Review Article

Post prandial glucose can be a substitute for HbA1c in low resource setting: answering the diagnostic dilemma

Binay Kumar1*, Nidhi Prasad2, Ravi Shekhar3

1Department of Pathology, NSMCH, Patna, Bihar, India
2Department of Community Medicine, IGIMS, Patna, Bihar, India
3Department of Biochemistry, IGIMS, Patna, Bihar, India

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*Correspondence:
Dr. Binay Kumar,
E-mail: drbinay10@gmail.com

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ABSTRACT

Achieving a strict glycaemic control is the key factor in diabetes management and associated complications. Although HbA1c is the best indicator of overall glycaemic control during the previous 2-3 months and remains the gold standard for assessing glycaemic control in patients with diabetes. But in low resource setting areas where HbA1c is a costlier affair, postprandial plasma glucose estimation can be a good alternative in estimating glycaemic control. By analyzing the results from many previous papers on glycaemic profiles, we conclude that contribution of postprandial plasma glucose was relatively high in patients with fairly good control of diabetes (HbA1c <7.5%) and decreased progressively with worsening diabetes (HbA1c >10.2%). Whereas the contribution of fasting plasma glucose showed a consistent contribution with increasing levels of HbA1c. So, we can understand that post-meal glycemia was a better predictor of good or satisfactory control of diabetes (HbA1c <7.5%) than was fasting glucose. Postprandial plasma glucose is the prominent contributor in patients with satisfactory to good control of diabetes, whereas the contribution of fasting plasma glucose increases with worsening diabetes. Hence, PPG is better in predicting overall glycaemic control in the absence of HbA1c.

Keywords: Post prandial glucose, Diabetes, Fasting plasma glucose, Complications, Glycosylated haemoglobin

INTRODUCTION

Diabetes, a common non-communicable disease (NCDs), but is the most challenging health problems in the 21st century worldwide. Among all NCDs, diabetes singly account for more than 4 million deaths per year. It is current epidemic in economically developing and newly industrialized nations.1 The number of diabetics is projected to explode beyond 700 million by the year 2045.2 The overall estimated prevalence of prediabetes (A condition in which blood sugar is high, but not high enough to be classified as diabetes) was 10.3% (WHO criteria) or 24.7% (American Diabetes Association criteria), depending on which definition was used. This prevalence is higher than that of diabetes and implies that there is a large pool of individuals who may go on to develop diabetes in the future.3 Complications from diabetes, such as coronary artery and peripheral vascular disease, diabetic neuropathy, amputations, stroke, renal and eye complications like blindness- resulting in increasing disability, reduced life expectancy and enormous health costs in virtually every society.4-7 Screening, early detection, and treatment of NCDs, as well as palliative care, are important components of management. Specific targets and indicators have been set to bring down the burden of NCDs mortality by 25% by the year 2025—the so-called 25×25 target.8,9 In 2010, the American Diabetes Association approved a more
expensive assay of glycated haemoglobin A1c (HbA1c) as one of the three tests for diabetes and prediabetes screening. Many studies showed that relying only on FPG will result in missing 42% of cases of diabetes, postprandial plasma glucose has closer association to glycrosylated haemoglobin than fasting plasma glucose, therefore targeting postprandial plasma glucose should be our focus.10

Many recent studies revealed Vitamin D extra skeleton activity, it has a protecting role in cardio metabolic diseases, cancer and inflammatory condition. Deficient vitamin D level plays a crucial role in pathogenesis of insulin resistance, including obesity and diabetes.11

PATHOPHYSIOLOGY

In healthy subject’s plasma glucose range is maintained in narrow range of 72–144 mg/dl. This Physiological range is maintained by a fine balance between glucose influx (exogenous glucose delivery and endogenous glucose production) and glucose efflux (glucose utilization by insulin sensitive tissues such as the skeletal muscle and insulin insensitive tissues, particularly the brain).12 be defined as value of plasma glucose level measured after overnight (8–12 hour) fasting and after 2 hour of proper meal respectively.15 Pancreas plays a crucial role in maintaining blood glucose levels within a very narrow range through glucagon and insulin by their opposing and balanced actions and glucose homeostasis.13 For fasting level of blood glucose and PPBG value liver as well as pancreas are responsible. During sleep or between meals when blood glucose levels is low or during prolonged fasting, α -cells release glucagon and promote hepatic glycogenolysis and hepatic and renal gluconeogenesis and increase endogenous blood glucose levels and insulin drops resulting in higher FBG level. The increase glucagon to insulin ratio as seen in diabetes, where liver is involved in excess glycogen breakdown and gluconeogenesis. The elevated glucose levels after a meal, insulin secretion is stimulated from β cells and insulin enables insulin dependent uptake of glucose into muscle and adipose tissues and lowering its level. Moreover, insulin enhances glycogenesis, lipogenesis and incorporation of amino acids into proteins. Although many a times in spite of sufficient insulin in body, individual may have higher FBG level, mainly due to insulin resistance in case of impaired fasting glucose tolerance and diabetes mellitus. Body glucose level is maintained by a very complex integrated mechanism involving release of hormones and action of enzymes on key metabolic pathways resulting in a smooth transition normally from a high level of glucose influx following meals / glucose intake to a basal level after 2-3 hours or so. Excluding alimentary hypoglycaemia, renal glycosuria, hereditary fructose intolerance and galactosemia, the possible causes of post prandial reactive hypoglycaemia (PRH) include high insulin sensitivity, exaggerated response of insulin and glucagon like peptide 1, defects in counter regulation, very lean and /or anxious individuals, after massive weight reduction, women with lower body overweight etc.14 The PP- plasma glucose has closer association to HbA1C than fasting plasma glucose, therefore evaluating postprandial plasma glucose is worthwhile.10 Fasting and 2 hour postprandial plasma glucose can

<table>
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<th>Parameters</th>
<th>Normoglycaemia</th>
<th>Prediabetes</th>
<th>Diabetes</th>
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<td>FPG</td>
<td>&lt; 110 mg/dl</td>
<td>110-125 mg/dl (IFG)</td>
<td>≥126 mg/dl</td>
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<tr>
<td>2-h PG</td>
<td>&lt;140 mg/dl</td>
<td>140-199 mg/dl (IGT)</td>
<td>≥200 mg/dl</td>
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<tr>
<td>HbA1c</td>
<td>&lt;5.7%</td>
<td>5.7-6.4%</td>
<td>≥6.5%</td>
</tr>
</tbody>
</table>

* Individuals with random plasma glucose between 140-199 mg/dl is recommended to undergo OGTT IFG - impaired fasting glucose; IGT - impaired glucose tolerance.

A1C ≥6.5% (in adults) Normal HbA1c values and interpretation: normal nondiabetic range: 4.5-5.7%, serious risk of hypoglycaemia: <4.5, diabetic range: >6.5%, prediabetic range: 5.8-6.4%.

PREDIABETES

Prediabetes is a clinical condition where; individuals blood glucose levels is higher than normal physiological levels but lower compared to diabetic range. Up to 70% of prediabetic will eventually develop diabetes within a decade of initial diagnosis.16 Despite the worldwide prevalence of prediabetes and diabetes, many patients remain undiagnosed. This may be attributed to the current reference standards for fasting glucose (FG), and/or the inconvenience for individuals taking the 2hr oral glucose tolerance test (OGTT). However, recent studies have highlighted HbA1c along with OGTT probably being the more accurate diagnostic test for pre/diabetes evaluation associated with age, BMI, physical activity, income, education, race/ethnicity, etc.17,18 Postprandial glucose can be used in diagnosing it better.

AS AN ESTIMATION OF CARDIOVASCULAR RISK

It is well established that postprandial glucose level, is an independent risk factor for cardiovascular complications, in type 2 diabetes, with incidence rates 5- to 10-fold higher than microvascular disease. For this reason, the estimation of A1C and 2-h OGTT are good predictors for patients with CVD.19-22

| Table 1: Diagnostic criteria for diabetes and prediabetes (ICMR.diabetesGuidelines.2018). |
|-------------------------------------|-----------------|-----------------|------------------|
| HbA1c ≥6.5% (in adults) Normal HbA1c values and interpretation: normal nondiabetic range: 4.5-5.7%, serious risk of hypoglycaemia: <4.5, diabetic range: >6.5%, prediabetic range: 5.8-6.4%.

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AS A PREDICTOR FOR RETINOPATHY

It’s a common practice among people having diabetes, routinely check their blood sugar before meal but not afterward or they leave it until the next mealtime. But by that time blood sugar is again within the normal range yet, in the meantime, a marked rise in blood sugar may have gone unnoticed and remained high for a long period. As long as glucose remains unchecked after meal, major fluctuations can go unnoticed. Studies have revealed that a sharp increase in glucose after eating may influence the occurrence of resulting complications such as diabetic retinopathy.23

IN PLANNING FOR ADEQUATE DIET

When post prandial blood sugar spikes, it may be difficult to get the level right all the way down to normal. As per American Association of Clinical Endocrinologists (AACE)“By measuring Post Prandial sugar, we are able to determine whether or not nutritional adjustments or pre-meal bolus insulin required or not. It is noticed that sufferers who attain their pre-meal glucose goals but whose A1C stays excessive, PPG tracking and treatment is recommended.”24 Studies have shown that postprandial sugar level directly affects HbA1c, so despite the fact that glucose spikes after meal are effective for short period, nevertheless it can elevate HbA1c over the path of time.25 Most person measures their blood sugar before meal but not afterward. By that time the sudden spike in blood sugar after meal goes undetected and unchecked for a long period and when next check is done the level comes down to normal.26 Other studies have found out that sharp rise in glucose after meal might also additionally impact the prevalence of complications like diabetic retinopathy etc.

IN EXCLUSIVE CONDITIONS

In certain clinical conditions like cystic fibrosis, suspected type 1 diabetes and in children, adolescents and pregnant women A1C not recommended as diagnostic test for diagnosis.27 Other tests, such as fructosamine, glyated albumin and 1,5-anhydroglucitol is not validated and frequently used for the diagnosis of diabetes. Confirming diabetes in of people with an initial positive test. Currently approximately 40% to 90% people having asymptomatic hyperglycemia are mis diagnosed as diabetic on single test, a repeat confirmatory laboratory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. It is preferable that the same test be repeated (in a timely fashion) for confirmation.28

CERTAIN PHENOMENON

The dawn phenomenon is a medical condition characterized by a raised blood sugar early in the morning. This sugar surge results from declining levels of insulin and an increase in growth hormones. It is related to an inadequate dose of insulin in the night before or eating too many carbs. In non-diabetic the body respond to the rise in blood sugar by releasing insulin, thus maintaining steady glucose levels. This essentially nullifies the dawn phenomenon.29

Somogyi effect, also known as post-hypoglycaemic hyperglycaemia, is a response to low blood sugar during the night due to high insulin dose or less/inadequate carb intake. This Phenomenon is due to a rebound effect of the body when blood glucose levels drops too low in late-night resulting in activation of counterregulatory hormones such as adrenaline, corticosteroids, growth hormone, and glucagon leading to activation of gluconeogenesis cascade and hyperglycemia in the early morning.30

IN LOW RESOURCE SETTING

As per United Kingdom prospective diabetes study (UKPDS) HbA1c >7.0 % is significantly associated with increased risk of both microvascular and macrovascular complications.31,32 HbA1c is an excellent indicator for overall glucose exposure integrating both fasting and postprandial blood sugar Since it reflects the mean glycaemic values of previous 2–3 months. But due to high costing of HbA1c test it is difficult to use in resource poor community. So post-prandial and fasting plasma glucose estimation has taken into practice particularly in developing countries.33 However, circumstantial evidence indicates that there is no consensus amongst professionals whether FPG or PPG is a better predictor of glycaemic control when HbA1c testing is not available.34 Some of the studies indicated that in good or fair HbA1c values, PPG levels made the highest contribution whereas fasting hyperglycemia appeared as the main contributing factor in poorly controlled disease having HbA1c >9 %. So, in easier terms PPG reflects better as compared with FPG in estimating plasma glucose level. Diabetes complications such as retinopathy, nephropathy can be predicted well by the concentration of HbA1c, which are understood to be due to harmful advanced glycation end products.35-37

LIMITATION OF HB1AC

There are few limitations of A1c to use it as a diagnostic criterion like it should be regularly validated and calibrated standardized to the National Glycohemoglobin Standardization Program—Diabetes Control and Complications Trial reference. A1c may be misleading in individuals with various hemoglobinopathies, hemolytic or iron deficiency anemias, iron deficiency without anemia, Graves’ disease and severe hepatic and renal disease.38,39

DISCUSSION

Effective glycaemic control/reducing hyperglycaemia significantly decreases the morbidity and mortality resulting from microvascular and macrovascular complication of long term uncontrolled diabetes.40-43 Estimation of HbA1c remains the gold standard for assessment of glycaemic control but monitoring of PPG
can be more helpful than FBG for optimal glycaemic control and prevent long term diabetes complication alone in the absence of HbA1c, especially in developing countries.\textsuperscript{44}

Studies have shown better correlation of PPG than FPG to HbA1c and both equally correlated to fructosamine levels. Thus, PPG predicted overall glycaemic control better than FPG. Compared to HbA1c, fructosamine is not well correlated with mean blood glucose level. Hence, HbA1c is better than fructosamine in monitoring overall glycaemic control.\textsuperscript{45} Also in Type 2 Diabetes Mellitus subjects who had already reached their A1C goal, pp-SMBG at least twice a day was associated with further improvement in glyceria, lipids, and weight, as well as exercise and dietary habit.\textsuperscript{46} Most individuals with HbA1c values between 6.0% and 7.0% have normal FPG levels but abnormal 2-hour PCPG levels, suggesting that an upper limit of normal for FPG at 110 mg/dL (6.11 mmol/L) is too high and that attempts to lower HbA1c in these individuals will require treatment preferentially directed at lowering postprandial glucose levels.\textsuperscript{47} Attempts to treat patients aiming for ambitious A1C targets, will generally fail unless PPG is controlled.\textsuperscript{48,49} If a single blood test at any time of the day could diagnose diabetes it may be worthwhile as we may prevent long term complications and its related morbidity.

CONCLUSION

In the management of diabetes mellitus glycaemic control is the most important aspect to be looked for. Continuous monitoring of interstitial blood glucose provides an opportunity to better understand the glycaemic excursions in patients with type 1 and type 2 diabetes mellitus. Circulating glucose concentration can be assessed using a range of samples and variable technology, PPG strongly correlate with HbA1c and contributes significantly to overall glycaemic control. This is in line with contemporary evidence that showed strong relation between PPG and development of diabetes complications. Consequently, on the basis of recent studies we can claim that special attention should be given to monitoring and treating PPG until the ongoing debate are resolved through large randomized control trials. Hence monitoring of PPG can be helpful in achieving optimal glucose level and in preventing long term diabetes complication compared to FPG alone in the absence of HbA1c, especially in under privileged settings.

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