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Translating the HemoglobinA$_{1c}$ Assay into Estimated Average Glucose Values-A New Term to Replace HbA$_{1c}$

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Abstract

Glycated Hb (Hb A$_{1c}$) has been accepted as the gold standard measurement for the assessment of chronic hyperglycaemia for nearly three decades. There are thirty different laboratory methods available to measure glycated hemoglobin.

After three decades from using Hb A$_{1c}$, new researches and trials were conducted to find out the relationship between average blood glucose and glycatedhaemoglobin, and a linear regression equation was developedto measure average blood glucose from Hb A$_{1c}$.

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), they recommended the useof a new unit, i.e. mmol Hb A$_{1c}$/mol of total haemoglobin instead of the percentage.

Meanwhile byusing theequation can calculate the average blood glucose from glycated haemoglobin in mmol/mol.

This average blood glucose will be reported as "eAG" (estimated average glucose) and it will be used to monitor glucose control as eGFR (estimated glomerular filtration rate) is used to monitor renal function in chronic kidney disease patients.

Keywords: Estimated average glucose; eAG; HbA$_{1c}$; Glycated Hb; International Federation of Clinical Chemistry (IFCC)

Introduction

Standardization of Glycated Haemoglobin Hb A$_{1c}$ measurement: In the 1980s and 1990s an important issue that concerned Hb A$_{1c}$ measurement was the lack of standardization of the assay, and this meant that different analysers could have widely differing reference intervals and yield varying results with patient samples[1].Standardization of HbA$_{1c}$measurement has been proposed in different countries to ensure accuracy in HbA$_{1c}$ results [2].

Glycated Hb has been accepted as the gold standard measurement for the assessment of chronic hyperglycaemia for nearly three decades. There are thirty different laboratory methods available to measure glycated hemoglobin. Various analytical laboratory methods based on different assays principles, from ion-exchange chromatography to immunoassay and electrophoresis have been used to measure glycated hemoglobin. Such a lack of standardization resulted in wide variability and debates within results (4.0% to 8.1%) on the same sample making it difficult to compare patient's results among laboratories [3].

This disparity has always been a source of anxiety among health care providers. It becomes even more important in this age of heavy economical migration, when people travel long distances and take their native record with them. Therefore, having the same method and unit to measure Hb A$_{1c}$ is very critical need.

In 2007, the IFCC recommended that Hb A$_{1c}$results can be expressed as mmolHbA$_{1c}$ instead of Hb A$_{1c}$ percentage. Patients

using mmol/l or mg/dl for self-monitoring of day-to-day glucose control find it difficult to understand when their doctors discussed hemoglobin levels in percentages. To eliminate confusion and streamline these discrepancies, a consensus statementon the worldwide standardization of HbA_{1c} measurement was adopted in May 2007 by the ADA, European Association for the Study of DiabetesEASD, IDF and IFCC. It states that new IFCC reference system is the only valid anchor for implementing the standardization of the measurement of Hb A_{1c} [4].

Since 1stJune 2009, Hb A_{1c} results in the UK have been standardized to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) which will allow global comparison of results, with the equivalent normal non-diabetic range of IFCC-Hb A_{1c} being 20-42 mmol/mol.

It was also resolved that if the on-going "average plasma glucose study" was concluded successfully (i.e. confirmed the relationship between average blood glucose and Hb A_{1c}) then the $A_{1c.}$ Derived Average Glucose Equivalent would also be reported as an interpretation of Hb A_{1c} results[4].

Assays for Hb A_{1c} use technologies based on either charge differences high performance liquid chromatography (HPLC) or structure (boronate affinity or immunoassay combined with general chemistry) and newly techniques based on combined immunoassay and general chemistry[5].

In past decades, the trials such as DCCT (Diabetes Control and Complications Trial) and UKPDS (UK Prospective Diabetes Study) considered Hb A_{1c}as the gold standard of diabetes care [2,6,7].

Furthermore, the programs such as NGSP (National Glycohemoglobin Standardization Program) and associations such as AACC (American Association for Clinical Chemistry) (Kahn & Fonseca, 2004)[8] have worked on standardization of Hb A_{1c}values leading to present methods in measurement of Hb A_{1c}. Recently, NGSP certifies rapid Hb A_{1c}assays have become available, allowing office and home testing[7].

Switch to IFCC units

After three decades from using Hb $A_{1c.}$ new researches and trials were conducted to find out the relationship between average blood glucose and glycated haemoglobin, and a linear regression equation was developed to measure average blood glucose from Hb $A_{1c.}$

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), they recommended the use of a new unit, i.e. mmolHb A_{1c} /mol of total haemoglobin instead of the percentage [4].Meanwhile by using the equation can calculate the average blood glucose from glycated haemoglobin in mmol/mol.

This average blood glucose will be reported as "eAG" (estimated average glucose) and it will be used to monitor glucose control as eGFR (estimated glomerular filtration rate) is used to monitor renal function in chronic kidney disease patients. The A_{1c} -derived average glucose study was conducted in 10 different locations in North America, Europe, and Africa. The goal of the study was to report glycated haemoglobin results not in the usual Hb A_{1c} percentage format but as A_{1c} derived averages in the same units used in self-monitoring, (i.e., mg/dl or mmol/l). The study concluded that the estimated average glucose (eAG) can now be calculated from Hb A_{1c} using a linear regression equation[8,9].

The American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD) and International Diabetes Federation (IDF) have agreed that, in the future, HbA_{1c} is to be reported in the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units[10].IFCC reporting was introduced in Europe except for the UK in 2003;[11]the UK carried out dual reporting from 1 June 2009 [12]until 1 October 2011**(Table 1-5)**.

Conversion between DCCT and IFCC is by the following equation [12].

$$\text{IFCC HBA1c}\ \frac{\text{mmol}}{\text{mol}} = [\text{DCCT HBA1c}\,(\%) - 2.14] \times 10.929$$

DCCT- Hb A_{1c} (%)	IFCC- Hb A_{1c} (mmol/mol)
3.1	10
4	20
4.9	30
5.8	40
6	42
6.3	45
6.5	48
6.7	50
7	53
7.2	55
7.5	59
7.6	60
8	64
8.1	65
8.6	70
9	75
9.5	80
10.4	90
11.3	100

Table 1: Comparing DCCT- Hb A1c and IFCC- Hb A_{1c} Results.

The approximate mapping between HbA_{1c} values given

in DCCT percentage (%) and eAG (estimated average glucose) measurements is given by the following equation:[9].

$$eAG(mg/dl) = 28.7 \times A_{1c} - 46.7$$

$$eAG(mmol/l) = 1.59 \times A_{1c} - 2.59$$

Data in parentheses are 95% confidence intervals

HbA1c %	mmol/ mol	mmol/L	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)

Table 2: Show HbA_{1c} % corresponded to different laboratory values.

NGSP	IFCC	eAG	eAG
HbA1c (%)	HbA1c (mmol/mol)	(mg/dL)	(mmol/l)
4	20	68	3.8
5	31	97	5.4
6	42	126	7
7	53	154	8.6
8	64	183	10.2
9	75	212	11.8
10	86	240	13.4
11	97	269	14.9
12	108	298	16.5

Table 3: Show mapping between HbA_{1c} values given in DCCT percentage (%) and eAG (estimated average glucose) measurements.

mmol/mol	NGSP
40	5.8
41	5.9
42	6
43	6.1
44	6.2
45	6.3
46	6.4
47	6.5 *
48 *	6.5
49	6.6
50	6.7
51	6.8
52	6.9
53	7
54	7.1
55	7.2
56	7.3

Measure in IFCC, convert to NGSP

% = (mmol/mol+23.5)/10.93

2 x 6.5%
(47 and 48 both become 6.5)

Also occurs at: 5.4 (35 & 36)
7.5 (58,59), 8.6 (69,70)

Table 4: Show Conversion from IFCC into NGSP [9].

% NGSP	mmol/mol
6	42
6.1	43
6.2	44
6.3	45
6.4	46
6.5	48
6.6	49
6.7	50
6.8	51
6.9	52
7	53
7.1	54
7.2	55
7.3	56
7.4	57
7.5	58
7.6	60

Measure in NGSP, convert to IFCC

mmol/mol = 10.93 x % - 23.5

"missing" 47 mmol/mol

Also missing:
35, 59, 72 and 83 mmol/mol

Table 5: Show Conversion from NGSP into IFCC [9].

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