


Interpretation of hemoglobin A1C in primary care setting

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ABSTRACT

Diagnostic tests for diabetes have evolved with the emphasis shifting from blood glucose levels and/or oral glucose tolerance test to measurement of hemoglobin A1c (HbA1c) levels. With the advent of modern and standardized methods assaying the percentage of glycosylated hemoglobin, clinicians are relying more and more on HbA1c for the management of diabetic patients.

A brief review of literature shows, although HbA1c is an important tool in the diagnosis and management of diabetes, it is still far from being perfect. Clinicians need to be more aware about these limitations and take extra steps to avoid medical errors.

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1. Introduction

Diabetes is a disease with a historical background; reports of polyuria can be found as far back as 1500 BC. Diagnostic tests for diabetes have evolved progressively; with the era of ‘tasting the urine’ (thankfully) far gone. Over the last forty years, the emphasis has shifted from blood glucose levels and/or oral glucose tolerance test to measurement of hemoglobin A1c (HbA1c) levels. With the advent of modern and standardized methods assaying the percentage of glycosylated hemoglobin, clinicians are relying more and more on HbA1c for the management of their diabetic patients.

However, it may be that as clinicians we are relying too much on the ‘face-value’ of HbA1c. Recently, we came across a patient in our clinic for diabetes and was on insulin. He was found to have an HbA1c value of 6.9% when checked by a POC (Point-of-care) device. However, when he was informed about the results, he expressed his concerns as his fasting and pre-meal blood glucose readings at home were consistently ranging between 200 to 400 mg/dl. His blood glucose readings were reviewed closely and an HbA1c assay was ordered which showed the value of 7.2%. He was advised to check his blood glucose during night time and between meals to detect any hypoglycemic episodes which might be contributing to this low HbA1c level. He continued to check his blood glucose as advised till his next visit in 4 weeks. Review of the blood glucose readings did not show any hypoglycemic episodes; meanwhile his serum fructosamine levels were checked which were raised to 512 $\mu\text{mol/L}$ (Normal: 190–270 $\mu\text{mol/L}$). His insulin dose was increased and it

was decided not to use HbA1c for his diabetes monitoring till the reason of the falsely low value is clear.

This interesting encounter posed several questions for us: ‘To what extent should we rely on HbA1c values for our diabetic patients? Are there any alternative methods of glycemic control assessment? Are we inadvertently over-/undertreating our diabetic patients?’ A brief review of literature shows, although HbA1c is an important tool in the diagnosis and management of diabetes, it is still far from being perfect. Clinicians need to be more aware about the ‘imperfections’ of HbA1c which can result in either over- or undertreatment of patients and worsened outcomes.

Through this article, we share our experience with the medical community; in addition, we review the fascinating historical background of HbA1c while discussing the current and future challenges regarding its use in diabetes.

2. Definition

Glycosylated hemoglobin or hemoglobin A1C, is a hemoglobin-glucose combination formed nonenzymatically within the erythrocytes. Because the erythrocytes are freely permeable to glucose, concentration of HbA1c is directly proportional to the plasma glucose concentration. In addition, it is formed continuously throughout the life span of the erythrocytes; thus, quantifying the ‘glycemic history’ of the previous 120 days [1].

Moreover, fasting is not needed for HbA1c testing and the levels are not affected acutely by stress, exercise and smoking. All these factors make HbA1c an excellent method for diagnosis and monitoring of diabetes.

3. Background

HbA_{1c} was discovered by Rahbar in 1969 and was met with considerable skepticism. However, over the years, HbA_{1c} has emerged as the most important indicator of glycemic control, enabling the doctor and patient to assess the long-term impact of lifestyle changes and medication. Therefore, its discovery and incorporation in diabetes management is dictated to be one of the most significant advances made in medicine during the last four decades. The evolution of HbA_{1c} through years is demonstrated in Table 1.

Table 1. Medical breakthroughs regarding discovery and use of HbA_{1c} [2,3].

EVENTS
<ul style="list-style-type: none"> • 1958: Huisman and Meyering isolate Hemoglobin A_{1c} from other forms of hemoglobin • 1966: Holmquist and Schroeder identify five subtypes of hemoglobin A, including HbA_{1c}. • 1968: Bookchin and Gallop identify HbA_{1c} as a glycoprotein • 1969: Rahbar discovers that HbA_{1c} is elevated in patients with diabetes • 1975: Bunn characterizes the reactions involved in formation of HbA_{1c} • 1976: Cerami and Koenig propose HbA_{1c} as an indicator for blood glucose levels in diabetes • 1977: Total HbA₁ introduced in clinical laboratories as a tool for monitoring diabetes • 1993: DCCT establishes significance of HbA_{1c} as a clinical marker in Type-1 diabetes • 1998: UKPDS establishes the significance of HbA_{1c} as clinical marker in Type-2 diabetes • 2007: NGSP implements the criteria for standardization of HbA_{1c} assays • 2010: HbA_{1c} is validated as diagnostic test for diabetes and prediabetes

4. Drawbacks

Although HbA_{1c} levels are quite useful for the evaluation of glucose control, the progress of glycemic control and medications changes must be done while keeping in mind the limitations of the HbA_{1c} test. We outline the issues which need to be addressed by the clinicians when managing diabetic patients:

4.1. Detection methods

Point-of-care (POC) HbA_{1c} values, although cost-effective and feasible, should not be relied upon as the results can show a falsely low HbA_{1c}. Per published reports, the margin of error ranges between 0.5–0.7% when the POC values are compared with standard laboratory assays [4].

Accuracy and precision of HbA_{1c} assays have been achieved due to criteria implemented by National Glycohemoglobin Standardization Program (NGSP) since 2007. However, different HbA_{1c} values may still be observed when using different methods because of the susceptibility of each method to various hemoglobin (Hb) variants. This is particularly important for

clinicians managing populations with a high prevalence of Hb variants.

The standard assays being used and their analytical characteristics are provided in Table 2.

Table 2. Commercial assays recommended for HbA_{1c} [5].

ASSAYS	ANALYTICAL WEAKNESS
<ul style="list-style-type: none"> • Immunoassays (second- and third-generation) 	Interference by rare Hb variants
<ul style="list-style-type: none"> • Enzymatic assays 	No analytical interference by Hb variants
<ul style="list-style-type: none"> • Capillary electrophoresis 	No analytical interference by Hb variants
<ul style="list-style-type: none"> • Ion-exchange chromatography 	Interference by all Hb variants including carbamylated Hb
<ul style="list-style-type: none"> • Boronate affinity chromatography 	Measures total glycated hemoglobin, not just HbA _{1c}

4.2. Race and ethnicity

Medical evidence suggests that due to genetic differences in erythrocyte metabolism, HbA_{1c} levels may be higher in African American, Hispanic, Asian population when compared to White Caucasian individuals despite having similar plasma glucose levels. These differences, although small and insignificant, have been found to occur independent of diagnostic assays and hemoglobinopathies such as sickle cell trait [6].

4.3. Daily fluctuations and timing of blood glucose measurement

Large daily fluctuations in glucose levels can be seen in patients who have erratic eating and exercise habits. An improper timing of blood glucose measurement in such patients can miss significant glycemic periods leading to discordance between HbA_{1c} levels and plasma glucose levels [7]. For example, HbA_{1c} levels may be elevated when the blood glucose concentrations are much higher at times between glucose measurement. Similarly, lower than expected HbA_{1c} value can be seen with undetected nocturnal hypoglycemia.

4.4. Conditions causing false readings

Despite standardization of HbA_{1c} testing, any medical condition that prolongs or shortens the erythrocyte turn-over and/or survival time can interfere with HbA_{1c} levels. In addition, conditions causing carbamylation and increased glycation also interfere with HbA_{1c} values. These medical conditions are mentioned in Table 3 [8].

4.5. Medications

Although quite rare, the use of certain non-diabetic medications can affect the HbA_{1c} levels (Table 4). The

Table 3. Medical conditions that can lead to falsely elevated or low HbA1c levels [8].

CONDITIONS CAUSING HBA1C VARIATIONS	MECHANISM
<ul style="list-style-type: none"> ● Falsely high HbA1c levels: -Iron deficiency/ pernicious anemia -Hemoglobinopathies (Thalassemia, HbF, HbS) -Kidney disease -Jaundice ● Falsely low HbA1c levels: -Hemolysis -Splenic sequestration -Hemodialysis in CKD -Hemoglobinopathies -Erythropoietin treatment -Treatment of iron deficiency/ pernicious anemia -Blood transfusions -Pregnancy 	<ul style="list-style-type: none"> Low erythrocyte turn-over Multifactorial: Anemia Increased hemoglobin carbamylation, erythropoietin deficiency Bilirubin causes increased glycation Rapid cell turn-over Rapid cell turn-over Removal of urea leading to less carbamylation of hemoglobin Multifactorial: Hemolysis, transfusions Increased RBC production Increased RBC production Hemodilution Physiological changes

Table 4. Medications reported to cause interference with HbA1c levels [9].

FALSELY HIGH HBA1C	FALSELY LOW HBA1C
<ul style="list-style-type: none"> ● Aspirin at high doses ● Chronic opioid use 	<ul style="list-style-type: none"> ● Chronic alcohol use ● Aspirin at low doses ● Dapsone ● Antivirals ● Vitamin C and E ● Hydroxyurea

postulated mechanisms are altered red cell turn-over, altered glycation and interference with the assays.

5. Important points to consider

In view of the above stated drawbacks, extra vigilance should be exercised by the health-care providers. The following steps should therefore be taken before making medications adjustments:

- (1) Self-monitored blood glucose patterns should correlate with HbA1c levels. Therefore, patients should be encouraged to keep a log of their continuous/meter-calculated blood glucose readings; comparison between HbA1c and the average of the fifty most recent blood glucose readings should be made at every clinic visit. A better way to see this concordance is with estimated Average Glucose (eAG). eAG (mg/dL) which can be derived from HbA1c, has been validated as a tool in ADAG (A1c-derived average glucose) study to rule out racial and daily fluctuations (Table 5). eAG value then can be compared with the average blood glucose readings [10]. For example, if the eAG is higher than the patient's average glucose, patients should be asked to perform fingerstick testing at times when the blood glucose is highest, eg, after

Table 5. Equivalent values of HbA1c and eAG [10].

HEMOGLOBIN A1C (%)	ESTIMATED AVERAGE GLUCOSE (mg/dl)
● 6.0	● 126
● 6.5	● 140
● 7.0	● 154
● 7.5	● 169
● 8.0	● 183
● 8.5	● 197
● 9.0	● 212
● 9.5	● 226
● 10	● 240
● 11	● 269
● 12	● 298

meals. If the eAG is lower than the meter average, patients should check blood glucose during suspected periods of low blood glucose such as between meals and late night.

- (2) Point-of-care (POC) HbA1c methods should not be relied upon. Instead standard assays should be performed. However, clinicians should be aware of the limitations of these HbA_{1c} assays. In diabetic patients with no known hemoglobinopathy, when HbA_{1c} measurements do not correlate with the clinical impression, the possibility of an Hb variant should be evaluated. At the same time, it should be checked whether the HbA1c assay used is affected analytically by common Hb variants or no. If yes, then using an assay that is unaffected by these variants is important.

The same applies to patients with known hemoglobinopathies. Clinicians do not have to use alternate methods of monitoring glycemic control in such patients as long as the proper assay is used.

- (3) As mentioned above, certain medical conditions result in misleading HbA1c data despite using standard HbA1c assays. The American Diabetes Association (ADA) has acknowledged that in these patients, HbA1c can be unreliable; therefore, alternative measures such as fructosamine and glycated albumin can be considered. However, these methods should be used cautiously as they are not without pitfalls. The pros and cons of these tests are provided in Table 6 [11].

Table 6. Utility of fructosamine and glycated albumin testing in diabetes [11].

Advantages	Disadvantages
<ul style="list-style-type: none"> ● More reliable than HbA1c in certain medical conditions such as renal disease. ● Earlier detection of rapid blood glucose fluctuations ● Identification of impaired glucose levels before any noticeable changes in HbA1c occur ● More cost-effective 	<ul style="list-style-type: none"> ● Lack of standardized assays ● Lack of standard guidelines regarding what values should the clinicians be aiming for ● Prognostic strength is unclear due to limited medical evidence. ● As these methods estimate glycemic control over a shorter duration, more frequent testing is required.

- (4) Non-diabetic medications being used by the patients should be screened closely to rule out drug-induced interference with HbA1c. If possible, these medications should be discontinued; otherwise alternative methods for monitoring can be used.

6. Conclusion

The medical field has come a long way since the times of sweet tasting urine for diagnosing diabetes; with the development of more sophisticated biochemical analysis of glycosylated hemoglobin, both clinicians and diabetic patients have benefited. A glorious future for this parameter is on the horizon with emerging medical evidence proving its utility even in non-diabetic population.

However, maybe we should stop for a moment and heed Hippocrate's warning for the physicians to come: '...experience deceives, judgement is difficult'. Use of HbA1c is not without limitations; since in some clinical settings, it can be misleading and therefore, cannot be used either for diagnosis or as a true 'reflection' of glucose control. Physicians need to be aware of these limitations and have a more critical approach in order to avoid poor patient outcomes.

Disclosure statement

No potential conflict of interest was reported by the authors.

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