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Thalassemia and Glycated Hemoglobin (HbA1c): Pathophysiological Interferences, Analytical Challenges, and Clinical Management Implications: A Comprehensive Review

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Abstract: Background: Glycated hemoglobin (HbA1c) is the internationally recognized gold standard to assess long-term glycemic control in patients with diabetes mellitus. However, its efficacy is fundamentally undermined in thalassemia syndromes, which are one of the most prevalent inherited hemoglobin disorders worldwide due to ineffective erythropoiesis, altered red blood cell biology, chronic hemolysis, reduced red blood cell (RBC) lifespan, and confounding factors related to transfusion. Despite precise glycemic monitoring being clinically time-sensitive and urgent for thalassemia patients, who have significantly raised risk of endocrine disorders such as diabetes mellitus, a universally recognized clinical framework for addressing this diagnostic challenge remains absent.

Objectives: This comprehensive review critically analyzes the mechanisms through which different thalassemia subtypes, including α-thalassemia, β-thalassemia major (transfusion-dependent), β-thalassemia intermedia (non-transfusion-dependent), and compound hemoglobinopathies, influence HbA1c measurement across accepted analytical system. This research further assesses the evidence base for alternative glycemic indicators in thalassemia populations and presents evidence-informed clinical recommendations.

Methods: A narrative systematic review was performed using PubMed/MEDLINE, the Cochrane Library, Embase, and Google Scholar to identify peer-reviewed publications from 2000 to 2025, with particular emphasis on those published post-2015. The search terms used were thalassemia, hemoglobin A1c, glycated hemoglobin, HbA1c interference, fructosamine, glycated albumin, continuous glucose monitoring, hemoglobinopathy, diabetes mellitus, iron overload, and erythrocyte lifespan.

Results: The alpha-thalassemia trait does not substantially affect HbA1c assessment in standard high-performance liquid chromatography (HPLC) techniques. Conversely, HbH disease causes significant measurement errors in cation-exchange HPLC systems due to peak co-elution. The β-thalassemia trait is linked to a statistically significant, yet clinically minor, decrease in HbA1c levels, primarily resulting from a decrease in hemoglobin concentration. Transfusion-dependent β-thalassemia compromises the accuracy of HbA1c measurement through several procedures including Glycated albumin, fructosamine, and continuous glucose monitoring (CGM) offer clinically relevant, although not flawless, alternatives for glycemic evaluation in thalassemia settings.

Conclusion: Clinicians treating thalassemia patients with suspected or co-existing diabetes must exercise caution when interpreting HbA1c results, identify method-specific analytical limits, and consistently use alternative glycemic monitoring strategies. Efficient multidisciplinary coordination among diabetologists, hematologists, and clinical laboratorians is essential for achieving optimal glycemic surveillance and reducing the risk of both under- and over-treatment of diabetes among patients with thalassemia.

Keywords:Thalassemia; Glycated hemoglobin; HbA1c; Diabetes mellitus; Hemoglobinopathy; Fructosamine; Glycated albumin; Continuous glucose monitoring; Iron overload; Red blood cell lifespan

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Introduction

Thalassemia syndromes are the most prevalent single-gene disorders worldwide and pose a significant public health challenge in the Middle East, Mediterranean basin, South Asia, and sub-Saharan Africa. The prevalence is also increasing rapidly in non-endemic Western countries because of migratory patterns [1, 2]. According to the Global Burden of Disease (GBD) 2021 analysis, that includes data from 204 countries and territories, the global rate for thalassemia was 119,679 cases in 2021, with an estimated 13.1 million prevalent cases worldwide [3]. Southeast Asia shows the highest age-standardized mortality rate, whereas East Asia shows the highest incidence rates, emphasizing the geographic variability of this genetic disorder [4].

At the same time, diabetes mellitus has become increasingly recognized as the leading non-communicable disease of the 21st century. According to the International Diabetes Federation (IDF), 589 million persons aged 20 - 79 currently have diabetes, and this number is projected to rise to 853 million by 2050 [5]. The integration of these two global epidemics creates a clinically complex scenario marked by the significant coexistence of both conditions, especially in thalassemia-endemic regions where diabetes resulting from iron overload and pancreatic siderosis is disproportionately common.

Glycated hemoglobin (HbA1c) is formed by the nonenzymatic binding of glucose to the N-terminal valine residue of the hemoglobin β-chain. HbA1c act as an indicator of mean plasma glucose concentrations over the past 2 to 3 months, which aligns with the average erythrocyte lifespan [6,7]. The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated a direct correlation between HbA1c levels and diabetic complications. As a result, HbA1c is now universally recognized by the World Health Organization (WHO), American Diabetes Association (ADA), and the International Federation of Clinical Chemistry (IFCC) as the gold standard for both diagnosis and of longitudinal monitoring and diabetes mellitus [8].

However, the reliability of HbA1c as an indicator depends on a physiologically normal lifespan of erythrocytes, typically 90 - 120 days. In thalassemia, many genetic lesions impair the structure and production of hemoglobin chains, therefore, systematically violating this assumption. Thalassemia impairs erythrocyte biology through multiple intersecting mechanisms. Accelerated hemolysis reduces the lifespan of a red blood cell. Ineffective erythropoiesis results in structurally abnormal erythrocytes. Chronic transfusions introduce donor hemoglobin, whereas iron overload after repeated transfusions and increased gastrointestinal absorption result in multiorgan endocrinopathies, including pancreatic beta-cell failure [9,10].

Despite substantial research has addressed individual aspects of this clinical issue, a comprehensive, analytically rigorous synthesis of the mechanisms, magnitude, and clinical implications of thalassemia-HbA1c interference, coupled with a critical assessment of alternative monitoring strategies, remains essential to inform laboratory scientists, clinicians, and policymakers in thalassemia-endemic regions. This review meets this requirement by presenting a comprehensive, evidence-based analysis suitable to an international audience.

1.1. Classification and epidemiology of thalassemia

1.1.1 Genetic Basis and Classification

Thalassemia includes a heterogeneous group of genetic hemolytic anemias characterized by quantitative defects in globin chain production. Clinically significant subtypes are categorized by the specific globin chains involved [11].

Alpha-thalassemia (α-thalassemia) arises from deletions or mutations affecting one to four of the alpha-globin genes situated on chromosome 16p13.3 [12]. Individuals with a silent carrier state, characterized by a single affected gene, exhibit a normal phenotype. Alpha-thalassemia trait, which involves a two-gene deletion, leads to mild microcytic anemia. In contrast, HbH disease, caused by a three-gene deletion, results in moderately severe hemolytic anemia characterized by the accumulation of unstable HbH (β4 tetramers). Homozygous α-thalassemia (Hb Bart's hydrops fetalis, four-gene deletion) is considered incompatible with extrauterine life in the absence of intrauterine transfusions [13].

Beta-thalassemia (β-thalassemia) arises from more than 300 identified mutations in the HBB gene located on chromosome 11p15.5, resulting in either reduced (β+) or absent (β0) β-globin chain synthesis [14]. Beta-thalassemia minor (trait, carrier, or heterozygous form) typically presents as an asymptomatic condition characterized by mild microcytic anemia. Beta-thalassemia intermedia, also known as non-transfusion-dependent thalassemia (NTDT), is characterized by moderate anemia that does not consistently require regular transfusions. Beta-thalassemia major, also known as transfusion-dependent thalassemia (TDT), manifests in early childhood as severe anemia that necessitates regular lifelong transfusions [15].

Compound hemoglobinopathies such as HbE/β-thalassemia, which is the most common severe hemoglobinopathy worldwide, constitute a clinically significant hybrid disorder. These conditions exhibit variable phenotypic expression, ranging from transfusion independence to transfusion dependence, which further complicates the interpretation of HbA1c results [16].

1.1.2 Global Epidemiology

The prevalence of thalassemia is geographically concentrated, with the highest carrier frequencies reported in Cyprus (14%), Sardinia (10.4%), Southeast Asia (Thailand 5–8%), and the Mediterranean basin [1,2]. The Maldives reports the highest global carrier rate, estimated at approximately 18% [17]. In contrast, carrier prevalence in Middle Eastern and Gulf Cooperation Council (GCC) countries ranges from 2% to 14% [18]. The Maldives reports the highest global carrier rate, estimated at approximately 18% [17]. In contrast, carrier prevalence in Middle Eastern and Gulf Cooperation Council (GCC) countries ranges from 2% to 14% [18] .Rapidly changing migratory patterns have contributed to the emergence of thalassemia as a global health concern, with rising case detection in Western Europe, North America, and Australia [19].

The GBD 2021 study reported an age-standardized prevalence rate of thalassemia of 18.28 per 100,000 persons (95% UI: 15.29–22.02) in 2021. This was accompanied by a declining trend in age-standardized incidence rates, attributed to the implementation of preventive prenatal screening programs and reproductive genetic counseling [3]. Although overall incidence has declined, the total number of prevalent cases continues to increase due to improved survival associated with modern management, especially in higher-income countries [3,20].

1.2. Biochemistry of HbA1c: Formation, Measurement, and Standardization

1.2.1 Mechanism of HbA1c Formation

Hemoglobin A1c (HbA1c) is generated via a two-step nonenzymatic glycation process. During the initial reversible step, glucose interacts with the free N-terminal valine residue of the hemoglobin β-chain, forming an unstable aldimine (Schiff base) intermediate. This intermediate subsequently undergoes a spontaneous Amadori rearrangement, forming the stable ketoamine HbA1c. The rate of HbA1c formation is proportional to the mean ambient glucose concentration and red blood cell (RBC) lifespan. Both factors are significantly disrupted in thalassemia [7,21].

Because erythrocytes cannot regenerate hemoglobin, the cumulative glycation of circulating HbA serves as a direct indicator of average plasma glucose throughout the lifespan of red blood cells. Younger red blood

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cells (reticulocytes and mature erythrocytes) exhibit significantly lower glycated hemoglobin levels than older red blood cells, creating a biological gradient. Any condition that modifies the age distribution of circulating erythrocytes, as regularly observed in thalassemia, would modify the HbA1c value despite glycemic status [21, 22].

1.2.2. HbA1c Measurement Platforms and Their Principles

Diverse analytical platforms are employed for HbA1c quantification, each showing specific susceptibilities to interference from hemoglobin variations and thalassemia syndromes [23]. Ion-exchange high-performance liquid chromatography (HPLC) is widely regarded as the standard method for separating hemoglobin fractions according to charge differences. Despite HPLC is certified by the National Glycohemoglobin Standardization Program (NGSP) and is traceability to the International Federation of Clinical Chemistry (IFCC), it remains vulnerable to co-elution of abnormal hemoglobin peaks at the HbA1c elution position, which can result in inaccurate readings in various thalassemia subtypes [24,25].

Boronate affinity chromatography and affinity HPLC measure total glycated hemoglobin by binding it to boronate. These approaches are less susceptible to structural interference from hemoglobin variations; however, they fail to differentiate HbA1c from other glycated hemoglobin fractions and are influenced by the increased HbF levels and modified red blood cell lifespan [23, 26]. Immunoassays (turbidimetric and nephelometric) employ antibodies that target the glycated N-terminal hexapeptide of the β-chain; they are rapid and extensively automated but unable to detect hemoglobin variants, resulting in silent errors when variants fall outside the antibody recognition window [23,27]. Enzymatic assays, representing the most advanced methods, utilize endo-proteinase Glu-C to selectively cleave the N-terminal β-chain hexapeptide and detect HbA1c spectrophotometrically. These assays demonstrate favorable performance in specific hemoglobin variant contexts; however, their accuracy is remained unaffected by altered red blood cell lifespan in thalassemia [25,26].

Capillary electrophoresis (CE) separates hemoglobin species based on their charge-to-mass ratio and, similar to high-performance liquid chromatography (HPLC), can identify hemoglobin variants. However, CE encounters challenges related to parallel-capillary consistency and reduced efficiency during high-throughput analyses [23]

1.2.3. International Standardization of HbA1c

International standardization of HbA1c measurement is overseen by the NGSP, which certifies HbA1c assay methods against the DCCT/UKPDS reference standard. The IFCC reference method employs mass spectrometric quantification of specific β-chain hexapeptides following enzymatic digestion [23,25]. All major diabetes associations endorse dual reporting in NGSP (%) and IFCC (mmol/mol) units. However, existing standardization frameworks do not comprehensively address the systematic biases introduced by hemoglobin variants and thalassemia. The NGSP provides guidance on variant-specific method interference but does not certify methods for use in thalassemia populations [23,27].

1.3. Mechanism of HbA1c interference in thalassemia

1.3.1. Reduced Red Blood Cell Lifespan

The primary mechanism by which thalassemia alters HbA1c measurements is accelerated erythrocyte destruction [21,28]. In β-thalassemia major, intramedullary destruction of abnormal erythroid precursors, known as ineffective erythropoiesis, along with peripheral hemolysis of circulating erythrocytes, reduces the mean red blood cell lifespan from the normal 90 to 120 days to as few as 20 to 40 days in severely affected patients. A reduction in red blood cell (RBC) survival proportionally decreases the time available for glucose to glycate hemoglobin, resulting in HbA1c values that significantly underestimate actual mean plasma glucose, regardless of the measurement platform used

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(RBC) survival proportionally decreases the time available for glucose to glycate hemoglobin, resulting in HbA1c values that significantly underestimate actual mean plasma glucose, regardless of the measurement platform used [28,29].

This mechanism closely parallels other hemolytic anemias, such as sickle cell disease, hereditary spherocytosis, and G6PD deficiency, in which HbA1c underestimates glycemia. This similarity accounts for historical reports of patients with thalassemia and overt diabetes presenting with deceptively low HbA1c values [9,30].

1.3.2. Analytical Interference from Abnormal Hemoglobin Species

Thalassemia syndromes produce pathological hemoglobin species, including HbH (β4 tetramers), Hb Bart's (γ4 tetramers), elevated HbF (fetal hemoglobin, α2γ2), and HbA2 (α2δ2). These species physically co-elute or co-migrate with HbA1c on various analytical platforms, resulting in false-positive or false-negative HbA1c signals [24,25,28].

In cation-exchange high-performance liquid chromatography (HPLC) systems, such as the Sebia Capillaries 2 Flex Piercing (C2FP), the peaks corresponding to HbH and Hb Bart's migrate to positions that overlap with or are adjacent to the HbA1c fractions. Previous research indicates that standard HPLC does not provide accurate HbA1c measurements in the presence of Hb Bart's. Additionally, HbH disease necessitates the use of comparative or complementary assay systems [28,31]. In HbE/β-thalassemia, the HbE peak, resulting from a Lys to Glu substitution at β-chain position 26, elutes near to HbA1c on ion-exchange HPLC in curtain system configurations. This proximity increases the likelihood of inaccurate quantification [32].

Increased HbF, universally present in β-thalassemia major and, intermedia induces analytical interference in immunoassay and boronate affinity platforms. These techniques measure total glycated hemoglobin without differentiating between HbA-derived and HbF-derived glycated fractions [23,27]. The total effect depends on both the measurement method and the individual variant, underscoring the need to identify the measurement technique when interpreting HbA1c in thalassemia [24,31,33].

1.3.3. Transfusion-Related Confounders

Patients with transfusion-dependent β-thalassemia (TDT) generally undergo red cell transfusions every 2 - 4 weeks to maintain pre-transfusion hemoglobin concentrations between 9 -10.5 g/dL [15,34]. Each unit of transfused packed red blood cells provides a bolus of hemoglobin A (HbA) from healthy adult donors, which temporarily dilutes the recipient's aberrant hemoglobin. The administration of HbA via blood transfusion systematically confounds HbA1c measurement by increasing the proportion of normal adult hemoglobin accessible for glycation and resetting the age distribution of circulating erythrocytes to a younger demographic [9,34].

Each unit of transfused red blood cells (RBCs) comprises approximately 200 mg of elemental iron, which accumulates over time in the heart, liver, pancreas, and endocrine glands [34,35]. Iron overload-induce damage to pancreatic islet cells and insulin secretory deficiency are the principle causes of thalassemia-associated diabetes mellitus (TADM), a unique form of secondary diabetes that is mechanistically different from Type 1 or Type 2 diabetes yet require equally rigorous glycemic monitoring [35,36].

1.3.4. Iron Deficiency Comorbidity and Spurious HbA1c Elevation

Despite thalassemia syndromes typically resulting in falsely decreased HbA1c levels, the occurrence of iron deficiency anemia, especially in thalassemia patients with nutritional deficiencies or during gestational thalassemia, may paradoxically raise HbA1c values. Iron deficiency prolongs red blood cell lifespan by reducing production of reticulocyte, resulting in increasing the time available for hemoglobin glycation and leading to falsely increased HbA1c levels, in spite of glycemia being normal or near-normal [28,36,37].

The possibility for both falsely low and falsely high HbA1c values, depending on the interplay of hemolytic and iron-deficiency

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and most analytically challenging conditions in diabetes management. This complexity requires individualized clinical reasoning instead of exclusive reliance on algorithmic interpretation of HbA1c readings [37].

1.4. Evidence from clinical studies

1.4.1. Beta-Thalassemia Major

Many clinical research have shown that HbA1c is an unreliable indicator in transfusion-dependent thalassemia (TDT). A comprehensive case series and literature review by Gluvic et al. revealed that, in a male patient with transfusion-dependent thalassemia (TDT) exhibiting distal neuropathic pain and right toe ulceration, HbA1c levels significantly underestimated the real glycemic burden, as indicated by elevated fasting and postprandial glucose measurements. In this context, HbA1c indicates donor-derived hemoglobin A glycation and to a markedly reduced native red blood cell lifespan [10]. Several studies have established that HbA1c is not an appropriate primary monitoring tool in transfusion-dependent thalassemia (TDT), and instead recommend fructosamine or continuous glucose monitoring as better alternatives [9,10,38].

1.4.2. Beta-Thalassemia Trait

A significant cross-sectional study by Tsilingiris et al. examined the effect of β-thalassemia trait on HbA1c by comparing values between 100 heterozygous β-thalassemia carriers and 100 matched non-diabetic controls. The mean HbA1c values were nearly identical between the groups (33.6 mmol/mol [5.23%] versus 33.6 mmol/mol [5.22%]; $p = 0.857$). Within the β-thalassemia group, a positive correlation was observed between HbA1c and hemoglobin concentration ($r = 0.455$; $p < 0.001$). Anemic carriers demonstrated marginally reduced HbA1c levels compared to non-anemic carriers, with a definitive difference of 2.4 mmol/mol (0.23%). Multivariable analysis revealed that the β-thalassemia carrier status itself was not a significant predictor of HbA1c, even though hemoglobin concentration was a significant predictor [39].

This major discovery indicates that HbA1c remains a valid instrument for diabetes screening in non-anemic β-thalassemia carriers, while anemic carriers may exhibit a slight but measurable downward bias. The authors specifically argued against categorically excluding HbA1c from diabetes screening methods for individuals with β-thalassemia carrier status [39].

1.4.3. Alpha-Thalassemia

The α-thalassemia impact on HbA1c levels is complex. Xu et al. conducted a comprehensive investigation of HbA1c measurements across various α-thalassemia genotypes using multiple analytical platforms. It was demonstrated that individuals with α0-thalassemia (SEA deletion) and silent α-thalassemia exhibit HbA1c values comparable to those of non-thalassemia controls when assessed by standard HPLC. However, HbH disease introduces significant platform-specific errors, especially in systems where HbH peaks co-elute with HbA1c fractions [28,31].

A multicenter cross-sectional study conducted in southern China found that asymptomatic individuals with β-thalassemia trait had significantly lower HbA1c levels than controls, as measured by HPLC. β-thalassemia individuals were readily identified by their characteristic hematological profile (MCV <75 fL, MCH <24 pg, RDW-CV >13.5%). In contrast, α-thalassemia carriers displayed red cell parameters within the normal reference range, complicating routine thalassemia screening prior to HbA1c measurement [40]. In this case, glycated albumin accurately reflected the mean blood glucose level, highlighting the importance of alternative biomarkers when HbA1c discordance is observed [41].

1.4.4. Gestational Diabetes and Thalassemia

A case-control study of 41 patients with gestational diabetes mellitus (GDM) and β-thalassemia minor and 93 GDM patients without thalassemia found that β-thalassemia minor significantly affected HbA1c levels in late pregnancy (36 to 38 gestational weeks). The thalassemia group exhibited lower HbA1c values despite comparable blood glucose

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iron deficiency [42]. This study demonstrated that physiological hemodilution and erythroid hyperplasia during pregnancy, when combined with thalassemia-associated erythrocyte abnormalities, further increase the diagnostic discrepancy between HbA1c and actual glycemia in pregnant women, a group for whom accurate glycemic monitoring is essential [42

1.4.5. Analytical Method Comparison Studies

A comprehensive multicenter study conducted in Germany (Zechmeister et al., 2022) evaluated HbA1c interference caused by 33 hemoglobin variants by comparing the Tosoh G8 and G11 HPLC systems with the Abbott Alinity enzymatic assay. Significant discrepancies between analytical methods were observed across several variant classes, including those associated with thalassemia. Importantly, the enzymatic assay generated HbA1c results in the presence of rare variants that HPLC identified as erroneous. This discovery highlights the potential threats of undetected clinical mismanagement when separation-based technique is not utilized [31].

Chaila et al. (2022) compared HPLC (BioRad Variant II TURBO), turbidimetric immunoassay (Roche COBAS C501), enzymatic method (Abbott Architect C8000), and capillary electrophoresis (Sebia Capillarys) across 1,245 samples. The study revealed high overall agreement among methods in samples without hemoglobinopathies. However, the authors explicitly noted that hemoglobinopathy exclusion criteria were implemented, indicating that these method comparison results cannot be directly extrapolated to patients of thalassemia [33].

1.5. Thalassemia-associated diabetes mellitus

1.5.1. Epidemiology and Pathogenesis

Thalassemia-associated diabetic mellitus (TADM) has emerged as a clinically unique and potentially preventable condition resulting from transfusional iron overload. Published studies indicate that the prevalence of TADM in TDT patients ranges from 5% - 30%, depending on the country, serum ferritin levels, chelation adequacy, and duration of follow-up [34,35,36]. Iron overload results in progressive pancreatic siderosis, characterized by selective iron deposition in insulin-secreting beta cells. This process reduces both insulin secretion capability and insulin sensitivity through oxidative stress pathways [35].

As opposed to Type 2 diabetes, TADM is primarily characterized by beta-cell secretory failure. Although its present, peripheral insulin resistance constitutes a secondary mechanism. This distinction carries considerable therapeutic implications, as beta-cell-directed therapies, such as insulin, are often favored over insulin sensitizers during the initial management of TADM [35,36].

1.5.2. The Importance of Monitoring and the Limitations of HbA1c

A clinical paradox in TADM emerges when the condition that requires the most precise glycemic monitoring is also the context in which the universal monitoring standard, HbA1c, is persistently unreliable. Poor glycemic control in TADM accelerates the progression of diabetic microvascular complications such as retinopathy, nephropathy, and neuropathy, which are compounded by the pre-existing multiorgan damage associated with thalassemia [35,36]. Accurate glycemic monitoring is essential for patient survival, rather than serving solely as a diagnostic procedure.

Several studies have reported cases in which patients with thalassemia-associated diabetes mellitus (TADM) and significant hyperglycemia exhibited deceptively low HbA1c values. For example, one published case from Kuwait described a 46-year-old male with newly diagnosed diabetes and thalassemia trait who presented with an HbA1c level markedly discordant with his documented hyperglycemia (capillary glucose 25 mmol/L) and ketosis. Hemoglobin electrophoresis subsequently confirmed β-thalassemia trait as the underlying cause [30]. This case illustrates the clinical risks

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associated with HbA1c measurements in thalassemia management.

1.6. Alternative glycemic biomarkers in thalassemia

1.6.1. Fructosamine

Fructosamine is a stable ketoamine produced by the nonenzymatic glycation of circulating serum proteins, primarily albumin, and serves as an indicator of average plasma glucose levels over the previous 2 to 3 weeks. In contrast to HbA1c, fructosamine is unaffected by hemoglobin structure, red blood cell lifespan, or transfusion history, which makes it a theoretically advantageous indicator for thalassemia monitoring [43,44].

However, the accuracy of fructosamine measurements depends on the presence of normal serum protein level. Hypoalbuminemia, common among TDT patients as a due to malnutrition, hepatic dysfunction, and chronic disease states, reduces fructosamine concentration independently of glycemia and introduces an additional source of bias [44,45]. Moreover, fructosamine lacks the comprehensive clinical validation databases available for HbA1c and is not recommended as a primary monitoring instrument by major diabetes guidelines. Musa et al. indicated that Egyptian children with β-thalassemia major demonstrated significantly increase levels of both HbA1c and fructosamine in comparison to healthy controls. Fructosamine, in particular, demonstrated a highly statistically significant elevation ($p < 0.001$), supporting its use as a supplementary indicator of glycemic dysregulation [47].

1.6.2. Glycated Albumin (GA)

Glycated albumin (GA) is the proportion of albumin fraction with a ketoamine bond and functions as a marker of average plasma glucose concentrations over the previous 2 - 3 weeks. Glycated albumin (GA) is unaffected by red blood cell (RBC) lifespan, hemoglobin variations, or hemolysis, and therefore represents a theoretically preferable alternative to both HbA1c and fructosamine in thalassemia [47,48]. Glycated albumin (GA) is increasingly examined as the preferred short-term glycemic indicator in clinical contexts where hemoglobin A1c (HbA1c) is inaccurate such as end-stage renal illness, hemolytic anemias, and pregnancy [46].

A 2022 case report indicated that glycated albumin accurately represented mean blood glucose in an α-thalassemia patient with discordantly elevated HbA1c, while HPLC-derived HbA1c measurements were artifactually raised [41]. Nevertheless, glycated albumin (GA) has significant limitations. Conditions such as nephrotic syndrome, thyroid dysfunction, obesity, and liver disease modify albumin turnover independently of glycemia, thereby introducing confounding variables. Moreover, GA is more expensive and less accessible than fructosamine, and it lacks prospectively validated reference intervals for thalassemia populations [47,48].

1.6.3. Continuous Glucose Monitoring (CGM)

Continuous glucose monitoring (CGM) technology directly measures interstitial glucose concentrations in real time by electrochemical or optical subcutaneous sensors, representing the most comprehensive method for glycemic evaluation independent of erythrocyte biology. Metrics derived from continuous glucose monitoring (CGM), such as time-in-range (TIR), time-above-range (TAR), mean glucose, and glucose variability indices, provide clinically informative, erythrocyte-independent glycemic data [30,46].

A 2024 prospective study by Kaminski et al. demonstrated that continuous glucose monitoring (CGM) and glycated albumin provided a more accurate assessment of glycemic control than HbA1c and fructosamine in patients with end-stage kidney disease and burnt-out diabetes. This clinical model closely parallels the thalassemia-diabetes scenario [46]. A published case involving a Kuwaiti patient with β-thalassemia trait and newly diagnosed diabetes reported that continuous glucose monitoring (CGM) was initiated after

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and effectively guided basal-bolus insulin titration over an eight-week period [30].

However, continuous glucose monitoring (CGM) is limited by high cost, insufficient insurance reimbursement in thalassemia-endemic low- and middle-income countries (LMICs), calibration accuracy issues in patients with severe anemia, and the absence of thalassemia-specific validation studies [30,46].

1.7. Recent Advances in Thalassemia Treatment and Their Implications for Glycemic Monitoring

1.7.1. Standard of Care: Transfusion and Iron Chelation

The management of TDT relies on regular red cell transfusions administered every 2 to 4 weeks to maintain pre-transfusion hemoglobin levels between 9.5 and 10.5 g/dL. This approach suppresses ineffective erythropoiesis and prevents skeletal deformities, growth retardation, and extramedullary hematopoiesis [15,34]. Iron chelation therapy using deferoxamine (administered subcutaneously or intravenously), deferiprone (administered orally), or deferasirox (administered orally) is required to prevent transfusional iron overload. The shift from parenteral deferoxamine-based regimens to oral chelators, particularly deferasirox, has resulted in significant reductions in liver iron concentration and improvements in cardiac T2* MRI parameters in large real-world cohorts [35,38].

Iron chelation directly influences glycemic risk. Maintaining pancreatic iron levels below critical thresholds with effective chelation reduces the incidence of TADM and may enhance glucose tolerance [35]. Pines et al. (2024) indicated that patients transitioning from deferoxamine monotherapy to oral chelators experienced a mean annual reduction in liver iron concentration of 0.24 mg/g dry weight and a significant enhancement in cardiac T2* [38]. This therapeutic advancement has significant hematological implications for the interpretation of HbA1c. Patients who experience improved hemoglobin parameters as a result of more effective chelation may exhibit partially normalized erythrocyte biology, which could enhance, but not fully restore, the reliability of HbA1c measurements.

1.7.2. Emerging Therapies: Luspatercept and Mitapivat

Luspatercept (ACE-536), an activin receptor ligand trap that inhibits aberrant TGF-β signaling and promotes late-stage erythroid maturation, was evaluated in the pivotal BELIEVE Phase 3 trial (Cappellini et al., 2019). This study demonstrated that luspatercept significantly reduced transfusion burden in adult patients with transfusion-dependent thalassemia (TDT) [36]. Luspatercept received FDA approval for the treatment of transfusion-dependent thalassemia (TDT) in 2020. Mitapivat, a pyruvate kinase activator approved by the FDA in 2024 for both TDT and non–transfusion-dependent thalassemia (NTDT), enhances glycolytic flux in erythrocytes, thereby extending red blood cell (RBC) lifespan and reducing hemolysis [34]. Both agents may partially normalize red blood cell (RBC) lifespan and consequently improve, but not fully restore, the reliability of HbA1c measurements.

1.7.3. Gene Therapy: A Transformative Paradigm

Gene therapy constitutes the most significant advancement in thalassemia management over the past decade. Thompson et al. (2018) were the first to demonstrate that lentiviral transfer of a modified β-globin gene (LentiGlobin BB305, encoding HbAT87Q) into autologous CD34+ hematopoietic stem cells results in transfusion independence for most TDT patients with non-severe genotypes [21]. The Phase 3 HGB-212 trial conducted in 2024 reported that 16 of 18 patients (89%) with severe genotypes (β0/β0, β0/βIVS-I-110) achieved transfusion independence following treatment with betibeglogene autotemcel (beti-cel/Zynteglo) [22].

In addition to lentiviral approaches, CRISPR-Cas9-mediated gene editing targeting the

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3.1. Erythropoietin-directed gene-activated fetal hemoglobin production resulted in transfusion independence in approximately 91% of patients in a Phase 3 trial. Exagamglogene autotemcel (exa-cel/Casgevy) received approval from the FDA and the European Medicines Agency in 2023–2024 for the treatment of transfusion-dependent thalassemia (TDT) and severe sickle cell disease [22,34]. These curative therapies normalize erythropoiesis and eliminate transfusion dependence, thereby fundamentally altering the erythrocyte biology responsible for HbA1c interference. As a result, patients who have undergone gene therapy may exhibit near-normal HbA1c validity; however, long-term data regarding the reliability of glycemic biomarkers following gene therapy remain unavailable.

1.8. Recommendations for the Interpretation of HbA1c in Thalassemia

1.8.1. Proposed Clinical Decision Framework

Based on the synthesized evidence, the following clinical framework is recommended for the interpretation of HbA1c and alternative glycemic monitoring in thalassemia:

- For individuals with β-thalassemia trait (minor/carrier) who are non-anemic, HbA1c measured by standard high-performance liquid chromatography (HPLC) is considered acceptable for diabetes screening. Hemoglobin concentrations must be documented in conjunction with HbA1c results. If discordance is observed between HbA1c and blood glucose measurements, supplementary assessment with fructosamine or glycated albumin (GA) is recommended.

- In individuals with β-thalassemia trait (minor/carrier) and anemia, HbA1c values may be mildly yet clinically significantly underestimated. Measurement should be supplemented with fructosamine or glycated albumin. Continuous glucose monitoring (CGM) is recommended for patients with suspected or confirmed diabetes.

- In patients with β-thalassemia major (transfusion-dependent thalassemia), HbA1c is considered unreliable as a primary tool for glycemic monitoring. Glycated albumin is the preferred alternative biomarker for assessing glycemic control over a 2 to 3-week period. Continuous glucose monitoring (CGM) is recommended for real-time glycemic management. Fructosamine may be considered with caution if glycated albumin is unavailable.

- In individuals with α-thalassemia trait (one or two gene deletions), HbA1c levels are typically not significantly affected when measured by standard high-performance liquid chromatography (HPLC). Glycated albumin (GA) or fructosamine should be considered if there is discordance between HbA1c and clinical findings.

- In HbH disease (three-gene α-thalassemia), HbA1c measurements are unreliable on certain HPLC platforms. Prefer enzymatic assays when available; alternatively, utilize glycated albumin (GA) or continuous glucose monitoring (CGM).

- In HbE/β-thalassemia, HbA1c measurement is unreliable because of the effects of compound hemoglobin variants. If HbA1c assessment is necessary, enzymatic assay methods are preferred over high-performance liquid chromatography. Glycated albumin and continuous glucose monitoring are considered superior alternatives.

- Following gene therapy, the reliability of HbA1c should be prospectively re-evaluated. Until validation is achieved, supplementary monitoring with glycated albumin (GA) or continuous glucose monitoring (CGM) is recommended.

1.9. Evidence and limitations

Empirical formulas to estimate corrected HbA1c in the presence of anemia, such as Measured HbA1c plus (15 minus Hemoglobin in g/dL) multiplied by 0.4, have been proposed in clinical studies. However, these formulas lack universal validation and are not endorsed by any major diabetes society for

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measures may function as preliminary screening tools in research contexts; however, they should not substitute for validated alternative biomarkers in clinical practice.

1.10. Laboratory Level recommendations

For populations with a high prevalence of thalassemia, clinical laboratories should: (1) routinely report method flags and abnormal hemoglobin peak notifications alongside HbA1c results; (2) employ separation-based HbA1c methods, such as high-performance liquid chromatography (HPLC) or capillary electrophoresis, which can detect hemoglobin variants, instead of relying exclusively on immunoassay or enzymatic methods; (3) establish local standard operating procedures (SOPs) for HbA1c reporting in patients with known hemoglobinopathies; and (4) consistently communicate method-specific limitations to clinicians [23,25,27,31].

1.11. Knowledge gaps and future research priorities

Although the literature on thalassemia-related interference with HbA1c is expanding, significant research gaps persist. First, no large-scale, prospectively designed studies have evaluated longitudinal glycemic outcomes in thalassemia patients managed with alternative biomarker strategies such as GA or CGM compared to HbA1c-guided management. Second, the performance of continuous glucose monitoring (CGM) has not been validated in patients with severe thalassemia anemia. In this population, modified interstitial fluid composition and possible sensor calibration drift may compromise measurement precision. Third, reference intervals for glycated albumin remain unestablished in thalassemia-specific populations across several ethnic groups. Fourth, longitudinal monitoring studies post-gene treatment are necessary to characterize the timeline and degree of HbA1c normalization after curative intervention. Fifth, there is an imperative need for standardized clinical guidelines from prominent organizations such as the WHO, ADA, and TIF that incorporate thalassemia-specific glycemic monitoring protocols.

2. CONCLUSIONS

Thalassemia illustrates a condition in which the global glycemic monitoring standard, HbA1c, is mechanistically impaired, clinically misleading, and potentially harmful if utilized without recognition of its limitations. Multiple intersecting mechanisms contribute to these phenomena: analytical interference caused by abnormal hemoglobin variants, diminished red blood cell lifespan due to hemolysis and ineffective erythropoiesis, dilution of hemoglobin A from transfusions, and the paradoxical emergence of iron deficiency in the context of transfusional iron overload. The direction and magnitude of HbA1c bias contingent upon genotype, subtype, and analytical method, requiring interpretation that is both individualized and context-sensitive.

The increasing prevalence of thalassemia, together with the rising incidence of diabetes mellitus in regions where thalassemia is common, makes this diagnostic intersection a significant public health concern. Thalassemia-associated diabetes mellitus is a preventable and treatable complication that significantly affects patient survival and quality of life. However, mismanagement frequently occurs when glycemic monitoring relies solely on an unreliable biomarker.

Alternative biomarkers, such as fructosamine, glycated albumin, and continuous glucose monitoring, each provide clinically significant advantages in thalassemia management. Emerging evidence increasingly supports their routine integration into multidisciplinary thalassemia care pathways. The advent of curative gene therapy for thalassemia is expected to transform erythrocyte biology in affected patients and may ultimately restore the validity of HbA1c measurements. However, until this restoration is achieved, rigorous monitoring using validated alternative methods. We recommend that leading national and international diabetes and hematology societies establish

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guidelines, implement mandatory laboratory reporting on HbA1c method limitations in hemoglobinopathy contexts, and increase investment in prospective clinical trials to evaluate alternative biomarker strategies for this uniquely vulnerable patient population remains essential.

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