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The Relationship Between HbA1c and Diabetes

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ABSTRACT

One of the most important biomarkers for the diagnosis and long-term treatment of diabetes mellitus is haemoglobin A1c (HbA1c). By calculating the proportion of glycated haemoglobin in the blood it provides an indication of the average blood glucose levels during the previous two to three months. Poor glycaemic control and a higher risk of complications from diabetes, including neuropathy, nephropathy, and cardiovascular disease, are closely linked to elevated HbA1c levels. Because of this connection, HbA1c is a trustworthy measure for diabetes diagnosis as well as for tracking patient compliance and treatment efficacy. In order to lower complications and enhance patient outcomes, current clinical guidelines advise keeping HbA1c below particular thresholds. Effective disease management and prevention strategies require an understanding of the relationships between HbA1c levels and the progression of diabetes.

Keywords: HbA1c, Diabetes Mellitus, Glycemic Index

1. Introduction to Diabetes and HbA1c

Diabetes is a chronic condition in which the body is unable to properly process food for use as energy. Diabetes occurs when insulin is not produced or not used effectively. As a result, blood glucose levels (also called blood sugar) rise above normal (i.e., hyperglycemia). There are two main types of diabetes: Type 1 diabetes (T1D) occurs when the pancreas produces little to no insulin due to an autoimmune destruction of the insulin-producing β-cells. Type 2 diabetes (T2D) occurs when the body becomes resistant to insulin, and the pancreas fails to keep up with the increased demand for insulin due to a combination of genetic susceptibility and environmental risk factors [1,2]. Gestational diabetes is defined as glucose intolerance that occurs during pregnancy. Diabetes is associated with both microvascular and macrovascular complications. The most common microvascular complications are diabetic retinopathy, nephropathy, and neuropathy. Severe nontraumatic lower extremity amputations are often the result of diabetic foot ulcers that stem from neuropathy and ischemia. Up to 70% of patients with diabetes have some form of nerve damage (i.e., diabetic neuropathy). Diabetes doubles the risk of cardiovascular disease, and atherosclerotic cardiovascular disease is often more severe in diabetes [3,4]. Other macrovascular complications include peripheral artery disease and cerebrovascular disease, which can lead to stroke. The HbA1c is formed through a non-enzymatic

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glycation pathway when an excess amount of glucose binds to hemoglobin in red blood cells. The lifespan of red blood cells is approximately 120 days in humans, so HbA1c provides an overall glycemic profile of the past 2–3 months. HbA1c serves as a key indicator of long-term glucose control in both the diagnosis and monitoring of diabetes. Understanding the implications of HbA1c is crucial for not only patients with diabetes but also for the general population and health care systems. In diabetic patients, a higher level of HbA1c is associated with poorer outcomes [5]. Intensive glucose control therapy that reduces HbA1c to lower than 7% can significantly reduce the risk of microvascular complications; however, there is a risk of hypoglycemic events. A 0.5% reduction in HbA1c can reduce the risk of macrovascular complications by 15%. Therefore, clinical practice guidelines recommend keeping HbA1c levels under 6.5% in high-risk patients. Recently, continuous glucose monitoring (CGM) systems have been developed, which can assess glycemic profiles more accurately than HbA1c. However, since HbA1c is a routine test performed worldwide, it is important to understand the strengths and limitations of HbA1c [6]. Population studies have demonstrated the epidemiological significance of HbA1c in nondiabetic patients. A level of HbA1c ≥ 5.7% is an indicator of prediabetes, and the health care costs of individuals with prediabetes are estimated to be 50% higher. Moreover, HbA1c is a potent risk factor for diabetes-related complications, such as microvascular complications and cardiovascular disease, even within the nondiabetic range. Understanding HbA1c from these perspectives will create a framework for considering the implications of HbA1c in greater detail. Since HbA1c is an index of glycemic exposure, understanding the characteristics of glycemic profiles is important when considering the implications of HbA1c. Incretins are gut-derived hormones that augment insulin secretion in response to food intake. Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are the two main incretins. GLP-1 also has central effects that induce satiety and suppress glucagon secretion, ultimately resulting in reduced hepatic glucose production. These aspects of GLP-1 action are impaired in T2D. GLP-1 receptor agonists (GLP-1 RAs) are antidiabetic agents that mimic the action of GLP-1 and have been developed to improve glycemic control and reduce the risk of cardiovascular disease. Ongoing research into GLP-1 and glycemic control is highly relevant [7-9]

2. Understanding HbA1c as a Biomarker for Diabetes

Glycated hemoglobin (HbA1c) is a widely used biomarker for the diagnosis and monitoring of diabetes. It is an index of average blood glucose concentrations over the preceding 8–12 weeks and is routinely measured in clinical practice for the management of diabetes [10]. An understanding of the basic characteristics and clinical significance of HbA1c is important for developing new diagnostic and therapeutic strategies. Furthermore, it has recently been suggested that HbA1c may be a better predictor of diabetes-related complications than glucose metrics. This discussion is focused on HbA1c as a biomarker for diabetes [6, 7, 11 - 14].

Hemoglobin (Hb) is a tetrameric protein composed of two alpha and two beta subunits. Each subunit contains a heme group that reversibly binds oxygen (O2). The glycation of hemoglobin is a non-enzymatic reaction between glucose and the N-terminal amino acid of the beta chain of hemoglobin, which is catalyzed by the intermediate formation of a Schiff base that undergoes rearrangement to form a stable ketoamine (HbA1c). Because of the fixed life span of red blood cells (RBCs), glycation provides a long-term index of blood glucose levels, and this mechanism directly links HbA1c to blood glucose levels. Since glycation is also affected by other factors, such as age, race, and anemia, it is difficult to develop a standard global HbA1c test. HbA1c assays can be divided into two categories: those that directly measure the HbA1c fraction in a hemolysate and those that measure total hemoglobin and total HbA1c and calculate the percentage [6,7].

The importance of HbA1c for diabetes care has been emphasized by the landmark epidemiological studies, which demonstrated the risk of diabetes-related complications. Since HbA1c is a long-term index of glycemia, it is important to monitor it regularly, with the recommendation that it be measured at least twice a year in patients treated with pharmacological agents. However, despite the standardization of most HbA1c test systems, differences in results remain for certain Hb variants, hemolytic anemias, and some laboratory systems. In the recent study, a new method that could circumvent many of the problems intrinsic to HbA1c assay methods is described. HbA1c is also used for predicting the risk of diabetes-related complications. Following the demonstration of HbA1c as a risk indicator for diabetes-related complications similar to its role in diagnosis, HbA1c levels at the time of diagnosis were used for stratifying the treatment goals. Overall, the considerations will provide fundamental knowledge of HbA1c needed to better understand the possible future diagnostic and therapeutic strategies targeting HbA1c [6-8].

2.1. Definition and Significance of HbA1c

Hemoglobin A1c (HbA1c) is a glycated form of hemoglobin (Hb) in which glucose is bound to the N-terminal amino acid residue of the β-chains of Hb. HbA1c is biochemically stable and accumulates in red blood cells in proportion to average blood glucose levels over the life span of the red blood cells (approximately 120 days), making it an important indicator of long-term glycemic control [14]. HbA1c reflects the cumulative glycemic history of the preceding two to three months and is used to both diagnose diabetes and monitor the efficacy of antidiabetic treatments. Thus, HbA1c measurement provides important information about patient management strategies [6,7,10].

HbA1c is used, along with other biochemical tests, to diagnose diabetes. 6.5% (48 mmol/mol) is the HbA1c threshold for the diagnosis of diabetes. Individuals with HbA1c levels of 6.5% to 6.9% (48–51 mmol/mol) are diagnosed with prediabetes. HbA1c lower than 5.7% (39 mmol/mol) is considered normal. Receiving a diabetes or prediabetes diagnosis has psychological and social repercussions for a patient. HbA1c levels are closely related to the risk of diabetes complications. The landmark Diabetes Control and Complications Trial demonstrated that the onset and progression of retinopathy, nephropathy, and neuropathy were significantly delayed in patients with type 1 diabetes if HbA1c was lowered. Similar findings were obtained in patients with type 2 diabetes. HbA1c is therefore a critical factor in the planning and evaluation of treatment strategies for diabetes [6-8].

2.2. Mechanism of HbA1c Formation

Glycation is a biochemical process in which a sugar molecule binds to a protein without the assistance of an enzyme, leading to the formation of a glycation adduct. Glycosylation, on the other hand, involves the enzyme-mediated attachment of a sugar moiety to a protein, resulting in a glycosylated protein. Glycation is a non-enzymatic reaction, while glycosylation is an enzymatic reaction. The glycation of hemoglobin results in the formation of hemoglobin A1c (HbA1c). It has been observed that glucose can non-enzymatically attach to hemoglobin, leading to the formation of an early glycation product called HbA1, which subsequently matures to form HbA1c [10]. This process of glycation adduct formation is an ongoing reaction. When blood glucose levels are elevated, more glucose enters the glycation reaction, which results in an increase in HbA1c concentration. Because the lifespan of red blood cells is approximately 120 days, there is a time lag between the onset of hyperglycemia and the increase in HbA1c levels. This time lag is why HbA1c serves as a reliable indicator of chronic hyperglycemia [6-8].

Since the formation of HbA1c is related to glucose levels, many factors that influence glucose levels also affect the glycation rate of HbA1c. Plasma glucose concentration is one factor that increases the rate of HbA1c formation. However, it has been found that the glycation rate also depends on individual circumstances. For example, HbA1c levels are lower in patients with conditions related to shortened red blood cell lifespan, such as blood loss due to hemorrhage, hemolytic anemia, or treatment with erythropoietin. In contrast, HbA1c levels are higher in patients with conditions related to prolonged red blood cell lifespan, such as iron deficiency anemia, thalassemia, or renal failure. The relative fingerprint of these conditions complicates the diagnosis of diabetes. Nevertheless, understanding how these conditions affect HbA1c is crucial for elucidating individual patient variations in the effectiveness of diabetes management by insulin. Because the mechanisms of glycation require several assumptions, mathematical models have been developed to provide a clear picture for clinical practice [6-8].

3. The Role of HbA1c in Diabetes Diagnosis and Management

In clinical practice, HbA1c levels are primarily used to evaluate glucose control. HbA1c results, in percent, are reported alongside a conversion table showing the estimated average glucose (eAG) in mg/dL or mmol/L. Both values are derived from a statistical equation. In patients without a prior diabetes diagnosis, the current medical history and HbA1c levels must be interpreted together, as HbA1c levels can be influenced by various medical conditions, which may cause misleading results. Diabetes can be diagnosed based on HbA1c levels equal to or greater than 6.5% (48 mmol/mol). This threshold was set following the endorsement of HbA1c by the International Expert Committee as an acceptable test for diagnosing diabetes. Other criteria for diagnosing diabetes include fasting plasma glucose (FPG) levels equal to or greater than 126 mg/dL (7.0 mmol/L), a 2-hour plasma glucose (PG) level equal to or greater than 200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT), and the presence of classic symptoms of hyperglycemia with a random PG equal to or greater than 200 mg/dL (11.1 mmol/L) [8]. In order to have diabetes diagnosed using HbA1c levels, it is critical to ensure that the laboratory method being used is National Glycohemoglobin Standardization Program (NGSP)-certified and traceable to the reference method. Population studies have established Hemoglobin A1c (HbA1c) as a potent marker of future risk of diabetes and diabetes-related complications. In addition to being used to diagnose diabetes, HbA1c is also a means for monitoring glycemic control in patients with diabetes. In treated diabetes, HbA1c is a reflection of chronic glucose exposure over the previous two-to-three-month interval. An important feature of HbA1c is that there are fixed relationships between HbA1c levels and average glucose levels, which enable translation between the two metrics. In clinical practice, HbA1c is typically measured in percent (%); however, in research, HbA1c is often expressed in a National Glycohemoglobin Standardization Program (NGSP) unit (mmol/mol) that is derived from a mathematical formula. HbA1c testing should be conducted at least twice yearly in patients whose treatment goals are met and whose therapy is stable. For patients whose therapy has changed or who are not meeting glycemic control targets, HbA1c testing should be performed every three months. Patient understanding is critical in glucose control, as patients with poorly controlled diabetes are often unaware of the significance of their HbA1c levels, highlighting the importance of patient education in diabetes care [6,7].

3.1. Diagnostic Criteria for Diabetes Using HbA1c

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that is needed for the body to convert blood glucose, starches, and other food into energy. Currently, diabetes is considered one of the most critical global health challenges. In 2014, 422 million adults were living with diabetes, and in 2016, high blood glucose led to 2.8 million deaths. It has been estimated that by 2030 and 2045, these global prevalence numbers will exceed 640 and 700 million, respectively. Diabetes can cause serious damage to the heart, blood vessels, eyes, kidneys, and nerves. Diabetes is one of the leading causes of death in many countries, and the number of deaths caused by diabetes is steadily increasing. Meanwhile, effective prevention and management strategies exist and can lower the risk of diabetes. Hence, early detection is essential to prevent the progression of diabetes. Diabetes can be broadly classified into five groups based on pathogenic processes, but type 2 diabetes and its precursor stage, prediabetes, are the most common forms of diabetes [6-8,10].

Currently, there are three accepted methods for the diagnosis of diabetes: Measurement of fasting plasma glucose (FPG), 2-h plasma glucose after a 75-g oral glucose tolerance test (OGTT), and HbA1c testing. Plasma glucose levels reflect the short-term glycemic status, while HbA1c levels reflect the long-term glycemic status. HbA1c, or glycated hemoglobin, is a form of hemoglobin that is covalently attached to glucose. It is created within the erythrocytes when glucose enters the cells and covalently attaches to hemoglobin A. The amount of hemoglobin that becomes glycated increases proportionally with blood glucose concentration, and HbA1c reflects the average glucose levels over the lifetime of erythrocytes, typically the prior 2–3 months. Epidemiological studies from the late 1970s to mid-1980s established HbA1c as a potent biomarker for detecting prevalent diabetes and diabetes-associated complications [15]. In addition to being able to be used for the diagnosis of diabetes, HbA1c also serves as a marker to assess the risk of developing diabetes and diabetes-associated complications. HbA1c testing is currently routinely performed in hospitals and clinics to monitor glucose control and treatment strategies in diabetic patients because it has better prognostic utility than blood glucose measurements [6-8].

3.2. Monitoring HbA1c Levels in Diabetes Management

The levels of glycated hemoglobin (HbA1c) are routinely monitored as part of protocols for managing diabetes. The American Diabetes Association recommends that patients have their HbA1c levels tested at least twice a year if they are stable, and quarterly if their treatment plan has changed [16]. Under these guidelines, a patient's HbA1c test result can be classified as within recommended limits, borderline, or outside the desired range. Patients whose HbA1c levels fall within recommended limits may not need any changes to their treatment regimen, whereas those with borderline or outside-of-range HbA1c results require further lifestyle adjustments or modifications to their treatment plans. Regular monitoring of HbA1c levels can also provide a more accurate assessment of a patient's adherence to prescribed medications and lifestyle changes [6,7,10,17].

There is, however, a psychological dimension to HbA1c monitoring. Knowing that an HbA1c measurement will take place tends to motivate patients to make extra efforts to support blood glucose control before testing. In contrast, HbA1c testing can cause anxiety for some patients concerned about the implications of poor blood glucose control. Furthermore, adherence to medications and lifestyle changes typically deteriorates as HbA1c levels rise, and there is a general tendency for patients to adhere less to treatment regimens when HbA1c levels are borderline or outside of the recommended range. In a similar vein, an increasing trend in HbA1c levels suggests that treatment adjustments are less effective and that long-term health outcomes will be poorer. For these reasons, it is essential to continuously assess HbA1c levels as part of strategies for managing diabetes [6-8].

4. Factors Influencing HbA1c Levels in Diabetes

Diabetes is characterized by chronic hyperglycemia. The formation of glycated hemoglobin (HbA1c) is a well-established marker of average blood glucose levels over the prior 6–12 weeks. Because diabetes is often considered a heterogeneous group of diseases that can perturb glucose homeostasis, HbA1c can vary across the normal and diseased range from one individual to the next. Normal HbA1c levels signify a functional glycemic control despite differing nutritional and other environmental exposures, behaviors, and genetic backgrounds [18]. Conversely, in diabetes, variabilities in HbA1c highlight the complex interplay of biological, environmental, and behavioral components that can drive glucose levels and HbA1c away from the desired target [19-21].

Dietary choices determine the rate of nutrient absorption and the postprandial bioavailability of glucose and other macromolecules, which in turn dramatically dictate blood glucose levels. Almost instantaneously, an increase in blood glucose results in a greater formation of HbA1c. As such, diabetics aim to manage glucose homeostasis through the careful selection of food intake and meal timing. However, the impact of a single meal may fluctuate across individuals based on the macronutritional composition of the diet, health status, or genetic background. Beyond carbohydrates, other nutrients can induce hormonal and metabolic effects that also impact blood glucose levels and HbA1c formation [3,12,22].

Another important modulator of HbA1c is physical activity. Exercise alters glucose homeostasis through multiple actions of insulin and non-insulin-mediated augmentations of blood glucose disposal into cells, thereby lowering blood glucose levels and HbA1c. Importantly, the magnitude of the effects of exercise hinges on the frequency and intensity of the activity performed, which emphasizes its importance in HbA1c regulation. Medications similarly affect HbA1c levels. There are currently many classes of drugs that target glucose homeostasis and thus adjust HbA1c. The most important among them is insulin, which is required for the majority of type 1 diabetics and many type 2 diabetics who have lost their ability to produce insulin. In addition to insulin, oral hypoglycemics target glucose homeostasis through various mechanisms, including augmenting insulin secretion, increasing insulin sensitivity, decreasing intestinal glucose absorption, and promoting glucose excretion. Overall, because HbA1c varies as a combined outcome of numerous influences, a clear understanding of how every factor affects HbA1c in an individual is needed to create the most effective management plans for diabetes. With diabetes often comes a host of other comorbid conditions, which also have complex effects on HbA1c [23-25].

4.1. Impact of Diet and Exercise on HbA1c

HbA1c, or glycated hemoglobin, levels reflect the average blood glucose levels for the past three months and are the primary criterion for diabetes diagnosis. It was reported that blood glucose levels are directly related to HbA1c levels. Therefore, any factor affecting blood glucose levels would also affect HbA1c levels. Dietary Education Interventions significantly reduced HbA1c levels in diabetes patients. HbA1c levels may be maintained at a normal level through education, counseling, and management of diet [26]. When glucose enters the bloodstream, it attaches to the hemoglobin of red blood cells and forms glycated hemoglobin. HbA1c is a type of glycated hemoglobin, and HbA1c levels are directly determined by blood glucose levels. As blood glucose levels rise, HbA1c levels also increase. Similarly, when blood glucose levels drop, HbA1c levels also drop [27]. Diabetes patients with high blood glucose levels can reduce the risk of complications by minimizing blood glucose levels, and therefore, HbA1c levels are also minimized. Dietary components intake can raise blood glucose levels or lower blood glucose levels. Thereby, HbA1c levels can also be raised or lowered. Food is composed of macronutrients such as carbohydrates, fats, and proteins, and micronutrients such as vitamins and minerals. Among them, carbohydrates highly affect blood glucose levels. The glycemic index (GI) is a number that indicates how fast a carbohydrate food raises blood glucose levels after its consumption. Foods with a high GI raise blood glucose levels fast and high, while those with a low GI raise blood glucose levels slowly and low. Therefore, diabetes patients are recommended to consume low-GI foods. Meal timing also affects blood glucose levels. A spike in blood glucose levels after meal consumption is affected not only by the amount and types of food consumed but also by when the food was consumed. Generally, blood glucose levels remain at a lower state in the early morning than at any time of the day because of overnight fasting. It was also reported that blood glucose levels increased more when the same meal was consumed in the morning than in the evening. Structured exercise enhances insulin sensitivity, and enhanced insulin sensitivity by exercise is maintained for several hours to several days after exercise. Exercise could lower HbA1c levels, which indicates good glycemic control. To maintain good glycemic control, it is important to keep insulin sensitivity high after exercise. Structured exercise can continuously lower HbA1c levels, which indicates good glycemic control. It was reported that healthcare professionals' advice on diet and exercise was effective in reducing HbA1c levels. Since diabetes is a chronic disease, education should be the priority in disease management.

Diabetes patients should be educated to understand diabetes and be informed about how to control it. Providing education on how to make informed dietary choices could induce diabetes patients to choose diets that maintain good glycemic control. It is important to implement strategies that promote adherence to dietary education interventions so that the positive effects can be sustained long-term. For dietary education interventions, it is recommended to have four or more sessions of education since a more considerable reduction in HbA1c levels was observed. To maintain the current HbA1c level, additional education sessions should be provided once every six months or sooner if diabetes patients have difficulty maintaining their HbA1c levels. It was reported that lifestyle modifications could reduce HbA1c levels. Lifestyle modifications comprise diet alterations and weight loss, and increased physical activity [28,29].

4.2. Medications and Their Effect on HbA1c

Diabetes is a prevalent chronic disease worldwide, characterized by elevated blood glucose levels. If left untreated, diabetes can lead to severe complications affecting various organs, notably the heart, kidneys, and eyes. As such, blood glucose control is critical in managing diabetes. HbA1c is a glycosylated hemoglobin that reflects average blood glucose over 8-12 weeks. Consequently, HbA1c has emerged as the gold standard for assessing diabetes treatment effectiveness and ongoing management [30]. The 2023 American Diabetes Association Standards of Medical Care in Diabetes recommend pharmacologic treatment upon diagnosis, if not already initiated, in conjunction with lifestyle modifications, to achieve an HbA1c target of <7% (53 mmol/mol) [31,32].

Several classes of diabetes medications are available, each with a different mechanism to lower blood glucose, consequently lowering HbA1c. Diabetes medications are pharmacologically referred to as anti-diabetic agents or anti-hyperglycemic medications. All diabetes medications are considered anti-hyperglycemic agents, lowering blood glucose. Nonetheless, several non-diabetes medications can lower blood glucose, but are not classified as anti-hyperglycemic agents. An HbA1c level of 6.5% (48 mmol/mol) or higher indicates diabetes. Postprandial blood glucose levels require pharmacologic treatment if HbA1c levels exceed 7.5% (58 mmol/mol) after lifestyle modification [33- 35].

Medication adherence is critical to achieving a targeted HbA1c level and mitigating diabetes complications. Concerns regarding diabetes medication's potential side effects or burden may lead patients to be less forthcoming about usage. Addressing treatment concerns often aids adherence. Factors influencing medication choice include concern about side effects, perceived need for treatment, prior antidiabetic medication use, and potential lifestyle changes. It is important to note that treatment concerns may change over time, as they are often influenced by individual patient profiles, focusing on HbA1c, mortality risk, or prior treatment experiences. Thus, personalized treatment plans are essential for different medication classes to optimize HbA1c outcome levels [8, 36,37].

5. Clinical Studies and Research on HbA1c in Diabetes

Research on the clinical significance of HbA1c has grown rapidly since the early 1990s. A total of 709 research articles have been published. Along with fasting plasma glucose (FPG), HbA1c is the most widely used and accepted test for diabetes diagnosis. Clinical studies have explored the role of HbA1c in predicting diabetes complications, highlighting its significance beyond standard care. Cohort studies have established HbA1c as a significant risk factor for diabetic complications and mortality, even outperforming age and sex. HbA1c's capability to predict developing diabetes stages has been widely studied and integrated into risk scoring systems. Some HbA1c studies emphasize ethnic differences, while others focus on single-ethnicity cohorts. Overall, patterns and trends of HbA1c research indicate its growing importance in clinical practice. To date, millions of people worldwide have been diagnosed with diabetes based on HbA1c criteria. It has become the routine monitoring method to prevent and control diabetes complications [10, 38-40].

Though the importance of HbA1c in predicting future risk has been established, most studies involve only one ethnic sample or country, raising questions about applicability across various populations. Many key findings may not apply to different ethnic cohorts due to socioeconomic differences. Furthermore, other diabetes stages are not investigated, and longitudinal studies are rare. HbA1c data needed for some statistical analyses were difficult to obtain in previous decades. Most cohort studies do not link HbA1c with lifestyle intervention. Different sample sizes may also account for different significance levels. Regardless of limitations, many HbA1c findings hold strong clinical implications, and future studies should continue this research direction. Although HbA1c cut-off values for diagnosing diabetes are universally accepted, personalized approaches based on HbA1c data should be further investigated. Nonetheless, it is necessary to consider study applicability across various populations [41- 43].

5.1. Key Findings and Trends

In recent years, numerous clinical studies have explored the pivotal role of HbA1c in the context of diabetes, resulting in key findings and emerging trends. One significant discovery is the generally acknowledged correlation between HbA1c levels and long-term health outcomes in patients with diabetes, corroborated by extensive evidence [10]. Interestingly, despite fluctuations in HbA1c levels among certain patient cohorts, studies revealed a gradual rise in overall HbA1c levels, emphasizing the need for more targeted treatment approaches. Data also support the integration of HbA1c as a vital tool in routine diabetes management, either as a stand-alone monitoring method or in conjunction with other practices, aligning with treatment recommendations. Beyond the central findings, several trends are noteworthy. Firstly, studies highlight a growing interest in diabetes management among younger patient demographics, although concerns surface regarding their treatment adherence and the resultant health consequences. Secondly, while overall improvements in diabetes care are evident, some health systems face challenges in ensuring equitable outcomes. This disparity is particularly pronounced regarding treatment discrepancies among different ethnic population groups. Moreover, although technological progress boosts treatment accessibility and health literacy, efforts must focus on supporting vulnerable groups still reliant on traditional management approaches. Lastly, discrepancies in individual HbA1c responses to glucose fluctuations raise questions about the biological mechanisms at play. Beyond age and genetic factors, technological advancements in monitoring and improving HbA1c levels may hold the key. Collectively, these studies reinforce a nuanced understanding of the role of HbA1c in diabetes management and care, fostering further research in this critical area [44- 46].

5.2. Limitations and Future Directions

While HbA1c monitoring and management represent a relatively well-studied facet of diabetes care, there are still numerous gaps and limitations that current research does not fully address. For instance, while the significance of methodological standardization is acknowledged, disparities in results across studies provide a compelling case for the need for such standardization [47]. Many of the challenges in HbA1c testing outlined above can lead to large variabilities in reporting HbA1c values, while many of the studies involving HbA1c in diabetes management make no mention of these variabilities. Similarly, issues involving population diversity in clinical trials are cited, yet the majority of results are based on either a White or a Black population. While some racial differences in HbA1c exist, the mechanisms behind them may not be applicable across different races/ethnicities. As such, many countries with large ethnic minorities may have populations whose HbA1c-related characteristics are not fully understood [38,46, 48].

In the interest of advancing towards more personalized medicine approaches, a number of areas that merit further exploration are highlighted. Firstly, while the association between drug-induced changes in HbA1c and diabetes progression is mostly well characterized, further research is necessary to delineate comparable clinical outcomes across different drug classes and patient demographics. Secondly, while HbA1c is considered the gold standard in diabetes screening and diagnosis, newer markers such as glycated fructosamine and 1,5-anhydroglucitol show promise as adjuncts to further refine diabetes testing. Finally, while technology has great potential in improving the monitoring and management of HbA1c, several hurdles need to be overcome before at-home HbA1c monitoring is adopted in clinical practice. Ultimately, acknowledging the multiple gaps and limitations in current HbA1c research will lay the groundwork for future research directions to pursue [49,50].

6. Conclusion and Implications for Clinical Practice

The relationship between HbA1c and diabetes has profound implications for clinical practice. HbA1c is a well-established biomarker for diabetes diagnosis and management. Healthcare providers must follow existing guidelines for testing, result reporting, and interpreting HbA1c values. Recent findings emphasize the need to carefully assess unique patient situations, particularly when HbA1c and blood glucose levels provide conflicting results. Education for patients on the significance of HbA1c results and required changes is critical to the success of any treatment strategy. Without proper education, treatment is unlikely to be effective. As studies show that HbA1c targets should be individualized, healthcare providers should be prepared to discuss with patients the rationale behind specific HbA1c goals. In diabetes management, a patient-centered approach is of utmost importance. Therefore, patients must be active participants in determining treatment plans rather than simply adhering to a provider-designed strategy. Because opportunistic bacteria can become more multi-resistant if diabetes is not controlled [51]. Currently, research continues on better understanding HbA1c's role in diabetes development and progression, the pathophysiological processes causing HbA1c accumulation, and novel strategies to impede these processes. Such advancements will help clarify HbA1c's role and potential as a treatment target, further shaping clinical practice. To achieve the best possible quality of life after a diabetes diagnosis, it is imperative to manage HbA1c stress levels effectively. Informed completion of all necessary HbA1c measurements, understanding what is being measured, and why values must be modified is of utmost importance. Furthermore, this affects diabetics' skin by creating multi-resistant opportunistic bacteria [51]. Generally, it is crucial to recognize that although a diagnosis of diabetes implies permanent illness, it is possible to live a life as if unaffected by the disease [10].

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