Kuwait Research Journal of Agriculture and Life Science (KRJALS)

ISSN Print: 2790-6485 | ISSN Online : 2790-6477 Open Access

Sickle Cell Anemia and Hemoglobin A1c: Pathophysiological Interactions, Diagnostic Challenges, and Clinical Implications: A Comprehensive Review

Esraa S. Al-Fatlawey[1*], Ali M. Omara[2]

[1]Department of Pathological Analysis, Faculty of Science, University of Kufa, Najaf, Iraq.

[2]Department of Clinical Biochemistry, Faculty of Medicine, University of Al-Ameed, Karbala, Iraq.

*Corresponding Author

Esraa S. Al-Fatlawey

Department of Pathological Analysis, Faculty of Science, University of Kufa, Najaf, Iraq.

Article History

Received: 27.03.2026

Revise : 07.05.2026

Accepted: 09.05.2026

Published: 11.05.2026

DOI:10.61705/KRJALS.5.2.2026.17.29

Abstract:

Background: Sickle cell anemia (SCA) is an autosomal recessive blood disorder resulting from a point mutation in the beta-globin gene, which causes the synthesis of aberrant hemoglobin S (HbS). The accuracy of hemoglobin A1c as a glycemic biomarker, is impaired by chronic hemolysis and reduced red blood cell (RBC), posing a diagnostic issue for people with both sickle cell anemia and diabetes mellites (DM)

Objectives: This study examines the molecular pathophysiology of sickle cell anemia (SCA), the biochemistry involved in hemoglobin A1c (HbA1c) measurement, and the mechanisms by which hemoglobin S (HbS) interferes with HbA1c assays, both physiologically and analytically. It also reviews clinical methods for addressing these challenges.

Methods: A comprehensive literature review was conducted across Scopus, PubMed/MEDLINE, , and Web of Science for identifying peer-reviewed articles published between 1990 and 2025. The investigation employed the subsequent MeSH terms: sickle cell anemia, HbA1c, hemoglobin variations, glycated hemoglobin, glycated albumin, diabetes mellitus, and fructosamine.

Results: Polymerization of hemoglobin S (HbS) results in vaso-occlusion, persistent hemolysis, and organ destruction. The decreased lifespan of red blood cells in sickle cell anemia (17–29 days against the normal 90–120 days) results in a consistent underestimate of HbA1c levels. Analytical interference varies according to the testing technique employed. Ion-exchange high-performance liquid chromatography (IE-HPLC), immunoassay, boronate affinity chromatography, and capillary electrophoresis exhibit distinct interference patterns with HbS and increased fetal hemoglobin (HbF). Additional biomarkers, such as fructosamine and glycated albumin (GA), offer insights into shorter glycemic periods; yet each has distinct limits. Recent evidence suggests that continuous glucose monitoring (CGM) offers the most precise real-time glycemic evaluation in this demographic.

Conclusion: Clinicians should recognize the limitations of HbA1c in patients with sickle cell anemia and use tailored glycemic monitoring. For patients with SCA and diabetes, combine NGSP-certified HbA1c with alternative biomarkers and continuous glucose monitoring (CGM).

Keywords: Sickle cell anemia; hemoglobin A1c; HbS; glycated hemoglobin; hemoglobinopathy; fructosamine; glycated albumin.

Introduction

Sickle cell anemia (SCA) is the most common severe monogenic condition worldwide. It affects about 300,000 infants each year, with the highest prevalence in sub-Saharan Africa, the Middle East, India, and the Mediterranean region [1,2]. SCA arises from a single-nucleotide change (GAG to GTG) at codon 6 of the HBB gene on chromosome 11p15.5, which encodes the beta-globin chain. This mutation led to the production of abnormal hemoglobin S (HbS; α2βS2) instead of adult hemoglobin (HbA; α2β2), changing erythrocyte biochemical and physiological properties [3, 4].

The worldwide epidemic of type 2 diabetes mellitus (T2DM) simultaneously affects persons with genetic hemoglobin disorders. About ten percent of people with sickle cell disease (SCD) match the criteria for diagnosis of diabetes mellitus. This prevalence is affected by factors such as age, genetics, and disease-modifying therapies [5]. The combination of sickle cell anemia (SCA) and diabetes mellitus (DM) have a significant diagnostic challenge, particularly regarding the reliability of hemoglobin A1c (HbA1c), which is globally recognized as the gold standard biomarker for glycemic assessment.

HbA1c is produced via non-enzymatic glycation of the N-terminal valine residue in the β-globin chain of adult hemoglobin. The concentration reflects the weighted average blood glucose level over the past 90-120 days, that correlates with the usual lifespan of erythrocytes [6,7]. This relationship primarily depends on the predictability and stability of erythrocyte lifespan. In sickle cell anemia (SCA), persistent hemolysis markedly shortens erythrocyte lifespan, thereby reducing HbA1c readings. Moreover, the analytical interference resulting from structural HbS and elevated HbF affects commonly used laboratory test platforms [9].

This review enhances understanding of the molecular basis of sickle cell anemia (SCA) and the biochemistry of hemoglobin A1c (HbA1c). It covers the impact of SCA on the analysis and reliability of HbA1c biologically and outlines glycemic tracking strategies for this group. Knowing these relationships helps prevent undertreatment, misdiagnosis, and diabetes complications in patients with SCA.

1.1 Epidemiology of Sickle Cell Anemia

Sickle cell anemia (SCA) is a major global health issue. About 6–7% of people around the world have an abnormal hemoglobin gene [1]. Every year, almost 300,000 infants are born with SCA, a ratio expected to reach 400,000 in 2050 due to population shifts in high-incidence areas [10]. The sickle cell trait (HbAS) carrier frequency in some sub-Saharan African communities is 25–30% [11].

More than 100,000 people in the United States live with sickle cell anemia (SCA), with an elevated incidence within African Americans. In the Middle East, especially Saudi Arabia, Iraq, and Bahrain, trait frequency ranges from 2% - 25% depending on the area [13].

The HbSS genotype, known as sickle cell anemia (SCA), is the most severe and prevalent form of sickle cell disease (SCD)in people of African origin, accounting for more than 70% of cases. Other common genotypes include HbSC and HbSβ-thalassemia, both of them can cause hemolysis that affects HbA1c readings. Despite advances in medicine, life expectancy for SCA patients is still less than that of the general population, with an average of about 43 years in the United States [12,19].

1.Molecular and Cellular Mechanisms Fundamentals for the Pathophysiology of Sickle Cell Anemia

1.2.1 The HbS Mutation and Polymerization

Substituting hydrophilic glutamic acid (Glu) with hydrophobic valine (Val) at position 6 of the beta-globin chain creates a hydrophobic site on the HbS tetramer's surface [3,4]. In deoxygenated states, this region promotes contact between HbS

molecules, forming elongated polymer fibers in the erythrocyte [14,15]. Polymer formation within the cell alters the normal biconcave shape of red blood cells, leading to the stiff, sickle morphology [4].

HbS polymerization is acutely responsive to thermodynamic circumstances. Factors include intracellular HbS concentration, oxygen tension (pO2), temperature, intracellular pH (via the Bohr effect), inhibitory hemoglobins such as HbF and HbA, and other intracellular variables, such as 2,3-bisphosphoglycerate (2,3-BPG) [14,16]. Increased fetal hemoglobin (HbF) levels markedly impede polymerization because HbF lacks the βS chain and cannot participate in polymer fiber formation. This finding is the main reason for using hydroxyurea therapy [31].

1.2.2 Hemolysis and Chronic Anemia

Sickle erythrocytes carrying polymer are prone to both intravascular and extravascular hemolysis. Intravascular hemolysis produces cell-free hemoglobin, heme, and arginase. Cell-free hemoglobin sequesters nitric oxide (NO), leading to nitrate and methemoglobin, and reduces endothelial vasodilatory capacity [16]. Loss of NO induces endothelial dysfunction, platelet activation, and vasoconstriction, contributing to pulmonary arterial hypertension, anxiety, and leg ulcers—collectively termed the 'hemolytic vasculopathy' phenotype [18]. Extravascular hemolysis, handled by the spleen and liver, occurs when these organs recognize and remove rigid, antibody-opsonized, or phosphatidylserine-exposing sickle erythrocytes [16].

People with HbSS usually have hemoglobin levels of 6–11 g/dL and red blood cell lifespans of 17–29 days, much shorter than the normal 90–120 days [19]. Reticulocytosis is common and shows that the bone marrow is working hard to replace red blood cells. More rapid red blood cell turnover and shorter red blood cell lifespan are the main reasons HbA1c is unreliable in sickle cell anemia.

1.2.3 Vaso-Occlusion and Multi-Organ Damage

Vaso-occlusion (VOC) represents the primary pathological event in sickle cell anemia (SCA) and is responsible for most of its acute and chronic complications [18,20]. This process is multifactorial and includes: (a) adhesion of low-density sickle reticulocytes to activated endothelium through α4β1-integrin/VCAM-1 and BCAM/Lu–laminin interactions; (b) trapping of dense, rigid, irreversibly sickled cells within the microcirculation; (c) neutrophil-erythrocyte heterotypic aggregation mediated by E-selectin and P-selectin; and (d) platelet activation and thrombosis [18,20]. Sterile inflammation, mediated by TLR4 signaling, complement activation, and damage-associated molecular patterns (DAMPs) released from lysed erythrocytes, particularly cell-free heme, has been identified as a fourth pathophysiological mechanism in sickle cell disease (SCD) [16].

End-organ damage progressively accumulates throughout the lifespan. Major complications include acute chest syndrome, which is the leading cause of mortality, stroke, and silent cerebral infarction, avascular necrosis of the femoral head, sickle nephropathy characterized by hyperfiltration, proteinuria, and chronic kidney disease, hepatic sickle cell disease, retinopathy, and progressive functional asplenia resulting from splenic auto infarction [16,19]. The cumulative effects of recurrent ischemia-reperfusion injury and chronic hemolytic vasculopathy on target organs establish a pathological environment that complicates the interpretation of biomarkers such as HbA1c.

2. Materials and Methods

2.1 Biochemistry of Hemoglobin A1C

2.1.1 Formation and Physiological Basis

Hemoglobin A1c is formed via the non-enzymatic and irreversible glycation, referred to as the Amadori modification, of the N-terminal valine residue (Val-1) on the beta-globin chain of HbA [6,7]. This method has two stages. Initially, glucose reacts with the free amine group of Val-1 to produce a reversible Schiff base (aldimine).
Subsequently, this intermediate undergoes an irreversible Amadori modification, yielding the stable keto amine product, HbA1c.
[6]. Glycation occurs frequently during the

erythrocyte lifespan, leading to older cells with a greater proportion of glycated hemoglobin. Consequently, HbA1c signifies the weighted average glucose concentration over the past 90-120 days, with about half of the final value derived from the latest 30 days [7].

The American Diabetes Association (ADA) Standards of Care classified HbA1c values less than 5.7% as normal, values between 5.7% and 6.4% as a sign of prediabetes, and values of 6.5% or more as diagnostic of diabetes mellitus [6]. HbA1c has been validated in key prospective clinical trials, such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), as a dependable indicator of microvascular and, to a lesser degree, macrovascular issues related to diabetes [7].

2.1.2 Assay Methods and Their Principles

Various laboratory techniques are used worldwide to quantify HbA1c. The four primary platforms consist of: (1) ion-exchange high-performance liquid chromatography (IE-HPLC), which separates hemoglobin species based on ionic charge and adheres to the standards of the International Federation of Clinical Chemistry (IFCC); (2) immunoassay, using antibodies specific to the glycated N-terminus of the beta chain; (3) boronate affinity chromatography, which captures all glycated molecules irrespective of hemoglobin type; and (4) capillary zone electrophoresis (CZE), which distinguishes hemoglobin variants based on electrophoretic mobility [9]. Every analytical technique shows distinct susceptibility to influence from HbS, HbC, HbE, HbD, and HbF [9,21]. The National Glycohemoglobin Standardization Program (NGSP) maintains a certification program for HbA1c assay methodologies and regularly provides updated interference data about recognized hemoglobin variations.

2.2 Interference mechanisms of HbA1c in sickle cell anemia

2.2.1 Biological (In Vivo) Interference

The most clinically significant reason of HbA1c interference in sickle cell anemia (SCA) is biological. Because of the accumulation of HbA1c during the lifespan of erythrocytes, any condition that reduced red blood cell survival results in improperly lower HbA1c values relative to actual blood glucose levels [8,22]. In sickle cell anemia (SCA), the typical red blood cells lifespan is reduced to 17-29 days, in comparison with90-120 days in healthy individuals [19]. As a result, HbA1c often underestimates typical glycemia, potentially masking situation involving uncorrected or poorly managed diabetes [5,8].

This error has severe clinical consequences. Individuals with undiagnosed or poorly controlled diabetes may have a progressive microvascular problem, including nephropathy, diabetic retinopathy, and neuropathy, without the indication of rising HbA1c levels [5]. Several case studies have shown patients with sickle cell disease displaying significant diabetes issues despite having HbA1c levels below 4.2–5.0%, generally considered suggestive of euglycemia [5]. The quantitative impact of hemolysis on HbA1c reduction has been examined. A higher level of indirect bilirubin is a sign of hemolysis and shows an inverse connection with HbA1c (Spearman r = −0.44) in a cohort of 439 SCD patients at the University of Illinois Sickle Cell Center [24]. On the contrary, specific situations, like diminished reticulocytosis during aplastic crises, iron deficiency- associated sickle cell anemia (SCA), or blood transfusions from hemoglobin AA (HbAA) donors, may accidentally normalize or raise HbA1c levels by temporarily increasing the lifespan of red blood cells , which leads to misleadingly normal or elevated readings [22,25]. The interpretation of HbA1c in sickle cell anemia (SCA) must take into account current hemoglobin levels, reticulocyte count, lactate dehydrogenase (LDH), indirect bilirubin, and recent transfusion history.

2.2.2 Analytical (In Vitro) Interference

In addition to its in vivo effects, HbS causes analytical interference in several HbA1c testing systems due to alterations in the beta-globin chain structure [9,21]. The GAG-to-GTG substitution alters the ionic charge of the beta chain, resulting in distinct chromatographic retention in ion-exchange high-performance liquid chromatography

(IE-HPLC) systems.

Depending on the specific IE-HPLC analyzer, HbS may co-elute with the HbA1c peak, leading to falsely high results, or elute separately, resulting in incomplete integration and falsely low readings [9]. Point-of-care immunoassay devices pose a particular challenge, as certain antibodies are engineered to target the glycated N-terminal β-chain and may not cross-react with the structurally altered βS chain [9,21].

Individuals with homozygous HbSS do not possess circulating HbA, therefore removing the substrate required for HbA1c synthesis. Most IE-HPLC analyzers report HbA1c as a percentage of total hemoglobin; consequently, in the absence of HbA, results are typically reported as zero or as technically unmeasurable [26]. Boronate affinity methods capture all glycated hemoglobin species regardless of structural subtype and are generally regarded as less susceptible to analytical interference from hemoglobin variants. However, these methods do not differentiate HbA1c from glycated HbF or glycated HbS, which may result in inaccurate measurements when these species are present in high concentrations [9,21]. The NGSP publishes regularly updated tables that identify certified methods exhibiting clinically significant interference, defined as a deviation of greater than ±6% from reference values for HbS, HbC, HbE, HbD, and HbF [9]

2.2.3 The Sickle Cell Trait (HbAS)

The impact of sickle cell trait (HbAS), defined as heterozygous carriage of HbS, on HbA1c is more complex than the effect observed in individuals with homozygous HbSS. A retrospective cohort study involving 4,620 African Americans demonstrated that sickle cell trait was associated with a significant reduction in mean HbA1c by 0.29% (95% CI: −0.35 to −0.23%) compared to individuals without the trait (5.72% versus 6.01%) [22]. This modest yet statistically significant effect may be sufficient to influence diagnostic classification, especially at HbA1c thresholds used to diagnose prediabetes and diabetes. Other studies, especially those using continuous glucose monitoring (CGM) as the reference standard, have not demonstrated that sickle cell trait significantly affects the accuracy of HbA1c compared with CGM [29]. These inconsistencies may be due to differences in assay technique, fluctuation in HbS concentration, and differences in population demographics.

2.3 Clinical presentation and diagnostic approach

2.3.1 Recognizing HbA1c Unreliability

HbA1c interference should be considered in the following situations: (a) the HbA1c result is below 4.0% or above 15.0%; (b) the HbA1c value is inconsistent with self-monitored blood glucose (SMBG) or random/fasting plasma glucose measurements; (c) there is a significant change in the HbA1c result after a modification in the laboratory assay method; or (d) the patient is from an ethnic group with a high prevalence of hemoglobinopathies, such as sub-Saharan African, Middle Eastern, South Asian, or Mediterranean populations [8]. A high index of suspicion is crucial, especially in geographic regions such as Iraq, Saudi Arabia, and other Middle Eastern countries where sickle cell anemia is prevalent, and diabetes represents a significant non-communicable disease burden.

The current ADA Standards of Care explicitly state that HbA1c measurement should not be used for patients with HbSS, HbCC, or HbSC disease because of the combined effects of hemolysis-related biological interference and potential analytical interference. Diagnostic procedures for these genotypes must use plasma glucose criteria which include a fasting glucose level of at least 7.0 mmol/L or a 2-hour post-load glucose level of at least 11.1 mmol/L during an oral glucose tolerance test, or other alternative biomarkers [21].

The various mechanisms by which hemoglobin variations distort HbA1c measurements are many and assay dependent. Hemoglobinopathies can impact HbA1c values in three primary methods: by modifying chromatographic peak measurements, through altering glucose binding to hemoglobin,

and by elevating the risk of hemolysis, thereby decreasing the lifespan of red blood cells [22]. In the quantitative analysis utilizing cation-exchange chromatography, genetic hemoglobin variants may co-elute with HbA1c, and the glycated fractions of these variants may exhibit different elution profiles in comparison to HbA1c, producing either falsely raised or falsely diminished readings [8]. Currently, there are more than 30 different laboratory techniques commercially available to quantify the proportion of HbA1c in blood, and research has reported significant bias among these analytical methods; therefore, comparability and standardization of HbA1c results across various methods remain an important clinical concern [21,22]. Considering that approximately 7% of the global population are heterozygous carriers of hemoglobin disorders, the choice of an appropriate, interference-free assay method is not merely a laboratory consideration but a direct patient safety concern, especially in regions of the Middle East where carrier rates for structural hemoglobin variants are significantly higher than the global average [8,24].

In addition to structural hemoglobin variations, several other clinical disorders must be recognized as causes of unreliable HbA1c levels. HbA1c may be inappropriate diagnostic test in individuals treated with erythropoietin, those with anemia or patients undergoing hemodialysis or HIV treatment, as these disorders alter hemoglobin levels or erythrocyte turnover [23,25]. In South Asia and similarly impacted regions, the elevated incidence of anemia, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and hemoglobinopathies, combined with inadequately standardized HbA1c assay methodologies, complicates the interpretation of HbA1c values and undermines its reliability in both the diagnosis and monitoring of diabetes [22]. Falsely raised HbA1c in relation to mean blood glucose levels can occur when red blood cell turnover is diminished — as seen with vitamin B12, iron, or folate deficiency anemia. Conversely, elevated RBC turnover leads to a greater proportion of younger red blood cells and falsely diminished HbA1c values, as seen in conditions of acute and chronic blood loss, pregnancy, hemolysis, or treatment with erythropoietin [21,24]. Clinicians practicing in Iraq and adjacent nations must therefore consider the entire range of confounding factors, not only hemoglobinopathies, when analyzing HbA1c findings in their patient populations.

When HbA1c is considered unreliable, proven alternative biomarkers and monitoring mechanisms must be employed to ensure precise glycemic evaluation. Serum fructosamine and glycated albumin (GA) are considered useful tools for assessing short-term glycemic control, as these biomarkers not only reflect glycemic regulation accurately in hematologic disorders but also indicate postprandial glucose fluctuation [8,22]. Alternative assessments for glycemic control include continuous glucose monitoring (CGM), capillary blood glucose readings, glycated albumin, serum fructosamine, and 1,5-anhydroglucitol (1,5-AG), each providing distinct temporal insight into glycemic information [23]. Other glycated proteins such as glycated albumin, fructosamine, and the nutritional monosaccharide 1,5-anhydroglucitol, as well as direct glucose assessment testing by SMBG or CGM systems, may provide significant complementary data, particularly in situations when HbA1c results may be unreliable or are insufficient for evaluating the risk of adverse outcomes [25]. Clinicians must recognize that glycated albumin values may be unreliable in patients with conditions altering albumin metabolism, such as liver cirrhosis, nephrotic syndrome, or thyroid disease, further highlighting the need for individualized, context-sensitive glycemic evaluation in complex patient cases.

2.3.2 The Effect of Blood Transfusion

Chronic blood transfusion therapy, utilized in sickle cell anemia (SCA) to diminish the fraction of hemoglobin S (HbS), introduces donor hemoglobin AA (HbAA) erythrocytes that experience standard glycation during their lifespan. This process may normalize or increase HbA1c levels, making the measurement temporally relevant for individuals receiving regular transfusions.

Conversely, following extensive transfusion, HbA1c measurements may represent a mixture of donor and recipient erythrocytes with differing ages and HbS proportions, complicating interpretation.
McLean et al. (2020) demonstrated a significant association between HbA1c and fructosamine in a pediatric patient with sickle cell disease receiving chronic transfusion therapy, suggesting that transfusion may effectively correct the glycation substrate and enhance the reliability of HbA1c measurements [25].

2.3.3 Hydroxyurea and HbF Effects

Hydroxyurea therapy improves fetal hemoglobin (HbF) manufacturing by reactivating the gamma-globin gene. Elevated fetal hemoglobin (HbF) concentrations interfere with HbA1c evaluation on some analytical platforms. The gamma-globin chain of HbF is missing the Val-1 residue found in the beta chain, which is necessary for the glycation of conventional HbA1c. Additionally, increased HbF competes with adult hemoglobin (HbA) as a substrate.
Furthermore, certain IE-HPLC methods exhibit interference when hemoglobin F (HbF) levels are elevated [9]. Clinicians should recognize that hydroxyurea-induced increases in fetal hemoglobin (HbF) may further compromise the reliability of HbA1c measurements in patients with sickle cell anemia (SCA), beyond the effects of hemolysis.

2.4 Alternative Glycemic Biomarkers for Sickle Cell Anemia

2.4.1 Fructosamine

Fructosamine measures the total concentration of glycated serum proteins, predominantly glycated albumin, and indicates the mean blood glucose level over the preceding 2 to 3 weeks, which aligns with the albumin half-life of approximately 20 days [27,28]. Because fructosamine measurement relies on protein glycation rather than hemoglobin glycation, it is theoretically unaffected by red blood cell lifespan or hemoglobin structure. This characteristic makes fructosamine an appealing alternative in sickle cell anemia (SCA) [27,28].

A systematic review by Al-Aboud et al. and a cohort study conducted in West Africa by Diallo et al. found a strong correlation between fructosamine and fasting blood glucose, regardless of sickle cell trait status .in the Diallo cohort comprising 618 Nigerian participants, fructosamine demonstrated comparable performance to HbA1c in detecting type 2 diabetes, with both exhibiting an area under the curve (AUC) of 0.92. An estimated diagnostic threshold of ≥309.5 µmol/L also demonstrated consistent performance [28].
A 2023 study from the University of Illinois Sickle Cell Center reported that fructosamine demonstrated a poor correlation with 14-day time-paired mean glucose concentrations ($r = +0.02$, $p = 0.8$) in patients with sickle cell disease. In contrast, HbA1c exhibited a statistically significant correlation with 30-day glucose ($r = +0.36$, $p < 0.001$), even after adjustment for hemolytic markers [24]. A 2025 Ugandan study published in Diabetic Medicine reported that fructosamine and glycated albumin do not offer significant improvements in glycemic monitoring compared to HbA1c in patients with sickle cell trait [29]. The findings indicate that fructosamine does not regularly surpass HbA1c in this population. Its use should therefore be guided by local conditions and individual patient factors.

Additional limitations of fructosamine are its sensitivity to abnormalities in protein metabolism, such as hypoalbuminemia, hyperalbuminemia, nephrotic syndrome, hyperthyroidism, and obesity. Furthermore, there is a lack of universally validated reference intervals across populations and insufficient prognostic data linking fructosamine levels to long-term diabetes complications [27,28].

2.4.2 Glycated Albumin

Glycated albumin (GA) quantifies the proportion of albumin that is glycated and serves as an indicator of glycemic control over a 2-to-4-week period [27]. Glycated albumin (GA) is not influenced by hemoglobin structure or red blood cell (RBC) lifespan. Several studies indicate that GA may be more effective than fructosamine in hemodialysis patients and in conditions involving protein-metabolism abnormalities, since albumin is

measured as a percentage rather than an absolute concentration [27]. A 2024 prospective pilot study by Kaminski et al. found that GA was superior to both HbA1c and fructosamine in detecting glycemic burden among patients with end-stage kidney disease [39].

However, GA shows a negative correlation with body mass index and may underrepresent glycemia in obese individuals. This issue is therapeutically relevant given the increasing prevalence of obesity among SCA patients in rich nations.

2.4.3 Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) offers the most precise and immediate glycemic assessment, unaffected by hemoglobin characteristics. Continuous glucose monitoring (CGM) provides (a) average glucose concentration, (b) metrics for glucose variability, (c) glucose time-in-range (TIR, defined as the percentage of time maintained within 70–180 mg/dL), and (d) diagnosis of nocturnal and fasting hypoglycemia. A patient with sickle cell anemia (SCA) and diabetes mellitus (DM) benefits from continuous glucose monitoring (CGM), which provides an objective assessment that addresses the biological and analytical limitation of HbA1c [24, 27].

The 2025 Ugandan study (Niwaha et al.), employing continuous glucose monitoring (CGM) as the reference standard, estimated that HbA1c had the strongest correlation with CGM-measured mean glucose ($r = 0.88$), even in patients with sickle cell trait, anemia, and renal impairment, while fructosamine and glycated albumin each showed a correlation of $r = 0.84$. The authors concluded that replacing HbA1c with fructosamine or glycated albumin is unlikely to improve the precision of glycemic monitoring in this demographic [29]. This study largely focused on patients with sickle cell trait (HbAS) more than those with homozygous HbSS, who experience a significantly higher hemolytic burden.

More challenges to continuous glucose monitoring, or CGM, in low- and middle-income countries (LMICs), where most of sickle cell anemia (SCA) patients are located, encompass exorbitant costs, limited sensor accessibility, and insufficient infrastructure for data interpretation. Continuous glucose monitoring should be considered the preferred method for glycemic assessment in SCA patients when HbA1c result are inconsistent with clinical symptoms or plasma glucose measurements.

2.5 Management of Sickle Cell Anemia: Disease-Modifying and Curative Therapies

2.5.1 Hydroxyurea

Hydroxyurea (HU) has served as the primary pharmacological treatment for sickle cell anemia (SCA) since its FDA approval in 1998 for adults, with its indication expanded to pediatric patients aged two years and older in 2017 [31,33]. Hydroxyurea (HU) functions as a ribonucleotide reductase inhibitor that induces fetal hemoglobin (HbF) production via epigenetic reactivation of the gamma-globin gene, reduces neutrophil count, decreases endothelial adhesion molecule expression, and enhances erythrocyte deformability [31]. Cumulative evidence from the landmark MSH, BABY HUG, and TWiTCH trials, as well as a 2024 meta-analysis of 45 articles published between 2003 and 2023, demonstrate that a daily dose of 20 mg/kg results in an approximately 18% increase in HbF and significant reductions in transcranial Doppler velocity, tricuspid regurgitant velocity, albuminuria, and splenic dysfunction [31]. Current guidelines recommend initiating HU therapy at 9 months of age, irrespective of clinical severity, and continuing treatment indefinitely [31].

2.5.2 Novel FDA-Approved Therapies

Between 2017 and 2019, the FDA approved three novel disease-modifying agents: L-glutamine (2017), crizanlizumab (2019), and voxelotor (2019) [32,34,35]. L-glutamine, an amino acid that mitigates oxidative stress in sickle erythrocytes by enhancing the NAD redox potential, was associated with significant reductions in vaso-occlusive crisis frequency and hospitalization rates in the Phase III trial conducted by Niihara et al. [32,34]. Crizanlizumab, a humanized anti-P-selectin monoclonal antibody, demonstrated a 45%

reduction in annualized vaso-occlusive crisis (VOC) rates compared to placebo at a 5 mg/kg dose in the SUSTAIN trial [32,40].

The Phase III STAND study failed to replicate these advantages, leading the European Medicines Agency to revoke crizanlizumab's marketing authorization in June 2023 [31,33]. Voxelotor, an inhibitor of hemoglobin S polymerization that allosterically stabilizes the R-state of HbS, demonstrated a rise in mean hemoglobin levels of around 1.1 g/dL in the HOPE study [34,35]. However, post-approval registries identified safety issues, including a higher incidence of vaso-occlusive crises (VOC) and elevated mortality rates, prompting Pfizer to voluntarily withdraw voxelotor from international markets in September 2024. [31,33,40].

2.5.3 Gene Therapy and Curative Approaches

Hematopoietic stem cell transplantation (HSCT) from an HLA-matched sibling donor is the only recognized curative therapy for sickle cell anemia (SCA), preventing disease progression and facilitating transfusion independence. However, the transplant-associated mortality, donor scarcity, and the potential for graft-versus-host disease [34] limit the implementation of this therapy. The FDA's approval in December 2023 of two gene therapy products, exagamglogene autotemcel (Casgevy, Vertex/CRISPR Therapeutics), which utilizes CRISPR-Cas9 for the reactivation of fetal hemoglobin, and lovotibeglogene autotemcel (Lyfgenia, Bluebird Bio), which employs a lentiviral vector to express anti-sickling hemoglobin, represents a significant progression in the potential curative treatment of sickle cell anemia (SCA) [34,36]. Both therapies have shown significant rates of VOC removal in treated patients; yet, issues of long-term follow-up, accessibility, and cost remain.

2.6 Clinical recommendation and proposed algorithm

Based on the evaluated evidence, the subsequent stepwise recommendations are suggested for glycemic testing in patients with SCA:

Step 1: Determine genotype. Hemoglobin electrophoresis or HPLC must be conducted for all patients with SCA to ascertain the HbS genotype (HbSS, HbSC, HbSβ-thalassemia) before interpreting HbA1c values.

Step 2: Choose an NGSP-certified test technique. HbA1c measurements must be conducted using an NGSP-certified method that exhibits no clinically relevant interaction with HbS. Boronate affinity or immunoassay techniques are preferred over IE-HPLC platforms for patients with HbSS, where HbA is either absent or low.

Step 3: Establish correlation with plasma glucose levels. In individuals with sickle cell anemia, HbA1c values should be analyzed in conjunction with fasting and 2-hour post-load plasma glucose levels. When inconsistencies occur between HbA1c and plasma glucose measurements, additional biomarkers or glycemic evaluation techniques are advised.

Step 4: Evaluate fructosamine or glycated albumin. In individuals with HbSS or HbSC whose HbA1c is unreliable, fructosamine or glycated albumin may provide supplementary short-term glycemic information. Interpretation must take into account albumin concentration, renal function, and body mass index.

Step 5: Execute continuous glucose monitoring. In cases of persistent discordance or when clinical situations necessitate accurate glycemic evaluation, such as the perioperative period, pregnancy, or insulin introduction, continuous glucose monitoring (CGM) should be considered the reference standard.

Step 6: Modify according to transfusion status. In patients undergoing regular blood transfusions, HbA1c may be temporarily accurate due to the infusion of HbAA donor erythrocytes. The quantity and timing for each transfusion must be recorded alongside every HbA1c measurement.

4. Discussion

The relationship between sickle cell anemia and diabetes mellitus demonstrates how a molecular genetic condition can affect the reliability of a typically powerful clinical test indicator.

The pathophysiological basis is solid and well-

defined. Chronic hemolysis reduces red blood cell lifespan, restricts the timing for HbA1c accumulation, and consistently leads to lower HbA1c levels compared to actual mean glycemia [8,19,22]. Yet the clinical implications, including postponed diabetes diagnosis, insufficient assessment of glycemic management, and accelerated degeneration of diabetic organs, are still barely acknowledged beyond endocrinology facilities and specialized hematology.

The findings suggest that the issue transcends simple HbA1c underestimate. Analytical interference is complex and unique to each assay, with immunoassay, IE-HPLC, boronate affinity, and capillary electrophoresis showing unique susceptibilities [9,21]. The evaluation of HbF due to hydroxyurea creates an additional layer of uncertainty [9]. Recent data from extensive prospective cohort studies and continuous glucose monitoring (CGM)-referenced trials indicate that other measures, such as glycated albumin and fructosamine, are not effectively superior and possess a specific measurement limitations [24,27,29].

The current withdrawal of voxelotor and the revocation of crizanlizumab's European authorization demonstrate the persistent challenges in developing disease-modifying therapies for sickle cell anemia (SCA) and emphasize the continued importance of hydroxyurea (HU) as the primary pharmacological treatment [31,33,40]. Gene therapies such as Lyfgenia and Casgevy exhibit significant potential for curing sickle cell anemia in future generations. However, expense and access present substantial barriers in low- and middle-income countries, where the majority of patients with sickle cell anemia lives [34,36].

Essential future research priorities involve the prospective validation of continuous glucose monitoring (CGM)-referenced glycemic thresholds in homozygous HbSS patients with diabetes, the development of HbA1c correction algorithms that utilize hemolysis biomarkers such as reticulocyte count and indirect bilirubin , the establishment of population-specific reference intervals for fructosamine in areas with a high disease prevalence and the identification of pharmacological strategies to modulate and predict the impact of disease-modifying therapies, including gene therapy and hydroxyurea, on the reliability of glycemic biomarkers.

Conclusion

Sickle cell anemia compromises the accuracy of HbA1c as a glycemic biomarker via two distinct and cumulative mechanisms. Initially, biological underestimation arises from a reduced lifespan of red blood cells and hemolysis-induced decrease of HbA1c. Secondly, analytical interference arises from the existence of structurally aberrant hemoglobin S and elevated fetal hemoglobin, which affect several test platforms. Clinicians treating patients who have sickle cell anemia (SCA) must recognize that a 'normal' HbA1c level in this population may mask significant, clinically relevant hyperglycemia. Employing a multimodal strategy that incorporates plasma glucose criteria, genotype-informed assay selection, alternative short-term biomarkers like glycated albumin and fructosamine and continuous glucose monitoring is crucial for precise glycemic assessment and the prevention of diabetic complications in this at-risk demographic. With the aging SCA population and the increasing global incidence of diabetes, addressing this diagnostic gap is an essential goal for endocrinology, hematology, and laboratory medicine.

Acknowledgments

The authors wish to thank the academic and clinical staff at [AL-Sader Educational Hospital] for their support.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, et al. Global epidemiology of sickle hemoglobin in neonates:

a contemporary geostatistical model-based map and population estimates. Lancet. 2013;381(9861):142–151. doi:10.1016/S0140-6736(12)61229-X. [PubMed Search: Piel sickle hemoglobin neonates global epidemiology Lancet 2013]

2. GBD 2021 Sickle Cell Disease Collaborators. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000–2021: a systematic analysis from the Global Burden of Disease Study 2021. Lancet Haematol. 2023;10(8):e585–e599. doi:10.1016/S2352-3026(23)00118-7. [PubMed Search: GBD sickle cell disease global burden 2021 Lancet Haematol]
3. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, et al. Sickle cell disease. Nat Rev Dis Primers. 2018;4:18010. doi:10.1038/nrdp. 2018.10. [PubMed Search: Kato sickle cell disease Nature Reviews Primers 2018]
4. Sundd P, Gladwin MT, Novelli EM. Pathophysiology of sickle cell disease. Annu Rev Pathol. 2019;14:263–292. doi:10.1146/annurev-pathmechdis-012418-012838. [PubMed Search: Sundd Gladwin Novelli pathophysiology sickle cell disease Annual Review Pathology 2019]
5. Toperzer K, Moon A. Diagnostic limitations of hemoglobin A1c in the setting of compound hemoglobinopathy: a case report of sickle cell disease, alpha thalassemia, and occult diabetes. Cureus. 2026;18(1):e101623. doi:10.7759/cureus. 101623.
6. Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. Biomarker Insights. 2016;11:95–104. doi:10.4137/BMI.S38440.
7. ElSayed NA, Aleppo G, Aroda VR, et al.; American Diabetes Association. 6. Glycemic targets: Standards of Care in Diabetes—2023. Diabetes Care. 2023;46(Suppl. 1):S97–S110. doi:10.2337/dc23-S006. [PubMed Search: ADA Standards of Care glycemic targets 2023 Diabetes Care]
8. Bunn HF. Pathogenesis and treatment of sickle cell disease. N Engl J Med. 1997;337(11):762–769. doi:10.1056/NEJM199709113371107. [PubMed Search: Bunn pathogenesis treatment sickle cell disease NEJM 1997]
9. National Glycohemoglobin Standardization Program (NGSP). HbA1c assay interferences [Internet]. Columbia (MO): NGSP; 2023 [cited 2025 Jan 15]. Available from: https://ngsp.org/interf.asp. [Search: NGSP HbA1c assay interferences hemoglobin variants]
10. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. N Engl J Med. 2017;376(16):1561–1573. doi:10.1056/NEJMra1510865. [PubMed Search: Piel Steinberg Rees sickle cell disease NEJM 2017]
11. Weatherall DJ. Inherited hemoglobinopathies are an emerging global health burden. Blood. 2010;115(22):4331–4336. doi:10.1182/blood-2010-01-251348. [PubMed Search: Weatherall inherited diseases hemoglobin global burden Blood 2010]
12. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312(10):1033–1048. doi:10.1001/jama.2014.10517. [PubMed Search: Yawn sickle cell disease management 2014 JAMA]
13. Adyan Adnan Hashem, Siham Jasim Alkaabi. Detection of the mrkD Adhesion Gene and Phenotypic Assessment of Biofilm Formation., Al-Harf Journal, 25(1), 2026.
14. Al-Fatlawey,Esraa S., Kadhim, D. A. and Omara, A. M. (2026). 'Thalassemia and Glycated Hemoglobin (HbA1c): Pathophysiological Interferences, Analytical Challenges, and Clinical Management Implications: A Comprehensive Review' .,Kuwait Scientific Research Journal of Medical Sciences, 3(2), pp. 1-15
15. Al-Qurashi MM, El-Mouzan MI, Al-Herbish AS, Al-Salloum AA, Al-Omar AA. The prevalence of sickle cell disease in Saudi children and adolescents. Ann Saudi Med. 2008;28(5):388–391. doi:10.5144/0256-4947.2008.388. [PubMed Search: Al-Qurashi sickle cell disease

prevalence Saudi children Ann Saudi Med 2008]

16. Vekilov PG. Sickle-cell hemoglobin polymerization: Is it the primary pathogenic event of sickle-cell anemia? Br J Haematol. 2007;139(2):173–184. doi:10.1111/j.1365-2141.2007.06794.x. [PubMed Search: Vekilov HbS polymerization sickle cell anemia Br J Haematol 2007]
17. Gordeuk VR, Abdalla S, Ghalie RG, et al. Sickle cell vaso-occlusion: the dialectic between red cells and white cells. Exp Biol Med. 2021;246(14):1555–1570. doi:10.1177/1535370221999494. [PubMed Search: Gordeuk sickle cell vaso-occlusion red cells white cells Exp Biol Med 2021]
18. Telen MJ, Malik P, Vercellotti GM. Therapeutic strategies for sickle cell disease: towards a multi-agent approach. Nat Rev Drug Discov. 2019;18(2):139–158. doi:10.1038/s41573-018-0003-2. [PubMed Search: Telen Malik Vercellotti therapeutic strategies sickle cell disease Nat Rev Drug Discov 2019]
19. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease: life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639–1644. doi:10.1056/NEJM199406093302303. [PubMed Search: Platt Brambilla Rosse sickle cell disease mortality NEJM 1994]
20. Kato GJ, Steinberg MH, Gladwin MT. Intravascular hemolysis and the pathophysiology of sickle cell disease. J Clin Invest. 2017;127(3):750–760. doi:10.1172/JCI89741. [PubMed Search: Kato Steinberg Gladwin intravascular hemolysis sickle cell disease JCI 2017]
21. Mangla A, Ehsan M, Agarwal N, Maruvada S. Sickle cell anemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [updated 2023 Sep 4; cited 2025 Jan 15]. [PubMed Search: Mangla sickle cell anemia StatPearls 2023]
22. Hebbel RP, Vercellotti G, Nath KA. A systems biology consideration of the vasculopathy of sickle cell anemia: the need for multi-modality chemoprevention. Clin Appl Thromb Hemost. 2009;15(5):509–511. doi:10.1177/1076029609348522. [PubMed Search: Hebbel Vercellotti vasculopathy sickle cell anemia Clin Appl Thromb Hemost 2009]
23. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Sickle cell trait, hemoglobinopathies & diabetes: A1C test [Internet]. Bethesda (MD): NIDDK; 2025 [cited 2025 Jan 15]. Available from: https://www.niddk.nih.gov. [Search: NIDDK sickle cell trait hemoglobinopathies diabetes A1C test]
24. Lacy ME, Wellenius GA, Sumner AE, Correa A, Carnethon MR, Liem RI, et al. Association of sickle cell trait with hemoglobin A1c in African Americans. JAMA. 2017;317(5):507–515. doi:10.1001/jama.2016.21035. [PubMed Search: Lacy sickle cell trait HbA1c African Americans JAMA 2017]
25. Christensen DL, Witte DR, Kaduka L, Jørgensen ME, Borch-Johnsen K, Mohan V, et al. Moving to an A1C-based diagnosis of diabetes has a different impact on prevalence in different ethnic groups. Diabetes Care. 2010;33(3):580–582. doi:10.2337/dc09-1898. [PubMed Search: Christensen A1C diagnosis diabetes ethnicity Diabetes Care 2010]
26. Sun R, Layden B, Zapatar J, Galanter B, Lash J, Han J, et al. Markers of glycemic control in adults with sickle cell disease. Blood. 2023;142(Suppl 1):928. doi:10.1182/blood-2023-179278. [PubMed Search: Sun Layden glycemic control sickle cell disease Blood 2023]
27. McLean A, Wright F, deJong N, Skinner S, Loughlin CE, Levenson A, Carden MA. Hemoglobin A1c and fructosamine correlate in a patient with sickle cell disease and diabetes on chronic transfusion therapy. Pediatr Blood Cancer. 2020;67(9):e28499. doi:10.1002/pbc.28499. [PubMed Search: McLean HbA1c fructosamine sickle cell disease chronic transfusion Pediatr Blood Cancer 2020]
28. Yilmaz M, Ozyilmaz F, Koc N. Unmeasurable HbA1c result due to hemoglobinopathy. Int J Med Biochem. 2022;5(2):75–79. doi:10.14744/ijmb.2022.59480.
29. Nathan JD, Rao A. Clinical utility of

fructosamine and glycated albumin. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [updated 2025 Sep 14; cited 2025 Jan 15]. [PubMed Search: fructosamine glycated albumin clinical utility StatPearls 2024]

30. Diallo A, Charbit-Henrion F, Gissot V, Balestre E, Fontbonne A. Serum fructosamine and glycemic status in the presence of the sickle cell mutation. Diabetes Res Clin Pract. 2021;178:108980. doi:10.1016/j.diabres.2021.108980.

31. Niwaha AJ, Nyirenda MJ, Mwebaze R, et al. Glycated albumin and fructosamine do not improve the accuracy of glycaemic control assessment in patients with conditions reported to affect HbA1c reliability. Diabet Med. 2025;e70011. doi:10.1111/dme.70011. [PubMed Search: Niwaha glycated albumin fructosamine HbA1c accuracy sickle cell trait Diabet Med 2025]

32. Alzahrani BA, Alotaibi AS, Albakri MI, et al. The effect of different types of anemia on HbA1c levels in non-diabetics. BMC Endocr Disord. 2023;23(1):24. doi:10.1186/s12902-023-01280-y. [PubMed Search: Alzahrani anemia HbA1c non-diabetics BMC Endocrine Disorders 2023]

33. López Rubio M, Argüello Marina M. The current role of hydroxyurea in the treatment of sickle cell anemia. J Clin Med. 2024;13(21):6404. doi:10.3390/jcm13216404. [PubMed Search: Lopez Rubio hydroxyurea sickle cell anemia J Clin Med 2024 6404]

34. Migotsky M, Beestrum M, Badawy SM. Recent advances in sickle-cell disease therapies: a review of voxelotor, crizanlizumab, and L-glutamine. Pharmacy (Basel). 2022;10(5):123. doi:10.3390/pharmacy10050123.

35. Hassan O, Farhan H, Zahreddine N, et al. A review on disease modifying pharmacologic therapies for sickle cell disease. Ann Hematol. 2025;104:1209–1223. doi:10.1007/s00277-025-06216-1.

36. Coleman SR, Moonga M, Ward JM, Cooper HM. Hope on the horizon: new and future therapies for sickle cell disease. Biomedicines. 2023;11(9):2542. doi:10.3390/biomedicines11092542.

37. Achebe MM, Okam MM, Ilonze O, et al. Advances in the diagnosis and treatment of sickle cell disease. J Hematol Oncol. 2022;15(1):20. doi:10.1186/s13045-022-01237-z.

38. Ngwube A, Hoyt TR, Henry RL, et al. Current and future therapeutics for treating patients with sickle cell disease. Front Genet. 2024;15:1383007. doi:10.3389/fgene.2024.1383007.

39. Little RR, Roberts WL. A review of variant hemoglobins interfering with hemoglobin A1c measurement. J Diabetes Sci Technol. 2009;3(3):446–451. doi:10.1177/193229680900300307.

40. Bry L, Chen PC, Sacks DB. Effects of hemoglobin variants and chemically modified derivatives on assays for glycohemoglobin. Clin Chem. 2001;47(2):153–163.

41. Kaminski CY, Galindo RJ, Navarrete JE, et al. Assessment of glycemic control by continuous glucose monitoring, hemoglobin A1c, fructosamine, and glycated albumin in patients with end-stage kidney disease and burnt-out diabetes. Diabetes Care. 2024;47(2):267–271. doi:10.2337/dc23-1276.

42. Karkoska K, Jacob SA, McGann PT. Accelerated drug approvals and patient trust: impact of voxelotor and crizanlizumab for sickle cell disease. Blood Adv. 2025;9(11):2857–2862. doi:10.1182/bloodadvances.2025015822.