Glycosylated hemoglobin (HbA1C): A brief overview for clinicians

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Abstract

Glycosylated hemoglobin (HbA1c) is an index of estimated average blood glucose over the preceding three months, giving an estimate of long-term glycemic status. Its value is used both for the diagnosis and monitoring the blood glucose control of the patients with diabetes mellitus. Though a widely used tool the value of HbA1c is influenced by various factors which, if not kept in mind of the treating clinician may lead to a false diagnosis or false sense of diabetic control. The authors give a brief overview of the HbA1c and the factors affecting its value.

Keywords: Diabetes mellitus; Estimated average glucose; Glycosylated hemoglobin; Glycemic control

Introduction

Glycosylated hemoglobin (HbA1c) is the form of hemoglobin that is used widely to identify the average blood glucose levels of a person over the past three months and also can correlate to complications of high blood sugar (diabetes mellitus)[1,2]. It is recommended by international guidelines for evaluating the overall control of diabetes mellitus (DM)[1,2]. The World Health Organization (WHO) and the American Diabetes Association (ADA) also uses the value of HbA1c for the diagnosis of DM[3,4].

Pathophysiology and interpretation

HbA1C is formed by non-enzymatic glycation of the beta chain of hemoglobin A by the plasma glucose[5]. This glycation is irreversible and occurs continuously throughout the life span of red blood cells, which is 120 days (three months)[1,2]. The HbA1C or the fraction of glycated hemoglobin increases in a predictable manner according to the average level of plasma glucose. Therefore, it gives the blood sugar level estimate of the past three months, with the recent glucose levels having the greatest influence on its value[1,2]. Various researchers in their studies have shown that the mean blood glucose of previous 1 month, 2 months and 3 months contributes 50%, 40% and 10% respectively to the final result and thus mathematically calculating, the half-life of HbA1c is estimated to be 35.2 days (indicating that half of the glycation of hemoglobin occurred in the previous 35.2 days from the time of its estimation)[1,6,7].

The approximate relation between HbA1c values and eAG (estimated average glucose) measurements is given by the following equation (Table 1)[1]:

$eAG(mg/dl) = 28.7 \times A1C - 46.7$

$eAG(mmol/l) = 1.59 \times A1C - 2.59$

Table 1: Approximate relation between HbA1c values and eAG (estimated average glucose) measurements

HbA_{1c} (%)	HbA_{1c} (mmol/mol)	eAG (mmol/L)	eAG (mg/dL)
5	31	5.4 (4.2–6.7)	97 (76–120)
6	42	7.0 (5.5–8.5)	126 (100–152)
7	53	8.6 (6.8–10.3)	154 (123–185)
8	64	10.2 (8.1–12.1)	183 (147–217)
9	75	11.8 (9.4–13.9)	212 (170–249)
10	86	13.4 (10.7–15.7)	240 (193–282)
11	97	14.9 (12.0–17.5)	269 (217–314)
12	108	16.5 (13.3–19.3)	298 (240–347)
13	119	18.1 (15–21)	326 (260–380)
14	130	19.7 (16–23)	355 (290–410)
15	140	21.3 (17–25)	384 (310–440)
16	151	22.9 (19–26)	413 (330–480)
17	162	24.5 (20–28)	441 (460–510)
18	173	26.1 (21–30)	470 (380–540)
19	184	27.7 (23–32)	499 (410–570)

Recommendations and advantages of measuring HbA1c: The recommended value of HbA1c in diabetic patients is below 6.5% by the IDF (International Diabetes Federation) and below 7.0% by the American College of Endocrinology (ACE)[6]. WHO and the ADA defined the value of HbA1c above 6.5% as diagnostic of DM and 5.7% to 6.4% as pre-diabetes (the value needs to be reconfirmed the following day)[3,4].

It has been recommended by the various international diabetes control organizations (IDF, ADA) to check the HbA1c levels twice in a year for the patients with blood sugars within the targeted control and quarterly for the patients with uncontrolled blood sugars or the patients who underwent a change in the diabetic control therapy[8]. HbA1c measurement is recommended in patients for both (a) checking blood sugar control in pre-diabetic persons and (b) monitoring blood sugar control in diabetic patients with previous high levels of blood sugar. The major advantages of measuring HbA1c are that it is convenient to the patient as it does not require any special preparation or fasting, can be done at any time of the day, is relatively more stable at room temperature after collection and the variability in the levels is less as compared to the fasting blood sugar.

The two major studies, namely the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes[9] and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes[10] showed the evidence of HbA1c, as an important marker in assessing a patient's risk of microvascular complications (nephropathy, retinopathy) and hypoglycemia. The UKPDS study clearly demonstrated that the reduction in the level of HbA1c was accompanied by a significant decrease in diabetes related complication and one percent (%) decrease in HbA1c diminished the risk of myocardial infarction and microvascular complication by 14% and 37% respectively[10].

Limitations and pitfalls of HbA1c measurement: There are numerous factors that can influence the value of HbA1c[1,3,11]. They can be summarized as:

1. Abnormal hemoglobin- The patients with hemoglobinopathies (genetic or chemical alterations), fetal hemoglobin (HbF), methemoglobin can have variation in the HbA1c levels due to alteration in the RBC life span.
2. Red cell synthesis (defective erythropoiesis)- Falsely elevated levels of HbA1c are seen in Vitamin B12, folate and iron deficiency, decreased erythropoiesis renal insufficiency, and malignancy. Falsely low HbA1c can be seen if the patient is administered erythropoietin, iron, or vitamin B12, in patients with reticulocytosis, and chronic liver disease.
3. Abnormal Glycation- Increased value of HbA1c seen in alcoholism, chronic renal failure, decreased intra-erythrocyte pH, and

decreased value of HbA1c due to ingestion of aspirin, vitamin C and E, certain haemoglobinopathies, increased intra-erythrocyte pH.

4. Red blood cell destruction- Elevated HbA1c in cases where there is increased red blood cell life span (splenectomy, vitamin B12 or folate deficiency). Low levels of HbA1c in cases of decreased red blood cell life span (haemoglobinopathies, splenomegaly, glucose-6-phosphate dehydrogenase deficiency, sickle-cell disease, rheumatoid arthritis or drugs like anti-retrovirals, Ribavirin and Dapsone).
5. Assays- Increased HbA1c in hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiate use, variable values of HbA1c in haemoglobinopathies, and decreased HbA1c in hypertriglyceridaemia.
6. The levels of HbA1c levels have been found to decrease during the second trimester of a normal, non-diabetic pregnancy and rise during the third trimester[12].

The lack of availability and the high cost of conducting the assay for HbA1c in many developing countries is another limitation for its use.

Conclusions

During the last few decades, significant research has been conducted on HbA1c, increasing the knowledge on its utilization for the diagnosis and treatment of diabetes and also its limitations, as it can be affected by a variety of factors as stated above. HbA1c reflects the blood glucose concentrations over the previous three months provided there is normal and steady hemoglobin concentration with a normal erythrocyte survival. The clinicians should be made aware of this useful tool along with its pitfalls through proper dissemination of knowledge, especially in resource limited settings[13-26].

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