabetes, but can vary by about 15 percent from day to day, and therefore changes in therapy should be based on an average over several days [7]. Some have argued that nonfasting blood glucose measurements are a better marker of glycemic control than fasting values [6].

The effectiveness of SMBG in terms of improving glycemic control in patients with type 2 diabetes is less clear than for type 1 diabetes. Multiple observational studies have evaluated SMBG in type 2 diabetes, with some showing benefit [8,9] and others not [10-13]. Meta-analyses of randomized trials report conflicting results, with one reporting no benefit [14] and two subsequent analyses, limited to trials evaluating SMBG in non-insulin users, reporting a modest decrease in A1C in the SMBG group compared with control (pooled mean difference -0.24 percent) [15,16]. In one of the larger trials included in the meta-analysis, 610 patients with type 2 diabetes who were treated with oral agents were randomly assigned to SMBG or non-SMBG groups [17]. After 27 weeks, A1C decreased in both groups. However, there was a significantly greater reduction in A1C in the SMBG group (between group difference 0.25 percent). In contrast, other randomized trials have not shown a significant reduction in A1C with self monitoring of glucose versus no monitoring [18,19], and in one study of newly diagnosed patients, SMBG was associated with higher scores on a depression scale [19].

Studies of SMBG have multiple potential biases. Patients who comply with self-monitoring may have better lifestyle compliance as well, or may have worse glucose control and therefore are more motivated. Patients who are less motivated may not be willing to participate in randomized studies, so even randomized trials may represent only a selected patient population [20].

Monitoring blood glucose is a tool, not a therapeutic intervention. It provides important information with which motivated patients can modify their behavior and improve their A1C values safely. However, SMBG is expensive. In an economic analysis of self-monitoring of blood glucose (SMBG) using data from a UK trial [18], SMBG with or without training in patient-initiated management of SMBG feedback, was unlikely to be cost-effective [21].

Thus, self-monitoring of glucose may not be necessary at all, or only in unusual circumstances, for patients with type 2 diabetes who are diet-treated or who are treated with oral agents not associated with hypoglycemia. SMBG may be helpful in patients who take medications that can cause hypoglycemia. SMBG may also be useful for some type 2 diabetic patients who would take action to modify eating patterns or exercise, as well as be willing to intensify pharmacotherapy, based on SMBG results. The ADA recommends that patients with type 2 diabetes who are treated with insulin or oral hypoglycemic drugs monitor blood glucose daily [3,4].

**URINE TESTING** — Although measuring urine glucose is less painful and may arguably be easier than measuring blood glucose, it has significant errors that limit its accuracy as a reflection of glycemic control and is not recommended [22].

**Testing for ketonurias** — Measurement of urinary ketones is less subject to error because any positive value suggests the presence of ketonemia. The urine should be tested for ketones if the blood glucose concentration is above 240 mg/dL (13.3 mmol/L), during
periods of illness or stress, or if there are symptoms compatible with ketoacidosis such as nausea, vomiting, and abdominal pain [22].

The present of ketones in the urine does not always mean that the person has impending ketoacidosis. Ketonuria indicates that the person is in a catabolic state and is breaking down fat, and can occur in anyone who has a negative caloric balance while dieting. However, in the absence of a person purposely trying to restrict calories, the presence of urine ketones along with hyperglycemia is more serious than hyperglycemia alone. Under these circumstances, the person should be advised to retest every two to three hours, take measures to keep well-hydrated, and take extra insulin if indicated. Treatment of diabetic ketoacidosis is discussed separately. (See "Treatment of diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults".)

**SOURCES OF ERROR**

**Operator** — Errors in SMBG are most frequently attributed to operator-error [23]. Problems arise from failure to calibrate the meter correctly, dirty meters, inadequate hand washing, or improper storage of the test strips.

We recommend use of one of the newer glucose meters in which the patient adds a drop of blood to a strip already inserted into the meter. Patients who are motivated and test often usually get much more reliable results than those who are less interested or who test less often (such as non-expert clinicians) [24,25].

We also recommend the following steps to increase the accuracy of glucose monitoring:

- The glucose meter and strips should be brought in for clinic visits. The patient's method of testing should be observed periodically and any technical mistakes corrected. Patients should be queried regarding storage of strips.

- The glucose meter should be calibrated with a control solution (provided with the glucose meter) every few boxes of strips. If this is out of range, or if SMBG results do not seem consistent with expectations, we recommend that the patient bring the glucose meter in to be checked against meters of known accuracy or with a simultaneous lab value.

**Blood glucose meters** — Most glucose meters are reasonably accurate, and require only a small drop of blood. Even with newer meters, however, accuracy during episodes of hypoglycemia and in patients with poor peripheral tissue perfusion may be less than optimal [26-28].

In the past, glucose meters reported whole blood glucose values, which made it difficult to compare finger stick results with results from a laboratory, which are always plasma. However, the majority of available glucose meters now provide plasma or conversion to plasma readings rather than whole blood glucose values (by providing direct plasma readings or by multiplying the capillary whole blood value by 1.12). Thus, results from most available glucose meters and commercial laboratories should now be comparable.

**Glucose strips** — Some glucose strips have considerable batch to batch variation, and require recalibration to a meter every time a new batch is used. Many strips are packaged in groups (10, 25, 50, or 100) inside a can containing a desiccant to control humidity.
Common errors include leaving the lid off for periods of time, with exposure to heat, moisture, and humidity, and mixing lots of strips into one can for convenience. Patients often forget to match the code on the strip bottle to the meter code, with uncompensated batch variation causing erroneous glucose value readings.

**Site of testing** — Several blood glucose meters are now available that use sites other than the finger to obtain blood samples in an effort to reduce the discomfort involved with fingersticks. A study of one device that can be used to obtain samples from the arm found that it provided accurate results and was less painful than fingerstick testing [29].

Monitoring from alternate sites, such as the skin of the forearm, may give slightly lower results than those taken at the fingertips, since they may sample venous blood rather than capillary blood. While this should not be a problem if the patient uses one or the other site exclusively, the between-test variability will increase if multiple sites are used. In addition, during times when the blood glucose concentration is either rising rapidly (such as immediately after food ingestion) or falling rapidly (in response to rapidly acting insulin or exercise), blood glucose results from alternate sites may give significantly delayed results compared with fingerstick readings (figure 1) [30,31].

**Other sugars** — The FDA issued a safety alert in February 2006 that some glucose monitors (those using the enzyme glucose dehydrogenase pyrroloquinoline quinone or GDH-PQQ) will give falsely elevated readings in patients who have received treatments containing other sugars, including xylose as part of a d-xylose absorption test, maltose or galactose in IV solutions (IV immune globulin is formulated with maltose), or icodextrin in peritoneal dialysis fluids [32]. Not all glucose meters use this enzyme, and the test method used is identified in the package insert for the glucose strips. Several patient deaths were attributed to inappropriate insulin treatment for falsely elevated glucose strip readings.

**CONTINUOUS GLUCOSE MONITORING** — Real-time continuous glucose monitoring systems (CGMS) have the potential to improve glycemic control while decreasing the incidence of hypoglycemia [33,34]. However, the efficacy compared with SMBG is not certain, CGMS is expensive, and because of reliability issues CGMS does not eliminate the need for fingersticks. CGMS has the greatest potential value in patients with hypoglycemic unawareness who are at risk for or have severe hypoglycemia; unfortunately, currently available meters are most inaccurate in the low range of glucose.

CGMS may also be valuable in controlling daily fluctuations in blood glucose. Fluctuations in blood glucose, identified by continuous glucose monitoring, correlate more strongly than A1C levels with urinary markers indicative of activation of oxidative stress and free radical formation [35]. This has theoretical clinical implications, as free radicals have been implicated in endothelial damage and the formation of atherosclerotic plaques. One may therefore hypothesize that control of daily blood glucose fluctuations, in addition to management of chronic hyperglycemia in diabetic patients, could be important in protection against micro- and macrovascular disease [36]. However, in the DCCT, the degree of within-day and between-day variability in SMBG excursions had no influence on the development or progression of either retinopathy or nephropathy [37].

Most of the continuous blood glucose monitoring systems that are available, or in development, measure the glucose content of interstitial fluid using an electrochemical enzymatic sensor. Interstitial fluid is accessed by a needle sensor inserted subcutaneously
Some devices extract interstitial fluid across the skin using an applied electrical potential (iontophoresis). An older version of such a device gave unreliable readings, but there have been subsequent technological improvements.

With some devices, the patient receives no information while wearing the device. Results can be determined in a clinician’s office and graphed, providing useful information about the extent of within-day and between-day variations in blood glucose and the frequency of unrecognized hypoglycemia (figure 2). Newer devices provide the patient with real time results of glucose values on a continuous basis.

**Efficacy** — The effectiveness of continuous glucose monitoring (CGM) on glycemic control has not yet been established. Studies to date have demonstrated variable outcomes with regard to improving glycemic control and hypoglycemia:

- In one randomized trial of insulin-requiring diabetic patients (type 1 n = 75; type 2 n = 16), the group that had access to a continuous display had less time with hypoglycemia and hyperglycemia, more time at target glucose range, and less nocturnal hypoglycemia, although there was no difference in A1C levels.

- Another randomized trial compared SMBG (four or more times daily) and CGMS in poorly controlled insulin-treated patients (n = 128). Improvement in A1C was the same in both groups after 12 weeks, but those who used CGMS had less hypoglycemia measured in week 12.

- In a 26-week multicenter trial comparing CGM with SMBG in 322 motivated adults and children with type 1 diabetes, already receiving intensive insulin therapy (insulin pump or multiple daily injections) and performing self blood glucose monitoring on average six to seven times daily, there was a small but significant between group difference in A1C levels (-0.5 percent) favoring CGM in patients who were ≥25 years of age. In contrast, there was no between group difference in A1C levels in those 15 to 24 or 8 to 14 years of age.

The rate of severe hypoglycemia was low and did not differ between the two study groups. However, one patient (≥25 years of age) randomly assigned to CGM had six episodes of severe hypoglycemia.

- In another trial, 156 children and adults with poorly-controlled type 1 diabetes were randomly assigned to CGMS continuously, CGMS intermittently, or SMBG (five times daily) for three months. There was a significant 1 percent reduction in A1C in the continuous CGMS group compared with intermittent CGMS or SMBG. There was not a significant A1C reduction in the intermittent CGMS group.

Continuous glucose monitoring devices have also been used in conjunction with insulin pump therapy, an approach known as sensor-augmented insulin pump therapy. (See "Insulin therapy in adults with type 1 diabetes mellitus", section on 'Continuous subcutaneous insulin infusion (insulin pump)'). Studies are currently evaluating the efficacy of a fully automated closed loop system of insulin delivery based upon continuous glucose sensing. One small short-term study reported near normal glucose levels with the use of such a system and no hypoglycemic events.
**Reliability** — The interstitial fluid glucose sensor yields lower glucose values, compared with venous plasma glucose, when blood glucose concentrations are rapidly rising (figure 2) [39]. The reproducibility of results has also been called into question. When 11 adults (six type 1 diabetic patients, three type 2 diabetic patients, and two normal subjects) wore two interstitial fluid glucose sensors simultaneously, over 70 percent of the measurements differed by 10 percent or more, and 7 percent of the readings differed by over 50 percent [48].

The CGMS tend to be less accurate in the lower glucose range (<70 mg/dL or 3.9 mmol/L) and may be inadequate for reliably detecting hypoglycemia. In one study, 91 children and adolescents wore one or two CGMS; the absolute median difference between over 400 paired hypoglycemic blood glucose values was 19 mg/dL (1.0 mmol/L), with 42 percent of values falling within 15 mg/dL (0.9 mmol/L) of the reference glucose [42].

These studies emphasize that continuous glucose sensing devices should not be relied upon exclusively to give patients information about their blood glucose concentrations. Patients must continue to do several fingersticks daily to calibrate the currently available devices and to verify that the sensor readings are accurate.

Preliminary data from studies of implantable CGMS in adults with type 1 diabetes showed that 96 to 98 percent of the sensor glucose results fell within an acceptable margin of error after 5 to 90 days of continuous use [40,49,50]. When subjects were allowed to see and use these data to guide therapeutic decisions, they were able to maintain significantly fewer episodes of hypo- and hyperglycemia [40].

In two studies comparing four continuous glucose monitors, the clinical accuracy was similar among the four during euglycemia (96 to 99 percent), but was higher for two of the monitors (Navigator and Glucoday) during hypoglycemia (96 to 97 versus 84 percent) [51].

**Cost** — Currently available CGMS instruments are relatively expensive. Initial costs are approximately one to two thousand dollars for devices that directly sample subcutaneous fluid, with additional costs for supplies ranging between two and four hundred dollars per month. Costs are lower for the iontophoretic device.

**USING THE INFORMATION** — For most patients with type 1 diabetes, testing blood sugar levels before and at intervals after meals; before, during, and after exercise; and occasionally during the night will provide useful information for adjusting insulin and carbohydrate intake. At a minimum, monitoring should be used to avoid and/or help treat potentially dangerous hypoglycemia. (See "Cases illustrating problems with intensive insulin therapy for diabetes mellitus", section on 'Morning hyperglycemia'.)

However, this regimen will be effective only if the patient is able to use the information to make appropriate dietary or therapeutic adjustments. As an example, patterns of glycemic control can be most easily identified if the blood glucose values are entered in columns, corresponding to times of the day, and the relation to both food intake and exercise noted.

Many glucose meters provide data management features which can be downloaded onto a computer, allowing graphic representation of glycemic variation by time of day, or over a period of weeks, allowing calculation of means, and visualization of trends and variances. Unless results are reviewed on a frequent basis to detect and address blood glucose patterns, self-monitoring will not fulfill its purpose. Relying on the automatic data storage of
the meters, without regularly reviewing the results, may detract from the clinical utility of monitoring.

Optimal use of the data obtained is best done in two stages:

- **Pattern identification** — Patterns, as opposed to intermittent problems, are best identified if there are a relatively large number of measurements. Thus, blood glucose values should be recorded four to seven times daily for several days and evaluated for patterns of variation which allow adjustment of doses or types of insulin at different times of the day.

- **Insulin algorithms** — Once a basic regimen of eating, exercise, and insulin dosing has been established, there will still be a day-to-day variability in blood glucose values due, among other factors, to the vagaries of insulin and food absorption. (See "Insulin therapy in adults with type 1 diabetes mellitus".) This can be effectively treated by an insulin algorithm in which the before-meal dose of short-acting insulin is adjusted according to the blood glucose value and, for patients who use carbohydrate counting, anticipated carbohydrate content of the meal. The adjustments should be small in patients who are very sensitive to insulin or who are taking low doses of insulin (as with a continuous insulin pump). (See "Cases illustrating problems with intensive insulin therapy for diabetes mellitus", section on 'Insulin algorithm' and "Cases illustrating problems with intensive insulin therapy for diabetes mellitus", section on 'Late afternoon hypoglycemia' and "Cases illustrating problems with intensive insulin therapy for diabetes mellitus", section on 'Late morning hyperglycemia'.)

The frequency of SMBG in patients with type 2 diabetes, while most often less than for patients with type 1 diabetes, is dependent on the glycemic targets set, and the treatments used. (See "Case illustrating blood glucose monitoring in type 2 diabetes".) If SMBG is initiated to improve glycemic control, patient education strategies are necessary to ensure successful management of SMBG feedback. In one small longitudinal study of patient views on SMBG, the frequency of testing decreased over time, often because patients did not know how to respond to high readings, and patients perceived that providers were more interested in A1C values than glucose logs [52].

With a well-educated and motivated patient, therapeutic advice can often be given over the telephone or even via fax or e-mail. It is important not to recommend many changes at the same time. Having made a change, it is usually best to wait several days until the effect of that change can be assessed from further blood glucose measurements.

**Patients with special needs** — Visually impaired patients may have difficulty using glucose meters; with help, this problem can be overcome with "talking meters" or large-screen meters. Patients or providers may contact:

American Association of Diabetes Educators (AADE)

444 N. Michigan Ave., Suite 1240

Chicago, IL 60611-3901

Tel: 1-800-338-3633

**INFORMATION FOR PATIENTS** — Educational materials on this topic are available for
patients. (See "Patient information: Diabetes mellitus type 1: Overview" and "Patient information: Diabetes mellitus type 2: Overview" and "Patient information: Self-blood glucose monitoring in diabetes mellitus".) We encourage you to print or e-mail these topic reviews, or to refer patients to our public web site, www.uptodate.com/patients, which includes these and other topics.

SUMMARY AND RECOMMENDATIONS

- Self-monitoring of blood glucose (SMBG) is an important component of the intensive insulin regimen recommended for most patients with type 1 diabetes. Patients with type 1 diabetes will usually require testing before and at intervals after meals; before, during, and after exercise; and occasionally during the night, to adjust insulin doses for meals and avoid hypoglycemic events. (See 'Type 1 diabetes' above.)

- The benefit of SMBG for patients with type 2 diabetes is less clear. SMBG may not be necessary for patients who are not taking medications associated with hypoglycemia. (See 'Type 2 diabetes' above.)

- Errors in SMBG may result from poor technique (improper calibration, dirty hands or machine), lower test sensitivity in measuring low blood glucose levels, improper storage of test strips, or interfering substances. (See 'Sources of error' above.)

- Blood is usually sampled from the fingertips. Alternative sites may be less painful, but can give less reliable results when there are rapid fluctuations in blood sugar. (See 'Site of testing' above.)

- Continuous glucose monitoring systems (CGMS) report blood glucose levels to the patient in real time. Some studies have shown fewer periods of hypoglycemia with CGMS, but there are concerns with reproducibility of glucose results, particularly in the lower glucose range, with currently available CGMS. Studies are currently evaluating the efficacy of a fully automated closed loop system of insulin delivery based upon continuous glucose sensing. (See 'Continuous glucose monitoring' above.)

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GRAPHICS

Change in blood glucose using forearm and fingerstick testing after a 75g oral glucose load at time 0 and intravenous insulin at time 115 minutes

Data from Jungheim, K, Koschinsky, T. Diabetes Care 2002; 25:956.
Accuracy of CGMS: Correlation of CGMS and simultaneous hemocue

Results of continuous glucose monitoring compared with intermittent values checked with a laboratory-quality assay. *Courtesy of Dr. David Nathan.*