Haemoglobin A1c (HbA1c): clinical relevance, history, and role in diabetes mellitus management – a South African perspective

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Abstract

Background: Diabetes mellitus (DM) is a growing health challenge in South Africa, with an increasing prevalence driven largely by urbanisation and lifestyle changes. Haemoglobin A1c (HbA1c) has emerged as a pivotal biomarker for diagnosing and monitoring diabetes. Its clinical utility is well established globally, yet its optimal use in the South African healthcare landscape remains an area of interest. This article provides a comprehensive review of HbA1c, outlining its historical discovery, biochemical basis, clinical applications, and interpretation challenges. Emphasis is placed on its role in South Africa, where access to laboratory testing and point-of-care diagnostics influences diabetes care.

Methods: A literature review was conducted using PubMed, Google Scholar, and local healthcare databases to evaluate HbA1c's effectiveness in DM diagnosis and monitoring. International and South African guidelines were analysed to assess the standardisation and applicability of HbA1c testing in diverse populations.

Results: HbA1c is vital in diabetes management, though its accuracy may be affected by haemoglobinopathies, ethnicity, age, and medical conditions. Technological advances, such as point-of-care testing (POCT), have improved accessibility, particularly in underserved areas. Personalised HbA1c targets are increasingly recommended to enhance patient-centred care.

Conclusion: While HbA1c is a valuable diagnostic and monitoring tool, healthcare professionals (HCPs) must be aware of its limitations in specific populations. Expanding access to HbA1c testing and integrating individualised glycaemic targets can improve diabetes management outcomes in South Africa.

Keywords: HbA1c, diabetes management, glycaemic control, point-of-care testing, South Africa, haemoglobinopathies, diagnostic accuracy

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Introduction

Diabetes mellitus (DM) is a growing healthcare challenge, including in South Africa, where it is largely driven by urbanisation and lifestyle shifts.[1] It is currently recognised as one of the top ten leading causes of mortality worldwide, reflecting a substantial 95% increase in death rates since the year 2000.[2] Hird et al.[3] reported a DM prevalence of 12.9% among urban black South Africans in their 2016 Durban Diabetes Study (DDS), which is one of the highest documented rates in sub-Saharan Africa—exceeding the International Diabetes Federation (IDF) estimate in 2021 of 10.8% in all ethnic groups for South Africa[4]—yet comparable to the 13.1% prevalence observed by Peer et al. (2012)[5] in urban black Africans in Cape Town. According to recent statistics from the IDF, 45.4% of people living with DM remain undiagnosed.[4]

Haemoglobin A1c (HbA1c) has emerged as a pivotal biomarker, not only for monitoring glycaemic control but also for diagnosing DM.[6] In the South African context, where healthcare access is often limited in rural and underserved areas, understanding the application, benefits, and limitations of HbA1c testing is crucial.[7] This review provides a comprehensive educational overview of HbA1c, highlighting recent developments, clinical significance, and practical considerations for South African healthcare professionals (HCPs).

HbA1c in historical context

Glycated, or glucose-bound, haemoglobin was first identified in the late 1960s by Dr. Samuel Rahbar, who, through haemoglobin electrophoresis of 1 200 blood samples, discovered an abnormal fast-moving haemoglobin fraction—later termed HbA1c.[8,9]

Early studies identified higher levels of HbA1c in individuals with DM.[8,9] By the 1980s and 1990s, pivotal research including the landmark Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) established that maintaining lower HbA1c levels significantly reduces the risk of numerous diabetes complications.[10,11]

The DCCT demonstrated that intensive insulin therapy via multiple daily injections or continuous subcutaneous insulin infusion (CSII) lowered HbA1c levels and improved long-term outcomes. Patients achieving an HbA1c of 7% experienced a 50% reduction in microvascular complications over six years.

Closer to home, Mjwara et al.'s[12] more recent (2021) prospective, cross-sectional study of 100 patients with Type 1 and Type 2 DM in KwaZulu-Natal, demonstrated that those with proliferative diabetic retinopathy (PDR) had significantly higher HbA1c levels than those without, underscoring the strong association between

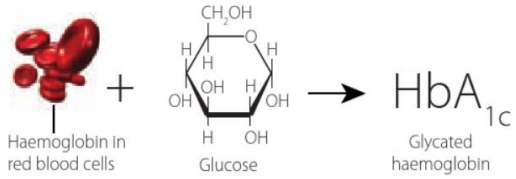

Figure 1: HbA1c Formation (Adapted from: Gough, S. et al.).[16]

poor glycaemic control and advanced diabetes complications. This finding highlights the critical role of routine HbA1c monitoring in identifying high-risk patients and preventing severe visual impairment. Consequently, HbA1c has become a cornerstone in monitoring DM.[6] Major international guidelines, including those of the American Diabetes Association (ADA), incorporate HbA1c as a diagnostic criterion for DM, a practice now common worldwide, including in South Africa as recommended by the most recent Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines.[13,14]

What is HbA1c? The biochemical basis

HbA1c is a glycated form of haemoglobin that forms when plasma glucose binds irreversibly to the haemoglobin within red blood cells (RBCs) as seen in Figure 1.[15]

Because RBCs have a lifespan of 120 days, HbA1c reflects blood glucose levels over the past two to three months. This makes it a key marker for long-term glycaemic control, providing a more comprehensive measure than daily glucose readings and offering a broader view compared to daily blood glucose measurements.[15]

Typically, HbA1c is reported as a percentage, with higher percentages indicating poor glycaemic control and a greater risk of diabetes-related complications.[15] In individuals without DM, the typical HbA1c range falls between 4% and 5.6%.

Clinical applications of HbA1c

HbA1c serves two principal roles in clinical practice:

Diagnosis of DM

An HbA1c level of 6.5% or higher, in two tests conducted at least three months apart, is diagnostic for DM. Levels between 5.7% and 6.4% indicate a high risk (prediabetes).[13] This test is particularly valuable because it does not require fasting and is less affected by short-term glucose fluctuations.

Monitoring glycaemic control

For patients with established DM, HbA1c is key for monitoring long-term glycaemic management. According to the SEMDSA guidelines, HbA1c testing should be performed every 6 to 12 months to assess glycaemic control.[13] An HbA1c target of < 7% is generally advised for optimal control, with more lenient targets (7–8%) for certain populations, such as the elderly. Personalised targets are essential, considering patient-specific factors like age, comorbidities, and risk of hypoglycaemia.[17]

The following table outlines the comparative characteristics and clinical considerations for interpreting fasting blood glucose (FBG) and random blood glucose (RBG) monitoring versus HbA1c measurements in diabetes care (Table I).

HbA1c interpretation challenges

The primary advantage of HbA1c is its independence from postprandial and illness-related glucose fluctuations. However, despite its widespread utility, HbA1c interpretation may be affected by several factors (Table II). For instance, research indicates that HbA1c levels may differ between men and women, even when blood glucose levels are similar. A study published in EClinicalMedicine found that erythrocyte properties influencing HbA1c levels may contribute to sex-based differences in diabetes diagnosis and management, potentially affecting mortality outcomes; specifically, the study suggests that HbA1c underestimates glycaemia in men compared to women, which may result in under-treatment and increased mortality risk in men.[18] Another study highlighted that sex hormones, such

Table I: Fasting blood glucose (FBG) and random blood glucose (RBG) monitoring vs. HbA1c measurements in diabetes care[6]

Consideration	FBG/RBG monitoring	HbA1c monitoring
Cost	Generally low-cost	More costly
Availability	Widely available in most laboratories and healthcare facilities.	Less universally available than glucose tests.
Glycaemic timeframe reflected	Reflects current, acute glycaemic status (FBG for fasting status, RBG for random sampling).	Reflects average glucose exposure over approximately 2 to 3 months.
Fasting requirement	FBG: Requires fasting (typically 8 hours). RBG: No fasting required; can be measured anytime.	No fasting required – can be measured irrespective of recent food intake.
Within-person variability	High variability observed between repeated measurements due to daily fluctuations.	Low within-person variability over time.
Impact of acute factors	Influenced by recent food intake, stress, illness, physical activity, and medications.	Largely unaffected by acue fluctuations (e.g. meals, illness, stress).
Patient factors influencing results	Affected by diurnal variation, medications, alcohol, smoking, and bilirubin levels.	Influenced by altered erythrocyte turnover (e.g. anaemia, haemoglobinopathies), renal impairment, liver disease, and pregnancy. *(See also HbA1c interpretation challenges).*
Test interferences	Susceptible to pre-analytical issues: sample handling delays, haemolysis, severe hyperlipidaemia, hyperbilirubinaemia.	May be affected by haemoglobin variants, severe hyperlipidaemia, and hyperbilirubinaemia.

*Table adapted from: Selvin E.[6]

Table II: Non-glycaemic factors influencing HbA1c levels

Category	Specific factor	Effect on HbA1C	Clinical consideration
Haematological	Haemoglobinopathies	Variable impact (possible interference)	Consider alternative glucose biomarkers in patients with known haemoglobinopathies.
	Iron deficiency anaemia	Slight increase in HbA1c	May cause a statistically significant rise; reassess post-iron therapy.
	Vitamin B_{12}/Folate deficiency	Mild increase in HbA1c	Limited clinical impact; interpret with caution.
	Erythropoietin therapy	Decrease in HbA1c	Avoid using HbA1c for DM monitoring in patients receiving erythropoietin.
Demographic	Age	HbA1c increases with age[18,19]	Alternative markers should be considered for individuals > 75 years.[18,19]
	Ethnicity	Higher HbA1c in some ethnic groups[20,21]	May result in overdiagnosis in African and Asian populations.[20,21]
	Biological sex	Higher HbA1c in women (possibly due to shorter RBC life spans, higher Hb and iron levels)	Variable impact on HbA1c depending on biological sex.
Physiological and metabolic	Pregnancy	Altered erythrocyte turnover	HbA1c may not accurately reflect glycaemia in gestational diabetes.
	Chronic Kidney Disease (CKD)	Variable impact, especially in CKD 4–5	Avoid HbA1c in advanced CKD; prefer blood glucose monitoring.
	Liver disease	Potentially lower HbA1c in cirrhosis	Frequent glucose monitoring is recommended in patients with liver disease.
Medications and supplements	Hydroxyurea	Possible HbA1c reduction	Use additional glucose markers in patients on hydroxyurea.
	Dapsone	Significant HbA1c reduction	Avoid using HbA1c in patients taking dapsone.
	Antiretrovirals (ARVs)	Uncertain effects	Data insufficient; interpret HbA1c cautiously.
	Vitamin E supplementation (in T2DM with deficiency)	Reduction in HbA1c	Requires further research; potential implications for monitoring.
Other	Hypothyroidism	HbA1c increases in untreated cases	Use glucose-based testing until thyroid function stabilises.
	Hyperthyroidism	No significant effect	HbA1c remains a reliable marker.
	Seasonal variation	Slight increase in winter	No clinical significance: monitoring remains valid.
	Acute inflammation	No major impact	Elevated HbA1c during acute illness should be confirmed later.
	Acute blood glucose fluctuations	HbA1c reflects long-term trends	Not suitable for detecting acute hyperglycaemia or hypoglycaemia.

*Adapted from Campbell L, Pepper T, Shipman K.[22]

as oestrogen and sex hormone-binding globulin (SHBG), can influence HbA1c in non-diabetic populations, suggesting that hormonal differences may partly account for observed variations.[19]

HbA1c levels can also vary by ethnicity due to genetic differences and variations in red blood cell lifespan, leading to potential misclassification of DM risk and treatment needs, particularly among black individuals who tend to have higher HbA1c levels for the same blood glucose levels compared to white individuals. While some studies report higher HbA1c levels in black individuals than in white, there is no clear evidence suggesting overdiagnosis. Therefore adjusting diagnostic criteria based on race may unintentionally worsen health disparities.[20] It is important to use HbA1c testing uniformly across populations while considering individual patient factors to ensure equitable DM diagnosis and management.

Thus, while HbA1c remains a fundamental tool in DM care, its interpretation should be contextualised within a broader clinical framework. Although certain non-glycaemic factors may influence levels, HbA1c continues to be a dependable and widely used indicator of long-term glycaemic control in most clinical scenarios.[15,23-25]

Recent advances and innovations

Technological innovations, particularly in POCT, have enabled more rapid and accessible HbA1c testing, allowing healthcare providers to make immediate decisions.[15] These devices are essential in rural and underserved areas in South Africa, where laboratory access is limited.[23] Additionally, emerging research emphasises individualised HbA1c targets tailored to the patient's overall health status, age, and life expectancy, ensuring more personalised and effective diabetes management.[15,23-26]

Diabetes management technology is advancing at an exceptional rate, with new tools being developed more rapidly than research can assess their effectiveness. However, the individual with DM

is key to treatment success; effective use of these innovations depends on personal selection, active engagement, and sustained support from healthcare providers. While technology can simplify diabetes management, it does not replace the need for ongoing self-care and education.

Public health implications in South Africa

The rising burden of DM in South Africa underscores the need for widespread and equitable access to HbA1c testing. Integrating HbA1c into community-based screening and health initiatives while empowering pharmacists to conduct POCT can significantly enhance early detection of DM and its management. Despite the benefits of HbA1c testing, cost remains a limiting factor in South Africa's public sector. Government policies to subsidise POCT in community clinics and train pharmacists for HbA1c screening could improve accessibility. Addressing cost barriers and ensuring quality control in POCT implementation are vital for effective use.[27]

Conclusion and recommendations

HbA1c remains an essential tool for DM diagnosis and monitoring response to treatment. However, healthcare providers must consider non-glycaemic influences such as ethnicity, age, and comorbidities when interpreting HbA1c results. Expanding HbA1c testing access, particularly through POCT**,** and adopting personalised treatment approaches are essential for improving DM care outcomes in South Africa.

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