

Mean Plasma Glucose Level - A Surrogate Marker to Glycated Haemoglobin Level For Assessment of Glycaemic Control

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Abstract

The purpose of present study was to find out a suitable alternative to glycated haemoglobin (HbA1c) for the assessment of glycaemic control in diabetic individuals. For the purpose of the study (HbA1c), fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and random plasma glucose (RPG) levels of 500 individuals were assessed. Mean plasma glucose (MPG) was calculated by using the equation $(FPG + PPG)/2$. On correlation analyses, it was found that correlation of MPG with HbA1c was better than that of FPG, PPG or RPG with HbA1c. Thus MPG seems to be a suitable alternative to HbA1c in the situations where high cost, medical conditions or standardization issues preclude the use of HbA1c assays. We suggest using a cut-off of 145.8 mg/dl for MPG to predict HbA1c $\geq 6.5\%$. For those centers that are estimating HbA1c levels, we suggest eMPG-I (Estimated Mean Plasma Glucose-Indian) study equation $(28.455 \times HbA1c) - 46.78$ for predicting the estimated mean plasma glucose of a patient in mg/dl, as it is easier to converse with the patients in terms of glucose levels.

Key Words

Diabetes, Plasma glucose, HbA1c, Glycaemic control

Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both (1). Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease (2,3). The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India. India currently faces an uncertain future in relation to the potential burden that diabetes may impose upon the

country (4). The most important aspect in the management of diabetes mellitus is glycaemic control. It is a cornerstone in reducing morbidity and mortality of the disease (5). The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels (6).

Control of blood glucose in patients with diabetes can be assessed by several methods. These include assessment of glycosylated haemoglobin (HbA1C), fasting plasma glucose (FPG), and postprandial plasma glucose (PPG) (7). High concentrations of glucose can

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increase the glycation of common proteins such as haemoglobin, forming HbA1c. It is important to note that HbA1c is neither considered dysfunctional nor harmful (8). A1c, which remains the gold standard for assessing glucose homeostasis, is an integration of both fasting and postprandial glucose variations over a 3-month period (9). However, there are a large number of medical conditions that are associated with alterations in the HbA1c values. Haematological conditions such as the presence of haemoglobin variants, iron deficiency, and haemolytic anaemia, the presence of carbamylated haemoglobin in uraemia, a variety of systemic conditions, including certain forms of dyslipidaemia, malignancies, and liver cirrhosis, various medications, and finally, pregnancy are among the factors that influence the HbA1c measurement (10, 11). Also, as a parameter for the overall glycaemic control, HbA1c reveals little about individual daily glucose fluctuations (12). The introduction of other indices of glucose homeostasis in clinical practice such as fructosamine and glycated albumin (GA) may be regarded as an attractive alternative, especially in patients in whom the measurement of HbA1c may be biased or even unreliable (e.g. rapid changes of glucose homeostasis and larger glycaemic excursions, and patients with red blood cell disorders and renal disease). But further studies are needed to definitely establish that GA can complement or even replace conventional measures of glycaemic control such as HbA1c (13). Till date there is no consensus that among fasting, postprandial or random plasma glucose (RPG), which is a better predictor of glycaemic control. Some studies had shown better correlation of FPG with HbA1c (14), while others had suggested PPG to be superior as far as correlation with HbA1c is concerned (15,16). Mean plasma glucose levels (an average of fasting and postprandial glucose levels) can be a better predictor of short-term fluctuations in glucose level. The aim of the present study was to find out the correlation of mean plasma glucose levels with the gold standard of glycaemic control i.e. HbA1c, so as to contribute to better management of glycaemic control in diabetics.

Material and Methods

In this retrospective, observational study, we observed the HbA1c and FPG, PPG or RPG of 500 individuals (250 males and 250 females) who had visited the Central Laboratory of Shri Mahant Indresh Hospital, Dehradun. Estimation of plasma glucose levels was carried out in VITROS 5600 automated analyzer using Glucose oxidase-peroxidase method (17). HbA1c level estimation

was performed using Ion Exchange High Performance Liquid Chromatography system. Quality control was assured in the laboratory by running internal quality control samples, two levels twice daily as well as participation in monthly proficiency testing programs. In addition, we calculated mean plasma glucose (MPG) by using the equation $(FPG + PPG)/2$. The Pearson correlation coefficients between HbA1c and FPG, PPG, RPG and MPG were estimated. A P-value less than 0.05 was considered to indicate statistical significance.

Results

HbA1c, FPG, PPG, RPG and MPG levels of 500 individuals were assessed. We divided the individuals into three groups- Group I - HbA1c <6.5%, Group II- HbA1c 6.5-9%, Group III HbA1c ≥9%. On correlation analyses, it was found that in groups I, II and III FPG, PPG and MPG showed significant positive correlation with HbA1c levels, but correlation of MPG with HbA1c was marginally better. Further, correlation of RPG with HbA1c became significant only at levels Less than 6.5% (*Table 1*). The relationship between HbA1c and MPG is depicted in *Fig. 1*. The scatter plot suggests that there is a linear relationship between HbA1c and MPG. Linear regression analysis yielded the equation $(28.455 \times \text{HbA1c}) - 46.78$ for predicting the mean plasma glucose in mg/dl of a patient.

Receiver-operating characteristic (ROC) curve analysis performed to examine the performance of MPG to predict HbA1c ≥6.5% showed area under curve (AUC) to be 0.915 (95% confidence interval = 0.8785-0.9527). An MPG cut-off value of 145.8 mg/dl predicted an HbA1c less than 6.5%, with a sensitivity of 82.2% and specificity of 89.5% (*Fig. 2*).

Discussion

Diabetes mellitus is a group of complex metabolic disorders with a partial or absolute insufficiency of insulin secretion and with various degrees of insulin resistance. The main aim of therapy in diabetic patients is to control blood glucose levels and to avoid both over treatment and under treatment. Hence it is essential to monitor the effects of treatment on blood glucose levels. Control of blood glucose in patients with diabetes can be assessed by several methods. These include assessment of glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), postprandial plasma glucose (PPG) or random plasma glucose (RPG). Continuous glucose monitoring systems (CGMS) are an emerging technology that allow frequent glucose measurements to monitor glucose trends in real time. Their use as a diagnostic tool is still developing

Table 1. Correlation of HbA1c with FPG, PPG, RPG and MPG in the Various Groups

Investigations		HbA1c		
		Group I	Group II	Group III
Fasting Plasma Glucose (FPG)	r value	0.299	0.442	0.497
	p value	0.0002(S)	0.0001(S)	0.0001(S)
Postprandial Plasma Glucose (PPG)	r value	0.361	0.419	0.420
	p value	0.0001(S)	0.0001(S)	0.0001(S)
Random Plasma Glucose (RPG)	r value	0.0003	0.553	0.391
	p value	0.998 (NS)	0.0001(S)	0.0001(S)
Mean Plasma Glucose (MPG)	r value	0.372	0.477	0.493
	p value	0.0001(S)	0.0001(S)	0.0001(S)

Fig.1 Correlation of HbA1c with Mean Plasma Glucose Levels

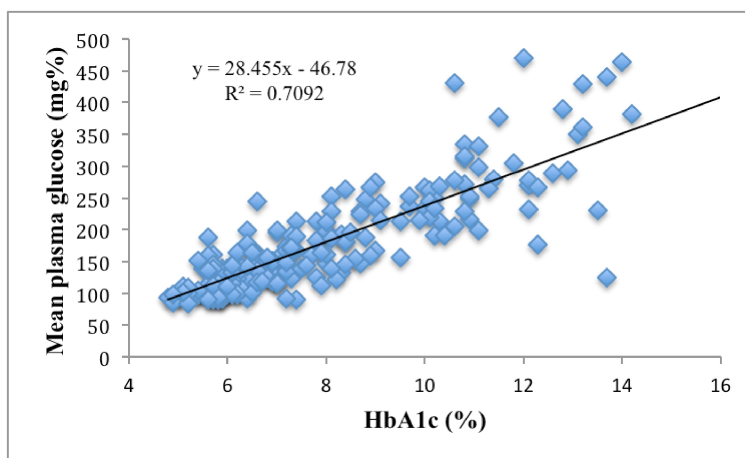
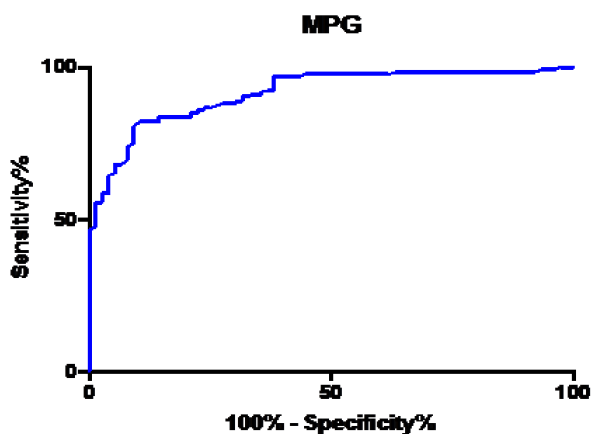


Fig 2. Receiver Operating Characteristic Curve Showing the Predictive Value of MPG for HbA1c 6.5%



and appears to be promising. Combining intermittent self-monitoring glucose system (SMGS) and CGMS combines the benefits of both. (18). But, cost is the deterrent in the use of both SMGS and CGMS, making them unreachable

for an average Indian (19).

The gold standard for assessment of glycaemic control at follow up remains the glycated haemoglobin level (20). Availability, affordability, standardization issues and

inability to predict glycaemic status in certain medical conditions made us ponder over the other options to assess the glycaemic status. So, the present study was carried out to find the correlation of FPG/PPG/RPG/MPG with HbA1c levels. We found that although estimation of plasma glucose in fasting and postprandial states correlated positively with HbA1c, but the correlation of MPG (a calculated average of fasting and postprandial glucose levels of a patient) with HbA1c was better. An MPG cut-off 145.8 mg/dl predicted HbA1c $\geq 6.5\%$, with a sensitivity of 82.2% and specificity of 89.5%. Ozmen *et al* (21) had suggested a cutoff MPG level of 10 mmol/l (180 mg%) to predict poor glycaemic control (HbA1c $> 7\%$) in type II diabetic subjects.

Many studies have been done to find out an alternative test to HbA1c, but so far there has been no agreement on this. Certain studies found that PPG had a stronger correlation with HbA1c as compared to the FPG, so a strict monitoring and control of PPG can help the clinicians to have an economical alternative test, compared to HbA1c for glycaemic control of their uncomplicated diabetic patients (15, 16). While there are also many reports showing the acceptable correlation between haemoglobin A1c level and fasting plasma glucose level (14, 20). Monnier *et al* (22) suggested that postprandial glycaemic excursions play a major role in the metabolic disequilibrium of patients suffering from mild or moderate hyperglycemia. On the contrary, fasting hyperglycemia appeared as a main contributor to the over all diurnal hyperglycemia in poorly controlled diabetic patients, whereas the role of postprandial glucose elevations decreased as patients progressed towards poor diabetic control. Kang *et al* (23) conducted a study in newly diagnosed Type 2 Diabetes mellitus (T2DM) patients and found that in patients with mild hyperglycemia, PPG is a predominant contributor, whereas the relative contributions of fasting blood glucose gradually increase from mild to severe hyperglycemia and obviously exceed PPG in the T2DM patients with HbA1c levels of $>9.0\%$. This finding implies that the initial pharmacotherapy may target PPG in those patients with mild hyperglycemia, but in patients with severe hyperglycemia fasting blood glucose should be targeted. In our study, we found that relative contribution of fasting plasma glucose towards HbA1c increased as the individuals progressed from good to moderate and poor glycaemic control. Mean plasma glucose derived from FPG and PPG, takes into account both fasting and postprandial glucose excursions. Our study showed that mean plasma glucose correlated

strongly with HbA1c level in patients having good as well as poor glycaemic control. Besides this, MPG is easy to calculate, less costly as compared to HbA1c or CGMS and is easily affordable. Thus MPG seems to be a suitable alternative to HbA1c in the situations where availability, high cost, standardization or medical conditions might be deterrent to the use of HbA1c estimation. MPG also seems to be a better predictor of shorter-term alterations in average blood glucose concentrations in selected set of patients (e.g. after change of therapy).

Translating HbA1c into estimated average blood glucose (eAG) has been a major focus of studies recently. The Diabetes Control and Complications Trial (DCCT) described the relationship between HbA1c and eAG based on daily 7-point profiles, and the study was done only in type 1 diabetes (24). Another multicenter study, the A1c-Derived Average Glucose (ADAG) study assessed a combination of CGM and frequent capillary glucose testing, and HbA1c levels over time to estimate the relationship between the two.

Linear regression analysis was used to determine the equation $28.7 \times \text{HbA1c} - 46.7$ for prediction of eAG. However, ADAG study had a few limitations, some ethnic/racial groups were underrepresented, primarily because of the withdrawal of one large Asian center in the study (25). In our study, we got the regression equation $(28.455 \times \text{HbA1c}) - 46.78$ to predict the mean plasma glucose of a patient. For the centers doing the estimation of HbA1c levels, we suggest that they should use Estimated Mean Plasma Glucose-Indian (eMPG-I) study equation for predicting the estimated mean plasma glucose of a patient in mg/dl as it is easier to communicate the results as average glucose to the patients.

Based on the results of our study, we suggest that estimated mean plasma glucose based on eMPG-I study equation may be a superior predictor of cardiovascular and other adverse outcomes in diabetics in Indian scenario.

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