Tests of Glycemia in Diabetes

AMERICAN DIABETES ASSOCIATION

Monitoring of glycemic status, as performed by patients and health care providers, is considered a cornerstone of diabetes care. Results of monitoring are used to assess the efficacy of therapy and to guide adjustments in medical nutrition therapy, exercise, and medications to achieve the best possible blood glucose control.

This position statement presents the recommendations of the American Diabetes Association on the tests used most widely in monitoring the glycemic status of people with diabetes and addresses both patient and physician/laboratory-based testing. It does not address tests for diabetes screening and diagnosis. The recommendations are based on the American Diabetes Association's technical review on the subject, which should be consulted for further information (1).

BLOOD GLUCOSE TESTING BY PATIENTS

— Within only a few years, self-monitoring of blood glucose (SMBG) by patients has revolutionized management of diabetes. Using SMBG, patients with diabetes can work to achieve and maintain specific glycemic goals. Given the results of the Diabetes Control and Complications Trial (DCCT) and other studies, there is broad consensus on the health benefits of normal or near-normal blood glucose levels and on the importance, especially in insulin-treated patients, of SMBG in treatment efforts designed to achieve such glycemic goals.

The subject of SMBG has been addressed extensively by two American Diabetes Association Consensus Conferences, which provide a comprehensive review of the subject.

Recommendations

1. Based principally on the DCCT results, it is recommended that most individuals with diabetes should attempt to achieve and maintain blood glucose levels as close to normal as is safely possible. Because most patients with type I diabetes can achieve this goal only by using SMBG, all treatment programs should encourage SMBG for routine daily monitoring. Daily SMBG is especially important for patients treated with insulin or sulfonylureas to monitor for and prevent asymptomatic hypoglycemia. Frequency and timing of glucose monitoring should be dictated by the needs and goals of the individual patient, but for most patients with type I diabetes, SMBG is recommended three or four times daily. The optimal frequency of SMBG for patients with type II diabetes is not known, but should be sufficient to facilitate reaching glucose goals. The role of SMBG in stable diet-treated patients with type II diabetes is not known.
2. SMBG is recommended for all insulin-treated patients with diabetes. SMBG may be desirable in patients treated with sulfonylureas and in all patients not achieving glycemic goals. Data indicate that only a minority of patients perform SMBG. Efforts should be made to substantially increase appropriate use of SMBG. Barriers to increasing use of SMBG include cost of testing, inadequate understanding by both health care providers and patients about the health benefits and proper use of SMBG results, patient psychological and physical discomfort associated with finger-prick blood sampling, and inconvenience of testing in terms of time requirements, physical setting, and complexity of the technique.

   Given the importance of SMBG to diabetes care, government, third-party payers, and others should strive to make the procedure readily accessible and affordable for all patients who require it. Thus, SMBG should be an important component of any health care benefits package.
3. Because the accuracy of SMBG is instrument and user dependent, it is important for health care providers to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. Use of calibration and control solutions on a regular basis by patients helps assure accuracy of results.
4. Optimal use of SMBG requires proper interpretation of the data. Patients should be taught how to use the data to adjust medical nutrition therapy, exercise, or pharmacological therapy to achieve specific glycemic goals. Although a number of SMBG methods store test results and with a computer interface can provide sophisticated analyses of blood glucose data, it is not known whether use of these data management systems yields better glucose control than patient review of results recorded in a logbook.

BLOOD GLUCOSE TESTING BY HEALTH CARE PROVIDERS FOR ROUTINE OUTPATIENT MANAGEMENT OF DIABETES

Recommendations

1. Blood glucose testing (e.g., laboratory glucose or finger-stick glucose) should be available to providers for use as needed. With the availability of SMBG and glycated protein testing, routine laboratory blood glucose testing by health care providers should no longer be used to assess glycemic control except to supplement information obtained from other testing methods and to test the accuracy of SMBG. When adjusting oral medication(s) in a patient not taking insulin, laboratory testing also may be appropriate.
2. Comparisons between results from patient self-testing of blood glucose

The initial draft of this paper was prepared by David E. Goldstein, MD, Chair; Randie R. Little, PhD; Rodney A. Lorenz, MD; John I. Malone, MD; David M. Nathan, MD; and Charles M. Peterson, MD. The paper was peer-reviewed, modified, and approved by the Professional Practice Committee and the Executive Committee, November 1996. For a Technical Review on this subject see *Diabetes Care* 18:896–909, 1995.

in the clinic and simultaneous laboratory testing are useful to assess the accuracy of patient results. If such testing is performed by health care providers using portable capillary blood testing devices rather than standard hospital or clinic laboratory methods, rigorous quality control procedures should be used. Participation in the College of American Pathologists voluntary proficiency testing program for home-use testing devices is recommended.

URINE TESTING — Historically, urine glucose and ketone determinations were the only practical way for people with diabetes to assess their glycemic status on a day-to-day basis. However, SMBG has supplanted urine glucose testing for most patients. Urine ketone testing remains an important part of monitoring, particularly in patients with type I diabetes, pregnancy with preexisting diabetes, and gestational diabetes.

Urine glucose testing

Urine glucose testing by patients in the home setting consists of semiquantitative measurements based on single voidings or, less often, by more quantitative "blocks" collected over 4–24 h. The rationale is that urinary glucose values reflect mean blood glucose during the period of urine collection. However, despite the relatively low cost and ease of specimen collection, the well-described limitations of urine glucose testing make SMBG the preferred method of monitoring glycemic status day-to-day.

For patients who cannot or will not perform SMBG, urine glucose testing can be considered an alternative that can provide useful, albeit limited, information. If patients choose to perform urine glucose testing, they should fully understand the test limitations. Specifically, patients should be taught that although urine glucose measurements correlate with blood glucose measurements, urine glucose testing provides only a rough estimate of prevailing blood glucose levels. Patients should be taught that urine glucose testing provides no information about blood glucose levels below the renal threshold, which for most patients is 180 mg/dl (10 mmol/l).

Test strips that quantify urinary glucose specifically rather than reducing sugars are recommended because of fewer drug and other interferences. Second-voided specimens do not appear to offer any appreciable advantage over first-voided specimens.

Urine ketone testing

Urine ketone testing is an important part of monitoring, particularly in type I patients. The presence of urine ketones may indicate impending or even established ketoacidosis, a condition that requires immediate medical attention. All people with diabetes should test their urine for ketones during acute illness or stress or when blood glucose levels are consistently elevated (e.g., >300 mg/dl [>16.7 mmol/l]), during pregnancy, or when any symptoms of ketoacidosis, such as nausea, vomiting, or abdominal pain, are present.

Ketones are normally present in urine, but concentrations are usually below the limit of detectability with routine testing methods. However, positive ketone readings are found in normal individuals during fasting and in up to 30% of first morning urine specimens from pregnant women. Urine ketone tests using nitroprusside-containing reagents can give false-positive results in the presence of several sulfhydryl drugs, including the antihypertensive drug captopril. False-negative readings have been reported when test strips have been exposed to air for an extended period of time or when urine specimens have been highly acidic, such as after large intakes of ascorbic acid.

Urine ketone testing materials should be available in the office/clinic setting. Health care professionals should be aware, however, that currently available urine ketone tests are not reliable for diagnosing or monitoring treatment of ketoacidosis. Blood ketone testing methods that quantify β-hydroxybutyric acid, the predominant ketone body, are now available. These may offer a useful alternative to urine ketone testing because β-hydroxybutyric acid determinations are reliable for diagnosing and monitoring treatment of ketoacidosis. More research is needed to determine if blood β-hydroxybutyric acid testing can be adapted for home use by patients as an alternative to urine ketone testing.

GLYCATED PROTEIN TESTING — Blood and urine glucose testing and urine ketone testing provide useful information for day-to-day management of diabetes. However, these tests cannot provide the patient and health care team with a quantitative and reliable measure of glycemia over an extended period of time. Measurements of glycated proteins, primarily hemoglobin and serum proteins, have added a new dimension to assessment of glycemia. With a single measurement, each of these tests can quantify average glycemia over weeks and months, thereby complementing day-to-day testing.

Glycated hemoglobin (GHb) testing

GHb, commonly referred to as glycated hemoglobin, glycohemoglobin, glycosylated hemoglobin, HbA_{1c}, or HbA_1, is a term used to describe a series of stable minor hemoglobin components formed slowly and nonenzymatically from hemoglobin and glucose. The rate of formation of GHb is directly proportional to the ambient glucose concentration. Since erythrocytes are freely permeable to glucose, the level of GHb in a blood sample provides a glycemic history of the previous 120 days, the average erythrocyte life span. GHb most accurately reflects the previous 2–3 months of glycemic control.

Many different types of GHb assay methods are available to the routine clinical laboratory. Methods differ considerably with respect to the glycated components measured, interferences, and nondiabetic range. Clinicians ordering GHb testing for their patients should be aware of the type of assay method used, the nondiabetic reference interval, potential assay interferences (e.g., labile intermediates, hemoglobinopathies, chronic alcohol ingestion, salicylates, carbamylation products in uremia, sample storage effects), and assay performance (e.g., some measure of assay precision, such as a coefficient of variation; CV <5% is desirable).

The GHb value has been shown to predict the risk for the development of many of the chronic complications in diabetes, analogous to using cholesterol determinations to predict the risk for development of cardiovascular disease. However, optimal use of GHb testing for this purpose will require the standardization of GHb assays, which is in progress. Until the standardization of methods is accomplished, reported results between laboratories may not be comparable, even if both laboratories use the same assay method. A national program, sponsored in part by the American Diabetes Association, to standardize GHb determinations to DCCT values began in mid-1996. On

an annual basis, manufacturers of GHb assay methods are awarded a "certificate of traceability to the DCCT reference method" if their assay method passes rigorous testing criteria for precision and accuracy. It is desirable that laboratories use only GHb assay methods that have passed certification testing. It is also desirable that all laboratories performing GHb testing participate in the College of American Pathologists proficiency testing survey for GHb started in mid-1996, which uses whole blood specimens in addition to lyophilized specimens.

GHb testing should be performed routinely in all patients with diabetes, first to document the degree of glycemic control at initial assessment, then as part of continuing care. Since GHb reflects a mean glycemia over the preceding 2–3 months, measurement approximately every 3 months is required to determine whether a patient's metabolic control has remained continuously within the target range. Thus, regular measures of GHb permit detection of departures from the target range in a timely fashion. For any individual patient, the frequency of GHb testing should be dependent on the treatment regimen used and on the judgment of the clinician. In the absence of well-controlled studies that suggest a definite testing protocol, expert opinion recommends GHb testing at least one or two times a year in patients with a history of stable glycemic control and quarterly assessments in patients whose therapy has been changed or who are in poor control.

Proper interpretation of GHb test results requires that health care providers understand the relationship between test results and average blood glucose, kinetics of GHb, and specific assay limitations. Data are available from the DCCT relating GHb to average glycemia, but these data should be used with caution if the GHb assay method is not certified as traceable to the DCCT reference method.

GHb values in patients with diabetes are a continuum; they range from normal in a small percentage of patients whose average blood glucose levels are in or close to the normal range to markedly elevated values, e.g., two- to threefold increases, in some patients, reflecting an extreme degree of hyperglycemia. Specific treatment goals should be individualized, but one must take into account the results of studies, such as the DCCT, showing a direct relationship between GHb values and the risk of many of the chronic complications of diabetes. The American Diabetes Association recommends that the goal of therapy should be a GHb of <7% and that physicians should reevaluate the treatment regimen in patients with GHb values consistently >8%. Again, these specific GHb values apply only to assay methods that are certified as traceable to the DCCT reference method.

Glycated serum protein (GSP)

Because the turnover of human serum albumin is much shorter (half-life of 14–20 days) than that of hemoglobin (erythrocyte life span of 120 days), the degree of glycation of serum proteins (mostly albumin) provides an index of glycemia over a shorter period of time than does glycation of hemoglobin. Measurements of total GSP and glycated serum albumin (GSA) correlate well with one another and with measurements of GHb, and they have been suggested as alternative methods for routine monitoring of glycemic control in patients with diabetes. In addition, in situations where GHb cannot be measured or may not be useful (e.g., hemoglobinopathies), the GSP assay may be of value in the assessment of the treatment regimen. Several methods have been described that quantify either total GSP or total GSA. One of the most widely used is called the fructosamine assay. Values for GSP vary with changes in the synthesis or clearance of serum proteins that can occur with acute systemic illness or with liver disease. In addition, there is continuing debate as to whether fructosamine assays should be corrected for serum protein or serum albumin concentrations.

A single measurement of GSP provides an index of glycemic status over the preceding 1–2 weeks, while a single measurement of GHb provides an index of glycemic status over a considerably longer period of time, 2–3 months.

Measurement of GSP (including fructosamine) has been used to document relatively short-term changes (e.g., 1–2 weeks) in glycemic status, such as in diabetic pregnancy or after major changes in therapy. However, further studies are needed to determine if the test provides useful clinical information in these situations.

Simultaneous measurements of GSP and GHb might complement one another and provide more useful clinical information than measurement of GHb alone. However, additional studies are needed to confirm the clinical utility of this approach.

Measurement of GSP, regardless of the specific assay method, should not be considered equivalent to measurement of GHb, since it only indicates glycemic control over a short period of time. Therefore, GSP assays would have to be performed on a monthly basis to gather the same information as measured in GHb three to four times a year. Unlike GHb, GSP has not yet been shown to be related to the risk of the development or progression of chronic complications of diabetes.

References

1. Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan D, Peterson CM: Tests of glycemia in diabetes (Technical Review). *Diabetes Care* 18:896–909, 1995