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*JAMA*. 2006;295(14):1688-1697 (doi:10.1001/jama.295.14.1688)

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# Assessing Glycemia in Diabetes Using Self-monitoring Blood Glucose and Hemoglobin A<sub>1c</sub>

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**T**HE PREVALENCE OF DIABETES IS increasing at an alarming rate, as are the associated personal and societal costs. While diabetes care should address a number of risk factors (dyslipidemia, blood pressure, tobacco use, etc), hyperglycemia itself not only defines the disease but is the cause of its most characteristic symptoms and long-term complications. Good glycemic control reduces the incidence and progression of microvascular disease in both type 1 and 2 diabetes.<sup>1-4</sup> The impact of hyperglycemia on cardiovascular disease is also becoming increasingly evident.<sup>5-7</sup> Although the Diabetes Control and Complications Trial found an increased incidence of hypoglycemia accompanying intensive glycemic control,<sup>8</sup> participants rated their overall quality of life as improved by better glycemic control.<sup>9</sup>

Assessing glycemia in diabetes, however, has always been a challenge. Until about 1910, overt symptoms of hyperglycemia were the only available metric of diabetic control.<sup>10</sup> The development of urine glucose testing allowed documentation of severe hyperglycemia, but was seriously lim-

**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 A<sub>1c</sub> (HbA<sub>1c</sub>).

**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. HbA<sub>1c</sub> 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 HbA<sub>1c</sub>, but standardization of assays has been well established. The main value of HbA<sub>1c</sub> is its use as a predictor of diabetic complications and the proven effect of improved control of HbA<sub>1c</sub> on complication risk. A reasonable target value for HbA<sub>1c</sub> is less than 7%. A new method for measuring HbA<sub>1c</sub> 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.

*JAMA.* 2006;295:1688-1697

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ited by being only semiquantitative, retrospective, and significantly affected by urine concentration. An important change in diabetes care occurred in the 1970s and 1980s as 2 methods became available: self-monitoring of blood glucose (SMBG) and hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) testing. Home urine testing became obsolete except when testing for ketones in situations of suspected ketoacidosis.

The information derived from these 2 assessment tools is fundamentally different. SMBG reveals the immediate,

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**Clinical Review Section Editor:** Michael S. Lauer, MD. We encourage authors to submit papers for consideration as a Clinical Review. Please contact Michael S. Lauer, MD, at lauerm@ccf.org.

See also pp 1681 and 1707.

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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 HbA<sub>1c</sub>. 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 HbA<sub>1c</sub>. We also describe important advances coming in the near future.

## METHODS

Titles and abstracts relevant to SMBG and HbA<sub>1c</sub> 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, HbA<sub>1c</sub>, 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  $\geq 100$  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.<sup>11</sup>

**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 (4.2 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 standards<sup>12</sup>; however, there are confounding variables.

Operator-related errors are a more significant source of error than are instrument-related errors.<sup>13</sup> A significant between-patient variance has been reported in glucose meter readings,<sup>14</sup> although the role of education in reducing user inaccuracies was demonstrated in a before-after study of 280 patients by Bergenstal et al.<sup>15</sup> Patient failure to calibrate the glucose meter regularly is a common cause of error.<sup>12</sup> Other common technique errors include improper use of control solutions, poor hand washing, and dirty meters.<sup>12</sup> Improper storage of test strips, which exposes them to humidity or excessive temperature, can falsely elevate results.<sup>15</sup> Certain drugs, such as ascorbic acid, acetaminophen, dopamine, and mannitol, can affect the accuracy of some meters.<sup>16</sup> Glucose meters are also less reliable in the lower ranges of glycemia<sup>17</sup> and may overestimate true

glucose values in the high glycemic range.<sup>14</sup>

A low hematocrit increases SMBG results<sup>18</sup> 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 readings<sup>19</sup> 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.<sup>20,21</sup> 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.<sup>22</sup> Frequency of SMBG varies directly with the intensity of treatment,<sup>23</sup> and cost inhibits its use,<sup>24</sup> either insured or out-of-pocket.<sup>25</sup> 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.<sup>26</sup> 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.<sup>38,43</sup> 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

Source	Design	Study Groups	No. of Participants	Setting	Favors SMBG	Outcome
<b>Insulin-treated diabetes*</b>						
Wing et al, <sup>27</sup> 1985	RCT	SMBG vs no SMBG	50	United States; two-thirds self-referred; ≥20% ideal body weight	No	No statistically significant difference in HbA <sub>1c</sub>
Kwon et al, <sup>28</sup> 2004	RCT	SMBG vs no SMBG	110	Korea; Internet-based	Yes	Significant improvement of HbA <sub>1c</sub>
Soumerai et al, <sup>24</sup> 2004	RCT	Free blood glucose monitors vs no monitors	3219	United States; health maintenance organization	Yes	Policy improved rate of SMBG; SMBG initiators had HbA <sub>1c</sub> reduction of 0.63% in patients with poor glycemic control (HbA <sub>1c</sub> >10%)
<b>Non-insulin-treated/ type 2 diabetes*</b>						
Fontbonne et al, <sup>29</sup> 1989	RCT	SMBG vs urine testing vs no SMBG	208	France	No/Yes	No statistically significant difference in HbA <sub>1c</sub> but significant correlation between test frequency and HbA <sub>1c</sub>
Allen et al, <sup>30</sup> 1990	RCT	SMBG vs urine testing	54	United States; Veterans Administration	No	No statistically significant difference in mean fasting plasma glucose, HbA <sub>1c</sub> , weight
Estey et al, <sup>31</sup> 1990	RCT	SMBG vs SMBG with education/compliance	60	Canada	No	More SMBG in education group but no statistically significant difference in HbA <sub>1c</sub>
Rutten et al, <sup>32</sup> 1990	RCT	SMBG vs no SMBG	129	The Netherlands	Yes	Significant HbA <sub>1c</sub> improvement of 0.4% vs increase of 0.5% in no SMBG group; included decision tree of results
Muchmore et al, <sup>33</sup> 1994	RCT	SMBG + carbohydrate counting vs none	23	United States; body mass index ≥27.5	Yes	Significant improvement in HbA <sub>1c</sub>
Jaber et al, <sup>34</sup> 1996	RCT	Pharmaceutical care (with SMBG) vs none	39	United States; African American	Yes	Significant improvement in HbA <sub>1c</sub> and fasting plasma glucose
Schwedes et al, <sup>35</sup> 2002	RCT	SMBG vs no SMBG	223	Germany and Austria	Yes	Significant improvement of HbA <sub>1c</sub>
Guerci et al, <sup>36</sup> 2003	RCT	SMBG vs no SMBG	689	France	Yes	Significant improvement of HbA <sub>1c</sub>
Davidson et al, <sup>37</sup> 2005	RCT	SMBG vs no SMBG	88	United States; predominantly Latino, low socioeconomic status	No	No statistically significant difference in HbA <sub>1c</sub>
<b>Type 2 diabetes</b>						
Faas et al, <sup>38</sup> 1997	Literature review	SMBG vs urine testing; SMBG vs no SMBG	617 (6 RCTs)	Type 2 diabetes; insulin-, and non-insulin-treated	No	No statistically significant difference in HbA <sub>1c</sub>
Coster et al, <sup>39</sup> 2000	Meta-analysis of RCTs	Monitoring (blood or urine) vs no monitoring	285 (4 RCTs)	Type 2 diabetes; insulin-, and non-insulin-treated	No	Nonsignificant improvement of HbA <sub>1c</sub> by 0.25%
Sarol et al, <sup>40</sup> 2005	Meta-analysis of RCTs	SMBG vs no SMBG	1307 (8 RCTs)	Type 2 diabetes, non-insulin-treated	Yes	Significant HbA <sub>1c</sub> improvement of 0.39%
Welschen et al, <sup>41</sup> 2005	Literature review	SMBG vs no SMBG	1159 (5 RCTs)	Type 2 diabetes, non-insulin-treated	Yes	Significant HbA <sub>1c</sub> improvement of 0.39%

Abbreviations: HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; 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.<sup>44-46</sup> Four Veterans Administration studies, however, each reported no benefit to SMBG,<sup>47-50</sup> although 6 of the 10 other retrospective or cross-sectional studies<sup>23,44-46,51-56</sup> did show benefit. A large cohort study of a managed care population of 24 000 patients found SMBG improved HbA<sub>1c</sub> by up to 1%.<sup>23</sup> A Canadian cross-sectional study found patients who were insured for SMBG had significantly lower HbA<sub>1c</sub> levels than those without coverage,<sup>52</sup> and a study of 115 patients found that HbA<sub>1c</sub> was not affected by simply prescribing SMBG.<sup>53</sup>

Tapping National Health and Nutrition Examination Survey (NHANES) data cross-sectionally, Harris found more SMBG among insulin-treated people, but no relationship between frequency of HbA<sub>1c</sub> and SMBG<sup>54</sup>; Blonde et al disputed this finding.<sup>55</sup> A recent evaluation from Italy found no effect of SMBG in people with type 2 diabetes not taking insulin,<sup>56</sup> consistent with their previous emphasis on the need for an educational link to SMBG.<sup>57</sup>

RCTs have had more positive results, including all 6 of those studying more than 100 participants (Table). Kwon et al randomly assigned 110 patients to usual care or Internet-based evaluation of SMBG, finding that with rapid feedback, SMBG proved beneficial.<sup>28</sup> Guerci et al in the Auto-Surveillance Intervention Active (ASIA) trial studied patients in 265 French physicians' offices, finding small but significant benefit from SMBG.<sup>36</sup> Schwedes et al, in a German RCT of non-insulin-treated patients, found improved HbA<sub>1c</sub> with SMBG.<sup>35</sup> A recent smaller study by Davidson et al stands out as a negative RCT. It found no effect of pre- and postprandial SMBG in 89 community clinic, non-insulin-treated participants of predominantly low socioeconomic status in Los Angeles, with educators blinded to group assignment.<sup>37</sup>

Two systematic reviews and 2 meta-analyses were reviewed (Table), all of people with non-insulin-treated diabetes. Faas, in 1997, noted no signifi-

cant evidence of benefit in type 2 diabetes, but recommended more studies.<sup>38</sup> The meta-analysis by Coster et al of 285 patients also found that blood or urine monitoring had nonsignificant effect.<sup>39</sup> The 2 most recent reports, however, were positive. Sarol et al, summarized 8 RCTs of 1307 patients, and found a significant reduction in HbA<sub>1c</sub> of approximately 0.4% among patients who performed SMBG.<sup>40</sup> Welschen et al recently reviewed the literature for non-insulin-using people with diabetes, concluding that SMBG does have a favorable effect on HbA<sub>1c</sub>,<sup>41</sup> although in a counterpoint, Davidson disputed the conclusion.<sup>26</sup>

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.<sup>1</sup> 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.<sup>58</sup> 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).<sup>58</sup>

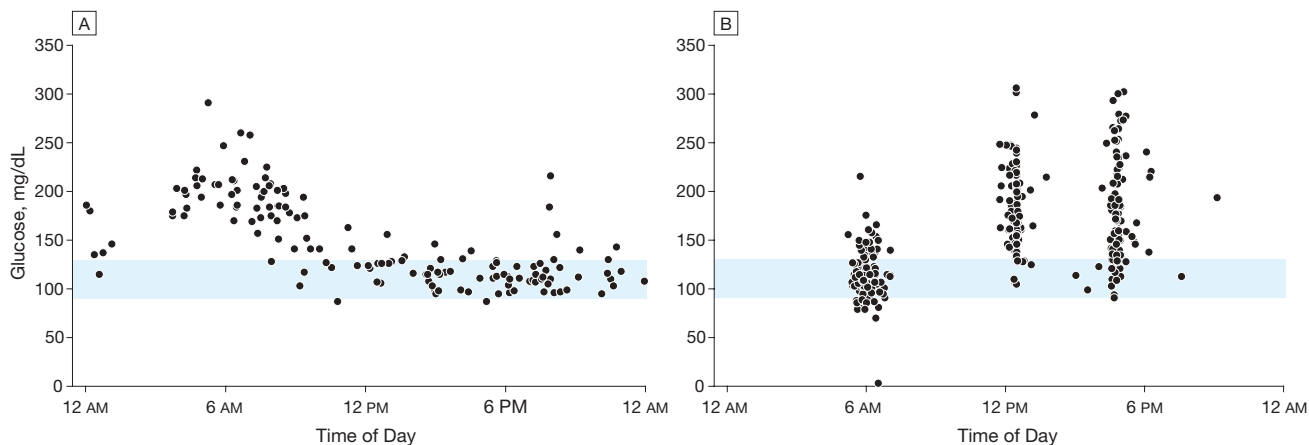
The optimal timing of SMBG testing also remains controversial. Monnier et al have made the most detailed analyses of this issue.<sup>59,60</sup> They found that the "extended post-lunch" (5 PM) values predicted HbA<sub>1c</sub> less than 7% with better sensitivity and specificity than did fasting glucose. 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 HbA<sub>1c</sub> after controlling for mean glycemia.<sup>61</sup>

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 diabetes<sup>62</sup> and women with gestational diabetes.<sup>63</sup>

Epidemiologic studies suggest that postprandial hyperglycemia is more predictive of adverse cardiovascular outcomes,<sup>64,65</sup> but these effects are relatively small and the data are drawn mainly from populations with mild diabetes or even HbA<sub>1c</sub> 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 HbA<sub>1c</sub>. In other words, if preprandial SMBG and HbA<sub>1c</sub> values are in a good range, there is little evidence to recommend testing after a meal.

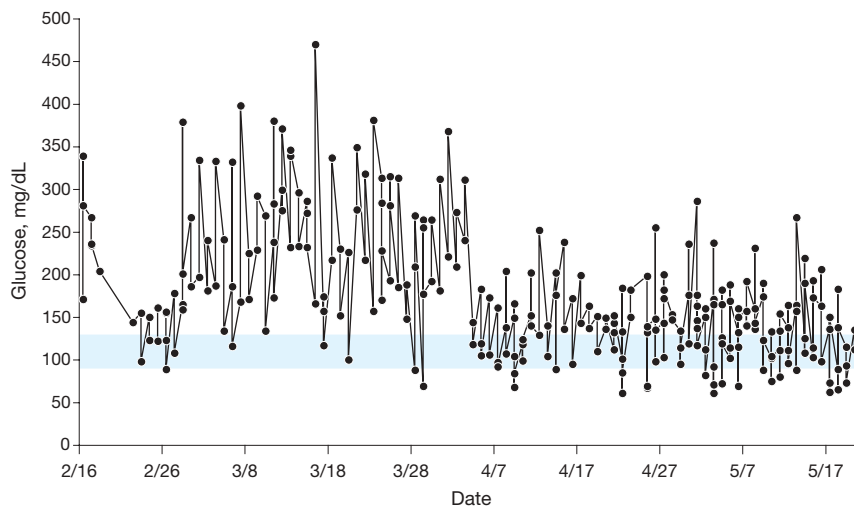
A consensus panel concluded that evidence is not adequate to support routine postprandial blood glucose testing.<sup>66</sup> Uncertainty about exact timing postprandially and exact meal content were cited. Our practice is to rely

**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 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.

on fasting, preprandial, and bedtime SMBG unless there is a special circumstance such as an unexplained discrepancy between HbA<sub>1c</sub> and SMBG results, pregnancy, or mild glucose intolerance. Also, given the potential seriousness of nocturnal hypoglycemia,<sup>67</sup> 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 insulinope-

nic very rapidly and ketoacidosis can develop quickly.<sup>68</sup>

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.

At present, there are several CGM products on the market and more are under development.<sup>69</sup> These monitors measure glucose concentration in subcutaneous interstitial fluid, which can reflect changes in blood glucose concentrations reasonably quickly.<sup>70,71</sup> Recent reports describe the use of CGM in clinical and research settings,<sup>72-74</sup> but the monitors are not easily used on a routine, clinical, long-term basis. Spectroscopy-based<sup>75</sup> and fluorescence-based sensors,<sup>76</sup> which could be entirely non-invasive, have been slow to develop.

The ultimate goal of CGM is to drive a closed-loop insulin delivery system, the "artificial pancreas."<sup>77</sup> This goal, in early stages of development, depends on the sensors being robust, accurate, and easy to use.<sup>69</sup>

### Hemoglobin A<sub>1c</sub>

In the late 1960s, a minor component of human hemoglobin A was noted to be increased in patients with diabetes.<sup>78</sup> By the mid-1970s, HbA<sub>1c</sub> was shown to decrease as glycemic control improved, and thus, the potential of HbA<sub>1c</sub> as a clinical and research tool was recognized.<sup>79</sup> Over the last 25 years, HbA<sub>1c</sub> testing has come into common use, serving as a convenient method for evaluating average glycemia over the previous several months.

HbA<sub>1c</sub> is defined as the stable adduct of glucose at the N-terminal amino group of the β-chain of hemoglobin A<sub>o</sub> (N-[1-deoxyfructosyl]hemoglobin).<sup>80</sup> 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.<sup>81</sup> 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 HbA<sub>1c</sub>. 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).<sup>82</sup>

A direct relationship exists between HbA<sub>1c</sub> 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 HbA<sub>1c</sub> 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 HbA<sub>1c</sub> corresponded to an increase in mean plasma glucose level of approximately 35 mg/dL (2 mmol/L).<sup>83</sup> One caveat in interpreting the linearity of this relationship is that HbA<sub>1c</sub> does not reflect blood glucose levels equally over the previous 120 days. Rather, recent changes in glycemic control are overrepresented in HbA<sub>1c</sub>. About 50% of HbA<sub>1c</sub> 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.<sup>84</sup>

**Standardization and Confounders.** Comparing study results and setting HbA<sub>1c</sub> 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 non-fasting state do not affect HbA<sub>1c</sub> test results, confounding conditions do ex-

ist. Hemoglobin variants commonly and unpredictably interfere with HbA<sub>1c</sub> measurements. Hemoglobin S or C carriers may have spuriously high or low HbA<sub>1c</sub> results measured by ion-exchange high-performance liquid chromatography due to coelution of the variant with either HbA<sub>1c</sub> or HbA, and results may be affected when using other methods as well.<sup>85</sup> With more than 700 hemoglobin variants reported, most clinically silent, unsuspected errors in HbA<sub>1c</sub> 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.<sup>86,87</sup> A hemoglobin variant should be suspected if the HbA<sub>1c</sub> 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 HbA<sub>1c</sub> may be more reliable. Bry et al have reviewed this topic<sup>88</sup> as has the NGSP Web site.

Many conditions also exist that alter HbA<sub>1c</sub> levels independent of the assay method. Any process that shortens erythrocyte lifespan decreases HbA<sub>1c</sub>, since glycation increases with age of the red cell. Kidney disease, liver disease, hemolytic anemia, hemoglobinopathies, and recovery from blood loss will all decrease HbA<sub>1c</sub> on this basis. Vitamins C and E have been reported to lower HbA<sub>1c</sub> measurements, possibly by inhibiting glycation.<sup>89,90</sup> Lower HbA<sub>1c</sub> 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 HbA<sub>1c</sub> in pregnancy.<sup>91</sup>

Iron-deficiency anemia, on the other hand, has been associated with increased HbA<sub>1c</sub>.<sup>92</sup> Any process that slows erythropoiesis, such as aplastic anemia, will increase HbA<sub>1c</sub> by causing an older erythrocyte cohort.

We studied whether glycemic lability, independent of mean glycemia, af-

fects HbA<sub>1c</sub>. Analyzing the SD of blood glucose in patients performing frequent SMBG, we found that after controlling for mean glycemia, HbA<sub>1c</sub> is not affected by glycemic lability.<sup>93</sup> Another report reached a similar conclusion on glycemia after lunch.<sup>62</sup>

#### Clinical Utility and Controversies.

The measurement of HbA<sub>1c</sub> 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 HbA<sub>1c</sub> 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 neuropathy.<sup>1</sup> 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 HbA<sub>1c</sub> achieved in the intensively treated group.<sup>3</sup>

Surprisingly, the relatively short period of intensive control imposed in the Diabetes Control and Complications Trial has now been shown to have long-lasting beneficial effects years after the HbA<sub>1c</sub> levels of the groups merge.<sup>94,95</sup> HbA<sub>1c</sub> is also the accepted measure of long-term glycemia in the Framingham<sup>65</sup> prospective cohort study and the long-term follow-up study to the Diabetes Control and Complications Trial,<sup>96</sup> both of which have found a lower risk for macrovascular complications with improved glycemia.

While abundant evidence demonstrates that improved HbA<sub>1c</sub> reduces the risk of complications, it is not clear whether regular assessment of HbA<sub>1c</sub> 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 HbA<sub>1c</sub> results were more successful in lowering future HbA<sub>1c</sub> results than those based only on blood or urine glucose testing.<sup>97</sup>

An outside analysis of the Diabetes Control and Complications Trial raised the theory that there are "fast glycaters" who, independent of glycemia alone, may be at greater risk of diabetic complications.<sup>98,99</sup> This theory is disputed,<sup>100,101</sup> however, and most evidence supports the conclusion that HbA<sub>1c</sub> correlates with complication risk because it reflects glycemia, not because it causes complications directly.

Recently, NGSP-certified rapid HbA<sub>1c</sub> assays have become available, allowing office and home testing. Point-of-care HbA<sub>1c</sub> 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 HbA<sub>1c</sub> testing may be superior to central laboratory testing in decreasing HbA<sub>1c</sub> levels in type 1 and type 2 diabetes.<sup>102,103</sup> 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 HbA<sub>1c</sub> testing.

In addition to HbA<sub>1c</sub>, 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 HbA<sub>1c</sub>. 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 HbA<sub>1c</sub> than fructosamine.<sup>104</sup> Even as an adjunct to home blood glucose monitoring, weekly fructosamine testing did not improve HbA<sub>1c</sub> levels.<sup>105</sup>

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 HbA<sub>1c</sub> was seen.<sup>106</sup> 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 HbA<sub>1c</sub> values among treatment groups.<sup>107</sup> 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.<sup>108</sup> Furthermore, the risk of hypoglycemia increases with lower HbA<sub>1c</sub>, at least in type 1 diabetes<sup>8</sup> (less clearly for type 2 diabetes<sup>109,110</sup>). Therefore, determining a glycemic target involves considering the individual risk-benefit ratio; there is no scientific basis for choosing a single, universal target HbA<sub>1c</sub>.

The ADA currently recommends that patients with type 1 and 2 diabetes achieve HbA<sub>1c</sub> levels less than 7%,<sup>58</sup> a level that confers a low risk of complications (eg, 9-year progression of rate of retinopathy <4%<sup>111</sup>). In some circumstances, such as elderly patients or those prone to hypoglycemia unawareness, target HbA<sub>1c</sub> should be adjusted upward, and some people with diabetes can achieve HbA<sub>1c</sub> of 6.5% or less. Studies to determine the ideal frequency of HbA<sub>1c</sub> 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.<sup>58</sup>

It remains controversial whether HbA<sub>1c</sub> 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<sup>112</sup> 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 HbA<sub>1c</sub> results 2 SDs above the mean (>6.1%).<sup>113</sup> At present, however, HbA<sub>1c</sub> testing is not accepted for screening or diagnostic purposes.<sup>58</sup>

**The Future of HbA<sub>1c</sub>.** The International Federation of Clinical Chemistry has developed a new, more specific reference method for measuring glycated hemoglobin.<sup>114</sup> Using mass spectroscopy and capillary electrophoresis, this method assays 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.<sup>115</sup> 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.<sup>115</sup>

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 HbA<sub>1c</sub> reference range could cause confusion for professionals and the public alike, given the decades-long effort to educate people about the importance of measuring HbA<sub>1c</sub> and the goal of maintaining HbA<sub>1c</sub> at less than 7%. One study found that simply modifying HbA<sub>1c</sub> reference ranges caused a deterioration in

glycemic control in patients.<sup>116</sup> 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 HbA<sub>1c</sub> 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 HbA<sub>1c</sub>.<sup>117</sup>

## 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 HbA<sub>1c</sub>, 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. HbA<sub>1c</sub>, 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.

**Author Contributions:** Dr Saudek had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Saudek, Derr, Kalyani.

**Acquisition of data:** Saudek, Kalyani.

**Analysis and interpretation of data:** Saudek, Derr, Kalyani.

**Drafting of the manuscript:** Saudek, Derr, Kalyani.

**Critical revision of the manuscript for important intellectual content:** Saudek, Derr, Kalyani.

**Obtained funding:** Saudek.

**Administrative, technical, or material support:** Saudek, Derr, Kalyani.

**Study supervision:** Saudek.

**Financial Disclosures:** Dr Saudek has delivered lectures sponsored by Lifescan Inc; has accepted insulin pumps for implanted insulin pump research from Medtronic MiniMed; and has received research support from DexCom Inc for studies of an implanted continuous glucose sensor. No products manufactured by the aforementioned companies were mentioned in this article. Drs Derr and Kalyani reported no financial disclosures.

**Funding/Support:** None disclosed.

**Role of the Sponsor:** The sponsor had no role in the design, conduct, or preparation of this manuscript.

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