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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: How should you assess glycemic control if the hemoglobin A1c is inaccurate or uninterpretable?

A: For adult outpatients with type 2 diabetes mellitus, hemoglobin A1c is the standard test used to gauge overall glycemic control during the previous 2 to 3 months and to titrate antidiabetic medications. But hemoglobin A1c does not provide an accurate assessment of frequency or severity of hypoglycemic events. Also, in some instances it may not truly represent glucose control, reflecting an average of high and low blood sugar values, or may not be reportable because of abnormal hemoglobin.

In these situations, an alternative test can be used along with capillary blood glucose testing, which remains the most reliable method of assessing glucose control in the short term. If an alternative test is used, it is important to clearly document it in the chart to reduce confusion, and also to educate the patient to better understand the disease-monitoring process.

HEMOGLOBINOPATHIES CAN INTERFERE WITH HEMOGLOBIN A1c

Many conditions that modify red blood cell production, destruction, or life span can affect the accuracy of hemoglobin A1c measurement (**Table 1**).[1–8]

Hemoglobinopathies can interfere with hemoglobin A1c testing, but this has become less of an issue as more laboratories use high-performance liquid chromatography in routine practice. The National Glycohemoglobin Standardization Program has published a list of commonly used hemoglobin A1c assays and expected interference from hemoglobin variants.[1] If the assay your laboratory uses is affected by these hemoglobin variants, consider other tests to measure long-term glucose control.

Suspect that a hemoglobinopathy or other condition is causing unreliable hemoglobin A1c readings if the hemoglobin A1c value[1–6]:

- Does not correlate with the expected value based on capillary blood glucose readings or laboratory plasma glucose readings
- Is inconsistent with frequently sampled plasma glucose values
- Is greater than 15%
- Changes significantly after the laboratory changes its testing method.

ALTERNATIVE METHODS TO ASSESS LONG-TERM GLYCEMIC CONTROL

Alternative tests to assess glycemic control include capillary blood glucose readings, continuous glucose monitoring, serum fructosamine, glycated albumin, and 1,5-anhydroglucitol.

Capillary blood glucose

Results from capillary blood glucose tests show glucose levels at a specific time and can be taken multiple times during a day. They are useful to identify glucose trends and inform medication adjustments.

This is the most common method to detect hypoglycemia and quantify its severity and frequency. Detecting hypoglycemia is especially important in patients receiving insulin or secretagogues or with other conditions that may predispose them to hypoglycemia. The hemoglobin A1c level can be above goal even if they have hypoglycemia. Capillary blood glucose monitoring relies on patient

Hemoglobin A1c is the standard but it is not perfect; alternatives are available

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TABLE 1

Common clinical conditions that can affect hemoglobin A1c[a]

Clinical condition	Effect on hemoglobin A1c	Mechanism or reason for effect
Asplenia	Increases hemoglobin A1c	Decreased red blood cell (RBC) turnover due to increased RBC life span
Chronic kidney disease	Effects vary based on severity of underlying disease and therapies	**Increased hemoglobin A1c** Carbamyl-hemoglobin production in uremic patients Erythropoietin deficiency **Decreased hemoglobin A1c** Shortened RBC survival Erythropoietin administration Hemodialysis (lowering of urea levels reduces carbamyl-hemoglobin concentration)
Chronic liver disease	Effects vary based on severity of underlying disease and therapies	**Increased hemoglobin A1c** Jaundice (increased glycation reaction in the presence of higher bilirubin concentrations) **Decreased hemoglobin A1c** Increased RBC turnover Antiviral drug therapies may decrease RBC life span
Hemoglobinopathies	Varies with testing method and assay	Multifactorial including anemia and rapid RBC turnover
Hemolytic anemia	Decreases hemoglobin A1c	Reduced RBC total volume Increased RBC destruction shortens RBC life span
Iron deficiency anemia	Increases hemoglobin A1c	Reduced RBC turnover prolongs RBC survival Greater malondialdehyde concentrations increase hemoglobin glycation reactions
Pregnancy	Decreases hemoglobin A1c in first 2 trimesters May increase hemoglobin A1c in third trimester	Increased RBC turnover decreases hemoglobin A1c Increased erythropoietin production decreases hemoglobin A1c Hemodilution decreases hemoglobin A1c
Transfusion	Variable hemoglobin A1c effects	**Increased hemoglobin A1c** Elevated glucose concentration in storage medium **Decreased hemoglobin A1c** Dilutional response
Vitamin B_{12} and folate deficiency anemias	Increases hemoglobin A1c	Reduced RBC turnover prolongs RBC survival

[a]This summation represents most current literature and clinical practice, but should be used as a guide only and should not replace clinical assessment or decision-making.

Based on information in references 1–8.

adherence to checking and recording glucose values several times a day and communicating the results to the care team.

The American Diabetes Association suggests using the estimated average glucose level, as calculated from the hemoglobin A1c, to give patients a reference to compare with the capillary blood glucose values they get at home. The formula is as follows[9]:

$$\textit{Estimated average glucose (mg/dL)} = 28.7 \times \textit{hemoglobin A1c (\%)} - 46.7$$

For example if the hemoglobin A1c is 7%, the estimated average glucose value would be $28.7 \times 7 - 46.7 = 154$ mg/dL. The American Diabetes Association has a conversion calculator on its website.[10]

Continuous glucose monitoring

Continuous glucose monitors measure interstitial glucose levels and are used to assess glucose trends over days to weeks. There are 2 main categories of these monitors: personal and professional.[11,12] Personal monitors are typically worn long-term for patient self-monitoring and come in 2 major types: real-time and intermittently scanned. Health insurance coverage requires specific criteria to be met for approval of either type.

In contrast, a professional continuous glucose monitor, if covered by insurance, is typically used for a shorter time, after which a medical professional retrieves the results. Results are either displayed in real time to the patient or are blinded to the patient.

Personal and professional monitors have shown similar performance qualities. However, both are less reliable for detecting hypoglycemia events than capillary blood glucose readings. In addition, their accuracy depends on reliable sensor placement and avoidance of certain prescribed and over-the-counter medications. Moreover, their use has not been studied in patients with end-stage liver or kidney disease, and they should be used cautiously in patients who have any condition that could affect measurement of interstitial glucose.

Serum fructosamine

Serum fructosamine, a circulating glycated protein (mostly albumin), can be measured to monitor glycemic control when hemoglobin A1c testing is inaccurate. Fructosamine levels provide an estimate of the average blood glucose levels in the preceding 7 to 21 days. This substance can be used to monitor rapid insulin titrations and has been shown to correlate more consistently with continuous glucose monitoring than hemoglobin A1c.[13–15]

Several formulas can be used to estimate the hemoglobin A1c based on the fructosamine level, eg:

$$\textit{Hemoglobin A1c (\%)} = 0.017 \times \textit{fructosamine level (µmol/L)} + 1.61$$

By this formula, a fructosamine level of 317 µmol/L converts to a hemoglobin A1c of 7%; a value of 375 µmol/L converts to a hemoglobin A1c of 8%.[16]

However, in patients with conditions associated with altered albumin metabolism, such as nephrotic syndrome, advanced liver disease, or protein-losing enteropathy, the correlation between fructosamine levels and glycemic control may be decreased.[14,15] Some suggest using a correction factor for the general equation, such as multiplying the fructosamine level by 4 and then dividing by the serum albumin level, but this practice has not been widely adopted.[2,15]

Hemoglobin A1c does not detect hypoglycemic episodes

Pregnancy is another condition in which fructosamine levels have limited use. In this situation, other tests, such as capillary blood glucose or continuous glucose monitoring, may have better validity and clinical applicability.

Glycated albumin

This is an emerging measure that may improve the overall predictive value of glycemic control. The proportion of serum albumin that is glycated provides an estimate of glycemic control in the previous 14 to 21 days. This value is easily converted to an approximate hemoglobin A1c value by dividing by 3. This is more straightforward than converting fructosamine to hemoglobin A1c and may provide better information regarding postprandial glucose values.[17]

However, glycated albumin values may not be reliable in patients with conditions that alter albumin metabolism such as nephrotic syndrome, hypo- or hyperthyroidism, or cirrhosis.[13]

1,5-Anhydroglucitol

1,5-Anhydroglucitol is a dietary polyol that competes with glucose for reabsorption in the renal tubule when circulating glucose concentrations are elevated. Lower circulating serum concentrations of 1,5-anhydroglucitol correspond with increased glycosuria and hyperglycemia within the previous 7 to 14 days.[18,19]

This test is not as reliable in patients with altered renal perfusion, though it provides valuable information in assessing same-day periods of hyperglycemia, particularly glucose values greater than 180 mg/dL. Also, 1,5-anhydroglucitol is not a reliable indicator of glucose control in patients on sodium-glucose cotransporter 2 inhibitors, which increase glycosuria.[20]

EDUCATING PATIENTS AND PROVIDERS ON ALTERNATIVE TESTS

Healthcare providers need to know that hemoglobin A1c does not correlate with capillary or venous blood glucose levels in some situations—otherwise, one might inappropriately escalate or de-escalate therapy. If alternative tests are used because of inaccurate or uninterpretable hemoglobin A1c values, clinicians need to document the clinical rationale. This documentation may prevent a hemoglobin A1c test from being ordered and falsely interpreted.

Many conditions can affect hemoglobin A1c measurements

Patient education is also important. Successful diabetes education efforts have led to widespread recognition of hemoglobin A1c as the standard diagnostic test for monitoring glycemic control. If a different test is used, the practitioner needs to explain the rationale to the patient and provide education on the alternative method. A diabetes educator, clinical pharmacist, or nurse may be able to facilitate this education.

If the patient has an abnormal hemoglobin variant, it should be added to the problem list. Consider adding ICD-10 code D58.2 (abnormal hemoglobin not otherwise specified) or D58 (other hereditary hemolytic anemias). Each facility can consider development and implementation of specific solutions.

Finally, insurance companies and other groups focused on quality metrics need to be informed of the inaccuracy of hemoglobin A1c testing for individual patients. With so many groups transitioning to population health data, a missing or inaccurate hemoglobin A1c test may affect the ability to assess glycemic control across a patient population and could affect assessment of performance measures for individual clinicians and practice groups. If data sets are automatically abstracted, the auditing software can penalize providers for not having tested hemoglobin A1c as a fundamental component of diabetes management.

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