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# ROLE OF HBA1C IN THE DIAGNOSIS OF PATIENTS WITH DIABETES MELLITUS

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## ABSTRACT

Globally, the incidence and prevalence of type 1 and type 2 diabetes mellitus (DM) has increased significantly over the past two decades and is expected to continue to increase in the future. Diabetes is associated with several chronic complications that lead to increased morbidity and mortality. In addition to people with diabetes, who receive adequate and timely medical attention, their blood glucose control should also be checked. Monitoring glycemic status is considered the cornerstone of diabetes care. The analysis of glucose data provides an evaluation of the effectiveness of therapy and leads to lifestyle adjustments and medications to safely obtain the best possible glycemic control. The most important techniques to evaluate the efficacy of glycemic control include patient self-control for blood glucose (SMBG) and the measurement of hemoglobin A1c (HbA1c). Hemoglobin A1C (HbA1c) is used as an indicator of average blood glucose monitoring over a period of months and is a source of blood glucose monitoring. This metric is easy to measure and relatively inexpensive to obtain. It involves micro-vascular complications related to diabetes.HbA1c, however, provides only an approximate measure of glucose control; it does not address short-term glycemic variability (GV) or hypoglycemic events.Continuous glucose monitoring (CGM) is a tool that helps doctors and people with diabetes overcome HbA1c limits in the treatment of diabetes. Large clinical studies support the modern view that the objective of HbA1c should be adapted to the risks and benefits of blood glucose control. This is probably more important in patients with diabetes, where reaching low HbA1c levels at the beginning of the natural history may be more beneficial.

**KEYWORDS:** Diabetes Mellitus, Micro-vascular, Hypoglycemic, HbA1c, Glycemic variability, Continuous glucose monitoring.

## INTRODUCTION

The measurement of hemoglobin A1c (HbA1c) has become an integral tool for the diagnosis and treatment of diabetes mellitus since its widespread introduction into clinical practice nearly two decades ago. It also serves as a surrogate marker for glycemic control and is a key indicator of the risk of micro-vascular and macro-vascular complications and diabetes mortality. Diabetes is a global endemic with a rapidly increasing prevalence in developed and developing countries.[1]T2DM is a group of metabolic diseases characterized by hyperglycaemia due to insulin secretion defects, insulin action, or both. Uncontrolled diabetics are characterized by hyperglycemia, hyperinsulinemia, protein glycosylation, and oxidative stress, which cause the onset of diabetic complications. Blood sugar is a continuous variable that decreases about twice a day in people without diabetes and up to about ten times in people with unstable diabetes. Glycemic exposure (which can be considered as average blood sugar per year) is the best-defined and proven cause of long-term diabetic complications. The analysis of glycated hemoglobin (HbA1c) in blood provides an indication of the average glucose levels in a person's blood in the last two or three months, ie, the expected red blood cell half-life (RBC).[2] HbA1c standard of care (SOC) for testing and controlling diabetes, especially type 2 diabetes.[3] Proteins are often glycated during various enzymatic reactions when conditions are physiologically favorable. However, in the case of hemoglobin, glycation occurs by non-enzymatic reaction between glucose and the N-terminal end of the β chain, which is a Schiff base.[4,5] During the rearrangement, Schiff's base will become Amadori products, being the most popular HbA1c (Fig. 1).

In Fig-1 shown that, in the primary phase of glycosylated hemoglobin formation, hemoglobin and blood glucose react reversibly to the aldimine. In the irreversible secondary phase, aldimina gradually becomes a stable form of ketoamine.[6]The main sites of hemoglobin glycosylation are in the order of their prevalence β-Val-1, β-Lys-66 and α-Lis-61. Normal adult hemoglobin

consists predominantly of HbA (α2β2), HbA2 (α2δ2) and HbF (α2γ2) in the composition of 97%, 2.5% and 0.5%, respectively. Approximately 6% of total HbA is designated HbA1, which in turn is composed of the HbA1a1, HbA1a2, HbA1b and HbA1c fractions defined by their electrophoretic and chromatographic properties. HbA1c is the most abundant of these fractions, accounting for about 5% of the total HbA fraction. As noted above, glucose in open-chain form attaches to the N-terminus to form an aldimine before performing an Amadori rearrangement to form a more stable ketoamine. This is a non-enzymatic process that runs continuously in vivo. The formation of glycosylated hemoglobin is a normal part of the cycle of physiological functions. However, as the average plasma glucose increases, so does the amount of glycosylated hemoglobin in the plasma. This specific characteristics of the hemoglobin biomarker is used to estimate the average blood glucose level in the last two or three months.[7] In this review, we have described the current trends in diabetes prevalence, diagnostic and prognostic of HbA1c, analytical aspects in HbA1c assays, and physiological changes due to hemoglobin glycation.

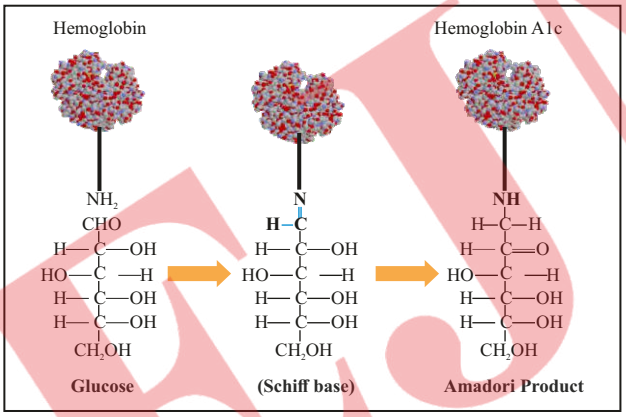


*Fig 1: Formation of Glycated Hemoglobin (HbA1c) from the Binding of Glucose to Hemoglobin*

## History of HbA1c

HbA1c was first discovered in 1955, but elevated HbA1c levels in patients with diabetes were not observed until 1968.[8] It took another 8 years for HbA1c to correlate with blood glucose levels in patients in the hospital with diabetes and to control glycaemia.[9] Biochemically, HbA1c formed by a non-enzymatic reaction in which glucose binds to the amino-terminal valine of one or both hemoglobin A beta chains. Blood sugar concentration, duration of exposure to red blood cells (RBC) at different concentrations, and amounts of RBC. HbA1c more accurately reflects the previous 2-3 months of glycemic control associated with the normal lifespan of 120-day red blood cells.[10] HbA1c represents the percentage of circulating hemoglobin that is glycosylated. Glycation is a non-enzymatic process and a measure of the time course. As a biomarker, it reflects the average blood sugar of the last 8-12 weeks. It is currently used both for the diagnosis and treatment of diabetes and is recommended as the gold standard for the assessment of diabetes-related outcomes. Historically, high levels of HbA1c in diabetics were first reported by Rahbaret al in 1968, and became the most important indicator of glycemic control in the decades that followed. It is widely used to assess the suitability of diabetes treatment. However, for a given HbA1c, there is a wide range of average glucose concentration values, and for any given average glucose value, there is a wide range of HbA1c values.[11-15] As a long-term indicator of glycemic control, it may not accurately reflect improvements or acute deterioration in blood glucose levels. Current factors that affect blood glucose should be taken into account, since HbA1c represents a weighted average of glucose with a 50% contribution compared to the previous month.[16] HbA1c should be interpreted with caution. In non-pregnant adults, HbA1c is falsely low in diseases that reduce the amount of glycosylated erythrocytes, such as hemolysis, splenomegaly, chronic kidney disease, liver cirrhosis, hemorrhage, blood transfusions, use of erythropoieticstimulants and some hemoglobinopathies (ie, HbS, HbC, HbF). Alternatively, HbA1c increases in other hemoglobinopathies and in diseases that cause a reduction in red blood cell turnover, such as iron deficiency anemia or vitamin B12.[17-19]

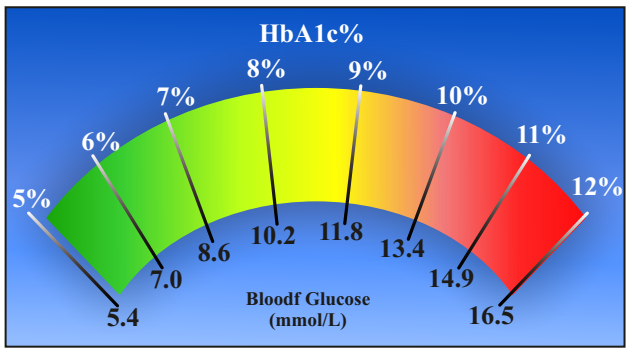


*Fig 2: HbA1c as Indicator of Diabetes Control (20)*

Figure 2 shows that a new guideline for American doctors on the pharmacological treatment of type 2 diabetes recommends HbA1c targets between 7% and 8%, compared to existing guidelines that suggest that HbA1C is greater than 7% Risk of diabetes complications such as retinopathy and neuropathy. New guidelines from the American College of Physicians (ACP) have been developed based on data that has been reviewed using existing guidelines and

clinical trials and that provide inconsistent evidence of reducing diabetes complications through intensive glycemic control (20).

**HbA1c Test Diagnosis for T2DM Patients**

The A1c test is the most common diagnostic tool for the treatment and investigation of T2DM.[21,22] Measures the average blood sugar level of a person in the last three months. The higher a person's blood sugar level, the higher the percentage of test result. Unlike the fasting plasma glucose (FPG) tests, which measure blood-free glucose after fasting, the A1c test is less variable and reflects the average amount of glucose linked to hemoglobin in the past three months, Recent diagnostic criteria The T2DM proposed by the Committee of International Experts on the basis of A1C suggests that values ≥ 6.5% (48 mmol / mol) indicate T2DM and identify 6.0-6.4% of those at high risk of progression to T2DM.[23] The American Diabetes Association (ADA) also recognizes that A1c levels indicate ≥6.5% of DM2, while 5.7-6.4% indicate a high risk of progression to DM2, while 5.7-6 4% indicate a high risk of progression to T2DM, although these criteria are based on both the FPG and the 76g oral glucose tolerance test (OGTT).[24] Despite the numerous strengths associated with the use of A1c (e.g., highly-standardized with low intra-person variation, timely, fewer requirements for sample collection and storage), it has little validity and, therefore, remains a point of discussion that limits its wider application (for example, A1c test 6.5% diagnosis threshold: sensitivity = 44%, specificity = 79%)[25-27] Studies suggesting that a close dependence on FPG and OGTT has also led to a diagnosis and diagnostic treatment of T2DM and pre-diabetes worldwide.[28]

It has long been recognized that the onset of T2DM often occurs years before clinical diagnosis and treatment (often up to seven years) and that these delays are often associated with an increase in metabolic disorders, clinical manifestations, and the risk of death.[29,30] Diagnostic validity of the A1c test was examined at various diagnostic cut-off levels for the diagnosis of T2DM.[31,32] In addition, the choice of optimal diagnostic thresholds depended on the fact that the benefits of diagnosis and treatment depended on the damage exceeded by everyone. Specific population of patients examined. Heterogeneity was also observed in the diagnostic performance of A1c assays in groups of patients of different ethnicity.[33] years,[34] hemoglobin variants: homoglobinopathies[34] and diseases such as HIV[36] and anemia[37] due to the A1c-disordarchance of glucose. This heterogeneity underlines the population-specific diagnostic performance of the A1c test as well as the optimal diagnostic threshold for determining the presence or absence of T2DM.

**HbA1c Test Prognosis for T2DM Patients**

HbA1c is not only a useful biomarker for long-term blood glucose control, but also a good predictor of lipid profile; therefore, monitoring blood glucose control with HbA1c may have additional benefits of identifying diabetes patients who are at a greater risk of cardiovascular complications.[38] High levels of HbA1c were associated with an increased risk of recurrence of atrial tachyarrhythmia in patients with type 2 diabetes mellitus and paroxysmal atrial fibrillation undergoing catheter ablation.[39] Even an increase of 1% in HbA1c concentration was associated with about 30% increase in all-cause mortality and 40% increase in cardiovascular or ischemic heart disease mortality, among individuals with diabetes.[40] Whereas reducing the HbA1c level by 0.2% could lower the mortality by 10%.[40] Vaag[41] has suggested that Improved glycemic control in patients with type 2 diabetes may be more important than the treatment of dyslipidemia to prevent micro-vascular and macro-vascular complications. Based on the follow-up of 12 months of 1,433 patients with stable angina undergoing coronary angiography, it was concluded that high baseline HbA1c was an independent predictor of the severity of coronary heart disease and an unfavorable outcome in patients with stable angina.[42]

HbA1c 6.5% is insufficient to be used only for the diagnosis of DM after transplantation in patients with kidney transplantation. However, the combined use of the HbA1c limits of 5.8% and 6.2% would reduce the number of oral glucose tolerance tests by 85% and the use of an algorithm with HbA1c in combination with FPG. It was more effective A good diagnostic strategy or exclusion of DM.[43] After transplantation Poor glycemic control (HbA1c 8%) was associated with reduced survival in the general population of diabetic patients on maintenance hemodialysis, suggesting that moderate hyperglycemia increases the risk of mortality for all causes of patients with hemodialysis of maintenance of diabetes in the Han Chinese population.[44] investigated the usefulness of HbA1c levels in predicting clinical disease in children genetically predisposed with multiple autoantibodies. They observed that a 10% increase in HbA1c levels in the samples every 3-12 months predicted the diagnosis of clinical disease, suggesting the usefulness of HbA1c as a time predictor for the diagnosis of type 1 diabetes in children with multiple autoantibodies.[45]

**Range of HbA1c in T2DM**

Non-diabetes is generally in the range of 4.0% to 5.6% HbA1c. Pre-diabetes generally has HbA1c levels of 5.7% to 6.4%, while those with HbA1c levels of 6.4% or more have diabetes.[46,47] People with diabetes live

healthily (diet and exercise) and maintain HbA1c levels below 7.0%. Diabetes-related complications are directly proportional to HbA1c levels increasing. HbA1c levels also increase the risk of such complications. Excessive use of vitamin C, B and E, as well as an increase in cholesterol, liver and kidney diseases can also lead to abnormally high levels of HbA1c.[48,49]Dyslipidemia, which is an imbalance of lipids and fats circulating in the blood, is another debilitating disease associated with diabetes.[50,51] However, maintaining a healthy glucose level is of fundamental importance for type 2 diabetics to be useful. in preventing vascular complications of micro and macropathologies.[52] HbA1c is also regularly used to evaluate gestational diabetes in pregnant women.[53] Other researchers used serum fructosamine and blood sugar to detect GDM.[54,55] Both Tests will allow Health professionals determine whether pregnant women with related risk factors before pregnancy have developed diabetes that may not have been diagnosed. If HbA1c levels are not carefully controlled for acceptable glycemic control, higher HbA1c levels can cause cardiac dysfunction of the developing fetus in the long axis.[56,57] There is a direct correlation between reduced HbA1c levels low mortality rate. Maintaining a healthy HbA1c level significantly reduces the risk of cardiovascular disease in diabetics. [58]

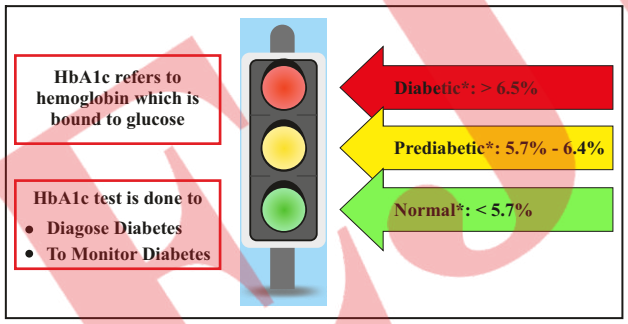


***Fig 3: HbA1c Test Measures Percentage of HbA1c in Blood. It Reflects the Average Glucose Over a Period of Past Two to Three Months (8-12 week)***

## Conclusion

HbA1c is an accurate and easy-to-manage test with on-site results availability. It can be an effective tool for diagnosing and prognosis of diabetes, especially in low- and middle-income countries and in hard-to-reach populations. Although HbA1c has been approved for the diagnosis of diabetes, certain screening strategies and reduction intervals are still under discussion in most countries around the world. However, the combination of FGT and HbA1c significantly increases the diagnostic accuracy of these individual tests. The prognostic potential of HbA1c lies in its unique ability to evaluate retrospective glycemic control and to predict the lipid profile in diabetic patients. As the diabetes epidemic continues to grow worldwide, the HbA1c test can continue to be implemented as part of the diagnostic and prognostic tool, improving patient care and improving patient outcomes achieve good clinical results.

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