Clinical usefulness of glycated albumin

Arun Kumar D[1], Sridevi Anantharaman[2], Swaminathan S[3]

[1]Senior Lab Technologist, Department of Biochemistry, Apollo Speciality Hospitals, Vanagaram, Chennai - 600 095
[2]Consultant, Department of General Medicine, Apollo Speciality Hospitals, Vanagaram, Chennai - 600 095
[3]Senior Consultant & Head, Department of Biochemistry, Apollo Speciality Hospitals, Vanagaram, Chennai - 600 095, India

ABSTRACT

Glycated albumin refers to albumin to which glucose has bonded. The amount of glycated albumin decrease or increase as and when plasma glucose changes. Glycated albumin is measured when diabetes therapy is initiated to determinethe medication regimens and doses to assess over all efficacy of therapy. Currently endocrinologists use only HbA1C to monitor diabetic control over the preceding 2-3 months. However HbA1C does not accurately reflect the actual state of glycemic control in patients with anemia, variant hemoglobins and also in chronic kidney diseases. Glycated albumin accurately reflects changes in plasma glucose during a short term of 2-3 weeks and will be useful to monitor changes in glucose level after 2 hours of meal and it correlates well with such changes. Fructosamine measures total concentration of glycated serum proteins including albumin which can fluctuate due to acute or systemic illness or chronic liver disease. Glycated albumin measures the ratio of GA to total albumin and hence minimizes interference due to GA and Non-GA. This article enumerates the research finding during the last decade on the clinical usefulness of GA and recommends its use as a routine glycemic control marker to assess short term changes in plasma glucose.

Keywords: GA, HbA1C, HD, T2DM, PG

Since glycation among various proteins is increased in diabetic patients compared to non-diabetic subjects, glycated protein can be used as a glycemic control indicator. Currently, among various glycated proteins, HbA1c is used as the gold standard of glycemic control. However, HbA1c does not accurately reflect the actual status of glycemic control in some conditions with rapid changes in glycemic control and in patients with anemia (hemolytic anemia, iron deficiency anemia, etc.) and variant hemoglobin. In comparison, glycated albumin (GA) more accurately reflects changes in plasma glucose during the short term and postprandial plasma glucose. GA also reflects glycemic control in patients with hematologic disorders; However GA does not reflect glycemic control in patients with disorder of albumin metabolism. GA is a glycemic control indicator which overcomes most of the disadvantages of HbA1c, and could be therefore expected to replace HbA1c as the standard glycemic control indicator in the near future. However, it is necessary to accumulate more evidences from large research studies on the effective directions for measuring GA [1].

HbA1c does not accurately reflect the actual status of glycemic control in some conditions where plasma glucose changes during short term, and in patients who have diseases such as anemia and variant hemoglobin. In comparison, another index of glycemic control, GA, more accurately reflects changes in plasma glucose during short term and also postprandial plasma glucose [2]. The glycation of albumin is ten times faster than glycation of Hemoglobin, so GA is likely to reflect the variation in blood glucose and postprandial hyperglycemia in combination with HbA1c and its value. 1, 5-anhydroglucitol (AG) is a marker of glycemia-induced glycosuria, since reabsorption of filtered 1, 5-AG in the proximal tubule is competitively inhibited by glucose. It is an indicator to identify rapid changes in hyperglycemia. Understanding the characteristics of the indicators above, it is important to use them suitably for each diabetes subject and to recognize glycemic control

Corresponding Author Address: Dr. S. Swaminathan, Senior Consultant & Head, Department of Biochemistry, Apollo Specialty Hospitals, Vanagaram, Chennai – 600 095, Tamil Nadu, India; E-mail: glorynathan@gmail.com

conditions more accurately [3]. While HbA1c reflects the long-term glycemic control state of preceding 2-3 months, it does not accurately reflect glycemic control in the clinical state in which glycemic control improves or deteriorates in the short-term. It is also known that HbA1c in patients with hematological disorders such as anemia and variant hemoglobin shows an abnormal value. In addition, HbA1c mainly reflects the mean plasma glucose but does not reflect the postprandial plasma glucose [4].

In current clinical practice, long-term glycemic control is assessed by quarterly measurements of HbA1c, since the degree of hemoglobin glycosylation depends not only on the level of glycemic control, but also on the lifespan of red blood cells, patients with hemoglobin disorders or anemia of any cause may have erroneous HbA1c levels, and consequently receive inappropriate treatment. Patients with chronic kidney disease (CKD) often suffer from various types of anemia, and consequently, they are frequently treated with iron and/or erythropoietin therapy or frequent blood transfusion. Thus, serum GA is a potentially useful glycemic index in diabetic patients with CKD, since it is not influenced by anemia and associated treatments. GA may also reflect the status of blood glucose more rapidly (2-3 weeks) than HbA1c (2-3 months), and is beneficial in those with wide variations in blood glucose or at higher risk for hypoglycemia [5].

Categorization of glycemic control into arbitrary quartiles by GA level led to better glycemic control in a significantly higher proportion of Hemo Dialysis (HD) patients with diabetes than those assessed by HA1c. Multiple regression analysis demonstrated that hemoglobin in addition to plasma glucose (PG) emerged as an independent factor associated with HbA1c in HD patients with diabetes, while PG, body mass index (BMI) and albumin were an independent factor associated with GA [6]. GA to HbA1c ratio is known to be inversely related with BMI and insulin secretory capacity. However, the reasons for this association remain unknown. It was found that HOMA-β or HOMA-IR indirectly influences GA/HbA1c in T2D and prediabetes group through affecting fasting and postprandial glucose level. The relationship between GA/HbA1c and BMI is due to the direct effect of BMI on GA/HbA1c in NGT group, while in Type 2 Diabetes Mellitus (T2DM) and prediabetes groups and this association is mostly as a result of BMI influencing blood glucose through insulin resistance or secretion [7].

The GA/HbA1c ratio was ≥ 3.0 in all pregnancy fulminant type 1 diabetes mellitus (P-FT1DM)

patients, whereas it was < 3.0 in 8 of 10 P-T2DM patients and all NP-T2DM patients. The GA/HbA1c ratio was also elevated in P-FT1DM patients at the diagnosis compared with T2DM with or without pregnancy [8].GA reflects shorter term glycemic control state than HbA1c. GA is useful for early detection of deterioration of glycemic control state after discharge from educational admission [9].

GA is recognized as a reliable marker for short-term glycemic monitoring in diabetic patients. Serum GA was strongly correlated with HbA1c in both groups. Fasting plasma glucose and postprandial glucose were correlated with GA in unstably maintained HbA1c group, whereas they were correlated with HbA1c in stably maintained HbA1c group. The GA/HbA1c ratio tended to increase as HbA1c increased. Postprandial glucose and BMI affected the GA/HbA1c ratio [10]. A positive correlation was determined for fructosamine and GA in both normal and diabetic cats, suggesting that serum GA may be a useful glycemic control indicator that could substitute for fructosamine to monitor glycemic control in diabetic cats [11].

GA could be a better marker for glycemic control than HbA1c in diabetic patients, especially for evaluating glycemic excursion, which is considered to be a major cause of diabetic angiopathy [12]. Although unknown influences on GA or HbA1c may exist, GA may be a useful marker for monitoring short-term variations of glycemic control during treatment of diabetic patients [13]. GA and HbA1c levels were found to be correlated to one another. Fasting plasma glucose (FPG) was significantly correlated with GA and HbA1c. BMI showed a significant negative correlation with GA levels, whereas there was no correlation of BMI with HbA1c levels. Multivariate regression analysis revealed that only FPG was positively correlated with HbA1c, while FPG was positively and BMI was negatively correlated with GA. Only BMI was negatively correlated with the ratio of GA to HbA1c. These results clearly demonstrate that GA levels are negatively influenced by BMI in diabetic patients [14].

GA/HbA1c ratio could be an useful marker for differential diagnosis in patients with abnormal serum ALT level in a clinical setting [15]. GA could be used to determine the glycemic control due to short half-life than erythrocytes which makes it an alternate reliable disease marker in diabetes [16]. GA reacts with albumin ten times more rapidly than hemoglobin with glucose and has shorter half-life which makes it more reliable for indicating glycemic states. The Bovine serum

albumin (BSA) aggregation was reviewed in terms of structural and biological impacts of glycation on the protein followed by reporting documents which indicate possibility of GA to be used as specific marker for diabetes. Some of the studies related to the models of GA emphasis on In vitro studies. It is interesting to note the relationship found between in vitro glycation experiments and the propensity of proteins to form amyloid structures, a point that could be further explored as to its significance in hyperglycemic states [17].

Several studies have suggested the potential of GA as an intermediate-term glycation index in covering the short-term effect of treatment. Furthermore, its role as a pathogenic protein affecting the worsening of diabetes and occurrence of diabetic complications is receiving attention as well [18]. GA/HbA1c showed better correlations with two variables of liver function viz ALT percentage and cholinesterase value than did fibrosis index based on the four factors (FIB-4) and with all four variables than did the aspartate aminotransferase to platelet ratio index (APRI). Hence GA/HbA1c ratio is associated with the degree of liver fibrosis in HBV-positive patients [19].

Among healthy individuals, GA levels were roughly estimated at approximately three fold higher than HbA1C levels. While measured HbA1c levels in patients with CLD were generally lower than estimated HbA1c levels, GA/3 values were generally higher than estimated HbA1c levels. Such discrepancies linearty increased in accordance with a decrease in ChE levels. On the other hand, in CLD-HbA1C levels were highly correlated with estimated HbA1c levels while no significant correlation between CLD-HbA1c and ChE was noted. Therefore CLD-HbA1c has been found to be a superior chronic glycemic control marker than HbA1c or GA in diabetic patients with CLD[20] The presence of platelets reduced advanced glycation end products (AGEs)-induced endothelial cell responses associated with CVD progression and the presence of endothelial cells reduced platelet adhesion and activation responses, as compared with individual exposures. In general, the presence of irreversibly GA promoted CVD development to a greater extent than reversible GA. This suggests that under diabetic conditions, platelets and endothelial cells can negatively feedback on each other, likely via enhanced adhesion, to elicit a reduced response associated with CVD progression [21]

GA is considered a more reliable marker than HbA1c for monitoring glycemic control in diabetic hemodialysis patients. GA predicted the risk of all-cause and cardiovascular mortality in diabetic hemodialysis patients, suggesting that GA ≤ 25% is an appropriate target for improving survival in diabetic hemodialysis patients [22]. Albumin could be the best model of glycation for monitoring diabetic pathophysiology and should be valuable to know if glycation of albumin could contribute to variability in drugs response during diabetes [23].The reference intervals of GA and HbA1c in the healthy pregnant women were 11.5-15.7% and 4.5-5.7%, respectively. GA levels were found to be lower than HbA1c levels in pregnant women with proteinuria. In the obese group, GA levels were lower than those of the control group with BMI < 25 and HbA1c levels were higher than those of the control group.GA appears to be a useful marker for pregnant women, since it can be measured easily and changes rapidly and markedly[24].

Stepwise multivariate regression analysis identified FPG and age as positively associated, and BMI and smoking as negatively associated with serum GA levels and serum GA levels were significantly lower in smokers than in nonsmokers. Smoking was identified as a significant negative explanatory variable for serum GA levels. These findings suggest that the inflammation-induced acceleration of albumin metabolism may be involved in the mechanism by which smoking is associated with serum GA levels [25]. GA significantly correlated to all continuous glucose monitoring (CGM) parameters and standard deviation of glucose (SD) significantly correlated to GA in multiple regression analyses. These results suggest that GA may be a different marker from HbA1c for diabetic complications, because GA, but not HbA1c may reflect not only short-term average glucose but also fluctuation of glucose [26].

Although no intergroup differences were observed for HbA1c serum GA was significantly higher among patients with hypothyroidism than controls and significantly lower among patients with thyrotoxicosis. Serum GA had a significant positive correlation with serum TSH and significant inverse correlations with free T3 and free T4. Cautions are necessary when evaluating serum GA levels in patients with thyroid dysfunction [27]. The changes in GA levels in relation to the blood glucose control in the dialysis patients matched those in non-dialysis patients. HbAlc levels for diabetics with ESRD were lower than indicated by their blood glucose control. When assessing blood glucose control based solely on HbAlc, erroneous results may be obtained. In such cases, GA may be used instead of HbAlc [28].

GA concentrations appear to be stable even in the presence of high intra-day fluctuations in mean blood glucose concentrations. Simulation of a

decrease in mean blood glucose concentrations resulted in a faster change in GA compared to HbA1c. GA also provided a time to 90 % power of the effect of a hypothetical antidiabetic drug that was 16 days shorter than when using HbA1c. These results indicate that GA could be used as alternative marker to assess blood glucose control in diabetic patients with CKD and also to follow an individual patient over time [29]. Dialysis status significantly impacted HbA1c levels without a significant effect on GA. In diabetic hemodialysis patients, HbA1c levels significantly underestimate glycemic control while those of GA more accurately reflect this control [30].

Although GA level could be a better indicator of glycemic control than HbA1c level in patients on HD who have diabetes and anuria, this conclusion might not be applicable to patients with massive proteinuria or to those on peritoneal dialysis. Further studies are required to confirm the target GA level that is necessary to ensure a good prognosis for patients with diabetes who are on HD because no clear consensus has yet been reached. In addition, more data are needed to determine at which stage of kidney disease measurement of GA becomes preferable to assessment of HbA1c level [31]. In T1DM, the GA concentration is independently associated with the presence of nephropathy. Abrogating the biologic effects of increased GA has novel therapeutic potential in the management of renal complications in diabetes [32]. GA provides a significantly better measure to estimate glycemic control in HD patients with diabetes and that the assessment of HbA1c in these patients might lead to underestimation likely as a result of the increasing proportion of young erythrocyte by the use of erythropoietin [33].

Conclusion

This review article presents cumulative data from the research field during the last decade. The contents of this article highlights the merits and demerits of the three glycemic control markers viz HbA1c, fructosamine and GA. While HbA1c is still considered the gold standard for monitoring a diabetic patient's glycemic control during the proceeding's 2-3 months, but does not pin point changes in glycemic control within a short period of 2-3 weeks. Among HbA1c and GA ,GA may serve not only as a short term glycemic control marker but also be useful to decide the type of antidiabetic drugs to be given when initiating treatment for a newly diagnosed T2 DM based on its level 2-to 3 weeks after initiating treatment. The contents of this paper will certainly make awareness among clinicians to make use of GA as a routine diabetic control marker to decide about the type of antidiabetic drug to be given. Once clinical laboratories start measuring GA as routine test, diagnostic companies manufacturing kits for GA will work out the cost of such kits to make it affordable to clinical laboratories. It is also important to gather more information/evidence from large scale clinical trial studies on the effective directions for measuring GA as a routine diabetic control marker.

Conflicts of Interest: None

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