

Personal View: Should haemoglobin A1C be used for diagnosis of diabetes mellitus in Malawi?

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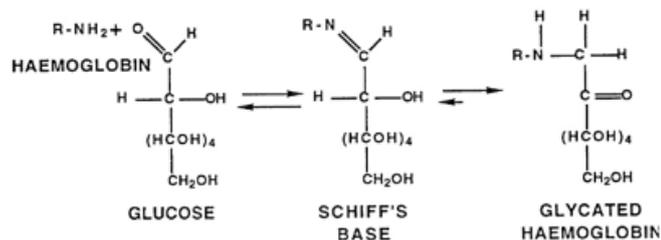
Introduction

Glycated haemoglobin (haemoglobin A1c or HbA1c) level has long been utilised for assessment of long-term glycaemic control in patients with diabetes mellitus.¹ More recently it has also been included as a criterion for the diagnosis of type 2 diabetes mellitus.² However, use of HbA1c as a diagnostic tool for diabetes is controversial.³ This article discusses some of the limitations, and explores whether HbA1c should be recommended for diagnosis of diabetes mellitus in Malawi and similar settings.

HbA1c formation and structure

HbA1c is modified haemoglobin, with a glucose linked to the N-terminal valine of the beta chain.⁴ It is made in vivo by the non-enzymatic attachment of glucose to haemoglobin.⁵ This occurs first by formation of a labile adduct aldimine, which is a Schiff base, that then rearranges to form a more stable ketoamine (Figure 1).⁶ The rate at which this reaction occurs is related to the prevailing glucose concentration, and it is expressed as a percentage of the total haemoglobin.⁷

Figure 1: Formation of glycated haemoglobin (HbA1c)



HbA1c in monitoring diabetes control

The potential utility of HbA1c in management of diabetes was proposed in 1976 by Ronald Koenig and Anthony Cerami⁸; and a 1985 World Health Organization (WHO) report recommended its use for practical assessment of long-term glycaemic control in patients with diabetes mellitus.¹ In individuals with a normal red blood cell lifespan, the level of HbA1c is related to the circulating plasma levels of glucose,⁹ as well as the average glycaemia of the previous 12 to 16 weeks, as this is the half-life of red blood cells.⁶ HbA1c is considered the gold-standard biochemical indicator of long-term glycaemic control in diabetic patients,¹⁰ as a good association has been demonstrated with the chronic microvascular complications of diabetes, such as retinopathy, nephropathy and neuropathy.^{2,11} HbA1c of less than 6.0% is considered normal, 6.0% to 7.5% is good control of diabetes mellitus, 7.6% to 9.0% is considered unsatisfactory control, and HbA1c of more than 9.0% is regarded as very poor control of diabetes mellitus. In Blantyre, Malawi, Cohen et al., in a survey of the management, control, and complications of diabetes mellitus in patients attending a diabetes clinic, found that 74% of patients had unsatisfactory levels of HbA1c (greater than 7.5%), and this was accompanied by a high frequency of microvascular complications.¹²

HbA1c and diabetes diagnosis

The diagnosis of diabetes has traditionally been based upon the detection of elevated plasma glucose levels, either after fasting, two hours after an oral glucose (75 g) tolerance test (OGTT), or, in symptomatic individuals, after a random blood glucose check.¹³ Recently, the American Diabetes Association and the WHO have recommended using HbA1c (greater than or equal to 6.5%) to diagnose diabetes mellitus.¹⁴ This was based, in part, on the ability for HbA1c to predict clinical outcomes. It has been established that HbA1c has a similar relationship with prevalent diabetic retinopathy as that of both fasting and two-hour plasma glucose levels, and that lowering HbA1c can reduce microvascular complications.^{15,16}

Although HbA1c testing is currently more expensive than blood glucose measurements (the net cost of an HbA1c test is, on average, 13.6 times higher than a plasma glucose measurement³), it provides significant practical advantages. HbA1c testing can be performed at any time of the day and does not require any special pre-test preparation by the patient (for example, overnight fasting or glucose loading).^{17,18}

While the use of HbA1c for long-term glycaemic control is well accepted, there remains significant controversy on its use as a diagnostic tool, and many studies show significant discordance between fasting glucose and HbA1c tests.¹⁹

Factors affecting HbA1c levels

There are many common factors, including genetic and medical conditions, that influence HbA1c and its measurement, even when glucose levels are constant.^{20,21} Several studies have shown that in recent-onset, drug-naïve type 2 diabetes (controlling for age, sex and BMI), there is ethnic variability of HbA1c, despite similar fasting plasma glucose levels and similar or lower post-glucose load glucose levels.^{22,23} People of African descent and South Asians appear to have significantly higher levels of HbA1c (and therefore levels “diagnostic” of diabetes) across the full spectrum of glycaemia,²¹ compared to Caucasians.²⁴⁻²⁶ The optimal HbA1c threshold for detecting diabetes may thus vary by ethnic group²⁷; while the WHO currently recommends a diagnostic HbA1c of 6.5%, other studies have shown that in some races a lower threshold of 6.3% can be used for detecting diabetes in high-risk populations.²⁸

In addition to the ethnic limitations described above, a number of other disorders influence HbA1c, and their frequencies will depend on the setting. Conditions that alter red cell lifespan alter the HbA1c concentrations, with conditions that shorten red cell survival, such as haemolysis, decreasing HbA1c, and those disease states that prolong red cell survival increasing HbA1c,²⁹ owing to the change in the duration of contact of the red blood cells with glucose in the blood. Thus, decreased erythropoiesis caused by iron or vitamin deficiency may cause increased HbA1c; and increased erythropoiesis caused by haemolysis (for example, in malaria), administration of erythropoietin, iron, vitamin B12, and

reticulocytosis, will lead to its decrease. Decreased lifespan of red blood cells resulting from haemoglobinopathies, splenomegaly (also common in malaria) rheumatoid arthritis, or drugs (for example, antimicrobials such as ribavirin and dapson) can also decrease HbA1c.

Table 1: Some factors that influence glycated haemoglobin (HbA1c) and its measurement

Factor influencing HbA1c	Increased HbA1c	Decreased HbA1c
Erythropoiesis	Iron deficiency, vitamin B12 deficiency, decreased erythropoiesis	Administration of erythropoietin, iron or vitamin B12, chronic liver disease
Erythrocyte destruction	Increased erythrocyte lifespan, splenectomy	Decreased erythrocyte lifespan, haemoglobinopathies, malaria, splenomegaly, rheumatoid arthritis, drugs (e.g., antiretrovirals, ribavirin, dapson)
Glycation	Alcoholism, chronic renal failure, decreased erythrocyte pH	Ingestion of aspirin, vitamin C, vitamin E, increased erythrocyte pH
Assays	Hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin	Hypertriglyceridaemia

Modified from Gallagher et al.¹⁷

The relationship between HbA1c and HIV infection is also complex. Slama et al. found that at a fasting glucose of 125 mg/dL, median HbA1c values were 0.21% lower in HIV-infected men than in HIV-uninfected men, and that the magnitude of this difference increased at higher glucose values.³⁰

They also found that HbA1c discordance was associated with lower CD4 cell counts; high mean corpuscular volume (MCV); high mean corpuscular haemoglobin (MCH); and a regimen containing a protease inhibitor, a non-nucleoside reverse transcriptase inhibitor, and zidovudine.³⁰ The use of HbA1c could therefore lead to underdiagnosis or undertreatment of established diabetes mellitus, particularly in HIV-positive people on antiretroviral therapy (ART), or those with advanced disease.³⁰ This is significant since HIV and AIDS may have an impact on glucose metabolism, and there are an increasing number of people in Malawi who are dually affected by HIV and diabetes.³¹

Finally, HbA1c testing (whether laboratory analysis or point-of-care) requires a rigorous programme to standardise the assays,³² which may not be possible in many developing countries. Lack of standardisation would lead to a high degree of uncertainty with the results generated in these settings.³

Conclusions

HbA1c is a useful addition to the tools available to diagnose diabetes, and it has clear advantages. However, challenges including cost, assay standardization and multiple potential confounding conditions must be considered. Individual countries will therefore need to decide whether HbA1c as a diagnostic tool is appropriate in relation to prevailing circumstances. Malawi is resource-poor and has a high prevalence of conditions that can influence the performance of HbA1c (such as HIV, anaemia of various aetiologies, and disorders associated with increased red cell turnover, including malaria). It would therefore be premature to advocate the use of HbA1c to diagnose diabetes mellitus in Malawi. More research will be required to fully understand the utility of HbA1c and its limitations in the diagnosis of diabetes in Malawi and sub-Saharan Africa in general.

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