Assessing Glycemia in Diabetes Using Self-monitoring Blood Glucose and Hemoglobin A₁c

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Context With the increasing prevalence of diabetes, successful management of blood glucose control is increasingly important. Current approaches to assessing glycemia include the use of self-monitoring of blood glucose (SMBG) and hemoglobin A₁c (HbA₁c).

Objectives To assess the evidence underlying the use of these 2 modalities, to evaluate confounders and sources of error in each test, to describe upcoming developments, and to reach evidence-based conclusions on their optimal use.

Data Sources, Study Selection, and Data Extraction Reports identified from MEDLINE searches (1976-2005) using relevant terms were selected for quality and relevance to the stated questions. Particular attention was paid to larger cohort studies, clinical trials, meta-analyses, and established recommendations.

Data Synthesis If used properly SMBG gives an acceptably accurate reflection of immediate plasma glucose levels. Study results vary, but in general, the evidence supports a positive effect of regular SMBG for improving glycemia, particularly in individuals treated with insulin. The best timing of SMBG and its frequency are controversial issues, but the clinical recommendation is for regular monitoring with frequency depending on the treatment and the instability of glycemia. In the relatively near term, SMBG could gradually be replaced by continuous glucose monitoring. HbA₁c measures long-term glycemic control, reflecting a time-weighted mean over the previous 3 to 4 months. There are a number of physiologic and methodologic confounders that can affect HbA₁c, but standardization of assays has been well established. The main value of HbA₁c is its use as a predictor of diabetic complications and the proven effect of improved control of HbA₁c on complication risk. A reasonable target value for HbA₁c is less than 7%. A new method for measuring HbA₁c may cause significant changes in the recommended levels, the numbers reported, and even the name of the test.

Conclusion Assessing glycemia in diabetes can be a challenge, but approaches are available that promote successful management of blood glucose and may thereby lead to a significant reduction in morbidity and mortality related to diabetes.

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The information derived from these 2 assessment tools is fundamentally different. SMBG reveals the immediate,
hour-to-hour blood glucose, which in people without diabetes varies only about 50% throughout the normal day but may vary 10-fold in patients with diabetes. Long-term or month-to-month glycemia is assessed by HbA1c. In this review, we summarize the theoretical and methodological basis, standardization and confounders, evidence of clinical utility and controversies, and recommendations for use of SMBG and HbA1c. We also describe important advances coming in the near future.

METHODS

Titles and abstracts relevant to SMBG and HbA1c were retrieved in a search of MEDLINE, published in English, for the years 1976 to July 2005. Search terms included, in various combinations: self-monitoring of blood glucose, SMBG, glycated hemoglobin, HbA1c, mean glycemia, confounder, standardization, efficacy, alternate site testing, frequency, postprandial, continuous glucose monitoring, fructosamine, screening, recommendations, NGSP [National Glycohemoglobin Standardization Program], IFCC [International Federation of Clinical Chemistry]. In limiting the number of articles evaluated, preference was given to larger cohort studies, randomized trials (especially those that enrolled ≥100 patients), prior comprehensive reviews, meta-analyses, quality of peer-reviewed publications, and published guidelines.

EVIDENCE SYNTHESIS

Self-monitoring of Blood Glucose

With a small fingerprick and a microliter or less of blood, people with diabetes can know their blood glucose level at any time. This allows patients to relate events in their daily life and treatment regimen to glycemic results. The introduction of SMBG thus caused a shift in the focus of diabetes management from the physician’s office into the hands of the patient. Given proper understanding and communication with the health care professional, patients could, to an extent previously unheard of, take control of their own diabetes.

Current glucose monitors use glucose test strips impregnated with glucose oxidase, glucose dehydrogenase, or hexokinase to convert blood glucose into gluconic acid and hydrogen peroxide when a drop of blood is added to the strip. This reaction is then quantified by various means including colorimetric methods, reflectance photometry, absorbance photometry, and electrochemistry.11

Standardization and Confounders.

In general, results from glucose meters are not as accurate as those from laboratory methods, although they are far more accurate than the earlier approach of visual matching to colors. While standards for acceptable accuracy vary, the International Organization for Standardization (http://www.iso.org) recommends that more than 95% of readings be within 15 mg/dL (0.83 mmol/L) for glucose readings that are less than 75 mg/dL (+2 mmol/L), and within 20% for higher blood glucose values when compared with the standard YSI 2700 reference method (Yellow Springs Instruments, Yellow Springs, Ohio). Under optimal circumstances, many meters meet these accuracy standards12; however, there are confounding variables.

Operator-related errors are a more significant source of error than are instrument-related errors.13 A significant between-patient variance has been reported in glucose meter readings,14 although the role of education in reducing user inaccuracies was demonstrated in a before-after study of 280 patients by Bergenstal et al.15 Patient failure to calibrate the glucose meter regularly is a common cause of error.12 Other common technique errors include improper use of control solutions, poor hand washing, and dirty meters.12 Improper storage of test strips, which exposes them to humidity or excessive temperature, can falsely elevate results.13 Certain drugs, such as ascorbic acid, acetaminophen, dopamine, and mannitol, can affect the accuracy of some meters.16 Glucose meters are also less reliable in the lower ranges of glycemia17 and may overestimate true glucose values in the high glycemic range.14

A low hematocrit increases SMBG results18 because of the lower erythrocyte mass. Erythrocytes are relatively glucopenic, so the whole blood applied to strips normally has about 15% less glucose than plasma glucose, the difference lessened with anemia. Most meters today are calibrated to provide plasma glucose equivalent readings19 and assume a normal hematocrit.

To reduce pain and promote more frequent testing, blood may be drawn from sites other than the fingertips, such as the forearm and thigh. This alternate site testing is a good option for routine SMBG testing before meals but may lead to false results after eating, exercising, or with insulin treatment.20,21 For example, compared with finger blood, forearm blood glucose appears to rise more slowly and less high after a small meal, whereas after exercise, thigh and forearm glucose levels fall lower than does fingertip glucose. Therefore, fingertip testing is preferred in circumstances of rapidly changing blood glucose levels.

Clinical Utility and Controversies.

The age-adjusted percentage of adults with diabetes performing daily SMBG increased from 36% in 1994 to 58% in 2003.22 Frequency of SMBG varies directly with the intensity of treatment,23 and cost inhibits its use,24 either insured or out-of-pocket.25 Indeed, the cost of SMBG is considerable. The Medicare B program is said to have spent more than $460 million on SMBG reimbursement in 2002, more than half its Part B budget for the diabetes International Classification of Diseases, Ninth Revision code.26 It is therefore important to ask whether SMBG positively affects patient care.

Many studies have sought to answer this question (TABLE), but there are multiple sources of bias that are difficult to overcome. The population studied, the mode of treatment, duration of the trial, and study design all affect the generalizability of results. Uncontrollable bias is introduced if, for example, people who test regularly also have generally better
self-care habits, or conversely, if individuals who test more often have less stable diabetes, and more need to know their blood glucose level. Even with a randomized controlled trial (RCT) design, the education level of the patient, and in particular how he or she is taught to take action based on results, could significantly influence the efficacy of SMBG.38,43 No information is available on patients who chose not to take part in studies, which further limits generalizability. Finally, there is little reason to think that testing without acting upon the results would be helpful.

Table. Clinical Trials of Self-monitoring of Blood Glucose

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Study Groups</th>
<th>No. of Participants</th>
<th>Setting</th>
<th>Favors SMBG</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin-treated diabetes</strong></td>
<td></td>
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</tr>
<tr>
<td>Wing et al,27 1985</td>
<td>RCT</td>
<td>SMBG vs no SMBG</td>
<td>50</td>
<td>United States; two-thirds self-referred; ≥20% ideal body weight</td>
<td>No</td>
<td>No statistically significant difference in HbA1c.</td>
</tr>
<tr>
<td>Kwon et al,28 2004</td>
<td>RCT</td>
<td>SMBG vs no SMBG</td>
<td>110</td>
<td>Korea; Internet-based</td>
<td>Yes</td>
<td>Significant improvement of HbA1c.</td>
</tr>
<tr>
<td>Soumerai et al,24 2004</td>
<td>RCT</td>
<td>Free blood glucose monitors vs no monitors</td>
<td>3219</td>
<td>United States; health maintenance organization</td>
<td>Yes</td>
<td>Policy improved rate of SMBG; SMBG initiators had HbA1c reduction of 0.63% in patients with poor glycemic control (HbA1c &gt;10%)</td>
</tr>
<tr>
<td><strong>Non–insulin-treated/ type 2 diabetes</strong></td>
<td></td>
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</tr>
<tr>
<td>Fontbonne et al,29 1989</td>
<td>RCT</td>
<td>SMBG vs urine testing vs no SMBG</td>
<td>208</td>
<td>France</td>
<td>No/Yes</td>
<td>No statistically significant difference in HbA1c, but significant correlation between test frequency and HbA1c.</td>
</tr>
<tr>
<td>Allen et al,30 1990</td>
<td>RCT</td>
<td>SMBG vs urine testing</td>
<td>54</td>
<td>United States; Veterans Administration</td>
<td>No</td>
<td>No statistically significant difference in mean fasting plasma glucose, HbA1c, weight.</td>
</tr>
<tr>
<td>Estey et al,31 1990</td>
<td>RCT</td>
<td>SMBG vs SMBG with education/compliance</td>
<td>60</td>
<td>Canada</td>
<td>No</td>
<td>More SMBG in education group but no statistically significant difference in HbA1c.</td>
</tr>
<tr>
<td>Rutten et al,32 1990</td>
<td>RCT</td>
<td>SMBG vs no SMBG</td>
<td>129</td>
<td>The Netherlands</td>
<td>Yes</td>
<td>Significant HbA1c improvement of 0.4% vs increase of 0.5% in no SMBG group; included decision tree of results.</td>
</tr>
<tr>
<td>Muchmore et al,33 1994</td>
<td>RCT</td>
<td>SMBG + carbohydrate counting vs none</td>
<td>23</td>
<td>United States; body mass index ≥27.5</td>
<td>Yes</td>
<td>Significant improvement in HbA1c.</td>
</tr>
<tr>
<td>Jaber et al,34 1996</td>
<td>RCT</td>
<td>Pharmaceutical care (with SMBG) vs none</td>
<td>39</td>
<td>United States; African American</td>
<td>Yes</td>
<td>Significant improvement in HbA1c, and fasting plasma glucose.</td>
</tr>
<tr>
<td>Schwedes et al,35 2002</td>
<td>RCT</td>
<td>SMBG vs no SMBG</td>
<td>223</td>
<td>Germany and Austria</td>
<td>Yes</td>
<td>Significant improvement of HbA1c.</td>
</tr>
<tr>
<td>Guerci et al,36 2003</td>
<td>RCT</td>
<td>SMBG vs no SMBG</td>
<td>689</td>
<td>France</td>
<td>Yes</td>
<td>Significant improvement of HbA1c.</td>
</tr>
<tr>
<td>Davidson et al,37 2005</td>
<td>RCT</td>
<td>SMBG vs no SMBG</td>
<td>88</td>
<td>United States; predominantly Latino, low socioeconomic status</td>
<td>No</td>
<td>No statistically significant difference in HbA1c.</td>
</tr>
<tr>
<td><strong>Type 2 diabetes</strong></td>
<td></td>
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</tr>
<tr>
<td>Faas et al,38 1997</td>
<td>Literature review</td>
<td>SMBG vs urine testing; SMBG vs no SMBG</td>
<td>617 (6 RCTs)</td>
<td>Type 2 diabetes; insulin–, and non–insulin-treated</td>
<td>No</td>
<td>No statistically significant difference in HbA1c.</td>
</tr>
<tr>
<td>Coster et al,39 2000</td>
<td>Meta-analysis of RCTs</td>
<td>Monitoring (blood or urine) vs no monitoring</td>
<td>285 (4 RCTs)</td>
<td>Type 2 diabetes; insulin–, and non–insulin-treated</td>
<td>No</td>
<td>Nonsignificant improvement of HbA1c by 0.25%.</td>
</tr>
<tr>
<td>Sarol et al,40 2005</td>
<td>Meta-analysis of RCTs</td>
<td>SMBG vs no SMBG</td>
<td>1307 (8 RCTs)</td>
<td>Type 2 diabetes, non–insulin-treated</td>
<td>Yes</td>
<td>Significant HbA1c improvement of 0.39%.</td>
</tr>
<tr>
<td>Welschen et al,41 2005</td>
<td>Literature review</td>
<td>SMBG vs no SMBG</td>
<td>1159 (5 RCTs)</td>
<td>Type 2 diabetes, non–insulin-treated</td>
<td>Yes</td>
<td>Significant HbA1c improvement of 0.39%.</td>
</tr>
</tbody>
</table>

Abbreviations: HbA1c, hemoglobin A1c; RCT, randomized controlled trial; SMBG, self-monitoring blood glucose.
*Studies of type 2 diabetes are listed as non–insulin-treated; studies of type 1 and 2 are listed as insulin-treated.
Early nonrandomized reports of SMBG were positive.44-46 Four Veterans Administration studies, however, each reported no benefit to SMBG,47-50 although 6 of the 10 other retrospective or cross-sectional studies41-46,51-56 did show benefit. A large cohort study of a managed care population of 24,000 patients found SMBG improved HbA1c by up to 1%.23 A Canadian cross-sectional study found patients who were insured for SMBG had significantly lower HbA1c levels than those without coverage,52 and a study of 115 patients random assignment.37

In Los Angeles, with educators blinded dominantly low socioeconomic status prandial SMBG in 89 community clinic, RCT. It found no effect of pre- and post- Davidson et al stands out as a negative SMBG.57

The need for an educational link to tent with their previous emphasis on Guerci et al in the Auto- observational studies23,44-46,51-56 although in 6 of those reviewing the literature for non– insulin-using people with diabetes, concluding that SMBG does have a favorable effect on HbA1c,49 although in a counterpoint, Davidson disputed the conclusion.26

In sum, the larger, more recent trials reviewed in this article support the conclusion that SMBG, if effectively translated into action, improves glycemia. The data are most conclusive for insulin-using people, in whom SMBG as part of a complete regimen to improve glycemia does reduce long-term complications of diabetes.1 The evidence that links SMBG to improved glycemia in non–insulin-requiring type 2 diabetes is less definitive.

Recommendations for Use. Consistent communication between the patient and health care professional is essential to effective implementation of self-monitoring and maintenance of patient motivation. When patients monitor regularly, they should be taught how to act immediately on the results as well as communicate the results to the health care professional. The health care professional must in turn take note of and evaluate results, communicate treatment modifications based on the results, and include follow-up.

There are no definitive clinical studies on optimal frequency of SMBG, so this is best decided by the individual patient and clinician. The American Diabetes Association (ADA) recommends SMBG 3 or more times daily for type 1 diabetes and no specific frequency is recommended for type 2.28 It is reasonable to recommend more frequent SMBG in people with more unstable glycemia, those prone to hypoglycemia, and when treatment changes are made. We believe that glycemic goals should be individualized, but the ADA has recommended that adults with type 1 or 2 diabetes aim for preprandial plasma glucose between 90 and 130 mg/dL (5.0-7.2 mmol/L) and peak postprandial plasma glucose less than 180 mg/dL (<10 mmol/L).58

The optimal timing of SMBG testing also remains controversial. Monnier et al have made the most detailed analyses of this issue.59,60 They found that the “extended post-lunch” (5 PM) values predicted HbA1c less than 7% with better sensitivity and specificity than did fasting glucose. But in less well-controlled type 2 patients, a 3-point daily testing system was optimal, one fasting (8 AM), one postprandial (10 AM), and one postabsorptive (5 PM). In people with type 1 diabetes, a 4- to 8-point daily system was recommended. In another study, peak post-lunch blood glucose values did not affect HbA1c after controlling for mean glycemia.61

In diabetic pregnancy, when the object is to approach euglycemia for the benefit of the developing fetus, postprandial testing has proven efficacy for both women with pregestational type 1 diabetes62 and women with gestational diabetes.63

Epidemiologic studies suggest that postprandial hyperglycemia is more predictive of adverse cardiovascular outcomes,64,65 but these effects are relatively small and the data are drawn mainly from populations with mild diabetes or even HbA1c within the normal range. It is not at all clear, therefore, that postprandial glucose measurements are predictive of cardiovascular or other diabetic complications beyond their effect on HbA1c. In other words, if preprandial SMBG and HbA1c values are in a good range, there is little evidence to recommend testing after a meal.

A consensus panel concluded that evidence is not adequate to support routine postprandial blood glucose testing.66 Uncertainty about exact timing postprandially and exact meal content were cited. Our practice is to rely...
on fasting, preprandial, and bedtime SMBG unless there is a special circumstance such as an unexplained discrepancy between HbA1c and SMBG results, pregnancy, or mild glucose intolerance. Also, given the potential seriousness of nocturnal hypoglycemia, it is clinically indicated to test in the middle of the night if patients have any symptomatic evidence of nighttime lows and to make appropriate treatment adjustments.

Patients using insulin pumps are a subgroup with special need for frequent blood glucose monitoring, both to guide their bolus insulin dosing and because if insulin delivery is inadvertently interrupted, they become insulinopenic very rapidly and ketoacidosis can develop quickly. SMBG can be used most effectively by using data management features available on the glucose meter to calculate means, variance, and trends by time-of-day or over weeks and months. Most meters can now easily download results into a personal computer, so managed data (graphs, averages) can be quickly printed. The only requirements are that the time and date be correctly entered into the meter, and that the office have a connecting cable and simple software. Examples of such downloads are in Figure 1 and Figure 2. In our opinion, this data management capability is useful and underutilized.

The Future: Continuous Glucose Monitoring. Continuous glucose monitoring (CGM) is in its infancy as a practical clinical tool, but it is likely to change diabetes management. Moving from intermittent SMBG to CGM is a conceptual as well as a technical advance. With CGM, the continuous, sometimes extreme fluctuations of blood glucose are readily apparent. Alarms can be set to alert patients of high or low blood glucose concentrations. The immediate effect of every dietary and therapeutic intervention can be seen.

**Figure 1. Sample Data Downloaded From Blood Glucose Meters by Time of Day**

Sample data downloaded from blood glucose meters over the 90 days prior to the visit. In panel A, the patient clearly has good glycemic control during the day but levels are high between about 5 am and 7 am. This illustrates the “dawn phenomenon,” in which hyperglycemia occurs in the dawn hours. In panel B, the patient tests regularly 3 times daily and has much better, more stable glucose levels in the morning than at noon or at 5 pm, when the level is higher and more variable. Regimen adjustment could include more daytime insulin or oral agent coverage or modification of dietary intake.

**Figure 2. Sample Data Downloaded From Blood Glucose Meters Continuously**

Glycemic control is clearly worse throughout the month of March. The patient started a better nutritional plan in April and the results are evident. Discussion with the patient could include lessening antidiabetic treatment to avoid hypoglycemia.
At present, there are several CGM products on the market and more are under development. These monitors measure glucose concentration in subcutaneous interstitial fluid, which can reflect changes in blood glucose concentrations reasonably quickly. Recent reports describe the use of CGM in clinical and research settings, but the monitors are not easily used on a routine, clinical, long-term basis. Spectroscopy-based and fluorescence-based sensors, which could be entirely noninvasive, have been slow to develop.

The ultimate goal of CGM is to drive a closed-loop insulin delivery system, the “artificial pancreas.” This goal, in early stages of development, depends on the sensors being robust, accurate, and easy to use.

Hemoglobin A1c

In the late 1960s, a minor component of human hemoglobin A was noted to be increased in patients with diabetes. By the mid-1970s, HbA1c was shown to decrease as glycemic control improved, and thus, the potential of HbA1c as a clinical and research tool was recognized. Over the last 25 years, HbA1c testing has come into common use, serving as a convenient method for evaluating average glycemia over the previous several months.

HbA1c is defined as the stable adduct of glucose at the N-terminal amino group of the β-chain of hemoglobinAo (N-[1-deoxyfructosyl]hemoglobin). It forms as a posttranslational modification, in which glucose condenses with the free amine group on the N-terminal valine residues of the hemoglobin β-chain. The resulting Schiff base is unstable and undergoes an irreversible Amadori rearrangement to form a stable ketoamine. Glycation also occurs at certain lysine residues on the hemoglobin α- and β-chains; total glycohemoglobin or total glycated hemoglobin refer to measurement of these products as well as HbA1c. Glycated hemoglobin is quantified most commonly with methods that distinguish it from nonglycated hemoglobin on the basis of either charge (cation-exchange chromatography, electrophoresis, isoelectric focusing) or structural characteristics (affinity chromatography, immunoassays).

A direct relationship exists between HbA1c and mean glycemia because erythrocytes are continuously glycated during their 120-day lifespan and the rate of glycohemoglobin formation is proportional to the ambient glucose concentration. In the Diabetes Control and Complications Trial, an HbA1c of 6% (measured by ion-exchange high-performance liquid chromatography) corresponded to a mean plasma glucose level of 135 mg/dL (7.5 mmol/L), and each 1% increase in HbA1c corresponded to an increase in mean plasma glucose level of approximately 35 mg/dL (2 mmol/L). One caveat in interpreting the linearity of this relationship is that HbA1c does not reflect blood glucose levels equally over the previous 120 days. Rather, recent changes in glycemic control are overrepresented in HbA1c. About 50% of HbA1c is determined by glycemia during the 1 month preceding the measurement, 25% from the 30 to 60 days before the measurement, and 25% from the 60 to 120 days prior to the measurement.

Standardization and Confounders.

Comparing study results and setting HbA1c goals assumes reliability and comparability of methods. In the early 1990s, there were over 20 available methods, with widely varying reference ranges. The National Glycohemoglobin Standardization Program (NGSP) (http://www.missouri.edu/~diabetes/ngsp.html) was created to remedy this situation and has been highly successful. Currently, 99% of laboratories in the United States use certified assays that are traceable to the Diabetes Control and Complications Trial glycohemoglobin reference (ion-exchange high-performance liquid chromatography) with a total imprecision (coefficient of variation) of 4% or less. Reliable standardization of the assay is also increasing internationally.

While age, sex, ethnicity, and nonfasting state do not affect HbA1c test results, confounding conditions do exist. Hemoglobin variants commonly and unpredictably interfere with HbA1c measurements. Hemoglobin S or C carriers may have spuriously high or low HbA1c results measured by ion-exchange high-performance liquid chromatography due to coelution of the variant with either HbA0 or HbA, and results may be affected when using other methods as well. With more than 700 hemoglobin variants reported, most clinically silent, unsuspected errors in HbA1c results may occur. Chemically modified hemoglobin, such as carbamylated hemoglobin associated with uremia and acetylated hemoglobin formed after ingestion of large doses of salicylates, can falsely increase results. A hemoglobin variant should be suspected if the HbA1c reading is surprisingly high or low, or is significantly changed coincident with a change in laboratory method. In these cases, a boronate affinity chromatography method of measuring HbA1c may be more reliable. Bry et al have reviewed this topic as has the NGSP Web site.

Many conditions also exist that alter HbA1c levels independent of the assay method. Any process that shortens erythrocyte lifespan decreases HbA1c, since glycation increases with age of the red cell. Kidney disease, liver disease, hemolytic anemia, hemoglobinopathies, and recovery from blood loss will all decrease HbA1c on this basis. Vitamins C and E have been reported to lower HbA1c measurements, possibly by inhibiting glycation. Lower HbA1c levels are found in diabetic and nondiabetic pregnant women, probably due both to lower fasting blood glucose and a shortened erythrocyte lifespan, prompting a proposal for lowering the upper normal limit for HbA1c in pregnancy.

Iron-deficiency anemia, on the other hand, has been associated with increased HbA1c. Any process that slows erythropoiesis, such as aplastic anemia, will increase HbA1c by causing an older erythrocyte cohort.

We studied whether glycemic lability, independent of mean glycemia, af-
effects HbA1c. Analyzing the SD of blood glucose in patients performing frequent SMBG, we found that after controlling for mean glycemia, HbA1c is not affected by glycemic lability. An other report reached a similar conclusion on glycemia after lunch.62

Clinical Utility and Controversies. The measurement of HbA1c has been the primary index of glycemia in the Diabetes Control and Complications Trial, the United Kingdom Prospective Diabetes Study, and many other studies. It is therefore the basis upon which glycemic control is known to be a mediator of diabetic complications. The Diabetes Control and Complications Trial reduced mean HbA1c by 1.8% in the intensively treated group (7.3% vs 9.1%), and this difference resulted in a 76% (95% confidence interval [CI], 62%-85%) decrease in the development of new retinopathy, a 39% (95% CI, 21%-52%) reduction in microalbuminuria, and a 60% (95% CI, 38%-74%) decrease in the development of clinical nephropathy. Similarly, in type 2 diabetes, the United Kingdom Prospective Diabetes Study found a 25% (95% CI, 7%-40%) decrease in microvascular complications associated with the 10% reduction in HbA1c achieved in the intensively treated group.3

Surprisingly, the relatively short period of intensive control imposed in the Diabetes Control and Complications Trial has now been shown to have lasting beneficial effects years after the HbA1c levels of the groups merge.24,25 HbA1c is also the accepted measure of long-term glycemia in the Framingham26 prospective cohort study and the long-term follow-up study to the Diabetes Control and Complications Trial,20 both of which have found a lower risk for macrovascular complications with improved glycemia.

While abundant evidence demonstrates that improved HbA1c reduces the risk of complications, it is not clear whether regular assessment of HbA1c itself improves diabetic control. Larsen et al more than 15 years ago did find in an RCT of 240 patients with type 1 diabetes that treatment decisions made using quarterly HbA1c results were more successful in lowering future HbA1c results than those based only on blood or urine glucose testing.97

An outside analysis of the Diabetes Control and Complications Trial raised the theory that there are “fast glycators” who, independent of glycemia alone, may be at greater risk of diabetic complications.98,99 This theory is disputed,100,101 however, and most evidence supports the conclusion that HbA1c correlates with complication risk because it reflects glycemia, not because it causes complications directly.

Recently, NGSP-certified rapid HbA1c assays have become available, allowing office and home testing. Point-of-care HbA1c testing at the clinic visit gives patients immediate feedback and allows the physician to make timely therapy changes. RCT evidence suggests that point-of-care HbA1c testing may be superior to central laboratory testing in decreasing HbA1c levels in type 1 and type 2 diabetes.102,103 Benefits of home testing, including increased patient autonomy and self-knowledge, must be weighed against the possibility of misuse, misinterpretation, and avoidance of the regular medical care system. No evidence exists to evaluate home HbA1c testing.

In addition to HbA1c, 2 other long-term indices of glycemia, fructosamine and 1,5 anhydroglucitol (1,5-AG), are available but less widely used. Fructosamine, the product of posttranslational glycation of serum proteins, predominantly albumin, provides a reflection of glycemia over a shorter time frame than does HbA1c.104 The reliability of the fructosamine assay is variable, bringing into question its clinical utility. One study found the mean glycemia over a prior 2-week period was better predicted by HbA1c than fructosamine.104 Even as an adjunct to home blood glucose monitoring, weekly fructosamine testing did not improve HbA1c levels.105

Recently, the US Food and Drug Administration approved a measure of the 1,5-AG assay. This measures serum levels of a molecule that is excreted in the urine with competitive inhibition by glucose. Thus, glucosuria inhibits 1,5-AG reabsorption at the renal tubule level, 1,5-AG excretion increases, and the serum levels fall with hyperglycemia. One study found an increase in 1,5-AG within 2 weeks of initiating treatment in patients with poorly controlled type 2 diabetes before a change in HbA1c was seen.106 In another study of 76 patients with well-controlled type 2 diabetes, 1,5-AG levels correlated with the degree of daily glycemic excursion, despite similar HbA1c values among treatment groups.107 The assay is marketed and could be useful as a marker of postprandial hyperglycemia, presumably because glycosuria ensues postprandially. Further studies are needed, however, to make a convincing case that 1,5-AG actually reflects postprandial hyperglycemia.

Recommendations. The relationship between control and complications is continuous, with no single glycemic threshold below which the risk of complications is sharply reduced or eliminated.108 Furthermore, the risk of hypoglycemia increases with lower HbA1c, at least in type 1 diabetes (less clearly for type 2 diabetes109,110). Therefore, determining a glycemic target involves considering the individual risk-benefit ratio; there is no scientific basis for choosing a single, universal target HbA1c.

The ADA currently recommends that patients with type 1 and 2 diabetes achieve HbA1c levels less than 7%.26a a level that confers a low risk of complications (eg, 9-year progression rate of retinopathy <4%).111) In some circumstances, such as elderly patients or those prone to hypoglycemia unawareness, target HbA1c should be adjusted upward, and some people with diabetes can achieve HbA1c of 6.5% or less. Studies to determine the ideal frequency of HbA1c testing are lacking, but expert opinion suggests twice-yearly testing in patients meeting goals and quarterly testing in patients not meeting goals or in whom therapy is changed.26
It remains controversial whether HbA₁c should be accepted as a means of screening or diagnosing diabetes. It would provide a simple laboratory test that does not require the patient to fast and is not greatly affected by diet or activity level of the previous few days. Proponents also point to improvements in assay standardization that have improved sensitivity and specificity when compared with criterion standard oral glucose tolerance testing. Indeed, the specificity for detecting undiagnosed diabetes in one study was 97.4% for HbA₁c results 2 SDs above the mean (>6.1%). At present, however, HbA₁c testing is not accepted for screening or diagnostic purposes.

The Future of HbA₁c. The International Federation of Clinical Chemistry has developed a new, more specific reference method for measuring glycated hemoglobin. Using mass spectrometry and capillary electrophoresis, this method assesses the glycation of valine residues on hemoglobin. With this more specific measurement, the International Federation of Clinical Chemistry reference range is about 1.3% to 1.5% lower than NGSP values. The normal range would thus be approximately 2% to 4% rather than the present 4% to 6%, and all values in the diabetic range would be about 2% lower than we are used to. A strong correlation exists between the existing and the new assays, however, and a conversion equation has been developed.

It is likely that this new International Federation of Clinical Chemistry method will become the anchor for glycated hemoglobin assays worldwide, but debate is ongoing as to how the new results will be reported, and even what the new test will be called. Changing the HbA₁c reference range could cause confusion for professionals and the public alike, given the decades-long effort to educate people about the importance of measuring HbA₁c and the goal of maintaining HbA₁c at less than 7%. One study found that simply modifying HbA₁c reference ranges caused a deterioration in glycemic control in patients. The new anchor could be converted to NGSP-standardized results and be reported in the familiar units. An alternative proposal is to conduct a large international trial, better establishing the exact relationship of the new results to mean blood glucose, and to change the name of the test from HbA₁c to mean blood glucose equivalent. With a new reference range, new targets, and a new name, the results could be reported in familiar plasma glucose values rather than as percent HbA₁c.

**SUMMARY**

Management of glycemia in diabetes is crucially important to the prevention of both acute and long-term complications. The 2 fundamental approaches to assessment, SMBG and HbA₁c, provide fundamentally different but complementary information. Regular SMBG is to be encouraged, particularly in patients using insulin, although the frequency can vary widely dependent particularly on the glycemic stability of the patient and the need to follow treatment changes. HbA₁c, the criterion standard measure of chronic glycemic control and complication risk, should be measured every 3 to 6 months to assess the success of the treatment regimen. Changes in both approaches are ongoing but with proper control of glycemia, diabetes can be successfully managed.

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