



Relation Hba1c with Diabetes Diagnosis

Zaydi, Sultan Jubran H, Hawy, Ali Mohammed H, Shibly, Yousef Mohammed J, Majeri, Yahya Mohammed H, Tawhari, Abdullah Dawshi M, Thallami, Nasser Mohammed H, Zaydi, Hassan Hussain A

Laboratory

Abstract:

The HbA1c test has gained widespread recognition as a reliable and effective biomarker for diagnosing diabetes, offering substantial advantages over traditional methods like fasting blood glucose (FBG). Unlike FBG, which provides a snapshot of glucose levels at a single point in time, HbA1c reflects long-term glycemic control over the past 2-3 months. This paper delves into the relationship between HbA1c levels and diabetes diagnosis, focusing on its diagnostic accuracy, prognostic potential, and clinical utility. It explores how HbA1c serves not only as a diagnostic tool for identifying diabetes but also as a prognostic marker for assessing the risk of diabetes-related complications. Furthermore, the paper highlights the challenges associated with HbA1c testing, such as its susceptibility to interference from factors like anemia and variations in red blood cell turnover, which can affect its accuracy. The need for the standardization of HbA1c testing across different populations and healthcare settings is emphasized, as is the importance of continued improvements in testing methods and technologies to enhance diagnostic precision and overall patient care in diabetes management.

Keywords: HbA1c, diabetes diagnosis, fasting blood glucose, glycemic control, prognostic marker, diagnostic criteria, type 2 diabetes, accuracy, clinical utility.

Introduction:

Diabetes has become a global health crisis, with the prevalence of Type 2 Diabetes Mellitus (T2DM) increasing at an alarming rate, particularly in low- and middle-income countries. The rise in the number of cases is largely attributed to factors such as an aging population, urbanization, and changes in dietary habits and lifestyle, all of which are contributing to the growing burden on healthcare systems. According to the World Health Organization (WHO), diabetes is projected to become the seventh leading cause of death worldwide by 2030. T2DM not only leads to significant morbidity but is also a major risk factor for cardiovascular diseases,



kidney failure, neuropathy, and vision loss, all of which severely impact the quality of life and increase healthcare costs (Berglund et al., 2019; Benaiges et al., 2017). As such, addressing diabetes, especially through early diagnosis and effective management, is critical to preventing the onset of these debilitating complications (Lenters-Westra et al., 2022).

Timely diagnosis of diabetes plays a crucial role in preventing long-term complications, which are associated with higher morbidity and mortality rates. When diagnosed early, patients with diabetes can be treated promptly to manage their blood glucose levels, thereby reducing the risk of cardiovascular disease, retinopathy, nephropathy, and neuropathy. Traditional diagnostic methods, such as fasting blood glucose (FBG) and oral glucose tolerance tests (OGTT), are widely used but have limitations that hinder their effectiveness in large-scale screenings. FBG, for instance, measures blood glucose levels at a single point in time, which can be influenced by various factors, such as stress or time of day. OGTT, although more accurate, requires patients to undergo a glucose load, which can be inconvenient and time-consuming (Karnchanasorn et al., 2016). In contrast, the HbA1c test offers a more reliable and practical diagnostic option, providing a measure of average blood glucose levels over the past two to three months, and has been increasingly adopted as the gold standard for diabetes diagnosis (Sreenan & Tormey, 2016).

The HbA1c test is a blood test that quantifies the percentage of hemoglobin that has become glycated due to prolonged exposure to elevated glucose levels. It is advantageous over traditional diagnostic tests in several ways. First, it offers a more comprehensive measure of long-term glycemic control, making it less susceptible to short-term fluctuations in blood glucose levels (Benaiges et al., 2017). Second, HbA1c testing is convenient as it does not require fasting and can be administered at any time of day. This has made it particularly appealing for large-scale screenings and routine monitoring (Sreenan & Tormey, 2016). In addition, HbA1c is strongly correlated with the risk of diabetes-related complications, including cardiovascular diseases, nephropathy, and retinopathy, making it a valuable tool not only for diagnosis but also for prognostic assessment (Forbes et al., 2018). Given its ability to predict long-term outcomes and provide a stable measure of glycemic control, the HbA1c test has emerged as an essential part of diabetes management (Lenters-Westra et al., 2022).

The primary aim of this paper is to critically evaluate the role of HbA1c in the diagnosis and prognosis of T2DM. This study will assess the accuracy, reliability, and practical application of the HbA1c test in diagnosing diabetes, particularly in comparison with traditional diagnostic methods like fasting blood glucose (FBG) and oral glucose tolerance test (OGTT).



(Karnchanasorn et al., 2016). Moreover, the paper will explore the prognostic value of HbA1c in predicting long-term complications of diabetes, including cardiovascular diseases, nephropathy, and retinopathy, and its potential to guide clinical management decisions (Forbes et al., 2018). Through this comprehensive review, the paper will highlight the effectiveness of HbA1c in diagnosing and predicting outcomes for diabetes patients while also addressing potential challenges such as interference from conditions like anemia and seasonal variations in HbA1c levels (Chen et al., 2023; Berglund et al., 2019). The findings will contribute to a deeper understanding of how HbA1c can be integrated into clinical practice for better management and outcomes in individuals with diabetes (Sreenan & Tormey, 2016).

2. Background:

HbA1c, also known as glycated hemoglobin, forms through a non-enzymatic reaction between glucose and hemoglobin in red blood cells. When glucose circulates in the blood, it interacts with hemoglobin, attaching itself to the N-terminal of the hemoglobin molecule, forming a Schiff base. Over time, this Schiff base rearranges into a more stable structure, the ketoamine, resulting in the formation of HbA1c. The process is irreversible and reflects the cumulative exposure of red blood cells to glucose over their lifespan, which averages around 2-3 months (Chen et al., 2023). As red blood cells have a relatively long lifespan, this makes HbA1c an ideal marker for assessing long-term blood glucose levels. The more glucose a person is exposed to over time, the higher the amount of glycated hemoglobin in their blood, making HbA1c a reliable tool for monitoring glucose levels and diagnosing diabetes.

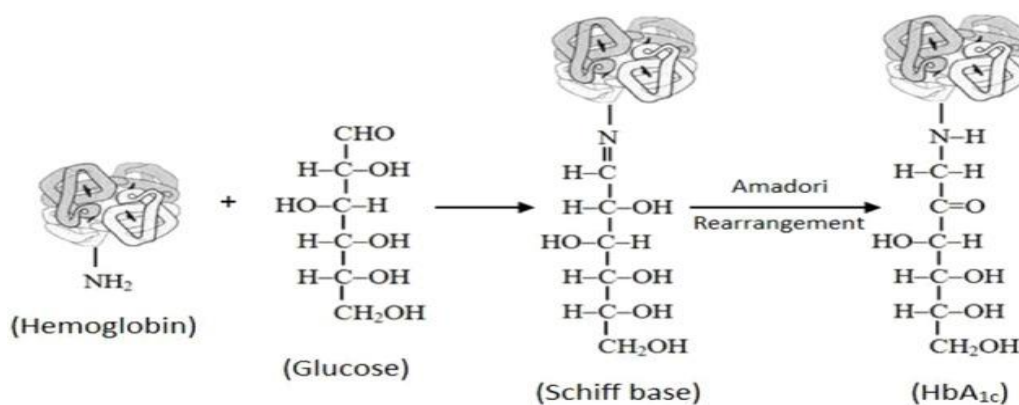


Figure 1: Formation of glycated hemoglobin (HbA1c) from the binding of glucose to hemoglobin



This figure illustrates the biochemical process leading to the formation of HbA1c. It shows how glucose molecules bind to the hemoglobin in red blood cells, leading to the non-enzymatic glycation process that results in HbA1c formation.

The relationship between HbA1c and blood glucose is direct and linear, meaning that an increase in blood glucose levels over time leads to a corresponding increase in the amount of glycated hemoglobin. As such, HbA1c serves as a strong indicator of an individual's average blood glucose concentration over a period of weeks to months, making it a valuable marker for long-term glycemic control (Niwa & Kakehi, 2018). However, it is important to note that certain factors can influence the accuracy of HbA1c measurements. For instance, conditions that affect red blood cell turnover, such as anemia or hemolytic diseases, can result in a skewed measurement of HbA1c. In these cases, the altered lifespan of red blood cells can either cause an overestimation or underestimation of HbA1c levels, leading to potential diagnostic inaccuracies (Chen et al., 2023). Additionally, certain genetic factors, like hemoglobinopathies, can also affect HbA1c formation, further complicating its use as a universal marker for blood glucose control.

Therefore, while HbA1c is a highly effective tool for assessing long-term glucose control, healthcare providers must consider these influencing factors when using it for diagnosing and managing diabetes. Its limitations highlight the importance of using HbA1c alongside other diagnostic methods, such as fasting blood glucose (FBG) and oral glucose tolerance tests (OGTT), to ensure the most accurate diagnosis and treatment plan for individuals with or at risk for diabetes.

3. HbA1c in the Diagnosis of Diabetes:

HbA1c has emerged as a cornerstone in the diagnosis of diabetes due to its ability to reflect long-term glycemic control, offering an advantage over other traditional diagnostic methods. The American Diabetes Association (ADA) has established a cut-off of $\geq 6.5\%$ for diagnosing diabetes using HbA1c, a level that indicates chronic hyperglycemia and poor long-term blood glucose control (Karnchanasorn et al., 2016). This threshold has been widely adopted, as it allows for an efficient and relatively straightforward method to diagnose diabetes without the need for fasting or complex procedures. For individuals at risk of developing diabetes, HbA1c levels between 5.7% and 6.4% are considered indicative of pre-diabetes, signaling that these individuals have an elevated risk of progressing to full-blown diabetes (Berglund et al., 2019).



When compared to traditional diagnostic methods like fasting plasma glucose (FPG), HbA1c has shown strong correlations, but the two differ in temporal relevance and the type of information they provide. HbA1c reflects the average blood glucose levels over a 2-3 month period, offering a more comprehensive picture of a person's long-term glycemic control. In contrast, FPG measures glucose levels at a single point in time, which, while effective, provides less insight into a person's overall glycemic status (Karnchanasorn et al., 2016). The comparison between these two diagnostic methods underscores their complementary nature. HbA1c is advantageous because it does not require fasting, making it a more convenient option for both patients and healthcare providers, though it has limitations in certain populations. Conversely, FPG is highly specific and reliable, but it requires fasting and provides a snapshot of glucose levels at one specific time, which can sometimes fail to capture the complexity of an individual's glucose regulation. The following table highlights the key differences between these two diagnostic tools:

Table 1: Comparison of HbA1c and FPG for Diagnosing Diabetes

Diagnostic Method	Sensitivity	Specificity	Advantages	Limitations
HbA1c	High	Moderate	Convenient, no fasting required	Not suitable for all populations (e.g., anemia, sickle cell)
FPG	Moderate	High	Fast and reliable	Requires fasting, single-point measurement

Despite its utility, there are several challenges associated with using HbA1c as the sole diagnostic criterion for diabetes. Certain conditions, such as anemia or hemoglobinopathies, can interfere with the accuracy of HbA1c measurements, making it less reliable in some populations (Niwa & Kakehi, 2018; Gargari et al., 2011). Additionally, factors like vitamin C supplementation can alter HbA1c levels, further complicating its use in certain individuals (Gargari et al., 2011). Furthermore, HbA1c variability—particularly in individuals with fluctuating glucose levels—can pose a challenge in its clinical application, making it more difficult to draw accurate conclusions in patients whose glucose control is inconsistent (Gagliardi et al., 2023). To address these limitations, HbA1c is often used in conjunction with other



diagnostic tests, such as FPG and oral glucose tolerance tests (OGTT), to provide a more complete picture of an individual's metabolic health.

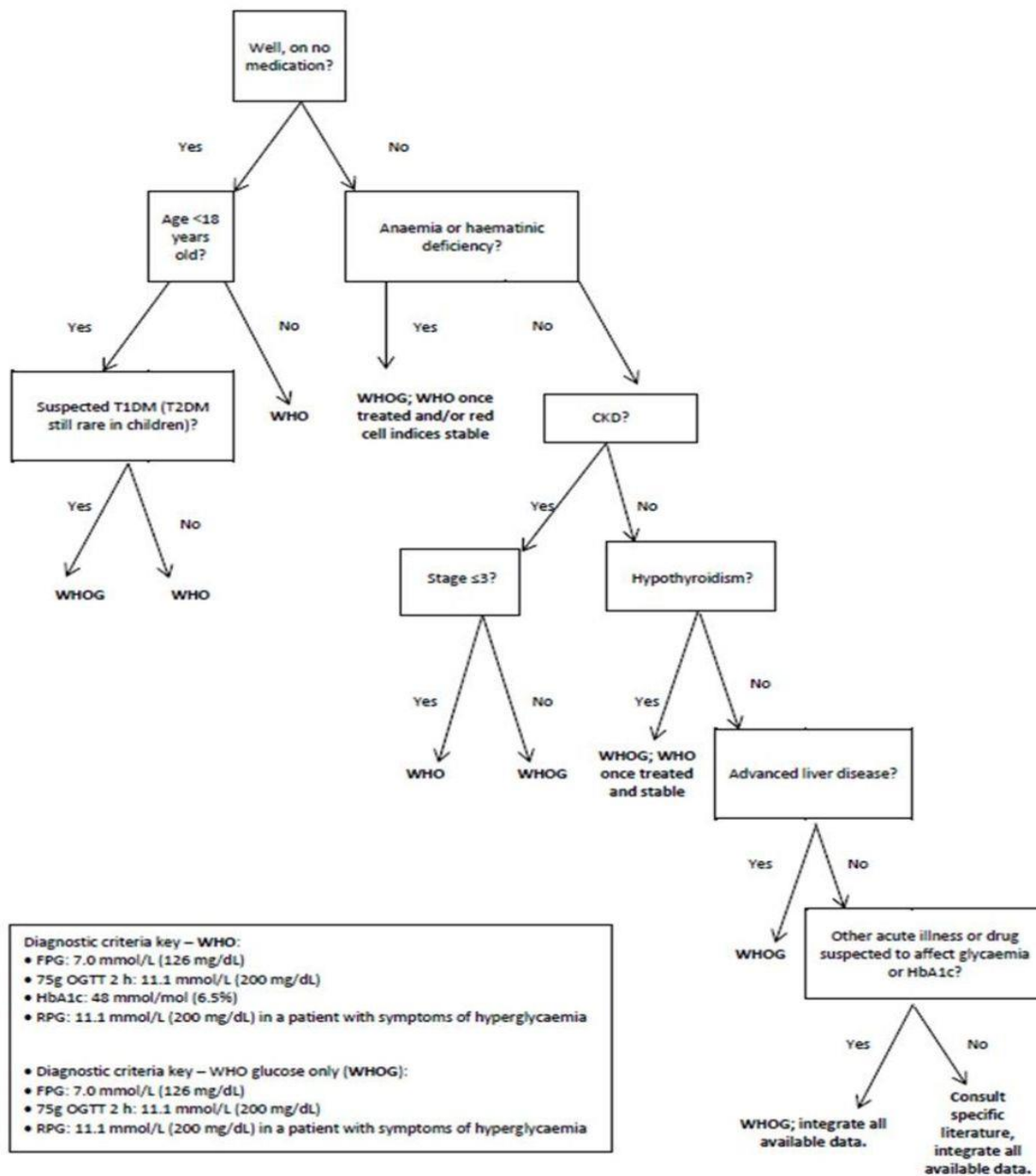


Figure 2: Flowchart for the selection of diagnostic strategy for T2DM



This flowchart illustrates how HbA1c can be integrated with other diagnostic tests, such as FPG, to offer a comprehensive strategy for diagnosing Type 2 diabetes (T2DM). By combining these tests, healthcare providers can increase diagnostic accuracy and ensure that individuals receive the most appropriate care.

Moreover, while HbA1c is most commonly used for diagnosing Type 2 diabetes, its utility extends beyond this population. For instance, HbA1c plays a role in diagnosing Type 1 diabetes in certain populations, particularly in those who present with mild symptoms or in the early stages of the disease (Wu et al., 2017). It has also shown promise in diagnosing gestational diabetes, with first-trimester HbA1c levels providing potential diagnostic value, although more research is needed to solidify its role in this context (Benaiges et al., 2017). Overall, while HbA1c is an invaluable diagnostic tool, it should be applied judiciously, taking into account various patient factors that might affect its accuracy, and always in conjunction with other clinical assessments to ensure accurate and timely diagnosis of diabetes across different patient populations.

4. Prognostic Implications of HbA1c:

HbA1c plays a critical role not only in the diagnosis of diabetes but also in predicting the long-term outcomes and complications associated with the disease. A growing body of research highlights the strong correlation between elevated HbA1c levels and an increased risk of both microvascular and macrovascular complications in individuals with diabetes. High HbA1c levels are particularly associated with an increased likelihood of developing retinopathy, nephropathy, and cardiovascular diseases (Forbes et al., 2018). These complications significantly impair quality of life and are leading causes of morbidity and mortality among diabetic patients, further emphasizing the need for early detection and effective management of blood glucose levels. Patients who have poor glycemic control, as reflected by consistently high HbA1c, are at a much higher risk of experiencing such complications, underlining the importance of maintaining HbA1c levels within the recommended target range to prevent these outcomes.

The relationship between HbA1c and insulin resistance is also a crucial aspect of diabetes management. HbA1c levels serve as an important indicator of insulin sensitivity, especially in individuals with Type 2 diabetes. Research has shown that HbA1c levels are more strongly correlated with insulin resistance than other commonly used markers of glycemic control (Chen et al., 2023). This relationship makes HbA1c a valuable tool for identifying insulin resistance in diabetic patients, enabling early intervention strategies aimed at improving insulin sensitivity and



potentially delaying or preventing the progression of diabetes. Given that insulin resistance is a key factor in the development of Type 2 diabetes, using HbA1c to monitor and manage this condition can help reduce the long-term burden of diabetes-related complications.

Additionally, HbA1c is increasingly recognized as a prognostic marker for cardiovascular diseases in diabetic patients. Higher HbA1c levels are associated with an elevated risk of heart disease, particularly in those already diagnosed with diabetes. This association is significant, as cardiovascular disease remains one of the leading causes of death among diabetic patients. Studies have demonstrated that elevated HbA1c levels not only increase the risk of heart disease but also predict poor outcomes in patients undergoing coronary procedures such as percutaneous coronary intervention (PCI) (Karnchanasorn et al., 2016). These findings emphasize the need for ongoing monitoring of HbA1c levels, particularly in diabetic individuals who are at risk of cardiovascular events, to guide treatment strategies and mitigate the impact of heart disease.

Furthermore, elevated HbA1c levels have been directly linked to increased all-cause mortality in diabetic patients, further supporting its role as a critical prognostic marker. Multiple studies have shown that individuals with poorly controlled blood glucose, reflected by high HbA1c, experience higher rates of mortality compared to those with well-controlled diabetes (Forbes et al., 2018). This relationship underscores the importance of achieving and maintaining HbA1c targets to reduce the risk of premature death and improve the overall life expectancy of individuals living with diabetes. As such, HbA1c not only serves as a marker of current glycemic control but also provides valuable insights into the long-term health outcomes and prognosis of diabetic patients.

5. Analytical Methods and Technological Advancements:

The accurate measurement of HbA1c is crucial for both diagnosing and monitoring diabetes. Several techniques are currently used to measure HbA1c levels, each with varying levels of precision and sensitivity. Ion-exchange chromatography, capillary electrophoresis, and immunoassays are the primary methods utilized in clinical practice (Lenters-Westra et al., 2022). Ion-exchange chromatography is widely regarded for its high precision and reliability in clinical settings. It separates HbA1c from other forms of hemoglobin based on the charge differences between them, providing highly accurate measurements. Capillary electrophoresis, on the other hand, offers a faster alternative with relatively high resolution, though it may be less commonly used than chromatography. Immunoassays, which detect HbA1c using antibodies specific to the glycated hemoglobin, are particularly useful for point-of-care testing due to their convenience,



though they may have limitations in terms of sensitivity and specificity when compared to other methods. The choice of method is significant because it can affect the diagnostic accuracy of HbA1c and consequently influence the management strategies for diabetes (Lenters-Westra et al., 2022).

Standardization of HbA1c testing has been an essential aspect of ensuring reliable and consistent results across different clinical settings and populations. To address variability in testing, international efforts have been made to standardize the measurement of HbA1c. The International Federation of Clinical Chemistry (IFCC) and the National Glycohemoglobin Standardization Program (NGSP) have been at the forefront of these efforts (Lenters-Westra et al., 2022). The goal of standardization is to minimize differences in results caused by variations in laboratory methods and equipment, which can lead to inconsistencies in diagnosis and treatment. Such standardization is crucial for ensuring that HbA1c serves as a reliable and accurate tool for diagnosing diabetes worldwide, especially as different populations may exhibit variations in hemoglobin structure that could influence test outcomes. Standardized HbA1c testing helps to reduce discrepancies in diagnostic thresholds and enables healthcare providers to more effectively identify and manage diabetes in diverse populations (Sreenan & Tormey, 2016).

In addition to these established methods, there have been significant technological advancements aimed at improving the accuracy and accessibility of HbA1c monitoring. Continuous glucose monitoring (CGM) technologies, for example, have transformed the way diabetes is managed by providing real-time data on blood glucose levels. These devices allow for more frequent and accurate tracking of glucose fluctuations throughout the day, which can then be used to refine HbA1c calculations and improve overall diabetes management (Sreenan & Tormey, 2016). CGM has become especially beneficial for individuals with Type 1 diabetes and those with frequent blood sugar fluctuations, as it enables more proactive adjustments to treatment. Furthermore, research is ongoing into non-invasive methods for measuring HbA1c, such as through optical sensing or using alternative body fluids like saliva or interstitial fluid (Niwa & Kakehi, 2018). These emerging technologies promise to reduce the need for blood draws, making diabetes monitoring more convenient and less invasive, and could potentially make HbA1c testing more accessible in remote or underserved areas. As such, these advancements in HbA1c measurement and monitoring are paving the way for more efficient and effective management of diabetes, which is essential in the fight against this growing global epidemic.



6. Clinical Utility and Impact:

HbA1c plays a central role in clinical decision-making by providing healthcare providers with valuable information about a patient's long-term glycemic control. This data is essential for guiding treatment decisions, including the adjustment of medications and the implementation of lifestyle changes aimed at improving blood sugar levels. HbA1c levels help in assessing the effectiveness of current treatment strategies and can indicate whether modifications are necessary. For instance, if a patient's HbA1c remains elevated despite adherence to a prescribed medication regimen, this may prompt the healthcare provider to consider intensifying therapy or adding additional medications to improve glycemic control. Additionally, monitoring HbA1c levels allows for early identification of suboptimal control, which is crucial in preventing the onset of complications like retinopathy, nephropathy, and cardiovascular diseases. By regularly assessing HbA1c, healthcare providers are better equipped to tailor individualized treatment plans that address the specific needs of diabetic patients, ultimately leading to more effective management of the condition (Gagliardi et al., 2023).

Beyond individual patient care, HbA1c testing plays a significant role in population health management by facilitating the early detection of diabetes and prediabetes. Routine HbA1c screening in at-risk populations helps identify individuals with elevated blood glucose levels who may not yet show symptoms of diabetes. Early detection enables timely interventions, such as lifestyle changes, weight management, and pharmacological treatments, which can significantly reduce the risk of progression to full-blown diabetes. Moreover, early diagnosis can prevent the development of severe complications associated with uncontrolled diabetes, improving the overall health outcomes of affected individuals and reducing the long-term healthcare burden. The ability to screen large populations with minimal effort and cost makes HbA1c a powerful tool in managing public health, particularly in regions with high rates of undiagnosed diabetes or prediabetes (Benaiges et al., 2017).

The cost-effectiveness of HbA1c testing further enhances its value as a diagnostic and management tool in clinical practice. Compared to traditional diagnostic methods, such as fasting plasma glucose (FPG) or oral glucose tolerance testing (OGTT), HbA1c is simpler, less invasive, and more cost-effective. This is particularly important in low-resource settings, where access to more complex testing procedures may be limited. HbA1c testing requires only a blood sample, which can be easily obtained without the need for fasting, and it provides reliable results that can be used for both diagnosis and ongoing monitoring. Its affordability makes it an attractive option



for large-scale screening programs, enabling healthcare systems to allocate resources more efficiently while still providing quality care. As a result, HbA1c is not only a convenient and reliable tool for diagnosing diabetes and prediabetes, but it also offers an economically viable solution for managing diabetes in both developed and developing countries (Gagliardi et al., 2023).

7. Conclusion:

In conclusion, the research underscores the pivotal role that HbA1c plays in diagnosing and managing diabetes. The findings confirm that HbA1c is an accurate, reliable, and convenient biomarker for assessing long-term glycemic control. It provides a comprehensive view of a patient's blood glucose levels over a period of 2-3 months, allowing healthcare providers to make informed decisions regarding treatment plans and adjustments. Despite its widespread use, it is essential to recognize that certain confounding factors, such as anemia, age, and seasonal variations, can influence the accuracy of HbA1c measurements. These factors must be considered in clinical practice to ensure that the results are not misinterpreted, especially in populations with conditions that may affect red blood cell turnover and HbA1c levels.

Looking ahead, continued research is vital to enhance the precision and reliability of HbA1c testing, particularly for individuals with health conditions that may skew results. For example, the influence of anemia and other blood disorders on HbA1c levels must be thoroughly investigated to develop more accurate methods of measurement for these populations. Furthermore, standardizing testing methods across diverse healthcare settings, as well as exploring innovative technologies, will increase the consistency of results and improve the global application of HbA1c testing in diabetes care. The integration of advanced monitoring technologies, including non-invasive methods and continuous glucose monitoring systems, promises to augment the diagnostic potential of HbA1c, making it even more effective in managing diabetes on a population-wide scale.

Ultimately, while HbA1c remains a cornerstone of diabetes management, ongoing efforts to refine its diagnostic and prognostic capabilities are necessary to further enhance patient outcomes. With improved accuracy, accessibility, and a deeper understanding of its limitations and potential, HbA1c can continue to contribute significantly to the prevention, diagnosis, and management of diabetes. Its integration into global health systems, coupled with advancements in medical technologies and research, will lead to better prevention strategies, more precise treatment plans, and improved health outcomes for individuals with diabetes.



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