

The Illusion of Control: The Critical Impact of Hemoglobinopathies on HbA1c Interpretation

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Abstract

Glycated hemoglobin (HbA1c) is a cornerstone of diabetes diagnosis and therapy. However, its reliance on normal hemoglobin biochemistry poses a significant challenge. Hemoglobinopathies, whether common or rare, can markedly affect HbA1c accuracy by altering red blood cell longevity, modifying glycation kinetics, and inducing method-specific analytical interference. This perspective delves into the mechanisms of interference and highlights prevalent conditions (such as HbS, HbC, HbE, and Beta-thalassemia). We illustrate the problems with a Sudanese example of sickle cell disease, where HbA1c readings were inaccurate and not useful. We advocate for the broader implementation of alternative biomarkers, including glycated albumin, fructosamine, and continuous glucose monitoring, in conjunction with proactive laboratory flagging systems that will help identify and address these issues. National and international guidelines should not overlook this diagnostic blind spot, especially where plenty of ethnic groups coexist and the prevalence of disease is high. Understanding the boundaries of HbA1c is not just a scientific detail; it is an essential element of both safe and equitable care.

Keywords: HbA1c, Hemoglobinopathy, Sickle Cell Trait, Thalassemia, Diabetes Diagnosis, Glycated Albumin, Analytical Interference

1. Introduction: A Flawed Gold Standard

Hemoglobinopathies, regardless of their prevalence, can significantly impact HbA1c accuracy by influencing red blood cell lifespan, affecting glycation kinetics, and causing method-specific analytical interference [1,2]. For decades, HbA1c has been regarded as the most effective method for assessing long-term blood sugar control. But this trust is based on a shaky assumption: that the patient has a normal red blood cell lifespan and a normal hemoglobin A (HbA) structure. Albumin is the protein that is most common in plasma. It accounts for approximately 60% of all the proteins in the blood. This protein, with a high molecular weight, maintains the pH level and osmotic pressure of blood. Albumin carries metabolic byproducts and acts as an antioxidant [3]. Glycated albumin (GA) is formed when proteins undergo glycation, and it accounts for approximately 80% of all glycation reactions in plasma. GA helps monitor blood sugar levels and is typically used in conjunction with tests that detect glycated hemoglobin. Patients with hemoglobinopathies or those on dialysis prefer the measurement of GA [4]. This assertion is invalid for millions globally who possess hemoglobin variations [5]. We contend that the inability to acknowledge this constraint renders HbA1c not a gold standard, but rather a possible fool's gold in these populations, resulting in considerable therapeutic detriment. This perspective has been drafted to focus attention on the underreported diagnostic pitfalls of HbA1c in individuals with hemoglobinopathies and to provide guidance for clinicians and public health administrators.

2. Global Burden and Ethnic Distribution

Hemoglobinopathies, as one of the most common single-gene illnesses worldwide, affect over 300,000 births each year [6]. The influence of geographic and ethnic factors is significant in the spread of these diseases. For instance, HbS is highly prevalent in Sub-Saharan Africa, with carrier rates exceeding 20% in some regions [7]. HbE is widespread in Southeast Asia, particularly in Bangladesh, Thailand, and Cambodia [8]. In contrast, HbC and HbD variants are more

commonly found in West Africa and certain regions of India. Recent screening data from Sudan suggest that up to 18% of the population may have a hemoglobin variation, highlighting the diagnostic challenges of HbA1c in standard diabetes management. These figures illustrate the importance of genetic context in the practical application of glycemic assessment tools, highlighting the significance of personalized medicine in managing diseases [9].

3. Mechanisms of Interference

There are several reasons why hemoglobinopathies can cause problems.

Altered Erythrocyte Survival: The 120-day lifespan of the RBC is a crucial factor in the production of HbA1c. Conditions that shorten this lifespan, such as the persistent hemolysis in sickle cell disease (HbSS) or beta-thalassemia, significantly reduce HbA1c [1, 10].

Structural Modification and Glycation Kinetics: Variants such as HbS, HbC, and HbE can significantly alter the charge and steric environment around the N-terminal valine of the beta-globin chain. These modifications have a profound effect on the rate of glycation [2].

Interference with analysis: The method is the most important thing. This is the most common cause of clinical mistakes [11].

Cation-Exchange High Performance Liquid Chromatography (HPLC): Variants such as HbS, HbC, and HbD may co-elute with the HbA1c fraction, resulting in a misleadingly high outcome [12].

Immunoassay: Antibodies may not efficiently bind to the glycated N-terminal sequence of a variant hemoglobin (e.g., HbC), resulting in a falsely low outcome [13].

Capillary electrophoresis and boronate affinity: Are usually stronger procedures. Boronate affinity measures total glycated hemoglobin and is relatively unaffected by most variations [14].

4. Clinical Scenarios: Recognizing the Red Flags

The clinician must be vigilant. Key scenarios that raise suspicion include instances where the HbA1c and glucose data don't match or

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when a patient from a high-risk ethnic group (African, Southeast Asian, Mediterranean, or Middle Eastern) receives an unexpected result [5, 15].

Table 1: Common Hemoglobinopathies and Their Typical Impact on HbA1c

Variables	Primary interference mechanism	Typical HbA1c impact	Clinical note
Sickle Cell Trait (HbAS)	Analytical (HPLC co-elution)	Falsely High (on HPLC)	Immunoassays are often accurate [12]
Sickle Cell Disease (HbSS)	Shortened Red Cell lifespan	Falsely low	HbA1c is unreliable [1,10]
Hemoglobin C (HbAC/CC)	Analytical (Immunoassay Ab binding)	Falsely low (on immunoassay)	HPLC may overestimate [13]
Beta-Thalassemia	Shortened Red Cell lifespan + Elevated HbF	Falsely low	HbF glycates more slowly than HbA [16]
Hemoglobin E (HbE)	Analytical + Altered Glycation	Often falsely low	Very common in South Asia [17]

(HPLC or electrophoresis).

3. Action: Stop using HbA1c that isn't reliable. Use different biomarkers:

Glycated Albumin (GA) or Fructosamine: These tests look at how glycation affects serum proteins. Changes in hemoglobin or red blood cells do not impact them. They are the better choice [3, 4, 18].

Continuous Glucose Monitoring (CGM): Offers an unmatched overview of glycemic patterns [19].

Glycated albumin is the non-enzymatic glycation product of albumin in plasma and, thus, emerged as a novel glycemic marker for the diagnosis of diabetes mellitus at the onset of the 21st century. The 12-week lifespan of hemoglobin affects HbA1c, while the longevity of albumin affects the plasma concentration of GA, which indicates the average blood glucose level 2–4 weeks before the measurements [20].

Glycated albumin was expressed as a percentage of total albumin using the following formula: $[(\text{glycated albumin concentration in g/dL} / \text{serum albumin concentration in g/dL}) \times 100 / 1.14] + 2.9$ [21].

5. A Path Forward: Mitigating Risk and Protecting Patients

We suggest a structured algorithm for keeping patients safe [Figure 1]:

1. Awareness: Teach all diabetes care providers about this widespread problem.
2. Investigation: If there is a difference, ask for a hemoglobin test

found, HbA1c is suitable for glycemic monitoring. However, caution is advised as HbA1c should be avoided if a variance is seen due to analytical and physiological interference. Clinical context and comorbidities should guide the interpretation of alternative indicators such as glycated albumin (GA), fructosamine, 1,5-anhydroglucitol, and CGM.

6. Case Scenario: Misleading HbA1c in a Patient with HbSS

A 7-year-old Sudanese girl with a known history of sickle cell disease (HbSS) came in for a regular metabolic checkup. Over the past three months, she had been getting more and more tired, urinating more often, and losing weight without meaning to. Even though she had never been diagnosed with diabetes mellitus before, his symptoms made doctors suspicious that she had hyperglycemia.

The first tests in the lab showed: HPLC revealed HbSS at 63.7%, HbF at 15.1%, HbA2 at 2.9%, with no HbA detected. Hemoglobin: 9.5 g/dL, Reticulocyte count: 8.5% Peripheral smear: significant reticulocytosis (10.5%) with Sickle, Boat, and Oat cells as well as anisopoikilocytosis; HbA1c (National Glycohemoglobin Standardization Program (NGSP)-certified method): < 2.0%, which is an apparent mistake (by HPLC).

The HbA1c result was considered invalid due to the paucity of HbA and the high reticulocyte count. The reduced lifespan of erythrocytes and altered glycation kinetics in HbSS patients are recognized to skew HbA1c readings, especially in the absence or minimal presence of HbA. To elucidate the glycemic state, the HbA1c was re-evaluated using an alternative methodology that is less influenced by hemoglobin variations. This resulted in a corrected HbA1c of 6.7%, which is in line with the early stages of diabetes. More tests to validate the results were:

Fructosamine: 306 $\mu\text{mol/l}$

Glycated albumin: 14.8%

Random plasma glucose: 8.1 mmol/L.

These readings are on the high end of the normal range, indicating potential early signs of diabetes or difficulty regulating glucose levels. In the case of HbSS, these markers are more accurate than HbA1c, especially when the patient has a high reticulocyte count and no HbA.

7. Clinical Insight

This case example highlights the diagnostic constraints of HbA1c in individuals with hemoglobinopathies, especially HbSS. It emphasizes the significance of method selection, variant screening, and the utilization of other biomarkers such as fructosamine, glycated albumin, continuous CGM, or other techniques for the detection of HbA1c. When HbA is not present, laboratories must mark HbA1c data as unreliable, and clinicians should consider glycemic indices in relation to

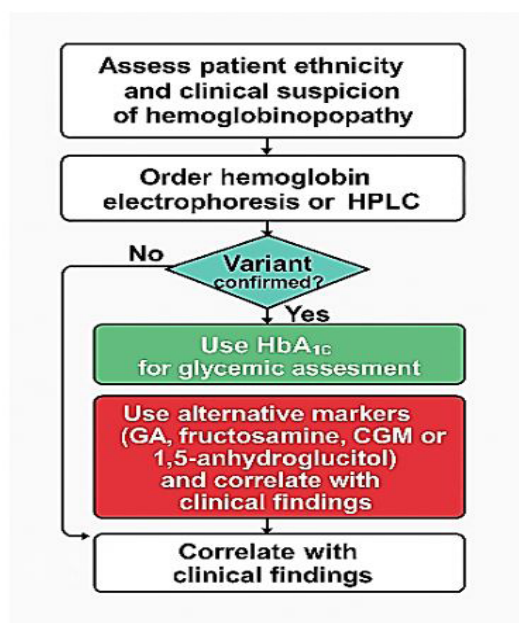


Figure 1: Diagnostic algorithm for Glycemic assessment in suspected Hemoglobinopathy. A stepwise clinical decision tool for glycemic evaluation of suspected hemoglobin variations. Ethnic background and symptoms of hemoglobinopathy are assessed first. Hemoglobin electrophoresis or HPLC is advised for a strong suspicion. If no variation is

hematologic background.

8. Laboratory Annotation and Flagging of HbA1c Result

The laboratory's reporting system automatically flagged the HbA1c result of < 2.0% since there was little quantifiable HbA on HPLC. The analyzer's algorithm, with its precision and reliability, identified a hemoglobin variation pattern that matched HbSS and subsequently halted the HbA1c output. It then said, "Result invalid due to absence of HbA; interpretation not recommended in the presence of variant hemoglobin." The high polychromatophilic smear added to this signal, prompting the clinical team to seek other glycemic markers.

9. Limitations of Alternative Glycemic Markers

Glycated albumin (GA) and Fructosamine serve as valuable alternatives to HbA1c; nonetheless, they possess certain limitations. Conditions that alter the breakdown of albumin, such as nephrotic syndrome, liver disease, or thyroid dysfunction, may affect GA levels [22]. Fructosamine, which indicates the extent of glycation on all serum proteins, may be influenced by total protein levels and lacks

standardization between laboratories [23]. CGM is a handy tool; however, it may be too expensive and difficult to set up in places with limited resources [24]. Consequently, doctors must analyze these markers within the comprehensive clinical framework, taking into account comorbidities, accessibility, and patient-specific variables.

10. Toward Diagnostic Reform: Policy and Practice Recommendations

The ongoing dependence on HbA1c in demographics with elevated hemoglobinopathy prevalence represents a systematic oversight. National diabetes guidelines ought to include screening techniques for hemoglobin variations, especially in multiethnic and high-risk areas [25]. Laboratory reporting systems should mark aberrant hemoglobin profiles and hide HbA1c findings when interference is anticipated [26]. Medical curricula and continuing education programs should also emphasize the drawbacks of HbA1c and encourage students to learn about alternative indicators [27]. These changes are necessary to ensure that diabetes care is equitable and that tests are accurate [Table 2].

Table 2: Proposed Reforms for Glycemic Assessment in Hemoglobinopathy Contexts.

Domain	Proposed Reform	Regional implementation strategy
Clinical Guidelines	Before interpreting HbA1c, change the national diabetes procedures to include hemoglobinopathy screening.	Collaborate with the Sudanese Endocrine Society and the Hematology Board to revise the diagnostic algorithms.
Laboratory Reporting	Flag HbA1c findings as invalid if HbA is missing or if variant interference is found.	Add auto-commenting systems to Laboratory Information Systems (LIS) that send notifications when variants are detected.
Diagnostic Algorithm	Use structured decision trees to check glycemic levels in people who carry variants.	Send out bilingual flowcharts and standard operating procedures (SOPs) to all diagnostic labs and outpatient clinics.
Biomarker Access	Encourage the use of GA, fructosamine, CGM, and 1,5-anhydroglucitol in patients who are not qualified for HbA1c testing.	Discuss with the Ministry of Health and donors the possibility of obtaining discounted access to other tests.
Training & Education	Start continuing medical education modules on how hemoglobinopathy might affect HbA1c levels.	Develop Arabic-English training kits for medical students, laboratory technicians, and healthcare professionals.
Patient Communication	In discharge summaries and counseling, talk about variant status and the limits of HbA1c.	Make bilingual patient brochures that describe different markers and monitoring regimens.

11. Conclusion

HbA1c is a handy tool; however, it has a significant limitation: it doesn't account for structural and kinetic hematologic variations. This is not a formal review but rather a point of view derived from

clinical practice and the existing literature. We call on guideline committees, laboratories, and clinicians to recognize HbA1c's limitations in subjects with hemoglobinopathies and adopt a more comprehensive biomarker approach for the safe care of diabetes.

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