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Research Article

Utility Of Glycated Albumin In Diagnosis Of Type 2 Diabetes: An Indian Perspective Study (Capitalize each word)

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Abstract

Glycated Albumin (GA) gives an estimate of short-term average glycemic status. It is used on monthly basis to assess glycemic control in diabetics to attain treatment goals and prevent long term complications. Recommendation of Glycated Hemoglobin (HbA1c) for diagnosis of diabetes mellitus has evoked mixed response worldwide. We reviewed a number of published articles to analyze the pros and cons of using both Glycated Hemoglobin (HbA1c) and Glycated albumin (GA) for diagnosis of Diabetes mellitus in India. We observed that HbA1c has some indisputable advantages over fasting plasma glucose estimation for diagnosing diabetes mellitus, a number of biochemical, clinical and economical factors limit its use as single diagnostic agent. Diagnostic methods and laboratories are insufficiently standardized for HbA1c in India. The clinician must consider the overall patient profile in addition to a number of local variations and disorders especially hemoglobinopathies /anemias before accepting an abnormal HbA1c value. Supportive or repeat tests may be required leading to increase in cost and delay in diagnosis. In the present Indian scenario, especially the fragmented unorganized health care sector in suburban areas, GA test can be accepted as an alternative to HbA1c test in diagnose of diabetes mellitus.
Keywords: Glycated Albumin, Glycated Hemoglobin, Diabetes Mellitus, Average Plasma Glucose, Indian Healthcare

1. Introduction

Haemoglobin A1c (HbA1c) has been the mainstay in the determination of glycaemic control in the management of diabetes mellitus (DM) for 30 years, and has been used in many clinical long-term studies[1,2]. The use of diagnostic markers has shown that early diagnosis and treatment also have the potential to prevent diabetic complications and cardiovascular disease. However, HbA1c ceases to be a reliable glycaemic control index if the erythrocyte lifespan has become altered; the HbA1c value is also affected by variant haemoglobins[3].

Glycated albumin (GA) reflects mean glycaemia over approximately 2–3 weeks. Compared with HbA1c, GA is characterised by more rapid and greater changes, and can be used to confirm treatment effects when initiating or changing medications. Glycated albumin can also be used for patients with anaemia or haemoglobinopathies for whom measured HbA1c levels may be inaccurate[4–7]. Recently, a user-friendly, highly accurate, automated enzymatic assay for measuring glycated albumin has been developed[8] and approved for clinical use in Japan. Studies using self-monitoring of blood glucose and continuous glucose monitoring have found glycated albumin levels to better reflect glycaemic fluctuation[9,10].

Several studies have shown that GA is a more reliable DM monitor and a better marker of glycaemic control than is HbA1c in patients undergoing haemodialysis and in patients with fluctuating and poorly controlled type 2 DM. [11-13] Moreover, serum GA is not affected by factors that affect haemoglobin metabolism. The International Expert Committee (IEC) recently proposed new diagnostic criteria based on measurement of HbA1c[14]. However, little attention has been paid to the utility of GA estimation compared with that of HbA1c in the diagnosis of DM. The GA assay is not widely available and is not standardised; thus, there is only very limited data to suggest that it would be useful as a diagnostic tool[15,16,17].

In this cross-sectional study, our aim was to establish the validity of GA as a measure of glycaemic control and to evaluate its utility as a diagnostic tool for DM in a community-based Indian population.

2. Materials & Methods

Our study enrolled randomly selected residents of in & surroundings of Melmaruvathur (one of the rural area in north-east Chennai, Tamilnadu, India). We randomly selected 1000 residents between September 2011 and May 2013. A total of 845 residents consented to participate in the study (response rate 82.3%). Of the 845 participants, 295 were excluded because they were being treated for DM, anaemia, thyroid disease, liver disease or nephropathy or were aged below 18, leaving 550 participants available for analysis (263 men and 257 women, mean age: 50.2 years, age range 22–76 years). All patients provided written informed consent before participation, and this Doctoral study was approved by the Institutional Ethics Committee (Regd. No. MAPIMS /958/PO/ac/09/CPCSEA) MAPIMS, Melmaruvathur Tamilnadu, India.

Body height, body weight and blood pressure were measured. The body mass index (BMI) calculated for each participant. After an eight-hour overnight fast, each participant had aliquots of whole venous blood, fresh serum and plasma samples (in sodium fluoride (NaF) anticoagulant tubes) taken for measurement of FPG and two hour plasma glucose levels (PG) using a standard 75 g oral glucose tolerance test (OGTT). Other biochemical tests were also performed (urea, creatinine, total protein, albumin, total cholesterol). Blood samples were assayed at the laboratory in The MAPIMS Hospital clinical biochemistry lab, Melmaruvathur.

Blood glucose concentrations were measured using a hexokinase/glucose-6-phosphate dehydrogenase method. Samples for HbA1c analysis were placed in EDTA tubes, kept cold until processing (within six hours) and measured using high performance liquid chromatography (HPLC) in the Bio-Rad variant II (manufacturer's reference range: 4–6%). The HPLC was performed according to the standardised calibration from the National Glycohemoglobin Standardization Program (NGSP)[18]. HbA1c levels were converted to NGSP levels (%). The inter assay coefficients of variation (CVs) were 1.85% and 1.34% for HbA1c at values 5.8% and 9.8%, respectively. Other serum biochemical measurements were measured using standard commercial methods on a Hitachi 7180 Biochemistry Automatic Analyzer (Hitachi Instruments Service, Tokyo, Japan).

GA was measured by an enzymatic method using the Lucica® GA-L enzymatic kit assay (Asahi Kasei Pharma Corp., Tokyo, Japan) (manufacturer's reference range: 8–16%). The inter assay CVs were 2.2% and 1.3% for GA of 16% and 44%, respectively, as determined using control serum samples. The diagnosis of DM was based on the 1999 WHO fasting PG (FPG) and/or oral glucose tolerance test (OGTT) criteria[19], with an FPG ≥ 125mg/dl (≥7.0 mmol/l), and/or 2-h PG of ≥ 200 mg/dl (≥11.1mmol/l) on an OGTT defining the presence of DM.

2.1 Statistical analysis

All data are shown as mean ± SD. For statistical analyses, the unpaired Student's t-test was used to compare groups. To analyse the effects of explanatory variables on GA level, stepwise multivariate regression analysis was performed, with GA as an objective variable; and with age and BMI as explanatory variables. Univariate regression analysis, as well as stepwise multivariate regression analysis, was performed with SAS 9 and SPSS 17.0. Correlation coefficients were calculated by simple regression analysis to analyse the correlations among GA, FPG, 2h-PG and HbA1c. A nominal p value <0.05 was considered statistically significant.

3. Results

No participants had a serum albumin concentration <40 g/l. No significant difference was observed for GA between genders, and mean HbA1c level and FPG were also similar between men and women. The unpaired t test analysis demonstrated a significant positive correlation between age and GA. In this population, the mean BMI was 24.8 kg/m2 in men and 23.1 kg/m2 in women. Adjusted BMI (ABMI) adjusted correlation between age and GA level was not significant (p=0.174).

3.1 Correlation between GA and FPG or HbA1c

There were significant and positive correlations of fasting serum GA with FPG (Figure 1a:r=0.8097, p<0.0001) and HbA1c (Figure 1b: r=0.8976, p<0.0001). Similarly, significant and positive correlations of GA were also found with PG (Figure 1c: r=0.6545, p<0.0001) 2 h after initiation of a 75 g OGTT, which did not differ significantly from that of HbA1c with FPG (r=0.8259, p<0.0001) and 2-h PG (r=0.7142, p<0.0001), based on the lack of significant differences in r-values. Regression analysis showed no correlation between GA and the other biochemistry measurements in our study. Thus, GA correlated better with FPG than with 2h-PG, whereas HbA1c showed similar correlations with both FPG and 2h-PG.

Figure a). Regression analysis of GA & FPG

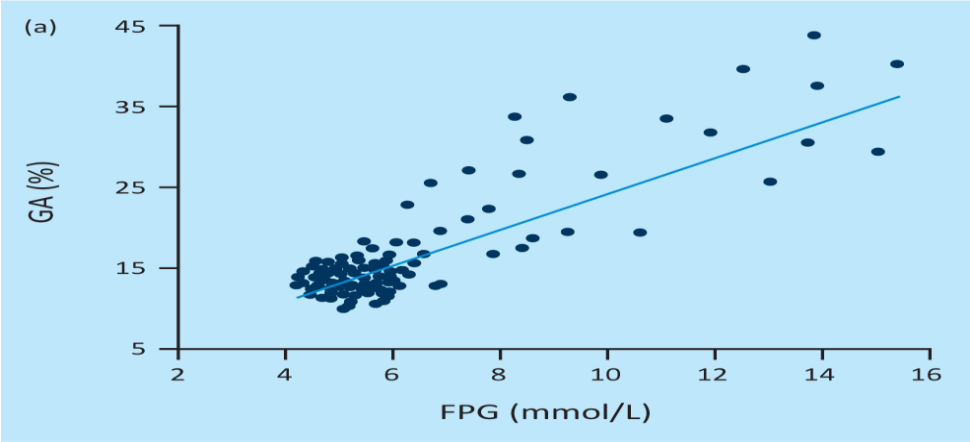


Figure b). Regression analysis between GA &HbA1c

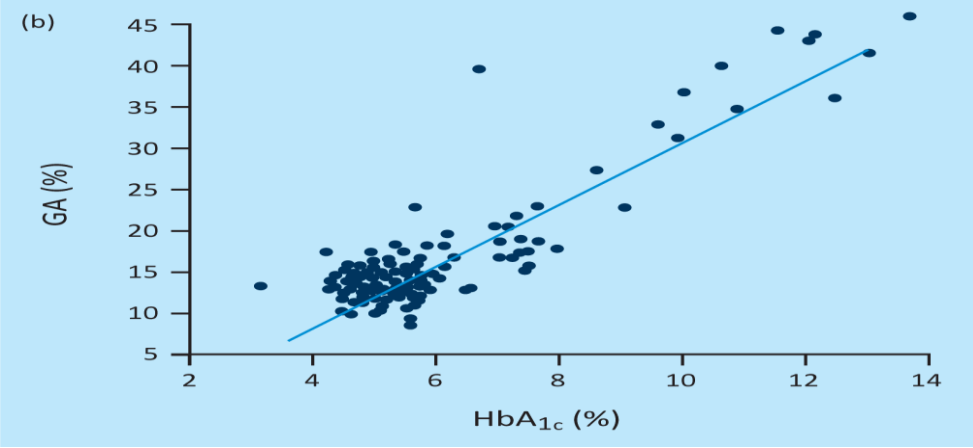
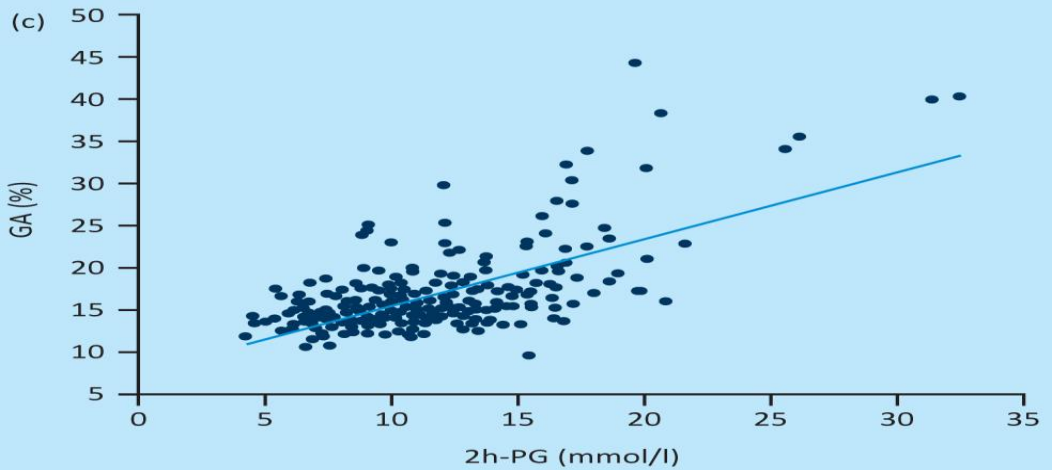


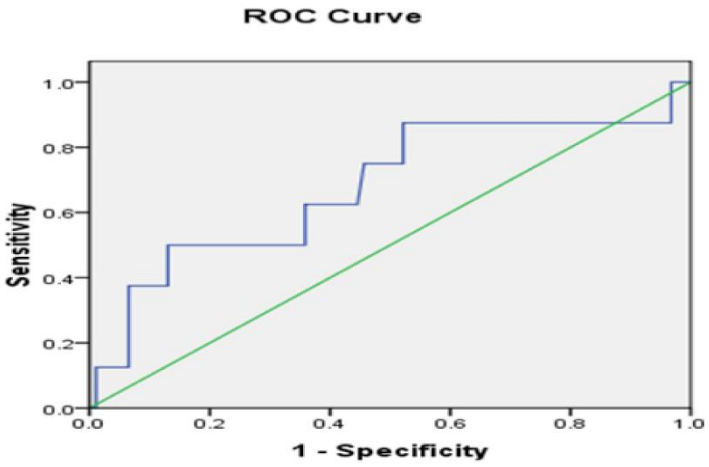
Figure c). Regression analysis between GA & 2 hrs OGTT



3.2 Performance characteristics of GA for undiagnosed DM

Figure 2 shows the ROC (receiver operating curve) analysis for GA predicting undiagnosed DM among 550 individuals. The AUC(area under the curve) of the ROC curve for GA (0.861 (95% confidence interval (CI); 0.787–0.917)) with a cut-off point of 15.7% predicting undiagnosed DM was similar to that for FPG (0.882 (95% CI; 0.812–0.934)) and that of HbA1c (0.861 (95% CI; 0.812– 0.934)). According to the ROC analysis, the cut off level for GA that best predicted DM was 15.7%, with a sensitivity of 73.3% and a specificity of 80.1%.

Figure d). ROC (receiver operating curve) for GA and FPG



4. Discussion

In this cross-sectional study, although age correlated with the GA level as in other studies, this effect was lost when adjusted for BMI (p=0.194). The GA and FPG levels also were not influenced by gender, in contrast to other reports indicating that females have lower FPG levels than do males. Among this Chinese population, the data showed that GA levels were negatively influenced by BMI, confirming the results of other studies[20]. Importantly, we examined the significance of GA as a diagnosis indicator of DM, correlating with FPG PG at the end of a two-hour 75-g OGTT. PG levels and 2h-PG after the initiation of the OGTT correlated with GA no less significantly than with HbA1c. GA was more highly correlated with FPG than with 2h-PG, whereas HbA1c showed similar correlations with both FPG and 2h-PG. Overall, we found highly positive correlations of GA levels with HbA1c (r=0.898) and FPG (r=0.810). Theses correlation coefficients are similar to those reported by previous studies[21]. The ROC analysis showed that a GA level of 15.7% was best for discriminating patients with DM from those without, with a sensitivity of 73.3% and a specificity of 80.3%. The area under the ROC curve was 0.861. These data support the contention that GA is a reasonable marker for the diagnosis of DM in a medical evaluation. Although, in this respect, its performance was similar to the use of HbA1c, there are other advantages that could be gained from the more widespread use of GA measurements. For example, GA has potential advantages over HbA1c in some instances, because GA reflects the mean PG level over the preceding 2–3 weeks[22]. Thus, it might be a better potential monitor of glycaemic control for patients with DM who suffer severe fluctuations in their glucose levels. It can also be used to confirm treatment effects when initiating or changing medication. The Japan Society of Clinical Chemistry (JSCC) has reported its recommended method for GA measurement from serum[23]. However, international standardisation for GA is clearly required if this assay is to become widely used. The Lucica® GA-L enzymatic kit assay that we used in this study has been automated for high throughput analysis, and is more suitable for such analysis than HPLC or other liquid chromatography methods.

Limitations of our study include a relative inadequate sample size. In addition, our study was cross-sectional: in the future, longitudinal studies need to be carried out to investigate whether GA is a potential tool for predicting diabetic complications. In conclusion, GA has the potential to be used as a measure of dysglycaemia for use in future research and clinical practice. Further investigations are needed to determine its worth as a robust monitor of glycaemic control and, thus, as means of diagnosing DM.

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