Measurements of glycemic control in diabetes mellitus

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INTRODUCTION

Diabetes is defined by elevated levels of glycemia (glucose and glycated hemoglobin), and controlling glycemia is an integral component of the management of diabetes. Measurements of instantaneous glucose levels (self-monitoring of blood glucose [with fingersticks and a glucose meter] and real-time continuous glucose monitoring [CGM]) are used to manage diabetes from hour to hour and from day to day, to aid in dose selection in insulin-treated patients, and for safety. Measures of chronic glycemia (eg, glycated hemoglobin or CGM-derived mean glucose, time-in-range, and glucose management indicator [GMI]) are used to determine the overall efficacy of diabetes management with the aim of reducing risk for long-term complications.

Glycated hemoglobin (A1C, hemoglobin A1C, HbA1c), which reflects average levels of blood glucose over the previous two to three months, is the most widely used test to monitor chronic glycemic control. It is used to diagnose diabetes and to monitor the efficacy of treatment. Other blood tests (eg, fructosamine, glycated albumin) that reflect average glucose levels over the preceding two to three weeks are sometimes used. There is also increasing use of CGM systems as a complement to A1C in some patients, particularly those with type 1 diabetes.

Biochemical tests and CGM metrics to estimate chronic glycemia will be reviewed here. Self-monitoring and continuous monitoring of glucose for the daily management of diabetes and the relationship between glycemic control and vascular complications are reviewed in more detail separately. (See "Glucose monitoring in the management of nonpregnant adults with diabetes mellitus" and "Glycemic control and vascular complications in type 1 diabetes mellitus" and "Glycemic control and vascular complications in type 2 diabetes mellitus".)

MEASURES OF CHRONIC GLYCEMIA

Glycated hemoglobin (A1C) — Glycated hemoglobin (A1C, hemoglobin A1C, HbA1c) is the most widely used clinical test to estimate mean blood glucose. It is used to diagnose diabetes and to monitor the efficacy of treatment (see "Clinical presentation, diagnosis, and initial evaluation of diabetes mellitus in adults", section on 'Diagnostic tests'). A1C was the measurement studied in clinical trials demonstrating the benefits of improved glycemic control on microvascular and macrovascular outcomes (figure 1 and figure 2) [1-3]. Based on US Food and Drug Administration (FDA) requirements, it is the primary endpoint for the demonstration of glycemia-lowering efficacy for new diabetes drugs.

Hemoglobin formed in new red blood cells enters the circulation with minimal glucose attached. However, red cells are freely permeable to glucose. A transient elevation in blood glucose concentration can lead to the non-enzymatic formation of aldimines (glucose bound to available amino groups, so-called Schiff bases, on internal lysines and N-terminal valines), which are proportional to the glucose concentration. This reaction reverses if the concentration returns to normal. However, the subsequent formation of ketoamines is irreversible, and glucose remains permanently attached to the protein over the course of its lifespan. When hemoglobin is glycated, the degree of glycation, specifically, the percentage of hemoglobin with glucose attached (A1C), reflects the average glucose exposure integrated over the half-life of hemoglobin in the red blood cell, which is approximately 60 days. The large majority of commercially available assays of glycated hemoglobin only measure the stable ketoamine and do not measure the labile (aldimine) fraction. Although the A1C reflects mean blood glucose over the entire approximate 120-day lifespan of the red blood cell, it correlates best with mean blood glucose over the previous 8 to 12 weeks. It is relatively unaffected by recent acute fluctuations in glucose levels.

Correlation with mean glucose — The strong positive correlation between mean blood glucose and A1C has been demonstrated in several studies that have calculated average glucose on the basis of frequently measured glucose levels, typically obtained from self-monitoring of blood glucose values (fingerstick) [4,5] or using continuous glucose monitoring (CGM) systems [4,6-11]. As examples:

- The Diabetes Control and Complications Trial (DCCT) estimated the mean blood glucose concentrations derived from seven measurements a day (before and 90 minutes after each of the three major meals, and before bedtime), performed once every three months and compared the average glucose concentration with A1C values in patients with type 1 diabetes [6]. A strong, linear correlation was observed between mean glucose and A1C

values in the DCCT data [8]. This study also demonstrated that postprandial glucose concentrations contributed substantially to A1C values.

- A large, international study (A1C-Derived Average Glucose [ADAG] study) calculated average glucose levels in 507 individuals (268 type 1, 159 type 2, and 80 without diabetes), using a combination of CGM and self-monitoring of blood glucose testing, and established a reliable regression equation that can be used to translate A1C results into an estimated average glucose value [12]. (See 'Standardization of the assay' below.)

- A small study captured average glucose by CGM obtained over three months in 25 participants (adults with type 1 and type 2 diabetes and also individuals without diabetes) and compared the calculated average glucose levels with the A1C at three months [8].

- Larger studies using approximately two weeks of CGM data to calculate average glucose have also demonstrated robust correlations of mean glucose from CGM with A1C [10,11].

Standardization of the assay — The National Glycohemoglobin Standardization Program (NGSP), established by DCCT investigators, has succeeded in standardizing more than 99 percent of the assays used in the United States to the DCCT standard [13]. A strict quality control program has improved precision and accuracy of assays in the United States and globally [14].

In addition, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference system for A1C insures traceability to a higher order reference method for standardization of A1C [14]. With this reference system, A1C results are reported globally in IFCC units (mmol/mol) and derived NGSP units (the same values as reported currently as percent of total hemoglobin) using a master equation (calculator 1).

Racial/ethnic differences — Several studies have shown that A1C values are higher in some race/ethnic groups (African American, Hispanic American, Asian American) than in White American persons with similar plasma glucose concentrations [15-20]. In general, the plasma glucose concentrations in these studies have been limited [15-20], other than in one study that employed CGM [20]. The differences in A1C across racial/ethnic groups are small (approximately 0.3 to 0.4 percentage-point difference in A1C) [18,20,21]. Race/ethnicity is a social construct that typically serves as a proxy for unmeasured factors in population-based studies. There are known glycemic and non-glycemic genetic factors that can influence A1C [22,23]. It is likely that genetic differences that are unequally distributed by race/ethnicity account for differences in A1C values that are independent of glycemia. (See 'Unexpected or discordant values' below.)

Importantly, the small observed differences in A1C by race/ethnicity have not been shown to significantly modify the association between A1C and cardiovascular outcomes [24], retinopathy

[25-27], or nephropathy [26]. In a cross-sectional study using the National Health and Nutrition Examination Survey (NHANES) 2005 to 2008, the prevalence of retinopathy was actually higher at a lower A1C level in African American compared with White American individuals (5.5 to 5.9 versus 6.0 to 6.4 percent) [25]. Racial/ethnic disparities in diabetes and its complications are major concerns. A focus of public health and clinical care should be to address inequities in health care access and the other social determinants of health that contribute to disparities in patient outcomes.

Point-of-care testing — Point-of-care devices are used to measure A1C in clinician's offices and clinics, using a fingerstick sample. There is concern about the analytical performance of some of these devices [28]. In one study, however, when point-of-care testing was performed as designed (by non-laboratory health care professional in the clinic), the results were comparable with laboratory-measured A1C [29].

Point-of-care testing is not recommended for diagnosis of diabetes or prediabetes, but it plays a valuable role in monitoring diabetes control in clinical settings as it can provide immediate availability of A1C results at the time of the patient visit. Immediate patient feedback at clinician visits regarding A1C values may improve glycemic control [30-32] by facilitating clinical decision-making and more efficient patient-provider communication [33]. Alternatively, although less convenient, patients may have blood samples obtained several days before a visit to perform laboratory-based A1C testing so that the results are available at the time of the visit.

Unexpected or discordant values — When there is a disparity between the A1C values and blood glucose values, we rely on the glucose values. Fasting plasma glucose or an oral glucose tolerance test can be used to diagnose diabetes. To assess glycemic control for management, glucose self-monitoring with fingersticks and a glucose meter or CGM may be used. Fructosamine or glycated albumin may be useful alternatives. (See 'Other biomarkers' below and "Clinical presentation, diagnosis, and initial evaluation of diabetes mellitus in adults", section on 'Diagnostic tests'.)

When A1C values are unexpected or discordant with other information (especially glucose measurements), the following factors should be considered:

- **Red cell turnover** – Falsely high A1C values in relation to a mean blood glucose values can be obtained when red cell turnover is low, resulting in a disproportionate number of older red cells. This can occur in patients with vitamin B12 or folate deficiency anemia. On the other hand, rapid red cell turnover leads to a greater proportion of younger red cells and falsely low A1C values. Examples include patients with chronic hemolysis (eg, thalassemia,

glucose-6-phosphate dehydrogenase deficiency); patients treated for iron, vitamin B12, or folate deficiency; and patients treated with erythropoietin [34-37].

- **Hemoglobin variants** – Depending upon the methodology, A1C can be altered (high or low) in patients with hemoglobin variants [14,38]. However, most modern methods for measuring A1C are no longer affected by the most common hemoglobin variants. The NGSP website contains comprehensive information on hemoglobin variant interference [14]. (See "Interactive diabetes case 8: Discordant values for A1C and home blood glucose values".)

- **Chronic kidney disease** – A1C values may be altered in the setting of chronic kidney disease. Most of the inaccuracy in the relationship between A1C and mean blood glucose occurs in the setting of advanced chronic kidney disease, hemodialysis, and erythropoietin treatment [39]. Decreases in measured A1C may occur with hemodialysis and altered red cell turnover, especially in the setting of erythropoietin treatment. (See "Management of hyperglycemia in patients with type 2 diabetes and advanced chronic kidney disease or end-stage kidney disease", section on 'Monitoring glycemia'.)

For patients who conduct self-monitoring of blood glucose and/or use CGM systems, it is useful to compare the average of the testing for the previous month, and ideally for the previous two to three months, with the A1C value obtained at that visit. With fingersticks, the meter-calculated average glucose can be used, and with CGM, the ambulatory glucose profile provides a mean sensor glucose value (figure 3). If there are discrepancies between the A1C and the device-calculated average glucose, further exploration is required. The accuracy of meters should be confirmed by comparing results against a clinic-based or laboratory assay, and clinicians and patients need to be sure that testing strips are not out-of-date.

- If A1C is **higher** than expected based on the mean glucose results, it is possible that the patient is falsifying his or her blood glucose results or has made an effort to improve glycemic control in the period before the appointment. Another explanation is that the blood glucose concentrations between measurements, such as at the postprandial peak, are much higher than the preprandial test results that patients typically obtain. Assessment of fingerstick blood glucose levels between meals may be revealing. An alternative is short-term use of CGM to evaluate glucose patterns. In addition, it is important to exclude the factors discussed above, which can falsely elevate the A1C (eg, low red cell turnover).

- If the A1C is **lower** than expected based on the mean glucose results, it is possible that blood glucose levels are low during times when testing is not being performed (such as undetected nocturnal hypoglycemia). In some patients, the timing of fingerstick blood

glucose monitoring requires adjustment. An alternative is to use CGM to detect nocturnal hypoglycemia, hypoglycemic unawareness, and/or frequent episodes of hypoglycemia. It is important to exclude reduced red cell survival (such as hemolysis) or conditions in which a disproportionate number of red cells are young (as with recovery from anemia or erythropoietin therapy). Occasionally, a blood transfusion may explain a factitiously low A1C level. Finally, although most assays are not affected by the most frequent hemoglobinopathies, such as sickle cell trait, clinicians should check with the laboratory to ensure that the assay used is not affected.

Other biomarkers — Virtually all proteins undergo nonenzymatic glycation [40]. Fructosamine and glycated albumin are both ketoamines, and the serum concentration of these proteins can also be used to estimate glycemic control (table 1). These biomarkers can be easily measured using validated assays in the laboratory but are infrequently used for monitoring glycemic control, primarily because they reflect a relatively short (two- to three-week) period of average glycemia, there are few data linking them to outcomes in randomized clinical trials, and there is no formal guidance on their use. However, in settings where A1C measurements are unreliable or unavailable, fructosamine or glycated albumin may be useful alternatives.

- **Fructosamine** – Fructosamine is inexpensive and easy to measure in the laboratory. There is a strong positive correlation between serum fructosamine and A1C values [41-45], but there are several considerations for the clinical use of fructosamine:

  - The turnover of serum proteins are more rapid than that of hemoglobin (28 versus 120 days). Thus, serum fructosamine values reflect mean blood glucose values over a much shorter period of time (two to three weeks) as compared with A1C.

  - Serum fructosamine will be affected if the serum protein concentration is abnormal [46]. Furthermore, falsely low values in relation to mean blood glucose values will occur with rapid serum protein turnover, as occurs in patients with protein-losing enteropathy or the nephrotic syndrome.

  - Epidemiologic studies have linked fructosamine to long-term outcomes [44], but there have been few trials that have evaluated fructosamine as a clinical outcome or conducted head-to-head comparisons with A1C. There is no consensus on target ranges for glycemic control or for diagnosis of diabetes. Prior studies have shown that fructosamine values of ranging from 266 to 312 mmol/L are approximately equivalent to an A1C of 7 percent [44,45,47].

- **Glycated albumin** – Glycated albumin assays are reported as a proportion of total albumin to minimize the effects of differences in serum protein concentrations. Like fructosamine,

glycated albumin reflects short-term (two- to three-week) glycemic control. Some studies have linked glycated albumin to long-term outcomes, with associations similar to those for A1C [44,48]. Considerations in the interpretation of glycated albumin assays are similar to those for fructosamine. Prior studies have shown that glycated albumin values ranging from 16 to 22 percent are approximately equivalent to an A1C of 7 percent [44,45,48].

- **1,5-anhydroglucitol** – Measurement of serum 1,5-anhydroglucitol (1,5-AG), a naturally occurring dietary polyol, is a biomarker that provides information on glycosuria [49-51]. During euglycemia, 1,5-AG is filtered and completely reabsorbed by the kidneys; as a result, serum concentrations remain stable. However, renal reabsorption of 1,5-AG is competitively inhibited by glucose. Within 24 hours of a rise in serum glucose to >180 mg/dL (10 mmol/L, the renal threshold for glucose excretion), serum 1,5-AG concentrations fall as urinary losses increase [52,53]. Thus, serum 1,5-AG measurements reflect blood glucose values over the past 24 hours, but they do not reflect the full range of glycemia.

  There are no data to suggest that complementary measurement of 1,5-AG assay improves glycemic control or reduces complications of diabetes more than measurement of A1C alone. Thus, we do not typically measure 1,5-AG concentrations. 1,5-AG concentrations are not interpretable in patients being treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors. Alpha-glucosidase inhibitors, dietary factors, and renal function can affect 1,5-AG concentrations.

CGM to estimate average glucose — Continuous glucose monitoring (CGM) data can be used to measure average glucose and may be used to supplement A1C data. Ambulatory glucose profiles generated by CGM contain graphics as well as glucose metrics, including mean glucose (figure 3). (See "Glucose monitoring in the management of nonpregnant adults with diabetes mellitus", section on 'CGM systems'.)

- **CGM: Ambulatory glucose profile** – The ambulatory glucose profile display (figure 3) of a CGM device contains graphics as well as glucose metrics: time (percent) in target range (70 to 180 mg/dL [3.9 to 10 mmol/L]), time (percent) in hypoglycemia (<70 mg/dL [3.9 mmol/L] and <54 mg/dL [3.0 mmol/L]), and time (percent) in hyperglycemia (>180 mg/dL [10.0 mmol/L] and >250 mg/dL [13.9 mmol/L]) [54]. Glucose variability is reported by standard deviation and percent coefficient of variation.

  The CGM ambulatory glucose profile also contains the glucose management indicator (GMI). GMI is an estimate of expected A1C based on the glucose data obtained over the monitoring period [9,55]. It is derived using a regression equation of laboratory A1C on CGM-measured mean glucose, primarily from individuals with type 1 diabetes [9]. GMI is an

additional tool to assess glycemia and should be differentiated from laboratory-measured A1C [56]. It may be similar, higher, or lower than laboratory A1C values. The value of GMI to provide information from CGM on management of diabetes control above and beyond mean glucose (and other CGM metrics) remains unclear.

Randomized clinical trials of persons with type 1 diabetes have demonstrated that CGM use can result in improvements in A1C [57-59] and reduce episodes of hypoglycemia [60-62]. Observational studies have linked time in range and other CGM metrics with clinical outcomes, also primarily in persons with type 1 diabetes [63-65]. There are no long-term clinical trials showing a direct benefit of CGM use on major microvascular or macrovascular complications [66]. There is growing interest in the use of this technology in persons with type 2 diabetes and other patient populations, including in pregnancy complicated by diabetes. CGM may be particularly useful in patients who need frequent glucose monitoring, such as in the setting of an intensive insulin regimen. More studies are needed to understand how to optimize the use of CGM technology in clinical practice, particularly for adults with type 2 diabetes.

GLYCEMIC VARIABILITY

The independent effect of glucose variability on complications of diabetes above and beyond average glucose or A1C is a topic of debate [9,67-69]. It is intuitive that glycemic instability is problematic [70]; sustained or repeated episodes of hypo- and hyperglycemia are of substantial clinical concern. Minimizing glucose variability and avoiding spikes and dips in glucose is an important goal in patients with diabetes. (See "Glycemic control and vascular complications in type 1 diabetes mellitus", section on 'Glycemic variability'.)

Because A1C reflects a weighted average of glucose exposure over the past two to three months, a given A1C may be associated with different continuous glucose monitoring (CGM) metrics of variability (typically calculated from up to 14 days of data) (figure 4). The approach to improving blood glucose control may be different depending upon whether an elevated mean blood glucose is associated with large fluctuations. As an example, optimal therapy of postprandial hyperglycemia requires changes in the nutrition prescription, the medication regimen, or both. A large meal containing a lot of quickly absorbed carbohydrate that is low in soluble fiber will cause substantial postprandial hyperglycemia. Changing the overall distribution of carbohydrate (eating somewhat less during each meal and more during between-meal snacks) and increasing the intake of soluble fiber should dampen the glycemic excursions after meals. (See "Nutritional considerations in type 1 diabetes mellitus" and "Nutritional considerations in type 2 diabetes mellitus".)

Large daily fluctuations in glucose are often explained by variability in eating or exercise habits and, sometimes, are due to omission of a pre-meal insulin bolus or injecting insulin after the meal. These problems should be corrected before making therapeutic changes such as increasing the insulin dose. (See "Cases illustrating problems with insulin therapy for type 1 diabetes mellitus", section on 'Case 1: Glycemic variability due to diet'.)

The use of CGM devices can help patients and providers visualize nuanced patterns of glucose and identify factors that may be contributing to glucose variability and daily highs and lows. (See "Glucose monitoring in the management of nonpregnant adults with diabetes mellitus", section on 'CGM systems'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Blood glucose monitoring".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Type 1 diabetes (The Basics)" and "Patient education: Type 2 diabetes (The Basics)" and "Patient education: Hemoglobin A1C tests (The Basics)")
- Beyond the Basics topics (see "Patient education: Type 1 diabetes: Overview (Beyond the Basics)" and "Patient education: Type 2 diabetes: Overview (Beyond the Basics)" and "Patient education: Blood glucose monitoring in diabetes (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Measurements of instantaneous glucose levels (self-monitoring of blood glucose [with fingersticks and a glucose meter] and real-time continuous glucose monitoring [CGM]) are used to manage diabetes from hour to hour and from day to day, to aid in dose selection in insulin-treated patients, and for safety. Measures of chronic glycemia (eg, glycated hemoglobin or CGM-derived mean glucose, time in range, and glucose management indicator [GMI]) are used to determine the overall efficacy of diabetes management with the aim of reducing risk for long-term complications. (See 'Introduction' above.)

- Glycated hemoglobin (A1C, hemoglobin A1C, HbA1c), which reflects average levels of blood glucose over the previous two to three months, is the most widely used test to monitor chronic glycemic control. It is used to diagnose diabetes and to monitor the efficacy of treatment. (See 'Glycated hemoglobin (A1C)' above.)

- As part of an effort to provide worldwide standardization of all A1C assays, A1C results are reported globally in International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units (mmol/mol) and derived National Glycohemoglobin Standardization Program (NGSP) units (the same values as reported currently as percent of total hemoglobin) using a master equation (calculator 1). (See 'Standardization of the assay' above.)

- A1C values are relatively higher in some races/ethnic groups (African American, Hispanic American, Asian American) than in White American persons with similar plasma glucose concentrations. These differences are small (approximately 0.3 to 0.4 percentage-point difference in A1C) and have not been shown to significantly affect treatment or modify the association between A1C and microvascular and macrovascular outcomes. (See 'Racial/ethnic differences' above.)

- Understanding the biological and patient-specific factors that can influence A1C and glucose is important for the interpretation of any discordance between A1C and glucose test results. When there is a disparity between the A1C values and blood glucose values, we rely on the glucose values. To assess glycemic control for management, glucose self-monitoring with fingersticks and a glucose meter or CGM may be used. (See 'Unexpected or discordant values' above.)

- Biomarkers such as fructosamine and glycated albumin are readily measured in the laboratory using validated assays but are infrequently used for the monitoring of glycemic control (table 1). There are few data linking these biomarkers to outcomes in randomized clinical trials, and there is no formal guidance on their use. However, in settings where A1C

measurements are unreliable or unavailable, fructosamine or glycated albumin may be useful alternatives. (See 'Other biomarkers' above.)

- CGM is helpful in the management of diabetes and particularly type 1 diabetes. CGM data can be used to measure daily glucose profiles and average glycemia and, as such, may be useful to supplement A1C data in some patients with diabetes (figure 3). (See 'CGM to estimate average glucose' above and "Glucose monitoring in the management of nonpregnant adults with diabetes mellitus", section on 'CGM systems'.)

- Understanding daily glucose patterns and the extent to which blood glucose concentrations vary is useful. For patients who test their own blood glucose at the same times every day, this variability can be evaluated simply by scanning down columns of blood glucose measurements over several days. The use of CGM devices can make the identification of within-day and between-day variation easier. (See 'Glycemic variability' above and "Glucose monitoring in the management of nonpregnant adults with diabetes mellitus", section on 'CGM systems'.)

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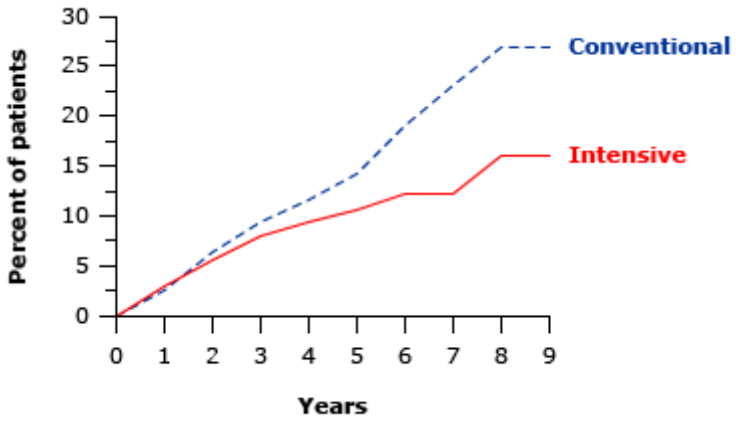
Topic 1807 Version 24.0

GRAPHICS

Strict glycemic control prevents moderately increased albuminuria (formerly called microalbuminuria) in patients with type 1 diabetes mellitus

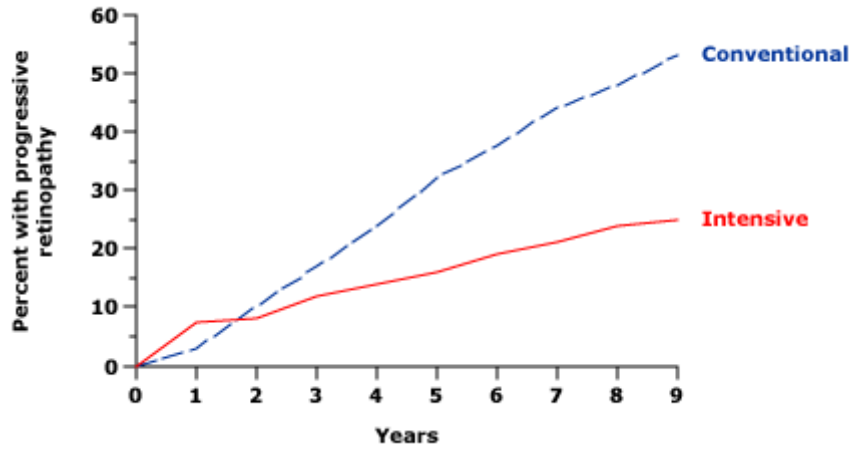


Cumulative incidence of moderately increased albuminuria (formerly called microalbuminuria) in patients with type 1 diabetes treated with either conventional or intensive insulin therapy for up to 9 years. There was an increasing benefit of intensive therapy over time ($p<0.04$).

Data from: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329:977.

Graphic 73143 Version 8.0

Strict glycemic control slows progression of retinopathy

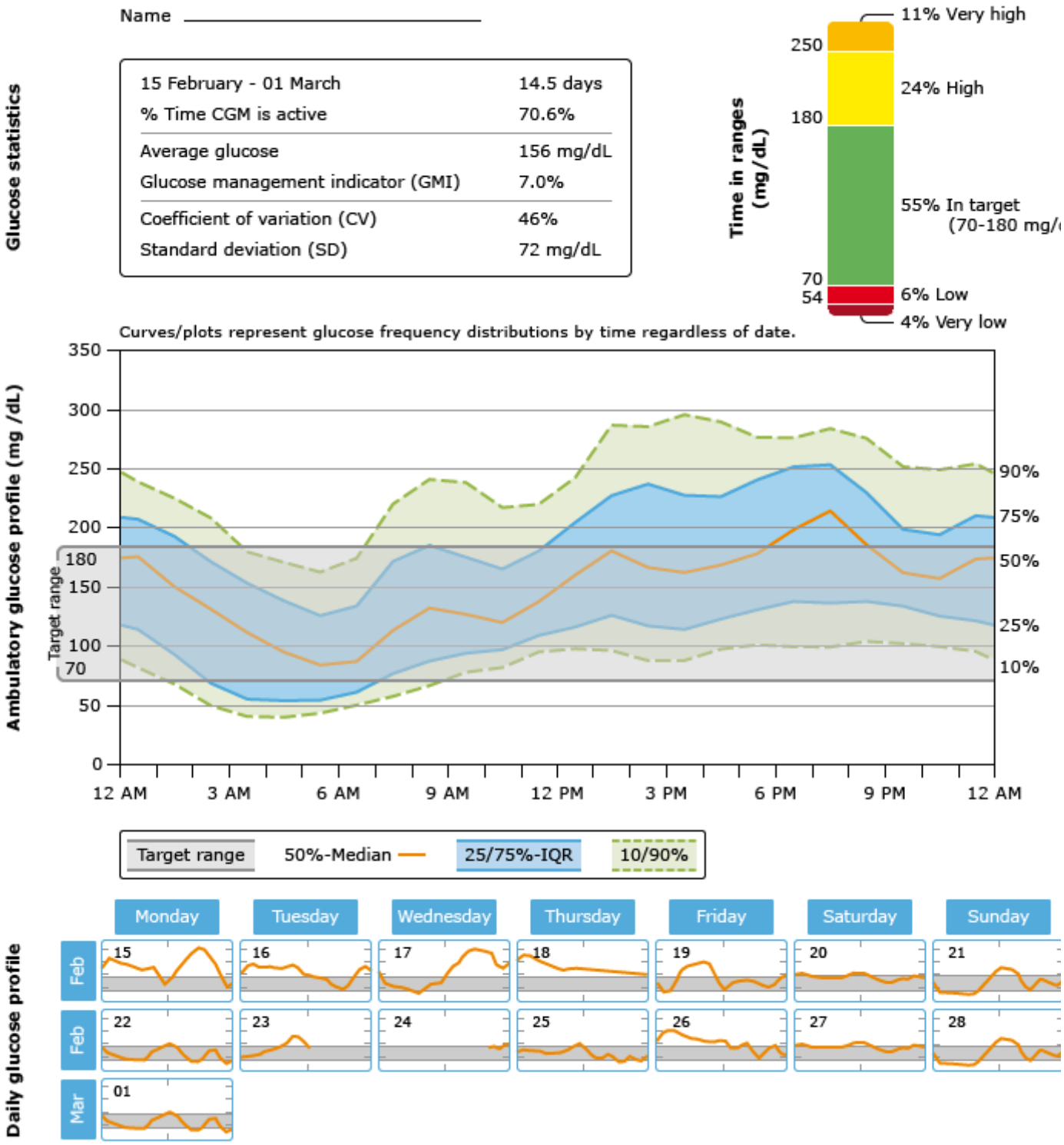


Cumulative incidence of progressive retinopathy in patients with type 1 diabetes and very mild to moderate nonproliferative retinopathy who were treated with either conventional (dashed line) or intensive (solid line) insulin therapy for 9 years. There was an increasing benefit of intensive therapy over time, although intensive therapy was associated with transient worsening in the first year ($p<0.001$).

Data from: Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329:977.

Graphic 61305 Version 8.0

Ambulatory glucose profile (AGP) report: Continuous glucose monitor



Graphic 119044 Version 2.0

Characteristics of traditional and nontraditional markers of hyperglycemia

	Brief description	Duration of glycemia reflected	Strengths	Limitations
Traditional markers of hyperglycemia				
Fasting glucose	Direct measure of circulating blood glucose	Acute/immediate	Direct measure; widely accepted; inexpensive	Requires fasting; affected by acute illness and stress; pre-analytical issues (sample stability)[1]; moderate within-person variability
A1C	Proportion of hemoglobin that is glycated	2 to 3 months	Reflects 2- to 3-month control Low within-person variability; no patient preparation needed; not affected by acute illness, stress, or recent activity levels	Affected by alterations in red cell turnover; some methods for measurement can give inaccurate results in the presence of certain hemoglobin variants*; requires whole blood; cost
Nontraditional markers of hyperglycemia				
Fructosamine	Total serum protein glycation	2 to 3 weeks	Does not require fasting; highly reliable automated methods are widely available; can be measured in serum or plasma; inexpensive	Affected by changes in serum protein metabolism (mostly albumin), thyroid dysfunction; limited evidence linking to outcomes
Glycated albumin	Proportion of albumin that is glycated	2 to 3 weeks	Does not require fasting; can be measured in serum or plasma	Affected by changes in albumin metabolism, thyroid dysfunction; method performance may vary; availability in the United States is limited; limited evidence linking to outcomes
1,5-AG	Monosaccharide filtered by the kidney and normally reabsorbed; reabsorption inhibited and it is excreted at high levels of glycemia, so serum levels drop	2 to 14 days	Does not require fasting; can be measured in serum or plasma; test is available from major laboratories in the United States; expense	Affected by changes in renal threshold for glucose, dialysis, or stage 4 or 5 kidney disease, pregnancy; limited evidence linking to outcomes

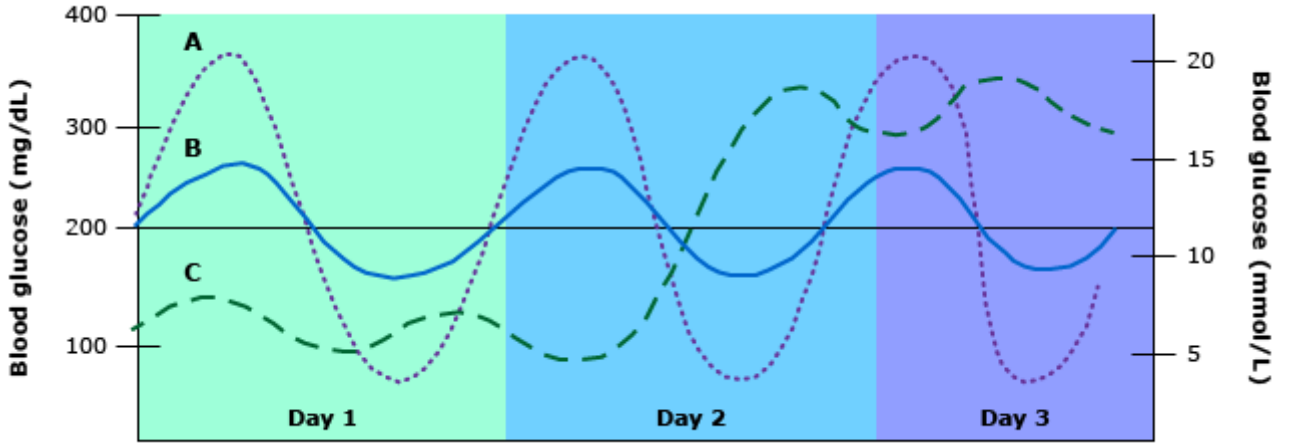
A1C: glycated hemoglobin; 1,5-AG: 1,5-anhydroglucitol.
* Refer to www.ngsp.org for comprehensive list.

Reference:

1. Gambino R. Glucose: A simple molecule that is not simple to quantify. Clin Chem 2007; 53:2040.

Graphic 129798 Version 1.0

Patterns of blood glucose control



Blood glucose excursions in 3 hypothetical patients who have the same mean blood glucose concentration of approximately 200 mg/dL (11.1 mmol/L, equivalent to an A1C value of approximately 8.2%) but who have different overall blood glucose control. Patient B (solid blue curve) has relatively small variations during the day and on different days; this patient should have little difficulty in lowering daily mean blood glucose concentrations without inducing hypoglycemia. In comparison, patient A (dotted purple curve) has marked blood glucose variations on the same day, and patient C (dashed green curve) has marked blood glucose variations on different days. These aspects of blood glucose control must be improved before the mean blood glucose concentration can be safely lowered. Increasing the intensity of insulin therapy can precipitate hypoglycemia in patients A and C since many of their blood glucose values are already in the low-normal range.

A1C: glycated hemoglobin.

Graphic 55747 Version 3.0

Contributor Disclosures

Elizabeth Selvin, PhD, MPH Other Financial Interest: Novo Nordisk [Honorarium for talk on hypoglycemia]. **David M Nathan, MD** Nothing to disclose **Joseph I Wolfsdorf, MD, BCh** Consultant/Advisory Boards: Ultragenyx DSMB [Glycogen storage disease type 1a]. **Jean E Mulder, MD** Nothing to disclose

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