Editorial: Rapidly Growing Importance of Glycated Haemoglobin (HbA1c) in Diabetic Management

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Abstract: Glycated Haemoglobin (HbA1c) has become an integral part of glucose management in diabetes mellitus patients as it corresponds to their average blood glucose level in past few weeks. The improved glucose management is clearly apparent to the healthcare professionals from the reduced and sustained HbA1c level in diabetics. HbA1c has also been recently advocated as a diagnostic marker for diabetes mellitus. During the past two decades, tremendous improvements have been made in the development of laboratory-based reference methods for HbA1c analysis and the development of secondary HbA1c reference material that is being used worldwide for the standardisation of HbA1c methods. The current generation of point-of-care (POC) instruments for HbA1c analysis lacks the generally-accepted analytical performance criteria, thereby stressing the need for critical improvement in POC devices and HbA1c methods.

Keywords: Glycated Haemoglobin (HbA1c), diabetes, glucose management, point-of-care devices.

Diabetes has been declared as the global epidemic by World Health Organization (WHO) due to the rapidly growing number of diabetics worldwide and unsustainable economic burden of around US$ 376 billion [1]. The numbers of diabetics predicted by WHO in 2004 [2] stated the increase from 171 million in 2000 to 366 million in 2030. However, the current estimates by International Diabetes Federation (IDF) [3] states 371 million diabetics, which has surpassed the estimates for 2030.

There is a rapidly growing importance of Glycated haemoglobin (HbA1c) [4, 5] in diabetic management. HbA1c has become a gold standard for glucose management in diabetes mellitus patients and has been recently advocated as a diagnostic marker for diabetes mellitus by American Diabetes Association (ADA) [6] and WHO [7]. The importance of HbA1c in diabetes was realised in 1969, when Samuel Rahbar and co-workers discovered higher concentrations of fast haemoglobin in diabetics in comparison to non-diabetics [8, 9].Subsequently, Trivelli established the relationship between fast haemoglobin, mean blood glucose concentrations and long-term diabetic complications [10].

In an healthy adult, there is 97% adult haemoglobin (HbA), 2.5% HbA_2 and 0.5% foetal hemoglobin (HbF), where 94% of HbA is in non-glycated form and the rest 6% is in glycated form (Figure **1**) [4]. The glycated haemoglobin further consists of ~1% minor components i.e. HbA1a and HbA1b, and ~5% major component i.e. HbA1c. HbA1c is formed by a two-stage non-enzymatic process (Figure **2**). The first stage is fast, where blood glucose binds to the N-terminal valine of the β-chains of haemoglobin to form an unstable aldimine intermediate (Schiff's base). The second step involves the slow Amadori rearrangement of the intermediate into a stable ketoamine i.e. HbA1c or its conversion back to glucose and haemoglobin.

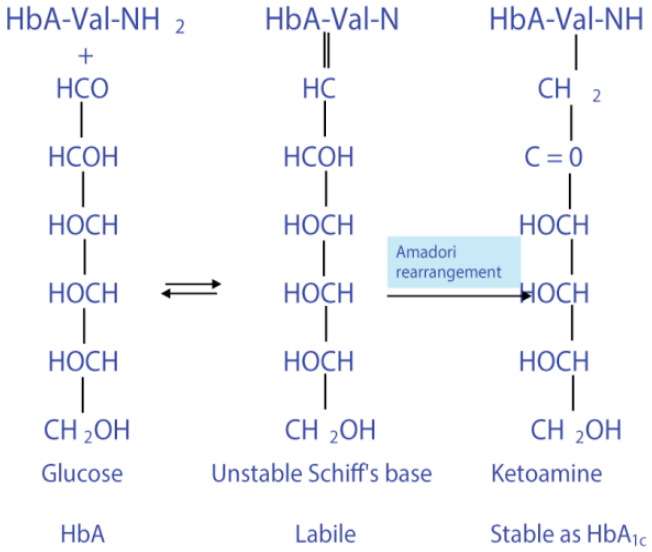

Figure 1: Haemoglobin types of healthy adults [4] Lenters-Westra *et al*. 2012]. Reproduced with permission from Elsevier Ireland Ltd.

It has been demonstrated that 50, 40 and 10 percent of given HbA1c value are the result of glucose exposure during the previous 30, 31-90 and 91-120 days, respectively. The treatment goal for diabetics aims to sustain the HbA1c concentration of less than

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ISSN: 1814-8085 / E-ISSN: 1927-5129/13

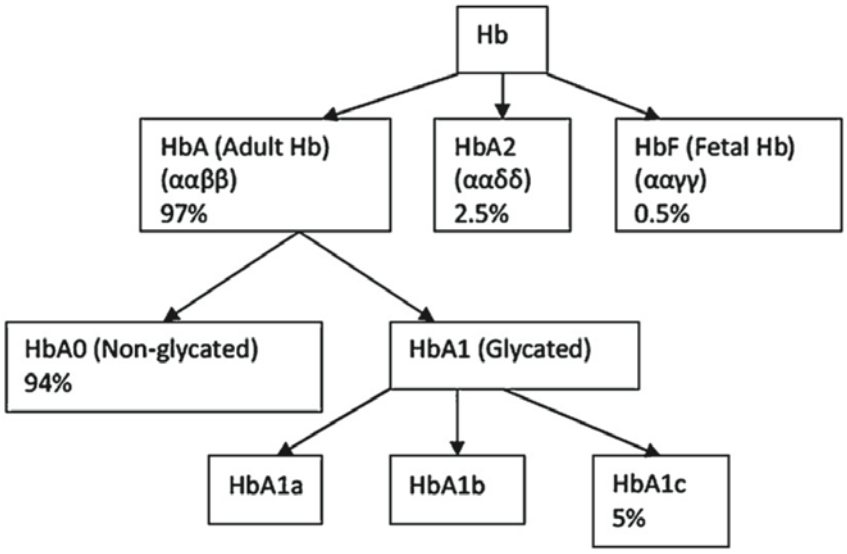

Figure 2: Formation of HbA1c [5] Higgins 2012]. Reproduced with permission from Elsevier Inc.

53 mmol/mol. The ADA recommends HbA1c measurement at least twice in patients with stable glycaemic control and four times in those having a change in therapy or higher HbA1c values. The decision pertaining to the change of treatment is advised to patients by the diabetic care professionals on the basis of their HbA1c level.

Until 1993, there was no reference material available for HbA1c, which resulted in high inter-laboratory CV and variability in results between different HbA1c methods. Therefore, it was difficult for physicians to use HbA1c in actual clinical practice. The work of National Glycohemoglobin Standardisation Program (NGSP)(started in 1996 by American Association for Clinical Chemistry (AAAC)) [11] and International Federation of Clinical Chemistry (IFCC) working group (started in 1994) for the standardisation of HbA1c in cooperation with manufacturers resulted in tremendous improvements in laboratory-based HbA1c methods. It resulted in the development of reference methods for HbA1c analysis [12] based on enzymatic cleavage of haemoglobin, mass spectroscopy and capillary electrophoresis. Additionally, the secondary HbA1c reference material, made from patient whole blood, was also developed, which is the basis for standardisation of HbA1c methods worldwide and is being widely used by the manufacturers [13]. Similarly, the national HbA1c standardisation programs were also carried out by Sweden and Japan. The study of the relation between the different standardisation programs resulted in the formation of master equations [14], which can predict the HbA1c values that will be obtained by various programs. The international agencies, i.e. ADA, IDF and European Association for the study of Diabetes (EASD), decided that HbA1c values should be reported worldwide in the same units (mmol/mol) similar to the existing glucose monitoring [15]. The studies conducted by the A1c-Derived Average Glucose (ADAG) study group provided a better understanding of the relationship between HbA1c and average blood glucose [16]. All these developments has resulted in enhanced convenience for the patient as the sample for HbA1c analysis can now be obtained at any time instead of at least 8 h fast, as required previously. Moreover, they have enabled the healthcare providers to use HbA1c in diabetes care. Sample processing is relatively simple for HbA1c while it needs stringent preparation and processing for glucose assessment, in addition to the fact that glucose measurement has moderate pre-analytic and biological variability versus little to no variations with HbA1c [17]. HbA1c assessment may be interfered by haemoglobinopathies or diseases that may increase red blood cells turnover.

There are numerous commercially-available HbA1c assays, which are based on two principles i.e. charge differences (employed in ion-exchange chromatography (high performance liquid chromatography) and electrophoresis-based assays) and structural differences (used in immunoassays and boronate affinity chromatography-based assays) [4]. The electrophoresis-based HbA1c assays are not used anymore in clinical settings. However, there is an immense need for point-of-care (POC) instruments for immediate HbA1c analysis, similar to that of blood glucose monitoring [18], as it will significant improve

the diabetic management. The HbA1c instruments are classified as CLIA-waived tests, which are not obliged to fulfil quality requirements in the same way as laboratory-based methods. Therefore, they suffer from poor analytical performance [19, 20] and interferences with haemoglobin variants. It has been shown that 6 out of the 8 POC instruments do not meet the generally-accepted performance criteria [21] and have high analytical coefficient of variance (CV), which could lead to tens of millions of people being wrongly diagnosed with diabetes and others who would not receive diabetes treatment. The current state-of-the-art is lacking a perfect method for HbA1c measurement, which stresses the need for more close interactions between clinical chemists (responsible for taking results) and healthcare providers (responsible for interpreting results). The clinical chemist should screen an appropriate HbA1c method having adequate analytical performance for clinical settings and provide them the desired information to properly interpret the results. This will enable the healthcare professionals to take more appropriate clinical decision for diabetic management.

The role of HbA1c in diabetic management has now been firmly established, where optimizing glycemic control is the key to prevent or delay the occurrence of diabetes chronic complications, which can be significantly reduced by achieving the ADA recommended HbA1c target of <7% [22]. The use of HbA1c in the diagnosis of diabetes mellitus has been recently advocated. HbA1c monitoring now forms an integral part of diabetes management. However, the analytical performance of HbA1c methods and POC instruments still requires critical improvement to reduce their maximum CV and bias to less than 1.9% and 2 mmol/mol, respectively, which are the widely accepted performance standards.

REFERENCES

[1] Zhang P, Zhang X, Brown J, Vistisen D, Sicree R, Shaw J, Nichols G. Global healthcare expenditure on diabetes for 2010 and 2030. Diabetes Res Clin Pr 2010; 87: 293-301. http://dx.doi.org/10.1016/j.diabres.2010.01.026

[2] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-53. http://dx.doi.org/10.2337/diacare.27.5.1047

[3] IDF Diabetes Atlas, 5th edition, 2012 update. http://www.idf.org/sites/default/files/5E_IDFAtlasPoster_2012_EN.pdf [Accessed on April 24, 2013].

[4] Lenters-Westra E, Schindhelm RK, Bilo HJ, Slingerland RJ. Haemoglobin A1c: Historical overview and current concepts. Diabetes Res Clin Pr 2013; 99: 75-84. http://dx.doi.org/10.1016/j.diabres.2012.10.007

[5] Higgins T. HbA_{1c} – An analyte of increasing importance. Clin Biochem 2012; 45: 1038-45. http://dx.doi.org/10.1016/j.clinbiochem.2012.06.006

[6] Gillett MJ. International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes: Diabetes Care 2009; 32(7): 1327-34. Clin Biochem Rev 2009; 30: 197-200.

[7] Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus http://www.who.int/diabetes/publications/report-hba1c_2011.pdf [Accessed on April 24, 2013].

[8] Rahbar S. An abnormal haemoglobin in red cells of diabetics. Clin Chim Acta 1968; 22: 296-8. http://dx.doi.org/10.1016/0009-8981(68)90372-0

[9] Rahbar S, Blumenfeld O, Ranney HM. Studies of an unusual haemoglobin in patients with diabetic mellitus. Biochem Biophys Res Commun 1969; 36: 838-45. http://dx.doi.org/10.1016/0006-291X(69)90685-8

[10] Trivelli LA, Ranney HM, Lai HT. Hemoglobin components in patients with diabetes mellitus. N Eng J Med 1971; 284: 353-7. http://dx.doi.org/10.1056/NEJM197102182840703

[11] National Glycohemoglobin Standardization Program. Background. http://www.ngsp.org/bground.asp [Accessed on April 24, 2013].

[12] Jeppsson JO, Kobold U, Barr J, Finke A, Hoelzel W, Hoshino T, *et al*. Approved IFCC reference method for the measurement of HbA1c in human blood. Clin Chem Lab Med 2002; 40: 78-89. http://dx.doi.org/10.1515/CCLM.2002.016

[13] Finke A, Kobold U, Hoelzel W, Weycamp C, Jeppsson JO, Miedema K. Preparation of a candidate primary reference material for the international standardisation of HbA1c determinations. Clin Chem Lab Med 1998; 36: 299-308. http://dx.doi.org/10.1515/CCLM.1998.051

[14] Geistanger A, Arends S, Berding C, Hoshino T, Jeppsson JO, Little R, *et al*. On behalf of the IFCC Working Group on Standardization of HbA1c: Statistical methods for monitoring the relationship between the IFCC reference measurement procedure for hemoglobin A1c and the designated comparison methods in the United States, Japan and Sweden. Clin Chem 2008; 54: 1379-85. http://dx.doi.org/10.1373/clinchem.2008.103556

[15] Sacks DB. ADA/EASD/IDF Working Group of the HbA1c Assay. Global harmonization of hemoglobin A1c. Clin. Chem 2005; 51: 681-3. http://dx.doi.org/10.1373/clinchem.2004.047431

[16] Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ, *et al*. Translating the A1c assay into estimated average glucose values. Diabetes Care 2008; 31: 1-6. http://dx.doi.org/10.2337/dc08-0545

[17] Waikato District Health Board (2012). Laboratory test reference guide. http://www.waikatodhb.govt.nz/lab/ [Accessed on Apr 24, 2013]

[18] Vashist SK, Zheng D, Al-Rubeaan K, Luong JH, Sheu, FS. Technology behind commercial devices for blood glucose monitoring in diabetes management: A review. Anal Chim Acta 2011; 703: 124-36. http://dx.doi.org/10.1016/j.aca.2011.07.024

[19] Little RR, Lenters-Westra E, Rohlfing CL, Slingerland R. Point-of-Care Assays for Hemoglobin A1c: Is Performance Adequate? Clin Chem 2011; 57: 1333-4. http://dx.doi.org/10.1373/clinchem.2011.165019

[20] Leca V, Ibrahim Z, Lombard-Pontou E, Maraninchi M, Guieu R, Portugal H, *et al*. Point-of-Care Measurements of HbA1c: Simplicity Does Not Mean Laxity With Controls. Diabetes Care 2012; 35: e85. http://dx.doi.org/10.2337/dc12-0751

[21] Lenters-Westra E, Slingerland RJ. Six of eight hemoglobin A1c point-of-care instruments do not meet the general

accepted analytical performance criteria. Clin Chem 2010; 56: 44-52.
http://dx.doi.org/10.1373/clinchem.2009.130641

[22] Timar B, Albai O. The relationship between hemoglobin A1c and chronic complications in diabetes mellitus: Rom J Diabetes Nutr Metab Dis 2012; 19: 115-22.

Received on 25-04-2013 Accepted on 06-05-2013 Published on 07-05-2013

http://dx.doi.org/10.6000/1927-5129.2013.09.43