HbA1C and diabetes – an overview

S Pathmanathan[1], **Noel P Somasundaram**[2]

Sri Lanka Journal of Diabetes, Endocrinology and Metabolism 2013; **3**: 104-107

Abstract

The hemoglobin A1C (HbA1C) assay has become the gold-standard measurement of chronic glycaemia for over two decades. It provides an average blood glucose level during the preceding 10 - 12 weeks. Its close association with risk for long-term complications, established in epidemiologic studies and clinical trials, has resulted in clinicians using HbA1C test results to guide their treatment decisions, and thus the assay has become the cornerstone of clinical practice. This brief review describes some important facts about HbA1C and its relevance and usefulness in clinical practice.

Introduction

Diabetes has been diagnosed for decades with the measurement of plasma glucose, either fasting (FPG) or post prandial (PPG) assessment or, much less frequently, with an oral glucose tolerance test (OGTT) (1). Fasting and 2-h OGTT only reflect the glucose level at a given moment of a single day and is not good in describing a chronic and complex clinical condition. The hemoglobin A1C (HbA1C) measurement, a biochemical parameter which could reflect hyperglycemia over a long period is more appropriate than a parameter describing it in the short term or in a given moment only (2,3). Today the HbA1C assay is widely accepted and used as the most reliable means of assessing chronic glycaemia and has become the cornerstone for the assessment of diabetes care.

HbA1C – an indicator of chronic glycaemia

It has been shown that HbA1C provides an average blood glucose level during preceding 10 - 12 weeks. But HbA1C truly does not reflect glycemic control over last three months as claimed. Rather, it is weighted to more recent weeks. The average glycaemia during the month preceding the HbA1C measurement contributes 50% of the result, during the 30-60 days prior to the HbA1C measurement contributes another 25%, and during the 60-120 days prior to the measurement contributes the final 25% (4).

The fasting blood glucose as well as post meal glucose excursions contribute to HbA1C levels. Post meal blood glucose contributes significantly when HbA1C is <7.5%. On the other hand, fasting blood glucose contributes more when HbA1C is >7.5% (5).

Diagnosing diabetes with HbA1C

The close association of HbA1c with risk for long-term complications has been well established in epidemiologic studies and clinical trials. The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated conclusively that risks for complications are related directly to glycemic control, as measured by HbA1C (6,7). DCCT study documented that maintaining lower blood glucose concentrations (assessed by HbA1C) resulted in a delayed onset and reduced the rate of progression of microvascular complications. Analogous to the DCCT, the UKPDS showed that intensive blood glucose control reduced the risk of microvascular complications. Both the UKPDS and DCCT documented that a small change in HbA1C values translates into a large alteration in the risk of diabetes complications in patients with type 1 or type 2 diabetes (6, 7).

This has led to the establishment of specific HbA1C targets for diabetes care with the goal of preventing or delaying the development of long-term complications. The major objective of diagnosing diabetes is to prevent premature mortality and complication-related morbidity. Therefore it seems logical to consider diagnosis in terms of risk of complications. American Diabetes Association (ADA)-organized international expert committee in 2010 recommended the adoption of the HbA1C assay for the diagnosis of diabetes at a cut point of 6.5% (8). This cut point was primarily derived from a review of studies that examined the association of HbA1C values with incident retinopathy. Retinopathy was chosen as the ultimate criterion because it is among the main complications of diabetes.

[1]*Senior Registrar in Endocrinology,* [2]*Consultant Endocrinologist, National Hospital of Sri Lanka, Colombo.*

World Health Organization (WHO) in 2011 officially recommended HbA1C testing for the diagnosis and monitoring of diabetes. They recommend that HbA1C can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement (9,10).

Standardization of HbA1C levels

Currently there are several methods available to measure glycated hemoglobin, and it is of utmost importance that these methods are standardized to report the same result for a single blood sample. The American Association for Clinical Chemistry (AACC) established a committee in 1993 to standardize GHB/HbA1C results so that clinical laboratory results are comparable to those reported by the DCCT and UKPDS, which established direct relationships between HbA1C concentrations and outcome risks in patients with diabetes. Three years later the National Glycohemoglobin Standardization Program (NGSP) was established to execute the protocol developed by the AACC committee (11,12). The ADA recommends that laboratories use only HbA1C assays that are certified by NGSP as traceable to the DCCT reference. These assays are listed on the NGSP website (http://www.ngsp.org) and are updated at least annually.

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) in 1995 developed a true reference method for HbA1C which is known as IFCC standardization. The IFCC reference method is technically demanding, time consuming, and very expensive and is not designed for routine analysis of patient samples. IFCC measurement is too specific as it only measures one molecular species of HbA1C: thus, non-HbA1C components are not included in final results. Therefore it was found that HbA1C values obtained by using IFCC method are 1.5 to 2 percentage points lower than the NGSP results traced to DCCT (13). To overcome this problem a "master equation" was developed to formulize the relationship between the IFCC reference method and the NGSP. The master equation allows for the conversion of the IFCC results to more customary HbA1c results (14).

In 2007, the IFCC recommended that HbA1C results be expressed as mmol HbA1c/mol Hb instead of an HbA1C percentage. To eliminate confusion on reporting of HbA1C, ADA, IDF and IFCC jointly issued a consensus statement in May 2007 which states that, HbA1C results were to be reported worldwide in IFCC units (mmol glycated Hb /mol total Hb) and derived NGSP units (%), using the IFCCNGSP master equation (15).

Table 1. The pros and cons of diagnosing diabetes with HbA1C

Reasons to prefer HbA1C	*Reasons not to prefer HbA1C*
HbA1C captures chronic hyperglycemia but not FPG	Cost of the assay
Fasting not needed	Not available on a large scale
Better associated with chronic complications than FPG	Standardization of HbA1C assay is poor
Microangiopathic complications (retinopathy) are associated with HbA1C as strongly as with FPG	Unreliable and cannot be used in many subjects. Eg: Pregnant women
No acute perturbations (e.g., stress, diet, exercise, smoking) affect HbA1C	May vary according to erythrocyte turnover rates (e.g., hemoglobinopathies) as well as other factors
Has a greater pre-analytical stability than blood glucose	Has significant differences in various ethnic groups Eg-African/African American (16)
	Has a poor sensitivity in diabetes diagnosis and would change the epidemiology of diabetes.

Table 2. Some of the factors that influence HbA1C and its measurement

Factors causing increased HbA1C	*Factors causing decreased HbA1C*
Iron deficiency anemia (17), vitamin B12 deficiency	Administration of erythro-poietin, iron, vitamin B12
Alcoholism	Chronic liver disease
Aplastic anemia	Hemolytic anemia
Chronic renal failure	Haemoglobinopathies (18)
Splenectomy	Hypersplenism, Splenomegaly Hypertriglyceridaemia.

Correlation of HbA1C with average glucose

ADA and the American Association of Clinical Chemists (AACC) have published the correlation between HbA1C levels and mean plasma glucose levels based on data from the international A1C-Derived Average Glucose (ADAG) trial. ADAG trial utilizes frequent patient self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM) in 507 adults (83% Caucasian) with type 1, type 2, and no diabetes. Correlation(r) of 0.92 is considered strong enough to justify reporting both an A1C result and an estimated average glucose result when a clinician orders the HbA1C test (19). For patients in whom HbA1C and measured blood glucose appear discrepant, the possibilities of hemoglobinopathy or altered red cell turnover should be considered (Table 2). Clinicians should also use the options of more frequent and different timing of SMBG or use of CGM. Other measures of chronic glycemia such as fructosamine are available, but their linkage to average glucose and their prognostic significance are not as clear as is the case for HbA1C (19,20). A calculator for converting HbA1C results into mean plasma glucose is available at http//professional.diabetes.org

Table 3. Correlation of HbA1C with average glucose

A1C (%)	*Mean Plasma Glucose*	
	mg/dl	mmol/L
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

HbA1C level and future risk of diabetes

Systematic review of various prospective studies confirms a strong, continuous association between HbA1C and subsequent diabetes risk. Persons with an HbA1C value of ≥6.0% have a very high risk of developing clinically defined diabetes in the near future with 5-year risks ranging from 25 to 50% and relative risks frequently 20 times higher compared with HbA1C <5%. However, persons with an HbA1C between 5.5 and 6.0% also have a substantially increased risk of diabetes with 5-year incidences ranging from 9 to 25%. The ideal decision about what HbA1C cut point is used for intervention should ultimately be based on the capacity for benefit as shown in clinical trials. Findings from various studies suggest that HbA1C range of 5.5 and 6.5% will capture a large portion of people at high risk, and if interventions can be employed to this target population, it may bring about significant absolute risk reduction (21,22). ADA recommends that patients with HbA1C of 5.7- 6.4% should be referred for lifestyle modifications with or without metformin to prevent the development of diabetes in these patients (1).

Conclusion

HbA1C has achieved importance in diabetes because of its value in the evaluation of glucose control and its relation to long-term microvascular complications. The utility and convenience of HbA1C compared with plasma glucose for the diagnosis and management of diabetes has to be weighed against the fact that it is not readily available in many countries and the cost remains unaffordable to most of our patients. Inaccuracies in measurement and poor standardization of HbA1C assays are still a common problem, even in western countries. Therefore it should be used in the management of diabetes only if the assays are standardized to criteria aligned to the international reference values.

References

1. American Diabetes Association. Standards of medical care in diabetes-2012. *Diabetes Care* 2012; **35**(Suppl. 1): S11-S63.
2. Goldstein DE, Little RR, Lorenz RA, Malone JI, et al. Tests of glycemia in diabetes. *Diabetes Care* 2004; **27**: 1761-73.
3. Sacks DB. A1C versus glucose testing: a comparison. *Diabetes Care* 2011; **34**: 518-23.
4. Beach KW. A theoretical model to predict the behavior of glycosylated hemoglobin levels. *Journal of Theoretical Biology* 1979; **81**: 547-61.
5. Curt L Rohlfing, Jack D England, Hsiao-Mei Weidmeyer, et al. Defining the relationship between Plasma Glucose and HbA1c. *Diabetes Care* 2002; **25**: 275-8.
6. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine* 1993; **329**: 977-86.
7. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352**: 837-53.
8. American Diabetes Association. Standards of medical care in diabetes - 2010. *Diabetes Care* 2010; **33**(Suppl. 1): S11-S61.

9. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus; 2011, www.who.int/diabetes/publications/report-hba1c_2011.pdf.

10. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Report of a World Health Organization Consultation. *Diabetes Research and Clinical Practice* 2011; **93**: 299-309.

11. Little RR, Rohlfing CL, Wiedmeyer HM,Myers GL, Sacks DB, Goldstein DE; NGSP Steering Committee. The national glycohemoglobin standardization program: a five year progress report. *Clinical Chemistry* 2001; **47**: 1985-92.

12. Little RR, Rohlfing CL. HbA1c Standardization: Background, Progress and Current Issues. *Lab Medicine* 2009; **40**: 368-73.

13. International Federation of Clinical Chemistry and Laboratory Medicine, IFCC Scientific Division, Mosca A, Goodall I, Hoshino T, Jeppsson JO, John WG, Little RR, et al. Global standardization of glycated hemoglobin measurement: the position of the IFCC Working Group. *Clinical Chemistry and Laboratory Medicine* 2007; **45**: 1077-80.

14. Hoelzel W, Weykamp C, Jeppsson J, Miedema K, Barr JR, Goodall I, et al. IFCC reference system for measurement of haemoglobin A1 in human blood and the national standardization schemes in the United States, Japan, and Sweden: a Method comparison study. *Clinical Chemistry* 2004; **50**: 166-74.

15. Consensus Committee. Consensus Statement, Consensus Statement on the Worldwide Standardization of the Hemoglobin A1c Measurement, the American Diabetes Association European Association for the study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation. *Diabetes Care* 2007; **30**: 2399-400.

16. Herman WH, Cohen RM. Racial and ethnic differences in the relationship between HbA1c and blood glucose: implications for the diagnosis of diabetes. *Journal of Clinical Endocrinology and Metabolism* 2012; **97**: 1067-72.

17. Tarim O, Kucukerdogan A, Gunay U, Eralp O, Ercan I. Effects of iron deficiency anemia on hemoglobin A1c in type 1 diabetes mellitus. *Pediatrics International* 1999; **41**: 357-62.

18. Randie R. Little, William L. Roberts, Review of Variant Hemoglobins Interfering with Hemoglobin A1c Measurement. *Journal of Diabetes Science and Technology* 2009; **3**(3): 446-451.

19. Nathan DM, Kuenen J, Borg R, et al. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008; **31**: 1473-8.

20. Robert M. Cohen, Christopher J. Lindsell, When the Blood Glucose and the HbA1C Don't Match: Turning Uncertainty into Opportunity. *Diabetes Care* 2012; **35**: 2421-13.

21. Zhang X, Gregg EW, David F. Williamson, et al. A1C Level and Future Risk of Diabetes: A Systematic Review. *Diabetes Care* 2010; **33**(7):1665-73.

22. Cohen RM, Haggerty S, Herman WH.HbA1c for the diagnosis of diabetes and prediabetes: is it time for a mid-course correction? *Journal of Clinical Endocrinology and Metabolism* 2010; **95**: 5203-6.