Calicut Medical Journal

Calicut Medical Journal 2009; 7(1): e3

Review Article:

HbA1c and Average Blood glucose

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Abstract:

HbA1c assay is the most widely accepted and reliable marker of chronic hyperglycemia as of today. Estimated average Glucose (eAG) level is derived from HbA1c by regression formula based on DCCT data. Self Monitoring of Blood Glucose (SMBG) is also now in vogue among diabetics. Comparisons are often done between average blood glucose (ABG) obtained through SMBG and eAG derived from HbA1c. It has been found recently that eAG is not a substitute for ABG derived from SMBG. Hence, a correction has been suggested in HbA1c derived eAG, based on a large clinical trial which correlates better with SMBG derived ABG.

Key Words: glycated haemoglobin, average blood glucose, self-monitoring blood glucose

Introduction

HbA1C assay is considered as a reliable and precise marker of assessing the status of diabetic control in patients. It has been popular for more than two decades for blood glucose monitoring. Landmark clinical trials have proved the merits of A1C monitoring for prevention of primary and secondary diabetic complications[1]. The positive correlation of A1C monitoring with diabetic complications shown in DCCT and UKPDS studies has made it a gold standard for monitoring therapeutic goal in diabetic. It helps in modifying the approach to the treatment of DM, and is a convincing tool to explain the importance of glycemic control in prevention of major DM complications.

Disadvantages of assessing HbA1C:

There are many factors that cause variation in A1C results. It does not reflect patterns of glycemic fluctuations, the effects of individual foods or exercise, or the immediate response to changes in therapy. Factors affecting A1C like erythrocyte turnover rate cause variation in results. Conditions that shorten erythrocyte life span, such as haemolytic anaemia or hypersplenism will decrease A1C. Conversely, diseases like aplastic anaemias, which results in aged red blood cells being in circulation associated with lack of new reticulocytes entering the pool, will cause A1C to progressively rise.[2]
Chemically modified haemoglobin, such as carbamylated haemoglobin associated with uraemia and acetylated haemoglobin formed after ingestion of large doses of salicylates, can falsely increase values.[3]
Kidney disease, liver disease, hemoglobinopathies, and recovery from blood loss will all decrease A1C. Vitamins C and E have been reported to lower A1C measurements, possibly by inhibiting glycation.[4, 5] Lower A1C levels are found in diabetic and nondiabetic pregnant women, probably due both to lower fasting blood glucose and a shortened erythrocyte lifespan.[6] Iron-deficiency anaemia, has been associated with increased A1C.[7]
There is also some evidence of wide fluctuations in A1C between individuals

that are unrelated to glycemic status, suggesting that there are “low glycators” and “high glycators”. [8] Different laboratories and methods used yield different A1C values.

Many studies have shown that A1C is an index of average blood glucose over the preceding few weeks to months. A1C truly does not reflect glycemic control over last three months as claimed. Rather, it is weighted to more recent weeks. The average glycemia during the month preceding the A1C measurement contributes 50% of the result, during the 30-60 days prior to the A1C measurement contributes another 25%, and during the 60-120 days prior to the measurement contributes the final 25%[9]

The fasting blood glucose as well as post meal glucose excursions contribute to HbA1c levels. Post meal blood glucose contributes significantly when A1C is <7.5%. On the other hand, fasting blood glucose contributes more when A1C is >7.5%.[10] HbA1C, though a valuable parameter, is being expressed as percentage and patients and clinicians may perceive small changes as unimportant although they are linked to large health effects. The aforementioned reasons preclude the use of A1C per se for diagnosis of DM.

So converting HbA1C to estimated average glucose (eAG) expressed in mmol/l or mg/dl will help in better understanding of the analytic changes. Other advantage of average blood glucose as seen in DCCT was that it was a predictor of the macro vascular complications of type 1 diabetes than HbA1c.[11]

HbA1C derived Average blood glucose:

Currently average blood glucose value (mg/dl or mmol/l) is derived from A1C report by a given formula based on DCCT data (average blood glucose (mg/dl) = (30.9 x HbA1C (%) – 60.6)[1]. However this A1C derived average blood glucose does not always correlate with clinical situation, it overestimates blood glucose levels. When a person achieves near normal glycemia as reflected by A1c value < 6% (eAG<135mg/dl), he is more likely to develop episodes of hypoglycaemia. This was observed in DCCT trial also.[12]

Recently International Federation of Clinical Chemistry (IFCC) has developed a new calibration standard that gives approx. 1.5-2.0% lower values. Existing A1C assay represents mixture of multiple glycated haemoglobins (young less glycated and old erythrocytes). Instead of that IFCC has suggested measurement of one standard, only A1C measurement, to be expressed in mmol / mol [13]. The advantage of the new value is that it reflects the actual blood glucose values but it has some disadvantages also. It is costly and needs re-education to patients and clinicians to avoid confusion.

The relationship between A1C and blood glucose is complex. On average, A1C of 6% corresponds to mean blood glucose of 135 mg/dl. For every increase in A1C of 1%, mean blood glucose increases by 35 mg/dl, Having lower average glucose at the same A1C may help explain why intensive DCCT treatment had increased incidence of hypoglycaemia and decreased microvascular complications compared with conventional treatment.[14] Earlier few studies which tried to correlate A1C to average blood glucose (e.g. Svendsen et al 1982, Nathan et al 1983), suffered from relatively infrequent monitoring and small number of patients. DCCT has many shortcomings including small study population, homogenous cohort, infrequent measuring of capillary glucose and absence continuous blood glucose estimation. These infrequent

glucose concentrations were not enough to compute a true 'average'. Therefore despite our confidence in the 'meaning' of A1C assay according to DCCT the relationship between A1C and average glucose is not well established. (Table 1)

Increasing awareness, frequent self-monitoring of blood glucose (SMBG) and availability of better, patient-friendly monitoring equipments that provide average blood glucose measures, has helped patient reach their glycemic control better. However, no formula-derived parameter can be better than real time SMBG derived average blood glucose, as reports are in same units as the patients' self monitoring of daily glycemia rather than as percent A1C.[15] An alternate way to overcome this is to establish an exact relationship of the new results to average blood glucose. With a new reference range, new targets, and a new name, reporting chronic glycemia in same units as the patients' self monitoring of daily glycemia rather than as percent A1C, will be advantageous and will give a better understanding of glycemic control.[16]

In order to do this a reliable regression model is required. An international study was needed to establish the relationship between A1c- average glucose across diabetes type, races, and ethnicities, where a confirmed mathematical relationship can be reported in the same unit as patients' self monitoring of daily glycemia.

On account of this correction, an international, multi-centric trial (A1c Derived Average Glucose (ADAG) study) with larger study population, different ethnic groups and heterogeneous patient groups (Type 1 DM, type 2 DM and non-diabetic) were initiated and completed recently.[17] The patients were subjected to frequent capillary blood glucose and continuous blood glucose estimations more frequently to establish the exact relationship between A1C and average blood glucose value This study showed a simple linear relationship between A1c level and average blood glucose with 90% of the estimated average glucose falling with in + 15% range of regression line. Based on these findings, a new regression equation was derived, i.e. $eAG_{(mg/dl)} = 28.7 \times A1C - 46.7$. The estimated average blood glucose value will be slightly lower than the present calculated value. This may explain why earlier patients with near normal HbA1C reported frequent hypoglycaemias.

conclusion

To conclude, calculating HbA1C has its own disadvantages. Currently used HbA1C derived average blood glucose according to DCCT trial overestimates blood glucose levels. The new formula by David M Nathan takes into consideration the mean value of multiple self-monitored blood glucose and hence is more representative of the actual mean blood glucose and claims a simple linear relationship between mean glucose and A1C levels. The reporting of the measured A1C as eAG, may now make a meaningful difference in setting up of treatment goals or adjusting treatment of diabetes mellitus.

Table 1

HbA1c	Existing average glucose according to A1c mg/dl (mmol/L) (DCCT)	Proposed A1c derived Average Glucose mg/dl (mmol/L) (ADAG)
5	100 (5.6)	96 (5.3)
6	135 (7.5)	125 (6.9)
7	170 (9.4)	153 (8.6)
8	205 (11.4)	184 (10.2)
9	240 (13.3)	214 (11.9)
10	275 (15.3)	243 (13.5)
11	310 (17.2)	273 (15.2)
12	345 (19.2)	303 (16.5)

Existing and proposed A1C derived average blood glucose values

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