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Challenges and Limitations of HbA1c as a Surrogate Marker in Assessing Glycemic Control: A Critical Review

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ABSTRACT

The gold standard for determining a patient's long-term glycemic control in individuals with diabetes mellitus is hemoglobin A1c (HbA1c). However, new research casts doubt on its validity because of a number of methodological, pathological, and physiological restrictions. Recent research raises doubts about the universality of HbA1c as a surrogate test by highlighting the impact of glycemic variability, red blood cell turnover, ethnicity, and coexisting medical disorders on HbA1c levels. The limits of HbA1c and other indicators that offer a more accurate depiction of glycemic control are critically examined in this overview of recent research.

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1- INTRODUCTION

Hemoglobin A1c (HbA1c) has long been regarded as the gold standard for assessing long-term glycemic control in individuals with diabetes mellitus, serving as a crucial diagnostic and monitoring tool in clinical practice [1, 2, 3]. By measuring glycated hemoglobin levels, HbA1c reflects the average blood glucose concentrations over the preceding 8 to 12 weeks, as endorsed by the American Diabetes Association (ADA) and the International Diabetes Federation (IDF) [4].

However, emerging research casts doubt on its validity as a universal indicator of glycemic control due to various methodological, pathological, and physiological factors [4]. Recent research shows that relying solely on HbA1c to gauge blood sugar control has some major blind spots. Take glycemic variability, for example—those rollercoaster-like spikes and crashes in blood sugar that are now recognized as a key driver of diabetes complications. HbA1c doesn't pick up on these fluctuations at all. Instead, it just gives a snapshot of your average glucose levels over a few months. The problem is that, two people with the exact same HbA1c result might actually have wildly different day-to-day blood sugar patterns. One person's levels could be relatively stable, while another experiences dangerous highs and lows—all hidden behind the same HbA1c number. This gap in measurement can lead to misunderstandings about a patient's true glycemic health, potentially leaving some at risk for complications that HbA1c alone failed to predict [5].

Furthermore, factors such as red blood cell turnover and other variables, including ethnicity, can significantly influence HbA1c readings, raising concerns about the accuracy of this measure across diverse populations [3, 6]. Recent research indicates that the relationship between HbA1c and actual blood glucose levels can vary among different racial ethnic groups, potentially leading to misclassification of diabetes risk and wrong clinical decision [3]. For example, African American has shown to have higher HbA1c levels than Caucasian at equivalent glucose concentrations, which could result in over treatment or under treatment of the effected individuals [3]. Given these complexities, relying solely on HbA1c for glycemic control assessment may result in incorrect diagnoses and heightened risk of diabetes-related complications [4].

In this review, the shortcomings of HbA1c are assessed, and other biomarkers that can offer a more thorough evaluation of glycemic management are investigated.

Biological Factors, Physiological and Ethnic Variability:

Regardless of glycemic state, a number of physiological and genetic factors affect HbA1c levels. Because HbA1c indicates glucose exposure across the lifespan of erythrocytes, the lifespan of red blood cells (RBCs) is important for interpreting HbA1c [1]. Despite inadequate glycemic management, conditions that impact RBC turnover, such as hemolysis, blood loss, or erythropoietin therapy, might produce deceptively low HbA1c values [2]. On the other hand, diseases such iron deficiency anemia that are linked to longer RBC lifespan may inadvertently raise HbA1c levels [3].

HbA1c levels are also influenced by racial and ethnic disparities; research shows that, for the same glucose concentrations, African, Asian, and Hispanic populations often have higher HbA1c values than Caucasians [6]. Hemoglobinopathies, such as sickle cell disease and thalassemia, are examples of genetic abnormalities in hemoglobin that can cause errors in HbA1c testing [7].

Hemoglobin in red blood cells undergoes non-enzymatic glycation to form HbA1c, a biomarker widely used to assess long-term glycemic control. However, the accuracy of HbA1c as a measure of glucose exposure is heavily reliant on the lifespan of red blood cells (RBCs). Any condition that alters RBC turnover can significantly impact HbA1c levels, leading to either falsely low or falsely elevated readings.
Conditions associated with shortened RBC lifespan result in falsely low HbA1c values because younger RBCs have had less time to accumulate glycated hemoglobin. Examples of such conditions include hemolytic anemia, where increased RBC destruction reduces the average age of circulating cells. Similarly, recent blood transfusions introduce younger donor RBCs into the bloodstream, further skewing HbA1c measurements. Chronic kidney disease (CKD) is another factor that shortens RBC survival due to uremic toxins and other pathological mechanisms. Erythropoietin (EPO) therapy, commonly administered to CKD patients to manage anemia, also contributes to this effect by stimulating the production of new RBCs, which dilutes the proportion of older, glycated cells.

Conversely, conditions that extend RBC lifespan lead to falsely elevated HbA1c levels. For instance, iron deficiency anemia, folate deficiency, and vitamin B12 deficiency are associated with prolonged RBC survival, allowing more time for hemoglobin glycation to occur. This discrepancy highlights the importance of considering underlying hematological and systemic conditions when interpreting HbA1c results.

Research evidence underscores the limitations of HbA1c as a universal marker of glycemic control. Cohen et al. (2020) demonstrated that, in patients with CKD, HbA1c readings tend to overestimate actual glucose exposure compared to alternative markers like fructosamine and glycated albumin. These findings suggest that HbA1c may not always accurately reflect glycemic status in individuals with altered RBC dynamics [4].

Moreover, ethnic variations in HbA1c levels further complicate its interpretation. Studies have consistently shown that African, Asian, and Hispanic populations exhibit higher HbA1c values than Caucasians, even when mean glucose concentrations are comparable. A landmark study published in the *New England Journal of Medicine* in 2017 revealed that African Americans had significantly higher HbA1c levels than Caucasians at equivalent glucose levels. This disparity could lead to misclassification of diabetes risk and inappropriate clinical decision-making, potentially resulting in overtreatment or under treatment of affected individuals.

These observations emphasize the need for caution when using HbA1c as the sole indicator of glycemic control, particularly in populations with diverse genetic backgrounds or comorbidities affecting RBC turnover. Clinicians should consider complementary measures, such as continuous glucose monitoring (CGM) or serum-based markers like fructosamine, to obtain a more accurate assessment of glycemic status in complex cases. By integrating these tools, healthcare providers can mitigate the risk of diagnostic errors and optimize patient care.

Disparity between Glycemic Variability and HbA1c:

Glycemic variability, which is becoming more widely acknowledged as a separate risk factor for complications from diabetes, is not taken into consideration by HbA1c, which measures mean glucose levels [7]. Some patients have frequent episodes of hyperglycemia or hypoglycemia that HbA1c is unable to detect, and patients with similar HbA1c readings may have quite distinct daily glucose swings [8].

According to new research, stable hyperglycemia is not as important in oxidative stress and endothelial dysfunction as postprandial hyperglycemia and glucose excursions [9]. Therefore, using HbA1c alone without taking into

account data from continuous glucose monitoring (CGM) may understate the risk of complications from diabetes, especially in individuals with type1 diabetes or type2 diabetes receiving insulin [10].

Although postprandial hyperglycemia and short-term glycemic swings are powerful indicators of problems from diabetes, HbA1c only measures an average blood glucose level. According to research, two people with the same HbA1c may have quite distinct glucose variability profiles, which could have an impact on their overall metabolic risk. Glycemic variability is an independent predictor of problems, as evidenced by a study in 2019, showed that individuals with equal HbA1c values had considerably varied glucose excursions as evaluated by continuous glucose monitoring (CGM) [11].

Non-Glycemic Factors' Effect on HbA1c Measurement.

A number of non-glycemic variables can change HbA1c readings, which could cause misunderstandings. Changes in erythropoiesis, increased hemoglobin carbamylation, and exposure to uremic toxins are some of the ways that kidney illness, a typical consequence of diabetes, impacts HbA1c levels [12]. Similarly, because of decreased erythropoietin synthesis and reduced glucose metabolism, liver disorders such cirrhosis might impact HbA1c [13].

Moreover, several drugs, such as vitamin B12, iron supplements, and erythropoiesis-stimulating medicines, can affect HbA1c levels without affecting glucose regulation [14, 15]. Because techniques like immunoassays and high-performance liquid chromatography (HPLC) may produce varied results in patients with hemoglobin variations, analytical variability among various HbA1c measurement methods also leads to inconsistencies [16].

Depending on the laboratory assay, hemoglobin variations such sickle cell disease (HbS), thalassemia (HbE), and hemoglobin C might cause errors in HbA1c readings. HbA1c readings were imprecise in communities with a high frequency of sickle cell trait, which resulted in an underestimating of glycemic control [15, 17].

Restrictions in predicting Complications from Diabetes

The prognostic usefulness of HbA1c for macrovascular consequences is unclear, despite its correlation with the risk of microvascular disorders such retinopathy and nephropathy [18].

Intense HbA1c lowering was strangely linked to higher mortality and did not significantly reduce cardiovascular events, according to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (ACCORD Study Group, 2008). According to this research, concentrating only on HbA1c may not be enough to prevent cardiovascular consequences when managing diabetes [19].

HbA1c cannot identify abrupt changes in glycaemia, but it does represent long-term glucose consumption. Because of this, it is less appropriate for tracking the results of short-term treatments, including dietary changes or adjustments to insulin medication. Individuals with acute hyperglycemia (such as diabetes brought on by steroids or surgery) may initially have a normal HbA1c, which could cause a delay in diagnosis and treatment.

Complementary Methods and Other alternative markers:

Continuous Glucose Monitoring (CGM)

Captures glycemic fluctuation and provides real-time glucose measurements. In order to get over HbA1c's drawbacks, supplementary and alternative markers have been suggested, such as TIR (Time in Range) By calculating the proportion of time a patient spends inside the target glucose range, CGM data offers a more dynamic and precise depiction of glycemic management [20, 21].
International guidelines now promote time-in-range (TIR) as a crucial indicator. TIR has a stronger correlation with diabetic complications than HbA1c, according to Beck *et al*., 2019 [22].

CGM represents a significant advancement in diabetes management, particularly in individuals who required tight glycemic control. CGM systems provide real-time glucose measurements capturing fluctuations in blood sugar levels throughout the day and night. This continuous monitoring offers several key benefits over traditional methods of glucose assessment, such as periodic finger-stick testing.

Measuring the fluctuations in blood glucose levels that can occur over short periods is essential because glycemic variability has been identified as an independent risk factor for diabetes complications, including cardiovascular disease and microvascular issues [1]. Traditional HbA1c measurements provide an average of blood glucose level

over several weeks, thus failing to reflect these potential dangerous spikes and drops in glucose that occur between measurements.

CGM devices use a small sensor that is typically inserted under the skin to measure glucose levels in the interstitial fluid. These sensors continuously collect data, usually sending alerts to the individual when their blood glucose levels fall outside preset target ranges. This immediate feedback empowers users to make timely adjustments to their diet, physical activity, or medication, thereby mitigating the risk of severe hyperglycemic or hypoglycemic episodes [1].

Continuous glucose monitors (CGMs) are game-changers in diabetes care, offering real-time insights that help tailor treatments to individual needs. Unlike HbA1c, which only shows an average glucose level, CGMs reveal daily highs, lows, and trends, letting clinicians see how factors like meals or exercise impact blood sugar. This leads to smarter adjustments in insulin doses or meal plans. Studies prove CGM users achieve better control and fewer complications, thanks to metrics like Time in Range (TIR) —the percentage of time glucose stays in a healthy zone—which predicts risks more accurately than HbA1c. By catching fluctuations HbA1c misses, CGMs empower patients and providers to act proactively, reducing long-term risks. As CGM technology improves and becomes more accessible, it's reshaping diabetes management into a personalized, data-driven partnership between patients and their care teams [1, 5].

Fructosamine

Fructosamine, which is a measure of non-enzymatic glycation of circulating proteins including albumin, globulins, and lipoproteins, has evolved to be a reasonable alternative to HbA1c measurement in situations where HbA1c is not reliable. It Reflect the last two to three weeks' worth of glycated plasma proteins. It helps anemic patients since it is not impacted by RBC lifetime.

Limitation: Affected by abnormalities of protein metabolism and albumin concentration [23].

Glycated Albumin (GA)

This indicator is helpful in situations that impact RBC turnover and represent shorter-term glycemic management, it represents glycemic state over a period of two to three weeks, which is helpful when glucose fluctuates quickly [24].

According to a meta-analysis study in 2022, **Glycated albumin (GA)** surpasses HbA1c in tracking glycemic variability and remains reliable in hemodialysis, anemia, or hemolysis. Unlike fructosamine, GA avoids protein interference, with fast, standardized testing. It accurately diagnoses diabetes and predicts complications but complements—not replaces—HbA1c. Clinical context and test availability should guide use. Global consensus on lab standards is needed to integrate GA into routine diabetes care [25, 26].

(1,5-AG) 1,5-Anhydroglucitol

1,5-AG is gaining attention for its effectiveness in blood glucose monitoring. It is a glucose analogue that is ingested through food and excreted by the kidney. Serum 1,5-AG levels decrease when urinary glucose exceeds the renal threshold, reflecting onset of hyperglycemia, but gradually normalize as blood glucose levels return to normal levels [27]. Unlike HbA1c, FA, and GA, 1,5-AG provides insights into average blood glucose, postprandial hyperglycemia, and blood glucose variability in 1-2 weeks [28,29]. In 2003, the FDA approved the Glyco-Mark kit for detecting serum 1,5-AG, establishing it as a new tool for short-term glucose monitoring [30]. In 2015, the Chinese Guidelines for the Clinical Application of Blood Glucose Monitoring proposed 1,5-AG as a new adjunctive indicator for blood glucose monitoring [31]. Researches on 1,5-AG in screening,management,and risk assessment of diabetes have been expanding. Furthermore, salivary 1,5-AG has been explored as a noninvasive index for screening and diagnosis of diabetes**.**

According to Xu *et al* (2024), 1,5-AG , a glucose analog, tracks hyperglycemia and glycemic fluctuations over 1–2 weeks, aiding diabetes screening, diagnosis, management, and complication prediction. Saliva-based 1,5-AG shows promise as a non-invasive marker. However, challenges remain: standardizing reference ranges, replacing costly LC/MS methods with simpler assays, and validating saliva testing. Addressing these gaps could enhance 1,5-AG's role in comprehensive diabetes care [32].

CONCLUSION

HbA1c is still a commonly used marker for long-term glycemic management, however in some patient populations; its limitations render it an unreliable solitary indicator. A combination of biomarkers that record postprandial glucose spikes, glycemic variability, and individual physiological variations should be used in diabetes monitoring in the future. HbA1c has significant drawbacks, such as its vulnerability to physiological changes, incapacity to measure glycemic fluctuation, and influence from non-glycemic factors, even though it is still a crucial tool for evaluating long-term glycemic management In a number of clinical situations, new data suggests that CGM, fructosamine, glycated albumin, and 1,5-AG are better indicators. Optimizing diabetes management requires a change in clinical standards toward customized glucose assessment.

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التحديات والقيود لإستخدام الهيموغلوبين السكري التراكمي كمؤشر بديل في تقييم التحكم في نسبة السكر في الدم

الـخـلاصـة:

يعد الهيموغلوبين السكري (c^1HbA) المعيار الذهبي لتقييم السيطرة على مستوى السكر في الدم على المدى الطويل لدى مرضى داء السكري. ومع ذلك، تثير أبحاث حديثة شكوكا حول دقته بسبب عدد من القيود المنهجية والمرضية والفيزيولوجية. وتشير هذه الدراسات إلى تأثير تذبذب مستويات السكر في الدم، ودورة حياة خلايا الدم الحمراء، والانتماء العرقي، والأمراض المصاحبة على مستويات c^1HbA، مما يثير التساؤلات حول صلاحيته كاختبار بديل شامل.

يستعرض هذا الملخص البحثي الحديث أهم القيود المرتبطة باستخدام c^1HbA، بالإضافة إلى مؤشرات بديلة قد توفر تقييما أكثر دقة للسيطرة على السكر في الدم.