25 Monitoring Diabetes

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Keypoints

- Glycated hemoglobin (HbA_{1c}) levels will increasingly be presented using the International Federation of Clinical Chemistry standard expressed as mmol/mol of unglycated hemoglobin. The equivalent of the current HbA_{1c} levels of 6.5% and 7.5% are 48 mmol/mol and 59 mmol/mol.
- For patients with type 1 diabetes (T1DM), blood glucose control should be monitored with measurement of HbA_{1c} every 2–6 months depending on the level and stability of blood glucose control and change in therapy.
- Patients with T1DM should be encouraged to self-monitor blood glucose with capillary blood glucose meters. With treatment regimens intended to produce intensive glycemic control testing should be frequent (e.g. four or more times a day).
- For patients with type 2 diabetes (T2DM), blood glucose control should be monitored using high precision methods for measurement of HbA_{1c} every 2–6 months depending on the level and stability of blood glucose control and change in therapy.
- For non-insulin-treated patients with T2DM, self-monitoring of blood glucose is unlikely to be cost-effective for well-controlled patients and should therefore only be used when training and support is available and a clear purpose for use identified.

Why monitor?

> "*The overall goal of diabetes management is to achieve as near normal physiological or ideal values as possible, without detriment to quality of life and, for glucose control in particular, without causing significant hypoglycemia*" [1].

Diabetes is a disorder of glucose homeostasis. It currently affects 285 million people worldwide and is expected to affect 435 million by 2039 [2]. For people without diabetes, glucose levels are maintained in the range of 4–6 mmol/L (80–110 mg/dL). When blood glucose levels increase as a result of glycogen conversion or eating carbohydrate-containing food, insulin is released restoring homeostasis through hepatic conversion of glucose to glycogen, and uptake of glucose into muscle and fat cells. Conversely, if blood glucose levels fall too low as a result of exercise or lack of food, glucagon is released causing hepatic conversion of glycogen to glucose.

People with type 1 diabetes mellitus (T1DM) lack the normal homeostatic mechanism to control levels of blood glucose, while people with type 2 diabetes mellitus (T2DM) have an impaired or absent response. In addition to insulin, which is the most important of the regulatory mechanisms, growth hormone, thyroxine and catecholamines are also important counter-regulatory hormones and lead to increases in blood glucose levels. The aim of monitoring glycemic control is to diagnose the nature of any impairment of homeostatic mechanisms, allow patients to understand the nature of their disorder, determine optimum times for initiating therapeutic intervention; and guide the day-to-day adjustment of management regimens.

Glycated hemoglobin (HbA_{1c}) and blood glucose are the two most frequently used measures of glycemia in current practice. Glycated hemoglobin provides information about overall control of glucose levels in the previous 6–8 weeks allowing assessment of the need for therapy and therapeutic response with minimal within-person variation in measurement. Blood glucose concentrations provide information about the day-to-day level of control, variation in control and response to therapeutic intervention. Measurement and interpretation of blood glucose, however, may be difficult because of potentially wide within-person variations in measures other than when fasting. Prospective observational and intervention studies have confirmed that HbA_{1c} levels are related to long-term disease outcomes [3,4]. Both HbA_{1c} and blood glucose therefore, along with a number of other tests, including measurement of urinary glucose for those who do not intend to aim for intensive glucose control, remain an option for helping to identify poor glycemic control and to facilitate the adjustment of therapy to achieve optimal glucose levels.

Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

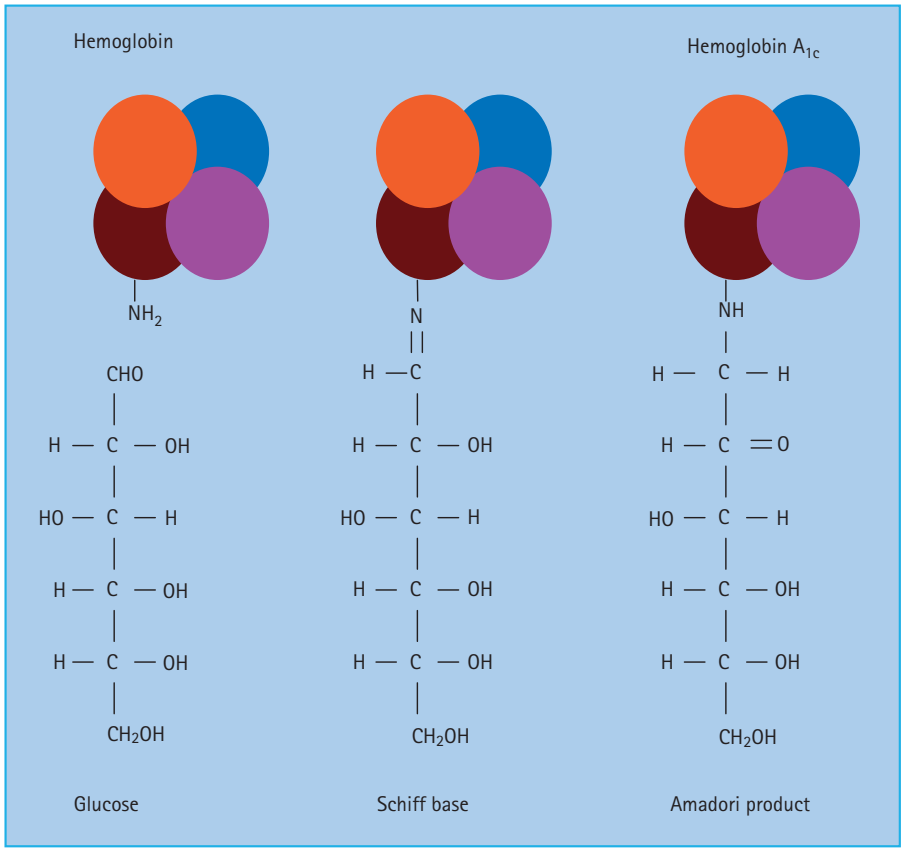

Figure 25.1 The Amadori reaction.

Tests and their characteristics

Glycated hemoglobin

Quality controlled HbA_{1c} measurement has a central role in the management of diabetes. Its pivotal role derives from its use in reports of the major outcome studies [5,6]; HbA_{1c} levels can be directly related to the risk of development of diabetic complications. Major national guidelines address this area and make recommendations about its use [5,7].

Hemoglobin reacts spontaneously with glucose to form glycated derivatives in a non-enzymatic manner. The process occurs slowly, with the extent of glycation determined by the concentration of glucose in blood. Human hemoglobin A undergoes such glycation to form HbA_{1c} from a reaction between the β-chain of hemoglobin A0 and glucose (Figure 25.1). Other compounds result from similar reactions on the α and β chains of hemoglobin and these can be measured as the total glycated hemoglobin.

Until the measurement of different glycated derivatives in the late 1990s, the difficulties of obtaining a common reference standard and the costs of the test made comparisons between laboratories difficult and availability limited. Many of these problems have been overcome, and the most common measured component, HbA_{1c}, is now widely accepted as a standard measurement of glycemic control.

Glycated hemoglobin can be affected by the presence of hemoglobin variants and uremia, but specific assays (e.g. high performance liquid chromatography rather than immunochemistry or affinity chromatography methods) can be used to obtain an accurate result. Vitamin C, hemolytic and iron deficiency anemia can also give abnormal results. Laboratories still differ in whether a result from a heterozygous patient with variant hemoglobin is reported as non-comparable to the Diabetes Control and Complications Trial/UK Prospective Diabetes Study (DCCT/UKPDS) standard, or whether it is not reported at all. Other conditions in which there is a rapid turnover of erythrocytes (e.g. polycythemia, anemia or blood transfusion) can also give inaccurate results (Table 25.1).

Table 25.1 Conditions that can affect the measurement of glycated hemoglobin.

Iron deficiency anemia
Hemoglobinopathies
Polycythemia
Blood transfusion
Hemolysis (hemolytic anemia)
Uremia caused by renal failure
High levels of vitamin C

Glycated hemoglobin serves as a retrospective indicator of the average glucose concentration over the previous 6–8 weeks. Approximately 50% of the variance in HbA_{1c} is determined by

the average blood glucose concentration over the previous month, 25% by the concentration over 30–60 days, and the remaining 25% by the concentration from 60 to 120 days.

Alignment of assays for HbA_{1c}

New International Federation of Clinical Chemistry standard

Soon after glycated hemoglobin measurements were adopted into routine use, it became clear that there were significant differences between results from differing laboratories. The differences arose because of the range of assays used and lack of agreement over a common reference standard. With the publication of DCCT [5] in 1993 a number of countries developed national programs to standardize measurement, which included external quality assurance schemes to ensure that measurements between laboratories could be compared [8]. With the development of more advanced assays it became possible to propose a new reference method based on assaying a specific component of HbA_{1c} (the β-N-terminal hexapeptide).

Despite these efforts to standardize HbA_{1c} there are over 30 different methods in use for measurement. Manufacturers provide calibration factors for individual machines, and there is a global network of laboratories that maintain and monitor the relationship between the different standards.

The new reference standard, agreed by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) was not initially viewed with enthusiasm because it would have lowered the reference range of HbA_{1c} by 1.5–2.0 percentage points, thus leading to confusion among both clinicians and patients and a potential deterioration in population glycemic control. A shift to the new reporting strategies, however, offers the opportunity for a global agreement about the requirements for manufacturers to supply equipment that can be standardized.

In Europe the new standard will be introduced to ensure laboratory and clinical practice is traceable to the IFCC reference method using units expressed as *mmol per mol* of unglycated hemoglobin. In addition, all results will be presented with both the DCCT aligned and the IFCC standard until at least June 2011. Thus, when HbA_{1c} results (DCCT aligned) are expressed as percent hemoglobin the equation deriving the relationship is:

$$\text{IFCC-HbA}_{1c}\ (\text{mmol/mol}) = [\text{DCCT-HbA}_{1c}\ (\%) - 2.15] \times 10.929$$

The conversion of integer HbA_{1c} (%) values to new units has an easy-to-remember numerical relationship known as "Kilpatrick's kludge" [9]. For example, for an HbA_{1c} of 7% subtract 2 = 5, and then subtract a further 2 = 3. Thus, a HbA_{1c} of 7% becomes 53 mmol/mol. For non-integer values the use of the formula or reference tables is required. The equivalent of the current HbA_{1c} targets of 6.5% and 7.5% are 48 mmol/mol and 59 mmol/mol in the new units (Table 25.2).

For both patients and clinicians, a shift to the new standard will reduce potential confusion between blood glucose levels and HbA_{1c} measurements. With current reference ranges it is relatively easy for confusion between a blood glucose value given in mmol/L to a value of a similar order to the HbA_{1c} (%) level but having different implications for clinical decision-making.

Table 25.2 IFCC aligned values for HbA_{1c}.

Current DCCT aligned HbA_{1c} (%)	IFCC HbA_{1c} (mmol/mol)
4.0	20
5.0	31
6.0	42
6.5	48
7.0	53
7.5	59
8.0	64
9.0	75
10.0	86

IFCC-HbA_{1c} (mmol/mol) = [DCCT-HbA_{1c} (%) − 2.15] × 10.929

Nevertheless, a considerable education initiative is needed to inform both patients and clinicians of the change.

Estimated average glucose measurements

As glycated hemoglobin levels are related to blood glucose concentrations and formulas, the American Diabetes Association (ADA) has proposed an alternative approach with the introduction of the estimated average glucose measurement (eAG).

Glycated hemoglobin provides information about the overall levels of glucose to which tissue is exposed. For a non-insulin-using patient with T2DM with regular fasting plasma glucose (FPG) levels of 6.5 mmol/L, an HbA_{1c} of around 53 mmol/mol (7%) would be expected, but prandial elevation of blood glucose makes an additional contribution to the rate of glycosylation, thus affecting individual results [10].

A large international study has recently established a strong correlation between continuous blood glucose monitoring results and HbA_{1c} ($r = 0.92$) in 507 Caucasian adults. The authors proposed a formula to derive eAG [11], and led to the recent ADA position statement recommending the use of the eAG measure [5]. Concerns about the extent to which the relationship between HbA_{1c} and eAG are generalizable, the limited information about applicability to all ethnic groups and the potential for patient confusion about the measurements have led to limited adoption outside the USA.

The extent to which eAG are related to diabetes complications is controversial. There are no long-term studies relating continuous blood glucose measurement to long-term diabetes outcomes. Instead, HbA_{1c} remains both a target of intervention in many trials, as well as a measure of success in improving glycemic control. This approach is based on the demonstrated relationships between HbA_{1c} and diabetes outcomes. There is therefore concern that the introduction of an eAG might lead patients and clinicians to place weight on measurement of blood glucose, while the assay is actually of HbA_{1c}.

Use of HbA_{1c} in the diagnosis of diabetes

Current guidance continues to recommend that the diagnosis of diabetes is based on at least two laboratory measurements of blood glucose ≥7 mmol/L or random samples of ≥11.1 mmol/L. In the event of uncertainty, an oral glucose tolerance test is pro-

posed. HbA_{1c} offers a potentially easier, non-fasting and therefore more acceptable test. Furthermore, there appears to be less intra-individual variation with HbA_{1c} than glucose testing. Previously, there were concerns that despite the variation in results of oral glucose testing within the same person, the alternative of a single HbA_{1c} test would be unsatisfactory because the threshold for screening (usually identified as 53 mmol/mol [7%]) would miss a substantial number of people with diabetes. There is also considerable potential for confusion, because current guidance for people with diabetes is to aim, if possible, for HbA_{1c} levels of 48–59 mmol/mol (6.5–7.5%) [7]. One possible alternative to simplify diagnosis is the combined measurement of fasting blood glucose and HbA_{1c}, making use of an algorithm developed from studies in which the two measurements were compared against the results of an oral glucose tolerance test [12]. There are ongoing discussions about the use of HbA_{1c} of a diagnostic test and, at the time of writing, it has been proposed that an HbA_{1c} of 48 mmol/mol (6.5%) would be diagnostic of diabetes. This test will not replace the glucose criteria as in many parts of the world HbA_{1c} is not available.

Point of care HbA_{1c}

Point of care testing for HbA_{1c} is now possible with clinic-based analyzers and may allow timely decisions on therapy changes when needed. A recent study of their use, however, carried out in a clinic setting, does not yet provide sufficient information about the benefits to justify their widespread deployment [13,14].

Measurement of fructosamine

Albumin is the main component of plasma proteins. Albumin contains free amino groups which can react non-enzymatically with glucose to form fructosamine. Measurement of fructosamine reflects glucose levels over the previous 1–3 weeks. Fructosamine measurement is not appropriate for routine use because the assay is markedly affected by excessive turnover or excretion of albumin in, for example, renal disease. In addition, fructosamine assays are not standardized in the same way as HbA_{1c} assays. Fructosamine testing remains useful in a number of circumstances, for example in pregnancy where glucose requirements change rapidly, or in the preconception period where motivation to improve control is high and the changes can be evaluated at shorter intervals. With the lower cost and increased standardization of HbA_{1c}, however, it is possible that more frequent measurements of HbA_{1c} may be an alternative strategy, particularly if evaluating potentially large improvements in the blood glucose over the preceding 4–6 weeks contributing to a clinically important change from a previous HbA_{1c} result [15].

Blood glucose

Blood glucose (or the level of glucose to which the body's organs are exposed) is expressed as the plasma glucose concentration. Blood glucose was traditionally given as whole blood values, but plasma glucose levels are now measured and reported by most laboratories. Blood samples for analysis need to be taken under controlled conditions to allow accurate measurement of glucose levels. Red blood cells may continue to metabolize glucose after collection, continuing glycolysis, and thus leading to reductions in glucose levels. This should be avoided by rapid centrifugation, collection onto ice and storage in a refrigerator. If blood is to be transported at room temperature it should be collected into fluoride-containing tubes which inhibit further glucose metabolism. If a patient has an intravenous line *in situ*, blood should be drawn from the arm opposite to the one with the line to prevent contamination of the sample from any infusion.

Blood glucose measurement is a term that is frequently used without precise definition. Measurement of glucose levels is usually carried out either on capillary or venous samples of blood. Most laboratories measure the level of glucose in plasma, which again differs from measurements made on whole blood. Table 25.3 shows the equivalent measurements from the different sites and samples taken.

Blood glucose levels are expressed in SI (Systeme International) units as millimoles/liter (mmol/L). The traditional unit for measuring blood glucose is milligrams/decilitre (mg/dL), although use of these units is now largely confined to the USA. To convert mmol/L glucose to mg/dL, multiply by 18 (Table 25.4).

Sampling and preparation of the sample affect measurement. Whole blood glucose is also affected by the concentration of protein (mainly hemoglobin) in the sample. Whole blood concentrations are therefore 12–15% lower than plasma concentra-

Table 25.3 Values for diagnosis of diabetes mellitus.

Time of measurement	Glucose concentration (mmol/L)*			
	Plasma		Whole blood	
	Venous	Capillary	Venous	Capillary
Fasting	≥7.0	≥7.0	≥6.1	≥6.1
2 h after a glucose load	≥11.1	≥12.2	≥10.0	≥11.1

* 1 mmol/L = 18 mg/dL.

Table 25.4 Correlation of HbA_{1c} with average glucose.

HbA_{1c} (%)	Mean plasma glucose	
	mg/dL	mmol/L
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

tions. Venous blood glucose levels are normally similar to arterial and capillary levels when fasting. The arterial and capillary levels most closely reflect the glucose concentrations at the organ level. After meals, venous blood will have lower glucose concentrations than arterial blood and can be as much as 10% lower.

Analytical techniques and quality assurance

A range of analytical techniques are used for the laboratory measurement of blood glucose levels. Chemical oxidation/reduction methods have a low cost for reagents and, although less specific, are still valid. Enzymatic analysis of glucose is more specific, although more expensive. The enzymatic reference method for glucose is the hexokinase/G6PDH method. The glucose oxidase methods are comparable, although the presence of reducing substances may cause error. Glucose oxidase methods are frequently used because of their convenience and lower cost. Measurements are accurate and precise with measurement coefficient of variance of around 2%. Self-measurement of blood glucose is possible using capillary blood glucose meters with test strip systems. Specific issues associated with their use are considered in the next section.

Capillary blood glucose meters use test strips that release gluconic acid and hydrogen peroxide from a blood sample. The reaction is quantified by one of a range of methods to measure blood glucose. Most of the currently marketed handheld capillary blood glucose meters give results as an equivalent to venous plasma glucose but this is not always the case. The same type of handheld meter may be calibrated to report whole blood glucose in one country and plasma values in another. Until this issue is resolved, the calibration of a meter should be checked and the thresholds for action set accordingly.

In a hospital or "site-of-care" setting, capillary blood glucose measurement can be used to replace venepuncture, with greater comfort and more rapidly available results. Standards have been laid down to ensure that bedside glucose determinations can be made accurately and include the need for well-defined policies which include adequate training, quality control procedures and regular maintenance of equipment [16]. Blood glucose meters may require entry of a number or insertion of a coding chip to ensure calibration to the batch of testing strips used.

Accuracy of blood glucose meters

Although laboratory methods of blood glucose measurement are accurate, the convenience and rapidity of capillary blood glucose meters means that, despite their higher coefficient of variance compared to laboratory testing and the possibility of user error, they are in wide use. The majority conform to international standards (www.iso.org), with 95% of readings within 0.83 mmol/L for readings <4 mmol/L and within 20% for higher glucose readings. The newer meters have minimized the possibility of user error by requirement for smaller volumes of blood for measurement and automated calibration methods. Operator error, however, remains a significant source of error, including failure to calibrate meters (some newer meters do not require external calibration), poor handwashing technique and dirty meters [17].

Measurement error can be minimized by careful training and consistent technique in making measurements, incorporating an allowance for the possibility of error in the reading when calculating insulin dose, and undertaking regular testing to identify results that do not fit the usual pattern, with retesting as necessary.

Despite their imprecision, blood glucose meters remain helpful at higher blood glucose values, where, for example, it is of less importance to distinguish a plasma glucose of 11 mmol/L from one of 14 mmol/L. In such circumstances, the aim of management is to achieve a substantial reduction in plasma glucose. At lower plasma glucose levels, however, the consequences of an imprecision of 15% are much greater. For many well-controlled patients aiming to keep their glucose levels in the range 4–6 mmol/L, the majority of readings below 4 mmol/L will result from the variance of the measurement rather than reflecting a true "low" value.

Measurement of urinary glucose

Measurement of glucose in urine has limited arguments in favor of its use for routinely monitoring diabetes. It is rapid, inexpensive, non-invasive and can provide a quantitative result, however, it does not reflect the changing levels of hyperglycemia with any accuracy and so interpretation may be difficult if not impossible. In addition, the renal threshold varies between individuals and varies during pregnancy and with aging. In any case, glucose is not excreted renally at levels where blood glucose is significantly elevated above that which should be targeted to minimize diabetic complications.

Urine fraction should be analyzed immediately, preserved at pH <5 to inhibit bacterial metabolism or stored at 4 °C. The enzyme used is glucose oxidase/peroxidase which may lead to false-positive results with hydrogen peroxide and false-negative test results with the presence of ascorbic acid.

Urine testing should no longer be used in most health care settings because of the availability of alternative and more accurate tests. For the moment it may have a role in resource-poor settings where identification and treatment of individuals with poorly controlled diabetes is the highest priority.

Monitoring in clinical practice

Glycated hemoglobin measurement is recommended to assess the maintenance of glycemic control and should be measured with high precision methods. Results should be reported in IFCC units (mmol/mol) or eAG (mmol/L or mg/dL) alongside the DCCT aligned (%) units. In general, HbA_{1c} measurements should be performed at least twice a year in patients meeting treatment targets and with stable glycemic control. An interval of 3 months between tests is usually recommended following changes in therapy or when levels are unstable, although a test after 2 months may provide some additional information [18].

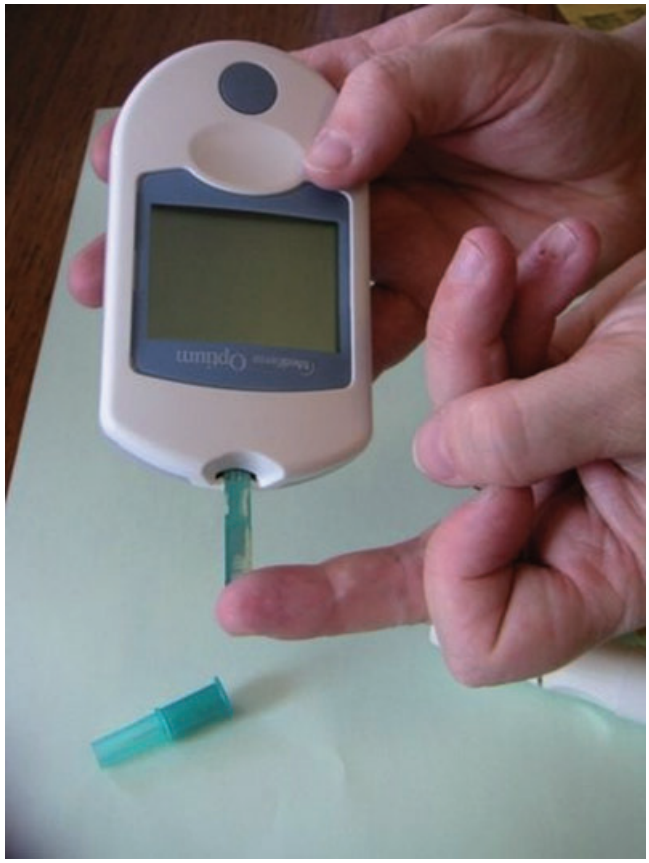

Figure 25.2 Correct technique for self-monitoring of blood glucose improves accuracy of testing.

Self-monitoring of blood glucose (SMBG) is a standard of care for patients with T1DM and necessary for insulin-treated patients with T2DM, although optimal use in this group is not established. SMBG may also be helpful for some non-insulin-treated patients with T2DM, although it is unlikely to offer benefit to well-controlled patients. SMBG requires a high level of motivation and if people using SMBG are not aware of how to interpret the results and what actions they should take, it is unlikely to be a clinically effective or cost-effective procedure. People with diabetes need to be taught how to perform the test accurately and how to use the data to adjust therapy in relation to food intake and physical activity. Correct technique involves obtaining the blood sample from the side of the finger pulp, wiping and using the second drop of hanging blood, using the meter correctly and disposing of the lancet (Figure 25.2). Alternative sites for sampling include the base of the thumb, forearm and thigh. Pre-meal readings will be the same between sites, but at times of rapid glucose change (in the post-prandial period or during hypoglycemia) forearm and thigh results will be different from the fingertip results.

Type 1 diabetes

For patients with T1DM, blood glucose control should be measured with HbA_{1c} every 2–6 months depending on the level and stability of blood glucose control and change in therapy. HbA_{1c} measurement should be provided either at site of care or carried out by the laboratory before clinical consultation. Patients should be encouraged to use SMBG using capillary blood glucose meters. With treatment regimens intended to produce intensive glycemic control, testing should be frequent (e.g. four or more times a day).

When using a typical basal bolus regimen including three injections of short-acting insulin and one or more injection of long-acting insulin, at least four time-points during the day need to be monitored, pre-breakfast, pre-lunch, pre-dinner and before bedtime. There is some evidence that tests 1 hour post meals may allow more accurate adjustment of pre-meal short-acting insulin although this needs to be offset against the greater inconvenience. Frequent glucose testing allows identification of periods during the day when plasma glucose levels are higher or lower than ideal and appropriate adjustment of the short-acting or bedtime injections. If the individual has regular routines and varies little in food intake and physical activity from day to day, then monitoring can take place at a frequency of less than four tests a day; for example, a daily fasting blood glucose with either 1 or 2 days a week with four-point sampling, or each day testing at one or more additional time-points to build a picture over the week. Until the dose of long-acting insulin has been established, a series of paired bedtime and fasting readings are needed.

Tight control brings with it the risk of hypoglycemia [4]. For some people (limited duration of life, inability to make the adjustments required for tight control) intensive control is inappropriate. Accepting less tight control allows use of less complicated regimens and less frequent monitoring.

For individuals using conventional rather than analog long-acting insulin, and with biphasic regimens more frequent monitoring may be required because of the less stable time course of the long-acting components of the insulin.

Glycated hemoglobin measurement complements blood glucose measurement by providing a check on the extent to which the glucose results are providing an accurate picture of overall blood glucose control. A schedule of blood glucose measurements indicating good control may need to be examined if an HbA_{1c} measure indicates that control is not so good. For example, timing of measurements and user technique may need reassessing.

SMBG should be carried out three or more times daily for patients using multiple insulin injections or insulin pump therapy. For patients using less frequent insulin injections, SMBG may be useful as an additional guide to the success of therapy and to support adjustment of insulin dose. In addition to measurement at defined time-points, additional checks on blood glucose levels can be made in relation to the risk of hypoglycemia, for example, before exercise or driving and in the presence of symptoms that may indicate hypoglycemia.

Glycemic targets for adults are for an HbA_{1c} of 48–59 mmol/mol (6.5–7.5%). Targets for children (aged 0–12 years) are higher because of the high risk of and vulnerability to hypoglycemia.

Adolescents and young adults are at particular risk with developmental and psychologic issues, but should nevertheless aim for control <59 mmol/mol (<7.5%).

Type 2 diabetes

For patients with T2DM, blood glucose control should be monitored using high precision methods for measurement of HbA_{1c} every 2–6 months depending on the level and stability of blood glucose control and change in therapy. HbA_{1c} measurements should be provided either at site of care or from the laboratory before clinical consultation.

Insulin-treated patients with T2DM need to make use of SMBG, particularly in the period of titration of insulin dose. For those patients using a long-acting insulin, fasting glucose readings can be used to guide incremental increases in insulin dose, with readings averaged over longer periods as the fasting glucose falls towards the target range. While fasting plasma glucose levels remain elevated, insulin dosage can be increased by up to 10%.

Although some patients report that they are able to gain motivation from regular blood glucose testing, others note their frustration when they are unable to make sense of what appears to be a random pattern of test results [19]. They report that health professionals do not appear interested in their carefully recorded results, and that this also leads them to question the value of the procedure. Many recent recommendations about the use of self-monitoring have stressed the need for self-monitoring to be accompanied by education about use of the results to promote optimal health behaviors. The extent to which understanding of test results might be improved by further support or training from health professionals is uncertain [19]. Other forms of evidence are therefore needed.

Evidence from large population-based clinical studies provides a mixed picture for the benefits of SMBG. Records from thousands of patients receiving care in the USA and Germany were examined to look at the outcomes of patients who were using SMBG compared with those who were not. Their results suggest that more frequent monitoring leads to improvements in glycemic control [20] and overall mortality [21]. Large studies of this type, however, have a high likelihood of bias. Although some statistical adjustments can be made for differences between users and non-users, there is likely to be a strong association between regular use of a blood glucose meter and take-up of other health promoting behaviors. In contrast, other studies using similar methods have identified no association between use of a blood glucose meter and improved outcomes [22]. Other research designs have therefore been used to identify an effect of SMBG.

Randomized trials provide an alternative approach to looking at the potential effectiveness of SMBG in improving outcomes for people with diabetes. Although they avoid potential bias through randomly allocating people to using or not using a meter, those people who agree to enter such a trial may not be completely typical of the wider group of people who might benefit from the intervention. Since the year 2000, there have been six randomized trials of at least 6 months' duration that compared the use of self-monitoring with no self-monitoring. These trials were summarized in a recent review. The overall identified benefit from use of self-monitoring in terms of improvement in glycemia was a decrease in HbA_{1c} of 0.2% [23]. Those trials that directly compared self-monitoring, and included state-of-the art patient education for both the SMBG user group and the non-user group, did not show a benefit [24]. These trials were also limited by including a substantial proportion of reasonably well-controlled patients. Other reviews have raised the possibility that, when used with patients who have less well-controlled diabetes, SMBG might be helpful [25]. Although most studies have focused their attention on potential benefits of SMBG, there is also the possibility of adverse outcomes. For example, two recent trials [26,27] have raised the possibility that, as the result of self-monitoring, some patients might become depressed or anxious compared to others not self-monitoring.

Most trials of self-monitoring have focused on the potential for SMBG to contribute to improved motivation and lifestyle adjustment. One recent trial has focused directly on adjustment of oral glucose-lowering medication. The study compared use of SMBG to titrate oral medication in comparison with usual care, and identified a small but significant improvement in glycemic control among patients allocated to self-testing compared with those assigned to usual care [28]. Further studies are needed to explore the extent to which there are long-term advantages of including SMBG compared to, for example, the more frequent use of HbA_{1c} measurement, as part of the management pathway for titration of glucose-lowering medication.

Some studies have also examined the costs that are associated with SMBG for non-insulin-treated patients. These studies vary in their assessment of the extent to which SMBG might be considered a cost-effective intervention. Some studies have used estimates of cost–benefit derived from selected cohort studies [29]. Other estimates of costs using more conservative estimates of SMBG efficacy and based on detailed cost data collected from clinical practice, suggest that any benefit in outcomes obtained from improved glucose control might be balanced out by the impact of a lower quality of life. Even when modeled over a long-term time horizon, use of SMBG failed to reach a conventional threshold of cost-effectiveness [27].

There are many unresolved questions about SMBG, including frequency and timing of testing, its value in new users and ongoing users, and if and how users act on the results. It is clear, however, that SMBG should only be used as part of a structured self-management program and when it serves an identified purpose in self-management.

Gestational diabetes mellitus

Women with diabetes should be advised to test fasting blood glucose levels and blood glucose levels 1 hour after every meal during pregnancy. Women should be able to adjust their insulin dose to maintain target blood glucose levels. Many oral glucose-lowering medicines are not recommended for use during preg-

nancy, particularly during the first trimester, so early training in the use of SMBG and insulin therapy is often necessary.

Monitoring diabetes in a hospital setting

Within a hospital setting, laboratory and point-of-care testing should be supported by certified quality assurance schemes. Some meters used in hospitals support quality assurance procedures by restricting access to trained personnel and transferring the results directly to the electronic patient record.

Blood glucose measurements should be available from meters situated on hospital wards. Measurement of glucose on admission to hospital is needed to identify hypoglycemia or hyperglycemia and to provide appropriate patient care. Confirmation from laboratory measurement is necessary for a proportion of these samples. Continuous monitoring may be appropriate for some patients while in hospital.

Critically ill surgical patients should have blood glucose levels maintained as close to 6.1 mmol/L as possible, and generally <7.8 mmol/L using an intravenous insulin protocol. Targets for non-surgical critically ill patients are less well defined, but some studies provide evidence for maintaining levels <7.8 mmol/L. For non-critically ill patients there is no evidence about optimum glycemic goals. Concerns about hypoglycemia mean that some institutions have concern about the safety of these goals as initial targets.

Self-management of diabetes in the hospital setting may be appropriate where adult patients are alert, able to self-manage their diabetes at home and have stable requirements for insulin. This may also provide an opportunity for providing support in learning techniques of insulin adjustment in line with carbohydrate intake.

Monitoring diabetes in a community setting

Glycated hemoglobin and SMBG testing are the two primary techniques for monitoring success in achieving glycemic goals, adjusting therapy and providing information to support lifestyle change.

Glycated hemoglobin testing

Glycated hemoglobin testing is usually carried out on a non-fasting venous sample obtained in EDTA tubes and sent to a locally accredited laboratory measured using one of the available techniques for measurement. In addition, capillary blood can be sent to the laboratory in capillary tubes or preserved as dry blood on a filter paper and sent to the laboratory, although chromatographic methods are less suitable for HbA_{1c} measurement in dry blood. Point-of-care testing systems are also available, either using an analyzer or small meters with test-strips.

HbA_{1c} provides a measure of glycemia that can be used to adjust treatment for patients with T1DM or T2DM. For patients with poorly controlled non-insulin-treated diabetes, advice about weight loss may bring about an improvement in glycemia, in the presence of some endogenous insulin secretion. Continuing poor control usually leads to initiation or increases in oral glucose-lowering medication as an appropriate further response. If these measures fail to improve glycemia, or there is concern about possible hypoglycemia, then characterizing the daily course of blood glucose in relation to food and physical activity may be appropriate.

To facilitate clinical decisions, patients are often asked to provide blood for HbA_{1c} testing before a clinic visit so that the results are available at a face-to-face consultation. Differences of 0.5% in HbA_{1c} in measurements made at the same laboratory using the same assays will indicate clinically relevant changes and provide a guide to the necessity of changes in treatment or facilitating lifestyle change.

Blood glucose testing

Blood glucose testing carried out by the patient with diabetes may enhance understanding of the impact of diabetes and treatment and adjust medication. For patients with T1DM and insulin-treated T2DM, the need to adjust insulin requires measurement, interpretation and appropriate adjustment to be carried out on a regular basis at home. Detailed records of blood glucose measurements and actions are needed to allow review by both the patient and their clinician. Blood glucose measurements are particularly helpful in situations where frequent adjustment of therapy is needed.

A single measurement of post-meal glucose used as a screening tool is likely to identify most inadequately controlled patients [10]. Blood glucose levels are usually high following meals, and thus contribute to overall blood glucose control. Some studies have been interpreted to suggest that post-prandial glucose levels correlate with development of complications better than fasting blood glucose levels (or that glycemic variability may be related to poor outcomes). Attempts to titrate oral hypoglycemic medication by taking account of post-meal measures, however, have not been successful [30].

Fasting blood glucose measurements can be used to inform management for patients with both T1DM and T2DM. Preprandial blood glucose levels are often equated with, but are not equivalent to, fasting blood glucose levels, which require an 8-hour fast. Preprandial measurements, however, may be useful for evaluating the impact of a complex insulin schedule, particularly with fast-acting analog insulin. For insulin treated patients, pre-breakfast levels, compared with the previous evening's readings, indicate the effectiveness of any long-acting insulin being taken.

For patients with non-insulin-treated T2DM, the within-person coefficient of variation of pre-fasting (pre-breakfast) blood glucose levels is low and measurements vary little from day to day. They are therefore a means of assessing day-to-day control and making adjustments to therapy or assessing the impact of lifestyle changes, although the cost-effectiveness in relation to HbA_{1c} testing has not been established. The frequency of fasting blood glucose measurement for non-insulin-treated T2DM has been suggested from once a week to once a day. The evidence for a particular frequency of testing, however, is lacking, and indi-

vidual variations (familiarity with ensuring measurement techniques, variation in lifestyle, availability of professional help in supporting patients in interpretation of measurements) will require that a judgment is made on the precise purpose of monitoring.

SMBG may provide some patients with T2DM, not requiring glucose lowering therapy, with insight about the impact of day-to-day activities on blood glucose. Evidence to support the use of SMBG in this way derives from qualitative and observational studies. Measurement of fasting glucose, if HbA_{1c} is unavailable, may be used as an alternative indicator of overall glycemic control. It is also possible that, in patients unable to achieve target HbA_{1c}, characterizing the extent of hyperglycemia 1–2 hours after a meal, aiming to reduce post-meal levels below 10 mmol/L may be a recommendation worth further evaluation.

A target capillary plasma glucose of 3.9–7.2 mmol/L is recommended on the basis of outcome studies such as UKPDS and DCCT in which HbA_{1c} was shown to predict complications. Most patients with T2DM treated with long-acting insulin also continue oral glucose-lowering medication. The recommended schedules for monitoring are derived from trials that have sought to achieve reductions in HbA_{1c} to within recommended levels [20]. The intensity of these schedules has not yet been evaluated in wider populations and those more representative of primary care populations. Fasting blood glucose levels carried out twice a week will allow the weekly or 2-weekly titration of the long-acting insulin to achieve tight control. Additional 4 or 7-point profiles may be helpful every 3–4 weeks to identify patterns of blood glucose control that require further attention, for example, to address the possibility of hypoglycemia or to identify high levels of post-prandial glucose that may require the use of pre-meal short-acting insulin.

Continuous blood glucose measurement

The need to provide more frequent SMBG measurements to document glucose excursions and guide insulin therapy has led to the development of innovative technologies that can provide nearly 300 measurements a day. Detailed data on the magnitude and duration of glucose fluctuations can be used to guide lifestyle and drug therapy in an attempt to produce a near-physiologic control of glucose levels.

There are a number of different systems currently available. All require calibration using capillary blood glucose measurement and utilize a subcutaneously implanted sensor that can remain *in situ* for up to 7 days. All the continuous glucose monitoring systems (CGMS) are intended for intermittent use in order to identify periods of hyperglycemia that can be corrected by changing therapy (e.g. increasing the dose of insulin or changing timing of injections), or detecting periods of biochemical hypoglycemia that may be too brief to cause symptoms but may nevertheless cause some impairment in cognitive function.

Evidence for effectiveness of CGMS in selected patients aged over 25 years with T1DM using intensive insulin therapy comes from a randomized trial with 322 people with T1DM in which those allocated to the CGMS arm experienced a 0.5% (6 mmol/mol) reduction in HbA_{1c} from 7.6 to 7.1% (60 to 54 mmol/mol) compared to conventional therapy [31]. Evidence for HbA_{1c} lowering is less strong in children, teens and younger adults, although there may be specific clinical circumstances in which CGMS might be helpful. Success correlates with adherence to the ongoing use of the device.

Use of CGMS has also been evaluated for pregnant women with diabetes treated with insulin. In a randomized trial those women randomized to continuous glucose monitoring had lower mean HbA_{1c} levels from 32 to 36 weeks' gestation compared with women randomized to standard antenatal care. The authors concluded that continuous glucose monitoring during pregnancy is associated with improved glycemic control in the third trimester, lower birth weight and reduced risk of macrosomia [32].

CGMS is now being used as a research tool among patients with T2DM, but the extent to which the procedure is useful to the patient or to the clinician remains unclear and its use cannot be recommended in routine clinical practice. Advocates of the procedure suggest that it might be useful as a means of helping patients to recognize aspects of their lifestyle that lead to hyperglycemia [33].

Resource-poor settings

Costs of SMBG using test meters remain high in relative terms, and testing with this equipment may not be appropriate in a resource-poor setting. Particularly for patients with T1DM, there is an urgent need for lower cost test strips, although a requirement for rigorous quality control procedures to maintain accuracy limits the potential for lower cost equipment.

Urine glucose testing remains a viable alternative to blood testing or HbA_{1c} measurement for patients in a country where health care resources are limited, or in a health care setting where costs of testing equipment are borne directly by the patient. There are few data on self-monitoring using urine glucose testing. A meta-analysis from 2005 [34] included two studies that compared SMBG and self-monitoring of urine glucose and reported a non-significant reduction in HbA_{1c} of 2 mmol/mol (0.17%) in favor of SMBG. Many patients, however, do not find the procedure acceptable or helpful [35]. Measurement of urine glucose should therefore not be seen as a substitute for SMBG, but can be used as an alternative where SMBG is not accessible, affordable or desired. Interpretation of information needs to be focused on the period between last voiding and the production of the current urine specimen. Most people have a renal threshold for glucose of around 8 mmol/L, so information about glucose levels is limited below this threshold. The renal threshold can drop during pregnancy, and so glycosuria is more likely in this situation.

The future

Current research is focusing on a number of non-invasive methods to enable continuous monitoring. Methods being con-

sidered include using infrared, electric currents and ultrasound. Currently available continuous monitoring systems require calibration, but are then able to record blood glucose levels at 5-minute intervals for up to 72 hours. Efforts are currently being made to develop integrated systems with glucose meters and insulin pumps. Computerized algorithms for controlling insulin pumps on the basis of blood glucose levels have been developed and have already been evaluated in the setting of intensive care. Mobile phones have also been linked to blood glucose meters to allow easy review of charted data, real-time feedback of support and integration of data with medical records [36].

Conclusions

Glycemic control should be monitored regularly for all patients with diabetes. The optimal method of determining risk of long-term complications is through HbA_{1c} measurement, although if this is not available, then examination of a series of blood glucose measurements, including fasting tests, may provide some guidance. Management of therapy depends on the clinical setting and the type and stage of the patient's diabetes. Patients with non-insulin-treated diabetes have little scope for adjusting therapy on the basis of routine SMBG measurements, although some individuals may benefit from exploring the extent of glycemic variability, self-titration of glucose-lowering medication or checking whether symptoms are related to low-blood glucose readings. For adult patients with T1DM and pregnant women treated with insulin, the evidence for active and regular blood glucose testing (including use of continuous glucose monitoring) to achieve intensive blood glucose control through adjustment of insulin dose in relation to lifestyle is strong. There is also good evidence for the routine use of SMBG for insulin-treated patients with T2DM. Rigorous trials of SMBG in well-controlled non-insulin-treated patients do not demonstrate a clinically important effect. Until further studies suggest settings or groups of patients where SMBG is likely to contribute to the impact of an educational intervention, it should be used only in circumstances where the information obtained through testing can be used to adjust treatment actively, enhance understanding of diabetes and assess the effectiveness of the management plan on glycemic control.

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