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 (MNT), 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 (2,3).

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 1 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 1 diabetes, SMBG is recommended three or more times daily. The optimal frequency of SMBG for patients with type 2 diabetes is not known, but should be sufficient to facilitate reaching glucose goals. When adding to or modifying therapy, type 1 and type 2 diabetic patients should test more often than usual. The role of SMBG in stable diet-treated patients with type 2 diabetes is not known.
2. SMBG is recommended for all insulin-treated patients with diabetes. SMBG may be desirable in patients treated with sulfonylureas or other insulin secretagogues 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 ensure accuracy of results. In addition, because laboratory methods measure plasma glucose, many blood glucose monitors approved for home use and some test strips now calibrate blood glucose readings to plasma values. Plasma glucose values are 10–15% higher than whole blood glucose values, and it is crucial that people with diabetes know whether their monitor and strips provide whole blood or plasma results.
4. Optimal use of SMBG requires proper interpretation of the data. Patients should be taught how to use the data to adjust MNT, exercise, or pharmacological therapy to achieve specific glycemic goals. Health professionals should evaluate at regular intervals the patient's ability to use SMBG data to guide treatment. 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.

The recommendations in this paper are based on the evidence reviewed in the following publication: Tests of glycemia in diabetes (Technical Review). *Diabetes Care* 18:896–909, 1995.

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Abbreviations: DCCT, Diabetes Control and Complications Trial; GSA, glycated serum albumin; GSP, glycated serum protein; MNT, medical nutrition therapy; SMBG, self-monitoring of blood glucose.

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 glucose-lowering 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 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.
3. Continuous ambulatory blood glucose monitoring may be used to determine 24-h blood glucose patterns and to detect unrecognized hypoglycemia; however, its role in improving diabetes outcomes remains to be established.

URINE GLUCOSE TESTING — SMBG has supplanted urine glucose testing for most patients. 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.

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).

Urine/blood ketone testing

Ketone testing is an important part of monitoring in type 1 diabetic patients, in pregnancy with pre-existing diabetes, and in gestational diabetes. The presence of ketones may indicate impending or even established ketoacidosis, a condition that requires immediate medical attention. Patients with type 1 diabetes should test 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.

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 available and are preferred over urine ketone testing for diagnosing and monitoring ketoacidosis. Home tests for β-hydroxybutyric acid are available.

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, also referred to as 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. Glycated hemoglobin is often reported as hemoglobin A_{1c}. HbA_{1c} has become the preferred standard for assessing glycemic control. In referring to this test, the term "A1C test" will be used.

The A1C test 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 the A1C test for this purpose requires the standardization of A1C test assays. Without standardization, reported results between laboratories may not be comparable, even if both laboratories use the same assay method. The National Glycohemoglobin Standardization Program (http://web.missouri.edu/~diabetes/ngsp.html), sponsored in part by the

American Diabetes Association to standardize A1C test determinations to DCCT values, began in mid-1996. On an annual basis, manufacturers of A1C test 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 A1C test assay methods that have passed certification testing. It is also desirable that all laboratories performing A1C testing participate in the College of American Pathologists proficiency testing survey for A1C testing started in mid-1996, which uses whole-blood specimens. Regardless of the assay method type and specific analyte qualified, all results should be reported as "% HbA_{1c}" or "% HbA_{1c} equivalents."

A1C 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 the A1C test 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 reached and been maintained within the target range. Thus, regular A1C testing permits detection of departures from the target range in a timely fashion. For any individual patient, the frequency of A1C 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 A1C testing at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control) and more frequently (quarterly assessment) in patients whose therapy has changed or who are not meeting glycemic goals.

Proper interpretation of A1C test results requires that health care providers understand the relationship between test results and average blood glucose, kinetics of the A1C test, and specific assay limitations. Data from the DCCT relating A1C test results to mean plasma glucose levels appear in Table 1 (4), but these data should be used with caution if the A1C test assay method is not certified as traceable to the DCCT reference method.

A1C test 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., >9.5%, 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 A1C test values and the risk of many of the chronic complications of diabetes. The American Diabetes Association recommends that the goal of therapy should be an A1C result of <7% and that physicians should reevaluate and, in most cases, significantly change the treatment regimen in patients with A1C test results consistently >8%. Again, these specific A1C values apply only to assay methods that are certified as traceable to the DCCT reference method.

Table 1—*Correlation between A1C level and mean plasma glucose levels (4)*

	Mean plasma glucose	
A1C (%)	mg/dl	mmol/l
6	135	7.5
7	170	9.5
8	205	11.5
9	240	13.5
10	275	15.5
11	310	17.5
12	345	19.5

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 glycated hemoglobin (A1C test). In situations where the A1C test cannot be measured or may not be useful (e.g., hemolytic anemias), 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 A1C test 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 the A1C test might complement one another and provide more useful clinical information than the A1C test 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 the A1C test, 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 by the A1C test three to four times a year. Unlike the A1C test, GSP has not yet been shown to be related to the risk of the development or progression of chronic complications of diabetes.

References

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