# COMPARATIVE ROLE OF GLYCATED HAEMOGLOBIN AND GLYCATED ALBUMIN IN THE MANAGEMENT OF DIABETES MELLITUS

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## ABSTRACT

Glycated haemoglobin (HbA1c) and glycated albumin (GA) are key biomarkers in the management of diabetes mellitus, each providing unique insights into glycaemic control. HbA1c, the traditional marker, reflects average blood glucose levels over approximately 120 days, making it essential for long-term monitoring. However, its reliability can be compromised by conditions such as anaemia, pregnancy, and chronic kidney disease. Glycated albumin, a newer marker, offers a snapshot of glycaemic fluctuations over a shorter period of 2 to 4 weeks, thus addressing some limitations of HbA1c. Recent advancements in GA measurement methodologies, particularly the Lucica GA-L® assay, have improved its precision and stability. Studies demonstrate GA's usefulness in scenarios where HbA1c may be less reliable, such as in patients with altered red blood cell life spans, during pregnancy, or in chronic kidney disease. GA also shows promise in monitoring short-term glycaemic changes and treatment responses, offering an advantage in assessing rapid fluctuations in glucose levels. Despite its advantages, GA is not a replacement for HbA1c but rather a complementary tool that can enhance diabetes management. The choice between HbA1c and GA should be guided by individual patient conditions and clinical contexts. Future research is needed to refine GA's diagnostic criteria, explore its effectiveness in diverse populations, and understand its role in predicting long-term diabetes complications. By integrating both markers into clinical practice, healthcare providers can improve the accuracy of glycaemic monitoring and optimize patient care.

**Keywords:** Diabetes mellitus, glycated haemoglobin, glycated albumin, sub-Saharan Africa

## INTRODUCTION

Diabetes mellitus (DM) is a long-term condition caused by insufficient insulin production leading to elevated blood glucose concentrations. This can happen due to either a significant reduction in insulin secretion by the pancreatic islets of Langerhans or a relative lack of insulin in individuals whose tissues do not respond effectively to the hormone [1]. The hallmark of untreated DM is persistent hyperglycaemia with its consequences. There are often related disruptions in fat and protein metabolism [2]. Alongside temporary metabolic issues caused by insufficient insulin action, chronic DM frequently leads to lasting complications, such as damage to the kidneys, eyes, nerves, and both large and small blood vessels. Early detection and effective management are crucial to prevent these complications [2].

Glycated haemoglobin (HbA1c) is the accepted benchmark for assessing glycaemic control in individuals with DM. HbA1c is the haemoglobin protein in red blood cells (RBCs) that has irreversibly bound to glucose molecules [3]. As RBCs have a lifespan of approximately three months, HbA1c represents typical blood sugar control over that period [4].

Recently, attention has focused on glycated albumin (GA) as a substitute marker of glycaemic regulation. This is premised on the fact that it is unaffected by dietary intake and the lifecycle of the RBCs [5]. It has also been shown to indicate shorter glycaemic control in comparison to HbA1c [6]. Furthermore, there are insinuations that it could be the better option when HbA1c result interpretation is challenging, particularly in haemoglobinopathies and anaemic conditions [5,6].

Despite the limitations of both glycated proteins in glycaemic control, it has been suggested that both are complementary [7]. In a study that determined the link between GA and HbA1c in glycaemic control in individuals with type 2 DM in Uganda, it was suggested that GA could be used alongside HbA1c in the African context [8]. In another study, GA was reported to offer additional insights into short-term glycaemic alterations, which could be beneficial for monitoring therapy adjustments [9]. GA in conjunction with HbA1c provided a comprehensive valuation of glycaemic control which is decisive for effective DM management and prevention of long term complications in a South African study [10]. While these reports are from Africa, it is uncertain if these observations apply to other races.

## GLYCATED HAEMOGLOBIN

Historically, HbA1c was first isolated and characterized as a glycoprotein in 1958 and 1968, respectively [11]. An author noted that patients with DM often have elevated levels of HbA1c [12]. The process by which HbA1c is formed was identified in 1975. The use of HbA1c as a biomarker for tracking glucose levels in DM patients was initially suggested in 1976 [13].

Proteins often undergo glycation during various enzymatic processes under physiologically favorable conditions. For haemoglobin, however, glycation results from

a non-enzymatic reaction between glucose and the N-terminal end of the β-chain, leading to the formation of a Schiff base. This Schiff base rearranges to produce Amadori products, with HbA1c being the most recognized. Initially, haemoglobin interacts with blood glucose to create a reversible aldimine. In the subsequent irreversible step, the aldimine gradually transforms into a stable ketoamine form [13]. The primary sites of glycosylation in haemoglobin, listed by their frequency, are β-Val-1, β-Lys-66, and α-Lys-61.

Normal adult haemoglobin primarily consists of HbA (α2β2), HbA2 (α2δ2), and HbF (α2γ2) in proportions of 97%, 2.5%, and 0.5%, respectively. Approximately 6% of total HbA is classified as HbA1, which includes the fractions; HbA1a1, HbA1a2, HbA1b, and HbA1c, distinguished by their electrophoretic and chromatographic characteristics [13]. Among these, HbA1c is the most prevalent, typically representing about 5% of the total HbA. In this process, glucose in its open-chain form binds to the N-terminal, forming an aldimine that subsequently undergoes Amadori rearrangement to yield a more stable ketoamine.

Physiologically, HbA1c formation is normal [13]. However, elevated level of mean plasma glucose causes the plasma HbA1c level to rise. This property of the haemoglobin biosignature is used to estimate average blood glucose levels during the past two to three months.

**HbA1c AS A CRITICAL BIOMARKER FOR GLYCAEMIC MONITORING: BENEFITS AND LIMITATIONS**

HbA1c (often referred to as A1C), serves as a key test for glycaemic monitoring because it accurately reflects average blood sugar levels and is closely linked to the long-term complications of DM. Its application may however, be inappropriate in certain clinical scenarios that affect haemoglobin metabolism, as these can lead to misleading results. Additionally, recent research indicates that HbA1c levels vary among different ethnic groups at similar glucose levels, though the underlying causes of these differences remain unclear [14]

Glucose binds covalently to haemoglobin through a series of reactions, forming various glycated haemoglobins (HbA1c being one). This can occur on one or both beta chains. HbA1c levels represent a balance between formation, breakdown, and destruction of RBCs. However, recent blood sugar levels (past 4 weeks) have a more significant influence due to the continuous turnover of RBCs [15].

In non-diabetic individuals or those with well-controlled DM, HbA1c typically falls between 4.6-6.4% of total haemoglobin [16]. HbA1c theoretically reflects the average glycaemic levels for a timeframe [4].This makes HbA1c a valuable tool compared to finger sticks, which only provide a snapshot of blood sugar at a specific time [4].

The HbA1c test accurately measures chronic blood glucose levels and is associated with the risk of complications related to DM [17]. Its use has expanded to include the diagnosis and screening of DM, supported by various

International Organizations and the World Health Organization. In 2010, the American Diabetes Association and the International Expert Committee made a proposition on diagnostic yardsticks for diabetes and pre-diabetes based on HbA1c values. Specifically, an HbA1c of 6.5% (48 mmol/mol) or higher indicates diabetes, while levels between 5.7% and 6.4% (39–46 mmol/mol) suggest pre-diabetes [18].

HbA1c has become essential in DM management [17]. It offers a unique window into a patient's blood sugar control, but like any tool, it has its advantages and disadvantages compared to other methods as indicated below.

**ADVANTAGES OF HbA1c**

i. Reflects Long-Term Control: HbA1c measures the percentage of RBCs with glucose attached. As RBCs have a lifespan of approximately 120 days, HbA1c reflects average blood sugar control during that period. This offers a considerable advantage compared to fingerstick tests, which only provide a momentary reading of blood glucose levels [4].
ii. Convenient Testing: Unlike blood glucose tests, which often require fasting or finger pricking, HbA1c could be done at any time of the day without any special preparations. This makes it a more convenient option for patients and healthcare providers [19].
iii. Improved Patient Monitoring: HbA1c allows healthcare professionals to track a patient's progress in managing their DM over time. By monitoring HbA1c levels, adjustments can be made to treatment plans to achieve optimal glycaemic control [4]. Ogbera and Kalu [20] highlighted the role of HbA1c as a consistent marker for monitoring the management of DM
iv. Stronger Link to Complications: Extensive research has shown a clear link between HbA1c levels and the development of long-term DM complications, such as retinopathy, neuropathy, nephropathy among others. Monitoring HbA1c helps identify patients at higher risk for these complications [18]. In a study that explored the relationship between HbA1c levels and lipid profiles in DM patients, an association between elevated HbA1c and dyslipidaemia was observed, indicating onset of complications [21].
v. Extremely Low Intra-Individual Variability Coefficient of Variation (CV) < 1%: This refers to how consistent HbA1c measurements are within the same person over time. A low CV (less than 1%) indicates that HbA1c results are highly reliable and reproducible, offering a clearer picture of average blood sugar control [22].
vi. Stability in Sample Material: HbA1c doesn't degrade easily in blood samples, allowing for flexibility in sample handling and transportation without compromising the accuracy of the test results [23].

vii. Not Altered by Acute Factors (e.g., Stress, Exercise): Unlike blood sugar levels, which can fluctuate due to temporary factors like stress or exercise, HbA1c reflects a longer-term average. This provides a more stable picture of blood sugar control that's not influenced by daily variations [4].

viii. Single Sample Required: HbA1c testing only requires a single blood draw, making it a less invasive and more convenient option compared to tests requiring multiple samples [18].

**DISADVANTAGES OF HbA1c:**

i. Not a Substitute for Day-to-Day Monitoring: While HbA1c reflects average blood sugar control, it does not capture the daily fluctuations that can occur. Patients with DM still need to perform regular blood glucose checks to manage their condition effectively, especially for insulin-dependent diabetics [24].

ii. Limitations in Certain Conditions: HbA1c can be inaccurate in certain conditions like pregnancy, anaemia, or recent blood loss. These factors can affect RBC turnover, leading to misleading HbA1c results [6, 24].

iii. Does Not Reflect Recent Changes: Due to the lifecycle of RBCs, HbA1c may not reflect recent changes in blood sugar control. This can be a disadvantage when evaluating the effectiveness of new medications or treatment adjustments [25].

**Comparison of HbA1c with Other Blood Sugar Evaluation Techniques**

***Self-Monitoring of Blood Glucose (SMBG) Levels***. This entails finger pricking to draw a small blood sample and measure glucose levels using a glucometer. It provides real-time blood sugar data but can be inconvenient and sometimes painful.

***Continuous Glucose Monitoring (CGM):*** CGM systems employ a sensor placed beneath the skin to continuously track glucose levels in the interstitial fluid, which is the fluid found between cells. They offer a more complete picture of blood sugar fluctuations throughout the day but are expensive and require regular sensor changes [24].

HbA1c is a valuable tool for DM management but should be used in conjunction with other methods like SMBG. Understanding the pros and cons of HbA1c testing allows healthcare providers to create a personalized approach to DM management for each patient. Although, HbA1c has traditionally been regarded as the yardstick for assessing glycaemic control in DM, recent studies indicate that another biomarker, GA, may also be significant in DM management.

**GLYCATED ALBUMIN (GA)**

Like HbA1c, GA is produced through the non-enzymatic binding of glucose to proteins in the blood, specifically albumin, which is the most prevalent protein in plasma. In contrast to RBCs, albumin has a shorter lifespan [26].

GA has become increasingly important for monitoring blood sugar levels in DM in recent

years. Being a fructosamine, it specifically measures the glycation of albumin, making it less affected by other serum proteins. This test does not require fasting and reflects short-term blood sugar levels due to albumin's half-life of about three weeks. Unlike HbA1c, GA is not influenced by haemolytic conditions or aberrant haemoglobin. It may serve as a more effective glycaemic marker in situations like anaemia, pregnancy, postprandial hyperglycemia, and in insulin users with DM. Furthermore, it is especially useful for DM patients undergoing haemodialysis. Recent research has shown a link between GA levels and the chronic complications associated with both types 1 and 2 DM [26].

Despite growing research on GA in recent years, it is not yet commonly utilized in routine laboratory settings, and there are limited commercial reagents available for its testing. Nonetheless, clinical studies indicate that GA holds promise as a valuable marker for managing DM [23].

## ALBUMIN GLYCATION AND THE BIOCHEMICAL PROPERTIES OF GLYCATED ALBUMIN

Albumin, a 66.7KDa protein consists of a single polypeptide chain with 585 amino acids, 17 disulfide bonds, and three homologous domains arranged in a helical configuration. Being the predominant plasma protein, it accounts for approximately 60% of total blood proteins with concentrations ranging from 3.0-5.0 g/dL and a half-life of 14 -20 days. The structure of albumin supports its physiological roles, including the regulation of pH and maintenance of blood osmotic pressure. Moreover, albumin functions as a potent antioxidant and the primary carrier for metabolic products, ions, nutrients, drugs, hormones, and fatty acids [27].

Like other proteins, albumin undergoes glycation as part of normal physiology. Fructolysine is the primary Amadori adduct produced from a reaction between glucose and lysine which can happen at 59 lysine sites on the albumin molecule. Notably, lysine 525 has been recognized as the main site for glycation based on *in vivo* and *in vitro* studies. The ketamines generated through the non-enzymatic glycation of proteins are collectively referred to as fructosamine. Among these serum fructosamines, GA constitutes about 80% of the total glycated proteins in plasma [28].

During the initial stage of glycation, a Schiff base is formed through the reaction between a reducing sugar and a free amine group within the polypeptide chain of plasma proteins. This is followed by a rearrangement that results in the creation of the Amadori product. In subsequent stages, the breakdown of both the Schiff base and the Amadori product, along with the autoxidation of sugars, leads to the formation of reactive dicarbonyl compounds, which are precursors to advanced Advanced Glycation End Products (AGEs) [26].

Essentially, the extent and length of hyperglycemia determine the glycation process. Extracellular proteins, like albumin, tend to undergo Amadori rearrangements more readily than intracellular proteins, such as haemoglobin because plasma proteins are directly exposed to glucose in the bloodstream

[26]. This may explain why the glycation rate of albumin is approximately 9 to 10 times higher than that of haemoglobin [29]. Additionally, in an *in vitro* study, it was found that the production of GA was about 4.5 times higher than that of HbA1c when equal concentrations of glucose were added to treated samples from healthy individuals [30]. This indicates that, even under the same *in vitro* conditions, GA forms more rapidly than HbA1c. Further oxidation in addition to irreversible processes occur in the advanced stages of protein glycation, resulting in AGEs formation at a higher rates in hyperglycaemia [31, 32].

The presence of AGEs receptors in a variety of tissues enhances their involvement in signal transduction, thus, causing oxidative stress via the activation of nuclear factor - κB (NF-κB) [33]. NF-κB regulates gene transcription of pro-inflammatory chemicals including interleukins 1, 6, and 8, tumour necrosis factor-α, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 [34]. This invariably results in increased formation of reactive oxygen species which has been implicated in the pathogenesis of DM and its complications [35].

Blood samples from a hospitalized DM patient over a period of one month showed a significantly reduced AGEs level with associated reduction of GA levels [26].

## LABORATORY MEASUREMENT OF GA

Fructosamine has been of significance when the determination of short term glycaemia is necessary. It is however fraught with low accuracy going by the influence of plasma proteins and molecules including uric acid and bilirubin among others. Additionally, the unavailability of fructosamine testing in every laboratory as well as non-standardized global protocol for its use are some of its demerits [36].

Laboratory techniques for evaluating/determining either plasma or serum GA have been designed since 1980s. Unfortunately, lack of standardization of the older GA assay techniques played a role to its unpopularity [37]. Methods including immunoassays, ion exchange high performance liquid chromatography and enzymatic assays involving ketamine oxidase and proteinase have been used for GA determination. However, information on the routine use of these methods is sparse [26].

The method of GA assay used determines its reference interval, since its levels varies depending on the analysed glycation sites and whether the method measures the GA molecule or its glycated amino acids. For example, glycated amino acids for GA levels are determined by colorimetry using thiobarbiturate, enzymatic and immunoassay methods whereas, the levels of GA are characterized by HPLC and other chromatographic technologies. Regardless of this disparity, there is between 2-5 fold increase in GA fraction in individuals with DM in comparison with normoglycaemic patients by the consistency of all methodologies used [38].

To overcome the limitations of prior methodologies, an enzymatic methodology with reduced operational time and ease of

performance was presented for evaluating GA levels. This method consists of three steps: albumin determination using particular proteinase, ketamine oxidase and bromocresol green reagent, followed by percentage GA computation. In the validation done for market introduction, excellent analytical performance was observed. There was no interference of glucose and bilirubin with the assay. However, ascorbic acid and haemoglobin minimally interfered with GA levels [39].

A new enzymatic method, Lucica GA-L® developed by Asahi Kasei Pharma Corporation, Tokyo according to reports was reproducible, accurate and had a strong association with HbA1c [40, 41]. Other manufacturers have also published comparable approaches for GA detection; however, instead of measuring individual GA levels, these assays use mathematical calculations and modelling to estimate percentage GA levels. Furthermore, the biological variance of GA evaluated by Lucica GA-L® is smaller than fructosamine and HbA1c [39].

The enzymatic method for GA determination consists of three steps. In the first step, glycated amino acids are liberated from a molecule of GA using an albumin-distinct protease. Glucosone and free amino acids are further separated by ketoamine oxidase. The amount of GA in the sample has a direct correlation with the final pigment. The second stage comprises the interaction of plasma albumin with bromocresol green in an acidic environment, which produces a coloured product that is proportional to total albumin content. In the third stage, the proportion of GA is obtained by a math calculation based on the two preceding reactions [26].

GA has good stability when frozen at extremely low temperatures. Kohzuma *et al*.[42] found that frozen samples stored at -80°C maintained steady GA levels over four years. Watano *et al*.[43] found comparable results for serum samples stored at -70°C, but noticed a significant increase in GA levels when samples were frozen at -20°C after 6 months.

Despite these characteristics, the GA test is not yet widely available in ordinary laboratory practice; however, it has been actively employed in clinical studies for diabetes during the previous decade. The increased number of GA research is largely attributed to the launch of the Lucica GA-L® enzymatic assay for GA detection, which has acquired recognition despite the lack of a clear international consensus [26].

## GA IN CIRCUMSTANCES THAT AFFECT HbA1c

HbA1c is of utility as a diagnostic tool and a test of reference for monitoring glycaemia in DM. Certain conditions, however, can limit its accuracy. These conditions include specific clinical situations or analytical methods that may produce erroneous HbA1c readings which do not accurately correlate with mean glycaemia and have a direct impact on patient identification and care. In such instances, GA may be an appropriate substitute to HbA1c. [6, 44].

### GA and Haematological Alterations

GA can be used as an alternative to HbA1c in cases where haematological alterations affect RBC lifespan or the structure and chemical characteristics of Haemoglobin. Haemolytic anaemias and bleeding incidences can lower HbA1c levels, but iron deficiency anaemias, thalassaemias, and haemoglobinopathies can raise HbA1c levels [45]. During the foetal stage, the primary type of haemoglobin in RBCs is foetal haemoglobin (HbF), which is steadily substituted with HbA following delivery. Because HbA1c is a glycation result of HbA, new-borns frequently have artificially low values [46]. However, interference with HbA1c tests can be method-dependent, and some analytical techniques may be unaffected by regular interferences such as haemoglobin variations [47].

**GA and Pregnancy**

The monitoring of glucose level is imperative in preganant women with pre-existing DM or those who acquire gestational DM. However, increasing iron demand in the later stages of pregnancy can have an impact on HbA1c levels [48].

In a prospective study on pregnant Japanese women with DM, a report showed a significant increase in HbA1c near the end of pregnancy, which was inversely related to ferritin levels and transferrin saturation. Contrariwise, GA levels remained stable throughout pregnancy, as it is not influenced by the physiological alteration characteristic of pregnancy [49].

**GA and Chronic Kidney Disease (CKD)**

In individuals with DM and chronic kidney disease (CKD), HbA1c may not reliably reflect glycaemic control due to several factors. CKD patients often have erythropoietin deficiency, leading to anaemia, which is managed with exogenous erythropoietin and iron supplementation, thus, affecting HbA1c levels [50]. Additionally, frequent blood transfusions and reduced erythrocyte lifespan from haemodialysis contribute to inaccurate HbA1c readings. Increased uraemia in CKD leads to the production of carbamylated haemoglobin that interferes with some HbA1c assays [51].

GA has been shown to give a more reliable evaluation of glycaemic control in advanced CKD stages. However, in cases of significant proteinuria and reduced serum albumin, there could be a falsely-altered GA levels. Therefore, a critical evaluation is necessary to choose the most appropriate glycaemic marker for these patients [39].

**GA in DM Diagnosis**

Certain researchers question the current cut-off points for the diagnosis of DM, this is in spite of the established role of HbA1c. Discrepancies exist between the proportions of patients diagnosed with DM by HbA1c compared to those identified by glycaemic tests Patients with conditions affecting HbA1c levels should be checked for diabetes utilising other indicators like GA. Although the enzymatic technique for GA was just established, there are limited reports on its diagnostic accuracy for DM [52].

## GA in Glucose Monitoring in DM

Unlike HbA1c, which reflects long-term glucose control over approximately 120 days, GA is formed over a much shorter period of 2-4 weeks. This rapid formation allows GA to better capture variations in glucose levels that may not be detected by a single plasma glucose measurement [53].

The degrees of glycation of GA and HbA1c illustrate their differences. GA production spans albumin lifespan, which is about 4 weeks, with the initial 2 weeks contributing to approximately half of its production. In contrast, HbA1c reflects glucose levels over the lifespan of erythrocytes, around 120 days, with the first month contributing to approximately half of its glycation [23].

GA is better suited to monitoring the commencement and adjustment of diabetic therapy than HbA1c because its levels respond faster to changes in glucose levels. Kohzuma *et al*. [44] found that GA was a more useful metric for evaluating insulin therapy responses in type 2 DM individuals with poor glycaemic control. GA also had a stronger connection with fasting glucose (FG) levels ($r = 0.75$) than HbA1c ($r = 0.54$). It was shown in a report that the ratio of GA to Hb1Ac was associated with the mean amplitude of glycaemic excursion as well as pancreatic islet function in patients with type 2 DM [54].

Overall, GA is advantageous for assessing mean glycaemia, glycaemic variability, as well as postprandial glucose levels more accurately than HbA1c. Elevated postprandial glucose levels are associated with a higher risk of cardiovascular diseases and microangiopathy, making the recognition of these fluctuations crucial. However, the exact reasons why GA is more directly related to postprandial glucose are unclear [26].

## GA in Predicting Long-Term Complications of DM

Chronic hyperglycemia considerably raises the chance of developing micro and macrovascular problems over time. HbA1c has been extensively studied and supported as a marker for predicting these complications in DM. However, there is ongoing dispute about whether mean glycemia or glycaemic variability is the primary cause of chronic damage in DM [55]. Recent research has investigated the prognostic validity of short-term glycaemic indicators, such as GA, as viable alternatives to HbA1c [56].

Selvin *et al*. [56] did a cross-sectional analysis of 1,600 persons from the Atherosclerosis Risk in Communities (ARIC) study and discovered that both GA and fructosamine were substantially linked with the prevalence of albuminuria, CKD, and retinopathy in type 2 DM. A longitudinal study involving 12,306 ARIC participants followed for over 20 years showed that fructosamine and GA were equally efficacious as HbA1c in predicting retinopathy and CKD. Even after controlling for HbA1c levels, GA levels > 23.0% had a significantly greater odds ratio (OR) for retinopathy onset than levels between 15.7% and 23.0% (OR > 8 vs. OR > 15). Furthermore, GA showed comparable associations with coronary heart disease, ischemic stroke, heart

failure, and mortality as HbA1c [57].

Nathan *et al*. [55, 58] used data from the DCCT and Epidemiology of Diabetes Interventions and Complications (EDIC) studies to determine the link between GA and chronic problems in type 1 DM. Their findings revealed that both GA and HbA1c were highly linked with the occurrence of retinopathy and nephropathy after a 6.5-year average follow-up period. However, no association was found with the 7-point glucose profile, and only HbA1c was linked to cardiovascular disease. Gan et al [59] elucidated the superiority of GA over HbA1c in glycaemic assessment in DM patients with advanced-stage CKD.

GA seems to be an effective predictor of microvascular problems in both types 1 and 2 DM. However, in terms of macrovascular outcomes, GA appears to be a good indication, particularly in type 2 DM. This disparity may be due to the many mechanisms involving the development of atherosclerosis and CVDs in type 1 DM [56].

## REFERENCE INTERVALS FOR GA

Japan Diabetes Society (JDS) determined a reference rangefor GA ranging between 12.3% and 16.9% in 2005 [60]. Later, Furusyo *et al.* [61] conducted a larger-sized study of 1,575 participants with GA reference range of 12.2%-16.5% reported, supporting the JDS findings. Using fasting glucose (FG) and/or HbA1c (≥ 126 mg/dL and > 6.5%, respectively) as reference tests, this study found a GA cut-off point of ≥ 15.5% with high sensitivity and specificity (83.3%) for detecting DM. In another study of 908 non-DM Japanese patients, 176 had fasting plasma glucose levels ranging from 5.5 to 6.9 mmol/l and HbA1c value less than 6.5% and were given an oral glucose tolerance test. The optimal GA value for the diagnosis of DM was 15.2%. [62]

Hwang *et al*. [63] assessed different GA cut-off points for DM and pre-diabetes diagnosis in 852 Korean adults using the criteria of American Diabetes Association. Cut-off mark of 12.5% and 14.3% were determined for pre-diabetes and DM, respectively. GA had higher sensitivity than HbA1c (66.4% vs. 52.5%), but poorer specificity (88.3% vs. 95.1%) for predicting 2-hour glucose levels ≥ 200 mg/dL. Combining GA values of 14.3% with FG ≥ 126 mg/dL increased sensitivity (77.5%, CI: 72.17–82.0%) for DM diagnosis. In a research of 2,192 adults in Taiwan, Hsu et al [64] found that a GA cut-off point of ≥ 14.9% for DM was associated with 78.5% sensitivity and 80.0% specificity. Furthermore, GA values corresponding to HbA1c levels of 5.7% and 6.5% were 14.5% and 16.5%, respectively.

Several studies have reported GA reference intervals in non-DM persons. These ranges include 11.9%-15.8% (N = 201 residents of North Carolina, USA), 10.2%-16.1% (N = 217 African immigrants in America), 10.5%-17.5% (N = 44 volunteers from a Canadian study), and 9.0%-16.0% (N = 252 Europeans) [65]. Young obese adults aged 10 to 18 years were diagnosed with DM using GA values > 12% and ≥ 14%, with 2-hour glucose and HbA1c as reference tests [66].

Information on the determination of reference intervals for GA is sparse in indigenous sub-

Saharan Africans.

**Advantages of GA**

i. Reflects Shorter-Term Glycaemic Control: Due to its shorter lifespan, GA provides an indication of blood glucose control over a shorter timeframe compared to HbA1c, which reflects longer-term control [67,68].

ii. Monitoring Recent Changes: HbA1c may not capture recent fluctuations in blood glucose due to the lifespan of RBCs. GA can offer a more current picture of recent glucose trends [69].

iii. Evaluating Treatment Effectiveness: GA may provide a quicker assessment of how new medications or treatment adjustments impact blood glucose control compared to HbA1c [70].

iv. Evaluating Glycaemic Variability: GA is particularly useful for monitoring glycaemic variability and very valuable for haemodialysis patients because its levels are unaffected by anaemia or haemolytic processes. Compared to fructosamine, GA has advantages, as it is uninfluenced by other serum proteins. The enzymatic methodology for GA analysis is generally simple and efficient, with high analytical precision and standardization. [53].

**Disadvantages of GA**

i. GA levels can be influenced by conditions affecting albumin metabolism. While GA readings are adjusted for total albumin, reduced serum albumin levels can be linked to increased glycation rates, whereas high protein metabolism can lead to lesser GA levels. Therefore, in circumstances such as hyper and hypothyroidism, liver cirrhosis, nephrotic syndrome with significant proteinuria, or other specific problems, GA may be misleading and ought to be used with caution [71].

ii. Obesity, smoking, hypertriglyceridaemia, inflammatory conditions and age are factors that can affect GA levels Additionally, ethnic differences have been observed, with GA and HbA1c levels being significantly elevated in Black individuals compared to Whites, highlighting the need for careful interpretation in different clinical contexts [56].

**HbA1c and GA in sub-Saharan Africa**

A South African study found that combining HbA1c and GA significantly improved the detection of dysglycaemia compared to using HbA1c alone [72]. In a separate study that examined the effectiveness of HbA1c, fructosamine and GA in identifying prediabetes among certain African population, it was reported that combining HbA1c and GA enabled identification of higher percentage of individuals with prediabetes [73]. Combining HbA1c and GA also improved the detection of

prediabetes in another African study [74]. The accuracy of DM diagnosis and monitoring were enhanced with the use of both markers in a South African study [10]. A report of meta-analysis on the use of GA for the diagnosis of DM in Africa supported its use in population with diverse haemoglobin variants [39].

A study reviewed the performance of HbA1c in various populations of African descent. The study showed that current HbA1c cutoffs may overestimate or underestimate glycaemic status depending on the specific African population, suggesting a need for adjusted diagnostic criteria [75].

In their study on the prevalence of gestational DM in Port Harcourt, Nigeria it was shown that HbA1c and GA could be useful in monitoring GDM in Nigerian women [76]. The same authors in another study posited that HbA1c was a reliable diagnostic tool in a Nigerian healthcare setting [77]. In another study in Bauchi, Nigeria, HbA1c was reported as a crucial marker in assessing diabetic complications such as retinopathy [78]. Salivary GA was shown as a biomarker for both periodontal health and DM management in another study [79].

A report showed a significant relationship between HbA1c and serum calcium in type 2 DM patients, thus contributing to the understanding of DM management in the Nigerian context [80]. Oladayo *et al*. [81] examined the role of HbA1c in assessing the risk of nephropathy in diabetic patients in, Zaria, Nigeria. The study reinforced the usefulness of HbA1c as a marker for monitoring kidney function in Nigerian diabetic patients [81].

These studies collectively underscore the relevance of both HbA1c and GA in DM across different African populations. While HbA1c remains a cornerstone for long-term glycaemic monitoring, GA offers advantages in assessing short-term glycaemic fluctuations, which can be particularly useful in regions with diverse healthcare challenges.

## CONCLUSION

In summary, both glycated haemoglobin and glycated albumin play important roles in the management of DM, offering different perspectives on glycaemic control. HbA1c remains the standard for long-term glucose monitoring, providing a dependable measure of average blood glucose levels over approximately 120 days. However, its accuracy can be compromised by various factors, including haematological disorders, pregnancy, and chronic kidney disease. In these cases, GA can serve as a valuable alternative, reflecting shorter-term glycaemic fluctuations with greater sensitivity.

GA's ability to capture glycaemic variations over 2 to 4 weeks makes it particularly useful for monitoring rapid changes in glucose levels and assessing treatment responses. Its stability in frozen samples and the development of standardized enzymatic assays, such as Lucica GA-L®, have significantly improved its reliability and precision. Despite these advantages, GA should not replace HbA1c but rather complement it, offering additional insights into glycaemic control when HbA1c is less reliable.

The integration of GA into routine clinical practice requires careful consideration of individual patient conditions and healthcare contexts. For instance, in settings with limited access to advanced diagnostic tools or where HbA1c results are frequently unreliable, GA provides a feasible alternative for assessing glycaemic control. Conversely, in regions where HbA1c is well-established and widely available, GA can serve as an adjunctive marker, enhancing the overall management of DM.

Future research should focus on refining the diagnostic criteria for GA and exploring its utility across diverse populations and clinical scenarios. This includes investigating its potential as a diagnostic tool for diabetes mellitus, its role in predicting long-term complications, and its applicability in different geographic and healthcare settings. By addressing these areas, we can better understand how to optimize the use of both HbA1c and GA in diabetes management, ultimately improving patient outcomes and advancing the field of glycaemic monitoring.

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