JOURNAL OF DIABETES, METABOLISM & ENDOCRINOLOGY
SINCE 2000
MEDWELL PUBLICATIONS

Clinical Uses of HbA_{1c} in Diagnosis of Diabetes Mellitus

Ibrahim A. Ali
Department of Physiology, Faculty of Medicine, The National Ribat University, Khartoum, Sudan

Key words: HbA_{1c}, diabetes mellitus, IFCC, Glycaemic status, diagnosis

Corresponding Author:
Ibrahim Abdelrhim Ali
Department of Physiology, Faculty of Medicine, The National Ribat University, Khartoum, Sudan. Email: hemamedicine@gmail.com

Page No.: 5-8
Volume: 1, Issue 1, 2020
ISSN: 2708-2709
Journal of Diabetes, Metabolism and Endocrinology

Abstract: HbA_{1c} is formed over a period of two to three months and reflects the glycaemic status of a patient over the past two to three months for this reasons HbA_{1C} test has been used for diabetics followup and diagnosis. The relationship between HbA_{1c} and average blood glucose is complex but has been studied by the Diabetes Control and Complications Trial (DCCT). A new internationally standardized method for reporting HbA_{1C} has been developed by the International Federation of Clinical Chemistry (IFCC). This will report HbA_{1C} in mmol per mol of hemoglobin without glucose attached. HbA_{1c} has now been recommended by an International Committee and by the ADA (American Diabetes Association) as a mean to diagnose diabetes and as a screening test for persons at high risk of diabetes. Also, the International Diabetes Federation and American College of Endocrinology (ACE) recommend HbA_{1c} values below 48 mmol moL^{-1} (6.5%). The 2010 American Diabetes Association Standards of Medical Care in Diabetes added the A_{1c} 48 mmol moL^{-1} (6.5%) as another criterion for the diagnosis of diabetes mellitus.

INTRODUCTION

HbA_{1c} is formed over a period of two to three months and reflects the glycaemic status of a patient over the past two to three months for this reasons HbA_{1c} test has been used for diabetics followup and diagnosis[1].

There is a correlation between the HbA_{1c} levels and mean plasma glucose levels on multiple testing over 2-3 months[2]. For example, an HbA_{1c} value of 6% corresponds to a mean plasma glucose level of 7.5 mmol L^{-1}, 135 mg dL^{-1} (Table 1).

The relationship between HbA_{1c} and average blood glucose is complex but has been studied by the Diabetes Control and Complications Trial (DCCT). A new internationally standardized method for reporting HbA_{1c} has been developed by the International Federation of Clinical Chemistry (IFCC). This will report HbA_{1c} in mmol per mol of hemoglobin without glucose attached[3].

Table 1: Comparing DCCT-Hb A_{1c} and Average blood glucose

DCCT-Hb A_{1c}(%)	Average blood glucose (mmol L^{-1})
5	5.5
6	7.5
7	9.5
8	11.5
9	13.5
10	15.5
11	17.5
12	19.5

From the we can see that average plasma glucose = $(2\times HbA_{1c})$-4.5[3]

According to a report published in 2009 by an International Expert Committee on the role of HbA_{1c} in the diagnosis of diabetes, HbA_{1c} can be used to diagnose diabetes and that the diagnosis can be made if the Hb A_{1c} level is 6.5% or more and HbA_{1c} level below 6% is considered normal[4].

HbA_{1c} results in the UK have usually been aligned to the assay used in the Diabetes Control and Complications Trial (DCCT), expressed as a percentage (DCCT-HbA_{1c}) - non-diabetic 'normal' range being 4-6%[5].

Diagnostic criteria for diabetes that made by (World Health Organization WHO report 2011) determined that HbA_{1c} of 6.5% was considered as the cut-off point for diagnosing diabetes. A value <6.5% does not exclude diabetes diagnosed using glucose tests[6].

Hba_{1c} test sensitivity: Glycated hemoglobin has been extensively investigated by clinical trials in 1979 Dunn *et al*.[7] suggested that HbA_{1c} is highly reproducible and responsive to changes in glucose tolerance as such it could be used to monitor the control of glycaemia.

In 1991, Mulkerrin *et al*.[8] reported very poor sensitivity (36%) and predictive value (44%) in their elderly sample (mean age 76 years old), thereby making HbA_{1c} neither useful in screening nor beneficial for diagnosing diabetes. However, in acutely ill hospitalized patients HbA_{1c}> 6% could reliably diagnose diabetes and level <5.2 % would reliably exclude diabetes[9].

In other words, the HbA_{1c} cut-off of 6.5% with very low sensitivity and very high specificity could be used as a supportive marker for the diagnosis of diabetes[10]. Although, HbA_{1c} cut-off 6.5% for diagnosis is too high, it gives acceptable sensitivity and specificity rates at 44.6 and 99.6%, respectively[11]. A study from Australia suggested the use of a 7% cut-off rate for HbA_{1c} when screening high risk populations[12].

Other studies have asserted that simultaneous measurement of fasting blood glucose and HbA_{1c} may be used to identify high risk patients at an early stage[13, 14].

In 1994, McCane *et al*.[15] recommended glycatedHb or fasting plasma glucose as an acceptable alternative for diagnosing diabetes instead of OGTT.

In one study most individuals with HbA_{1c} at 6-7% had normal FPG but usually abnormal 2 h post challenge Plasma Glucose (PCPG); only 58% of patients with HbA_{1c} in the 5-5.5% range had normal PCPG[16].

In a consensus statement: (2008) Society of Endocrinology[17] recommended the level of HbA_{1c} of 6.5-6.9% or greater, confirmed by Fasting Blood Glucose (FPG) or Oral Glucose Tolerance Test (OGTT) should establish thediagnosis of diabetes and HbA_{1c}>6.0% and impaired fasting glucose (>100 mg dL^{-1}) or random plasma glucose of 130-199 mg dL^{-1} should lead to further diagnostic workup and closer follow-up. By using these recommendations, we may identify a high proportion of individuals with undiagnosed diabetes may be identified who would otherwise only be diagnosed once they developed end organ damage.

MATERIALS AND METHODS

HbA_{1c} assay methods: A broad range of assay methods has being developed since $HbA_{1c}$was described in the late 1950. Roughly, there are two different methods for the measurement of HbA_{1c}: methods based on difference in charge and methods based on structural difference.

Ion-exchange chromatography, capillary electrophoresis and iso-electric focusing are all based on the difference in electrical charge.

Till 1999, the assays being used for measuring HbA_{1c} were boronate affinity chromatography (>50% of laboratories), cation or ion-exchange High Performance Liquid Chromatography (HPLC) methods (30%), immunoassay (15%) and electrophoretic methods (<5%)[18]. However, presently, cation exchange performed by HPLC is the most widely used assay method[19].

For the time being, only the High-Performance Liquid Chromatography (HPLC) is still in use. It is an efficient method; it meets the clinical requirements of reliability and interpretation and does not suffer from interference by Schiff base or carbamylatedhaemoglobin.

Affinity chromatography and immunochemical assays are the two main used methods based on structural difference. The latter is the one that is mostly applied.

HbA_{1c} accelerates faster in a cation-exchange resin. Ion exchange chromatography takes advantage of the lower isoelectric point that develops when glucose attaches to the beta chain N-terminal valine and HbA_{1c} acquires an extra negative charge.

The concentration of hemoglobin is measured using a spectrophotometer and quantified by calculating the area under each peak of the chromatogram compared with a calibrated chromogram[20].

RESULTS AND DISCUSSION

Relation of HbA_{1c} to glycaemic control in Diabetes Mellitus DM: Koenig *et al*.[21] examined the relationship between HbA_{1c} and glycaemiccontrol in poorly controlled diabetic patientsand found improvement in glycaemic control caused a reduction in the levels of HbA_{1c} after approximately 4 weeks.

In another study of newly diagnosed diabetic patients, initially elevated levels of HbA_{1c} were observed to decrease gradually in the weeks following the onset of dietary and insulin therapy with a tendency to level out after approximately 7 weeks[22].

HbA_{1c} and Diagnosis of DM: In 2000, it is estimated that the worldwide prevalence of diabetes wasapproximately 2.8% and is expected to grow to 4.4% by 2030[23].

It is important to remember that HbA_{1C} only reflects glucose concentrations over 4-8 weeks provided there is a normal hemoglobin concentration and normal red blood cell survival[23, 24].

The real international revolution and breakthrough for the clinical use of HbA_{1c} in diabetes came from the large prospective DCCT (Diabetes Control and Complications Trial) and UKPDS (United Kingdom Prospective Diabetes Study) studies showing that glycaemic control by the measured HbA_{1c} levels was related to risk of developing the micro vascular complications of diabetes[23].

Glycated hemoglobin is still not playing a major role in the diagnosis of gestational diabetes which still requires fasting and glucose tolerance measurements and not the glycated hemoglobin[4, 25]. HbA_{1c} levels decrease during the second trimester of a normal nondiabetic pregnancy and rise during the third trimester[26].

HbA_{1c} has now been recommended by an International Committee and by the ADA (American Diabetes Association) as a mean to diagnose diabetes and as a screening test for persons at high risk of diabetes[4, 6].

Also, the International Diabetes Federation and American College of Endocrinology (ACE) recommend HbA_{1C} values below 48 mmol moL^{-1} (6.5%)[4].

The 2010 American Diabetes Association Standards of Medical Care in Diabetes added the A_{1C} 48 mmol moL^{-1} (6.5%) as another criterion for the diagnosis of diabetes[27].

The appreciable advantage that make HbA_{1c} applicable for diagnosis of DM that it can be performed at any time of the day and does not require any special preparation such as fasting. These properties have made it the preferred test for assessing glycaemic control in people with diabetes[4].

The American Diabetes Association guidelines suggest that the HbA_{1c} testcan be performed at least two times a year forpatients with diabetes that are meeting treatmentgoals and have stable glycaemic control andquarterly for patients with diabetes whose therapyhas changed or that are not meeting glycemicgoals[25].

CONCLUSION

HbA_{1c} can be used as a diagnostic test for diabetes provided that stringent quality assurance tests are in place and assays arestandardized to criteria aligned to the international reference values and there are no conditions present which preclude its accurate measurements[6].

HbA_{1c} is expressed in (%) in NGSP (National GlycohemoglobinStandardization Program and mmol/mol in IFCC (International Federation for Clinical Chemistry). HbA_{1c} can indicate people with pre-diabetes or diabetes as follows[4, 6]:

- Normal: Below 42 mmol moL^{-1} (6.0%)
- Pre-diabetes: 42-47 mmol moL^{-1} (6.0-6.4%)
- Diabetes: 48 mmol (6.5%)

REFERENCES

01. Sacks, D.B., D.E. Bruns, D.E. Goldstein, N.K. Maclaren, J.M. McDonald and M. Parrott, 2020. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin. Chem., 48: 436-472.
02. Rohlfing, C.L., H.M. Wiedmeyer, R.R. Little, J.D. England, A. Tennill and D.E. Goldstein, 2002. Defining the relationship between plasma glucose and HbA1c analysis of glucose profiles and HbA_{1c} in the Diabetes Control and Complications Trial. Diab. Care, 25: 275-278.
03. Hicks, J., M. Muller, M. Panteghini and J. Garry, 2007. Consensus statement on the worldwide standardization of the hemoglobin A1c measurement: The American Diabetes Association. Diabetes Care, 30: 2399-2400.
04. International Expert Committee, 2009. International expert committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care, 32: 1327-1334.
05. Weykamp, C., W.G. John and A. Mosca, 2014. A review of the challenge in measuring hemoglobin A1c. J. Diabetes Sci. Technol., 3: 439-445.
06. WHO, 2011. Use of Glycated Haemoglobin (HbA_{1c}) in the diagnosis of diabetes mellitus. Report of a WHO Consultation. http://www.who.int/diabetes/publications/report-hba1c_2011.pdf.
07. Dunn, P.J., R.A. Cole, J.S. Soeldner and R.E. Gleason, 2013. Reproducibility of hemoglobin AIc and sensitivity to various degrees of glucose intolerance. Ann. Internal Med., 91: 390-396.
08. Mulkerrin, E.C., J.D. Arnold, R. Dewar, D. Sykes, A. Rees and M.S.J. Pathy, 2007. Glycosylated haemoglobin in the diagnosis of diabetes mellitus in elderly people. Age Ageing, 21: 175-177.
09. Greci, L.S., M. Kailasam, S. Malkani, D.L. Katz, I. Hulinsky, R. Ahmadi and H. Nawaz, 2007. Utility of HbA1c levels for diabetes case finding in hospitalized patients with hyperglycemia. Diabetes Care, 26: 1064-1068.
10. Tanaka, Y., Y. Atsumi, K. Matsuoka, A. Mokubo and T. Asahina et al., 2002. Usefulness of stable HbA1c for supportive marker to diagnose diabetes mellitus in Japanese subjects. Diabetes Res. Clin. Pract., 53: 41-45.
11. Rohlfing, C.L., R.R. Little, H.M. Wiedmeyer, J.D. England and R. Madsen *et al.*, 2007. Use of GHb (HbA1c) in screening for undiagnosed diabetes in the US population. Diabetes Care, 23: 187-191.
12. Kim, K.S., S.K. Kim, Y.K. Lee, S.W. Park and Y.W. Cho, 2008. Diagnostic value of glycated haemoglobin (HbA1c) for the early detection of diabetes in high-risk subjects. Diabetic Medicine, 25: 997-1000.

13. Rowley, K.G., M. Daniel and K. O'Dea, 2005. Screening for diabetes in Indigenous populations using glycated haemoglobin: Sensitivity, specificity, post-test likelihood and risk of disease. Diabetic Med., 22: 833-839.
14. Mannucci, E., A. Ognibene, I. Sposato, M. Brogi and G. Gallori *et al*., 2004. Fasting plasma glucose and glycated haemoglobin in the screening of diabetes and impaired glucose tolerance. Acta Diabetologica, 40: 181-186.
15. McCance, D.R., R.L. Hanson, M.A. Charles, L.T.H. Jacobsson, D.J. Pettitt, P.H. Bennett and W.C. Knowler, 1994. Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. Br. Med. J., 308: 1323-1328.
16. Woerle, H.J., W.P. Pimenta, C. Meyer, N.R. Gosmanov and E. Szoke *et al*., 2004. Diagnostic and therapeutic implications of relationships between fasting, 2-hour postchallenge plasma glucose and hemoglobin A1c values. Arch. Internal Med., 164: 1627-1632.
17. Saudek, C.D., W.H. Herman, D.B. Sacks, R.M. Bergenstal, D. Edelman and M.B. Davidson, 2008. A new look at screening and diagnosing diabetes mellitus. J. Clin. Endocrinol. Metab., 93: 2447-2453.
18. Little, R.R., C.L. Rohlfing, H.M. Wiedmeyer, G.L. Myers and D.B. Sacks et al., 2001. The national glycohemoglobin standardization program: A five-year progress report. Clin. Chem., 47: 1985-1992.
19. Gallagher, E.J., D. Le Roith and Z. Bloomgarden, 2009. Review of hemoglobin A1c in the management of diabetes. J. Diabetes, 1: 9-17.
20. John, W.G., 2003. Hemoglobin A1c analysis and standardization. Clin. Chem. Lab. Med., 41: 1199-1212.
21. Koenig, R.J., C.M. Peterson, R.L. Jones, C. Saudek, M. Lehrman and A. Cerami, 1976. Corelation of glucose regulation and haemoglobin A1c in diabetes mellitus. Eng. J. Med., 295: 417-420.
22. Ditzel, J. and J.J. Kjaergaard, 1978. Haemoglobin AIc concentrations after initial insulin treatment for newly discovered diabetes. Br. Med. J., 1: 741-742.
23. Wild, S., G. Roglic, A. Green, R. Sicree and H. King, 2004. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care, 27: 1047-1053.
24. Nathan, D.M., H. Turgeon and S. Regan, 2007. Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia, 50: 2239-2244.
25. American Diabetes Association, 2007. Standards of medical care in diabetes-2007. Diabetes Care, 30: S4-S41.
26. Nitin, S., 2010. HbA1c and factors other than diabetes mellitus affecting it. Singapore Med. J., 51: 616-622.
27. Stratton, I.M., A.I. Adler, H.A. Neil, D.R. Matthews and S.E. Manley *et al*., 2003. American diabetes association: Standards of medical care for patients with diabetes mellitus. Diabetes Care, 26: S33-S50.