Consensus Statement on Management of Post-Prandial Hyperglycemia in Clinical Practice in India

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Introduction

The primary aim of treating diabetes is to establish and maintain near-normal blood glucose levels, and to prevent micro and macro vascular complications. 1,2 There is a close correlation between the risk of complications and the glycated hemoglobin (HbA1c) values, which depend upon both fasting and postprandial glucose levels. Although pre-prandial and FPG concentrations are considered as the primary measures of daily glucose control, postprandial glucose (PPG) levels are equally important. 3

Abstract

Postprandial hyperglycemia (PPHG) is a detrimental factor in the evolution of diabetes related complications. Numerous studies have established the role of PPHG in development of atherosclerosis and associated cardiovascular conditions. It is seen that management of PPHG can be more troublesome than fasting plasma glucose (FPG). Currently, there are various strategies both monitoring as well as therapeutic to control PPHG but there is no uniformity in practicing these strategies. In the absence of any standard guidelines, widespread variations in the management of PPHG are observed among physicians and diabetologists. The objective of this document is to set forth uniform guidelines to manage PPHG. This will not only result in optimal management and prevention of long term complications of diabetes but also better co-ordination and collaboration among the care providers. Moreover, an Indian perspective that can take into consideration the issues relevant to Indian patient pool will be effective. An expert committee comprising of prominent physicians and researchers associated with diabetes care provided their inputs to provide a basic platform for the formulations of guidelines. Their inputs were supplemented by extensive literature search to collect the relevant evidences. An initial draft was prepared which was reviewed by the core committee. Inputs from other experts were also sought and an initial guideline version was formulated that was presented in a conference, discussed and debated among experts. The guidelines on PPHG were then finalised and published.

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PPG is an independent risk factor for the development of macrovascular complications associated with type 1 and type 2 diabetes and impaired glucose tolerance (IGT) stage. PPG has been linked to cardiovascular morbidity and mortality despite of HbA1c values being in the non-diabetic range.4-6

Objective: To assess relationships of diabetes and asymptomatic hyperglycemia at baseline to the risk of cardiovascular disease (CVD). Elevated FPG concentrations are not independently associated with increased cardiovascular disease (CVD) risk hence management of PPG becomes important.7, 8 That cardiovascular disease occurs more frequently in patients with Type II (non-insulin-dependent) diabetes and markers of cardiovascular disease such as oxidative stress, inflammation, endothelial dysfunction, and Carotid Intima- Media Thickness (CIMT) underscore the significance of PPG. In addition, post-meal hyperglycemia has also been connected with the incidence of carcinomas and cognitive dysfunction in elderly type 2 diabetic patients further providing reasons for strict PPG management.9,10

Numerous studies have shown that normalizing post-prandial blood glucose can be more challenging than maintaining a fasting glucose level. So, there is a need to employ intense measures for reducing PPG and excessive glycemic readings.

**Objective**

The objective of these guidelines is to provide India specific recommendations for the management of post-meal glycemia in patients with diabetes. These guidelines will present clinical data obtained from evidences to establish a crucial relationship between post-meal hyperglycemia and the development of diabetic complications. Though logic and clinical judgment remain critical components of diabetes care, following recommendations will assist clinicians and organizations to understand and address questions concerning post-meal glycemia management. The objectives of these guidelines are:

- To present clinical data on the relationship of post-meal hyperglycemia and the development of diabetic complications
- To explain the role of optimizing PPG management in reducing the burden of diabetes and its complications
- To identify and explain the management and role of various therapies in controlling post-meal plasma glucose

**Methodology**

Guidelines on PPG and other aspects of management of diabetes were formulated in a step-wise manner with due consideration given to opinion of experts and published literature on the matter. A core committee comprising of experts (healthcare professionals/researchers/clinicians) having expertise in treating diabetes was formulated. It was decided by the committee members that there is a pressing need of diabetes management guidelines in the Indian context. A separate group comprising of 6-7 individuals and one chairman was formed for each guideline. This group was responsible for formulating a draft version of a guideline. Extensive literature search was conducted on online databases such as Medline, Cochrane, Embase etc. to identify the relevant subject matter. Evidences included randomized or nonrandomized clinical trials, meta-analyses, evidence based reviews, case studies, cohort studies and epidemiological studies. Opinion of expert panel was also taken into account. The grading of evidences was done as below:

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of Evidence</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Meta-analyses or systematic review/randomized controlled trials</td>
</tr>
<tr>
<td>B</td>
<td>Controlled trials, no randomization/randomized uncontrolled trials</td>
</tr>
<tr>
<td>C</td>
<td>Observational trials/reviews/case studies</td>
</tr>
<tr>
<td>D</td>
<td>Opinion of expert panel</td>
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</table>

The initial draft of guidelines was presented to core committee who discussed all the aspects of guidelines and provided their inputs based on their clinical experience. This draft was posted on Diabetes India website to seek opinion from global and regional experts. Draft guidelines were further modified on the basis of comments received and the refined version was presented at a conference attended by nearly 200 experts. Each guideline was discussed and further comments were obtained from the group which resulted in the second draft of the guidelines. This draft was again sent to the core committee for their closing remarks and approval.

**Definition**

- American Diabetes Association (ADA) 2013 defines post-meal hyperglycemia as a 2-h plasma glucose level of more than 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT). It recommends the use of a glucose load equivalent of 75 g anhydrous glucose dissolved in water as prescribed by WHO.11
- A plasma glucose level of 7.8 mmol/l (140 mg/dl) or more, after 1-2 hours of food ingestion is defined as post-meal hyperglycemia by International Diabetes Federation (IDF) 2011.12

**PPG Epidemiology**

Post-prandial hyperglycemia is a widespread condition in Asia and often underdiagnosed. Dickinson et al found that Asian Indians displayed a marked rise in prandial glucose excursion after
consumption of 75-gm of bread meal. Another study conducted on 3,284 people with non-insulin-treated type 2 diabetes monitored daily plasma glucose profiles over a one-week period. Results demonstrated that a post-prandial blood glucose value of more than 8.89 mmol/l (160 mg/dl) was recorded at least once in 84% of these patients even among patients in apparently good glycaemic control, and that simple clinical characteristics identify subsets of diabetic patients with frequent post-prandial hyperglycaemia.

Subjects and Methods: Three self-assessed daily blood glucose profiles over a 1-week period, including 18 glucose readings before and 2 h after meals, were obtained from 3,284 unselected outpatients (men 51%; age 63±10 years).

Studies exhibit that patients with better control of fasting glucose can also have postprandial hyperglycaemia. This is called as isolated postprandial hyperglycaemia and is found to be quite common.

One of the studies demonstrated the prevalence of isolated postprandial hyperglycaemia in a cohort of 90 patients with type 2 diabetes. The patients were assessed with questionnaires, to obtain the demographic data as they visited the clinic for follow up. Result showed that isolated postprandial hyperglycaemia was prevalent in 24.4% of patients.

### Recommendations

- A 2-h plasma glucose level of more than 200 mg/dl (11.1mmol/l) during OGTT or with the use of 75 g anhydrous glucose will be defined as post-meal hyperglycemia. (Level D)

### Complications Associated with PPG

#### Cardiovascular diseases

PPG has been identified as an independent risk factor for cardiovascular disease (CVD) in patients with or without diagnosed diabetes, suggesting that PPG may be a better predictor of cardiovascular risk than is FPG or HbA1c alone (Table 1). Levitan et al performed a meta-analysis of 38 prospective studies and concluded that PPG appears to have a linear relation with CVD. Hyperglycemia even across the non-diabetic range was found to be associated with CVD. In a study conducted on Hoorn population it was observed that an increase of 5.8 mmol/l in post-load glucose was associated with higher cardiovascular mortality (RR 3.40) (p < 0.05).

Studies reported PPG excursion to be associated with increase in systolic and diastolic blood pressure. Giugliano et al showed that acute hyperglycemia in normal subjects significantly increases systolic and diastolic blood pressure. Backgroun: Acute hyperglycemia may increase vascular tone in normal humans via a glutathione-sensitive, presumably free radical-mediated pathway. The objective of this study was to investigate whether or not the vascular effects of hyperglycemia are related to reduced availability of nitric oxide.

Methods and Results: Acute hyperglycemia (15 mmol/L, 270 mg/dL) Similar results were obtained from studies conducted on a small group of healthy, non-obese normotensive subjects. Post-prandial blood pressure changes were observed in these patients during a 24-h period. It was reported that ingestion of a carbohydrate-rich meal induced an increase in systolic blood pressure, irrespective of the timing of meal ingestion.

It is thus evident that PPG is an independent risk factor associated with CVD and is reported to be associated with several cardiovascular complications including postprandial blood pressure, myocardial infarction (MI), CIMT and cardiovascular mortality. It is underscored that PPG is a more important factor than FPG or A1c in determining cardiovascular risks.

#### Nephropathy

Emerging evidence suggests that PPG may affect the development of nephropathy. PPG displays a stronger correlation with the incidence of diabetic microangiopathy compared to HbA1c levels. A study of 52 patients with Type 1 diabetes mellitus conducted between 1965 and 1983, showed a definite relation between the annual medians of PPG, the time interval between the onset of diabetes and the development of diabetic nephropathy. The respective rôles of arterial blood pressure

### Table 1: Morbidity and mortality related to postchallenge and postprandial hyperglycemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECODE study</td>
<td>10 prospective studies among 15,388 men and 7126 women not previously diagnosed with diabetes</td>
<td>2-hour blood glucose levels following 75-g OGTT better predictor of all cause and cardiovascular deaths from FPG levels</td>
</tr>
<tr>
<td>Chicago Heart Association</td>
<td>12,220 men with diabetes or asymptomatic hyperglycaemia</td>
<td>Increased risk of CVD mortality with higher PPG (after 50-g OGTT)</td>
</tr>
<tr>
<td>Temelkova-Kurktschiev et al</td>
<td>582 men and women at risk for type 2 diabetes</td>
<td>2-hour blood glucose levels and spikes more strongly associated with CIMT than FPG or HbA1c</td>
</tr>
<tr>
<td>Diabetes Intervention Study</td>
<td>1139 men women with newly diagnosed type 2 diabetes</td>
<td>PPHG but not FPG, significant risk factor for MI and mortality</td>
</tr>
<tr>
<td>Companion Postprandial Hyperglycaemia Study</td>
<td>93 men and 82 women with type 2 diabetes, not previously drug treated</td>
<td>Reduction of PPHG, but not FPG, associated with reductions in CIMT</td>
</tr>
</tbody>
</table>
and metabolic control in different stages of diabetic nephropathy were analyzed retrospectively in 52 sequentially-followed Type 1 diabetes.

The investigators from the Kumamoto study performed a 8-year follow up of type 2 diabetic subjects and found PPG to be a strong predictor of both retinopathy and nephropathy. An 8-year prospective study of Japanese patients with type 2 diabetes was performed.

Research Design and Methods: A total of 110 patients with type 2 diabetes (55 with no retinopathy [the primary prevention cohort] and 55 with simple retinopathy [the secondary intervention cohort]) In an Indian study of complications in subjects with a history of type 2 diabetes for more than 25 years, postprandial hyperglycemia was found to be associated with both diabetic nephropathy and neuropathy.

Retinopathy

Sufficient evidence suggests that postprandial hyperglycemia may lead to the development of retinopathy.

Data from the National Health and Nutrition Examination Survey showed that patients who had 2-hour postprandial glucose levels of 194 mg/dL had a threefold increase in the incidence of retinopathy, despite normal fasting glucose levels.

Two observational prospective studies from Japan demonstrated that post-meal hyperglycemia is a better predictor of diabetic retinopathy than HbA1c. A multiple regression analysis revealed that not only PPHG independently correlates with the incidence of diabetic retinopathy, but also was a strong predictor of the progression of this complication. Studies of Egyptian and Indian Pima populations revealed a similar increase in the incidence of retinopathy in subjects with normal fasting glucose levels but 2-hour postprandial glucose values of >200 mg/dL.

Neuropathy

In a population study, Beghi et al showed that elevated fasting and PPG levels in conjunction with prolonged disease duration were associated with an increased incidence of diabetic neuropathy.

Other Morbidities

Epidemiologic studies and meta-analyses show that type 2 diabetes increases the risk and tumor-specific mortality of certain cancers. PPG has also been connected with the incidence of cognitive dysfunction in elderly type 2 diabetic patients. One study reported that significantly elevated PPG excursions (11.1 mmol; 200 mg/dl) were associated with a disturbance of global, executive and attention functioning.

A study conducted in northern Sweden included 33,293 women and 31,304 men. 2,478 incident cases of cancer were identified. Relative risk (RR) of cancer for levels of both fasting and PPG was observed. Relative risk of cancer in women increased significantly by 1.26 in the highest quartile for fasting and 1.31 for post-load glucose compared with the lowest quartile. No significant association was found in men.

A large, prospective cohort study of 35,658 adult men and women (55) found a strong correlation between pancreatic cancer mortality and PPG levels. The relative risk for developing pancreatic cancer was 2.15 in people with PPG levels more than 11.1 mmol/l (200 mg/dl) compared with people who maintained PPG less than 6.7 mmol/l (121 mg/dl). This association was stronger for men than women, however, on the association of postload plasma glucose concentration with pancreatic cancer, which could provide insight into the role of abnormal glucose metabolism in the etiology of pancreatic cancer.

Objective: To determine the independent association between postload plasma glucose concentration and risk of pancreatic cancer mortality among persons without self-reported diabetes.

Design: Prospective cohort study.

Setting and Participants: Employees of 84 Chicago-area organizations, with an average age of 40 years at baseline, were screened from 1963 to 1973 and followed up for an average of 25 years. A total of 96 men and 43 women died of pancreatic cancer among 20,475 men and 15,183 women, respectively.

Main Outcome Measures: Relationship of pancreatic cancer mortality with postload plasma glucose levels.

Results: Compared with a postload plasma glucose level of 6.6 mmol/L (119 mg/dL).

Recommendations

- Measures should be taken to improve awareness, regarding CVD risk with PPG, among clinicians and the general public. (Level D)
- Emerging evidence suggests that PPG affect the development of microvascular complications. (Level C)
- Limited evidence also link PPG to occurrence of carcinoma in type 2 diabetic patients. However well designed, prospective, clinical studies would be necessary to differentiate and demonstrate the possible correlation between PPG and various treatment modalities to change of cancer risk in type 2 diabetes mellitus. (Level D)

PPG Goal

Various international bodies have proposed different optimal goals for post meal glucose. While IDF 2011 advocates a level of less than 9.0 mmol/l (160 mg/dl) (as
long as hypoglycemia is avoided), American College of Endocrinology Conference recommends 2-hour postprandial plasma glucose to be at a level lower than 140 mg/dl whereas ADA suggests more relaxed targets i.e lesser than 180 mg/dl. Similarly, according to European Association for the Study of Diabetes (EASD/IDF-Europe) postprandial target should be less than 7.5 mmol/l (135 mg/dl)\textsuperscript{11,12}

### Recommendations

Targets for glycemic control must be individualized (between 140 to 180 mg/dl) based on each patient’s clinical status, which includes socioeconomic circumstances, cognitive abilities, level of motivation, and other factors. (Level D)

### Management of Postprandial Glucose

Both pharmacological and non-pharmacological interventions are required to manage PPG. Control of PPG can be obtained through following approaches:

I. Screening tests

II. Self-monitoring of blood glucose (SMBG)

III. Non-pharmacological therapy

IV. Pharmacological therapy

V. Combination therapy

VI. PPG control in gestational diabetes mellitus (GDM) patients

#### I. Screening Tests

a. Postprandial glycemic screening: Based on the latest ADA recommendations for the testing of asymptomatic individuals, screening for PPG should be implemented in all adults who are overweight (BMI ≥ 25 kg/m\(^2\)) and have additional risk factors.\textsuperscript{11} Screening of PPG is also recommended for individuals having following conditions:

- IGT or IFG or HbA1c ≥ 5.7%
- High risk for CVD
- Established coronary artery disease (CAD)
- History of GDM
- Hypertension (≥140/90 mm Hg or on therapy for hypertension)
- Dyslipidaemia [triglyceride > 250 mg/dL (2.82 mmol/L) and/or high-density lipoprotein (HDL) cholesterol < 35 mg/dL (0.90 mmol/L)]
- Physical inactivity
- Polycystic ovarian syndrome
- First-degree relative with diabetes
- Other clinical conditions associated with insulin resistance (e.g. severe obesity and acanthosis nigricans)

b. Screening of Individuals with prediabetes/IGT\textsuperscript{11,12}: Already existing guidelines of IDF (2011) and ADA (2013) provide following recommendations for PPG screening in Individuals with prediabetes.

- It should be performed in individuals those have FBG level of 100 mg/dL (5.5 mmol/L).
- 2-h OGTT should be performed, using 140–199 mg/dL (7.8–11.0 mmol/L) as determinant of IGT
- If HbA1c is available, screening target should be 5.7–6.4%.

c. Screening of Individuals with type 2 diabetes: Ideally, PPG should be measured in all patients with type 2 diabetes, but particularly in patients with the following conditions:

- Those with high risk or with existing CVD
- Those with unstable glycemic control
- Those taking hypoglycemic medications (such as sulphonylureas, glinides, or all types of insulin)
- Those with chronic liver disease or end-stage renal disease
- Patients whose medication has been modified, or who are inadequately controlled
- Patients of GDM

### Recommendation

- PPHG should be routinely screened. (Level D)
- 2-hr glucose challenge shall be test of choice for screening. (Level D)
- Frequency of meal-based monitoring in patients with diabetes shall be individualized based upon the PPG control. (Level D)

#### II. Self monitoring of blood glucose (SMBG)

Meal-based SMBG may help the patients to monitor their meal choices and portion sizes according to the effect their food has on their glucose levels. Postprandial SMBG values often yield the highest glucose readings of the day and may motivate patients to avoid foods with high glycemic levels, encourage them for optimal physical activity to manage hyperglycemic excursions, or evaluate and adjust insulin doses. SMBG may facilitate significant improvement in glycemic control besides detecting postprandial excursion.

Schwedes et al investigated the effect of meal-related SMBG on HbA1c, compared to no SMBG in non–insulin-treated patients. In the 6-month study, patients in the intervention group achieved a significant reduction in HbA1c values compared with controls (1.0% vs 0.54%, P=.0086).\textsuperscript{33} Similarly, a study by Muchmore et al showed that meal-based SMBG (before and 2 hours after meals for the first month) combined with dietary carbohydrate counting led to a significant decrease in HbA1c values (1.54%, P<.05) from baseline over the 44-week study.\textsuperscript{34} Structured SMBG followed by therapeutic interventions results in greater HbA1c
reduction in people with non-insulin-requiring type 2 diabetes compared with programs without structured SMBG.\textsuperscript{35-37} Noninsulin-treated type 2 diabetes.

Research Design and Methods: This 12-month, prospective, cluster-randomized, multicenter study recruited 483 poorly controlled (A1C $\geq$ 7.5%).

There are no adequate randomized clinical trial data, but the following clinical situations demand PPG monitoring:

- Gestational diabetes
- In patients who achieve their pre-meal glucose targets, but whose HbA1c is inappropriately high and postprandial hyperglycemia is suspected.
- In patients with type 1 or type 2 diabetes treated with glucose-lowering agents aimed mainly to reduce PPG. PPG monitoring may be useful for dose titration of these medications. In these patients monitoring also helps to confirm patients’ response to the drug.
- Monitoring helps to evaluate the effect of changes in nutrition or exercise patterns.

Recommendations

- SMBG with appropriate patient education is effective for detecting and managing PPHG. (Level C).

III. Non-pharmacological Therapy

Apart from pharmacological approaches for achieving better control of PPG, few non-pharmacological strategies are also beneficial. Regular physical exercise and proper dietary measures are associated with optimal control of post-prandial glucose levels. Evidences exist to support the significance of these approaches in diabetes management.

a. Physical Activity: Physical exercise helps to attain glycemic control by virtue of its sensitization effect on insulin. Exercise also affects the glucose uptake stimulation regardless of the insulin action. There is evidence that postprandial exercising has a more potent effect in reducing glucose levels while the effect of exercise performed in the fasting state is relatively insignificant on fasting glycemia.

Effect of exercise was studied in 10 sedentary men with type 2 diabetes treated with oral agents. Their fasting and post-meal plasma glucose was not significantly different at the beginning of exercise (12.4 $\pm$ 1.3 vs 11.1 $\pm$ 1.1 mmol/L respectively). However, post-meal plasma glucose levels reduced significantly after exercise (7.6 $\pm$ 1.1 mmol/L) compared with the fasting state (10.0 $\pm$ 1.0 mmol/L; $P = 0.009$). Insulin levels were higher at the beginning of the exercise bout performed in the fed state (177 $\pm$ 26 vs 108 $\pm$ 19 pmol/L; $P < 0.05$) and during exercise. Increased levels of insulin after meal probably suppressed glucose production resulting in beneficial post-meal glucose levels in the fed state unlike the fasted state where insulin levels did not increase.\textsuperscript{38}

Postprandial high intensity exercise reduces both glucose concentrations and insulin secretion. The beneficial effects of exercise on PPG homeostasis are more related to the total energy expenditure than to the peak of exercise intensity.\textsuperscript{39,40} min at 98.3 $\pm$ 5.1 % V.(O2)

The physical activity is considered as one of the mainstays in type 2 diabetes mellitus treatment. Appreciable amount of energy expenditure with one hour aerobic exercise after meal helps to control post-prandial hyperglycemia.

b. Dietary Modification: Carbohydrates are the most common dietary component in postprandial glycemic excursion. Other macronutrients can also influence the glycemic excursion, such as dietary fiber content and fats, which decrease glucose absorption. The postprandial glycemia depends on the amount and type of carbohydrates ingested.\textsuperscript{41} Most of the modern starch-rich foods have a relatively high glycemic index (GI), including potatoes, white and brown bread, rice and breakfast cereals.\textsuperscript{42} Foods with a lower GI (legumes, and most fruits) contain starches and sugars those are less glycemic by nature (e.g. fructose, lactose) and take more time to get digested and absorbed. The product of the carbohydrate content of the diet and its average GI is termed as dietary glycemic load (GL). GL has been applied as a “global” estimate of post-meal glycemia and insulin demand. The GI and GL of individual foods have been reliable measures to predict how a mixed meal would affect postprandial glucose and insulin levels.\textsuperscript{43,44}

The use of GI can provide an additional benefit for diabetes control apart from carbohydrate counting.\textsuperscript{44}

Traditional Indian diets are carbohydrate-rich; sometimes, as high as 80% of the macronutrient composition comes from this proximate principle. The higher glucose load in the Indian diet leads to greater prandial glycemic excursion, increased glucosidase and incretin activity in the gut which leads to higher lipemic peaks and associated cardiovascular disease.\textsuperscript{45}

An Indian trial was conducted upon T2DM patients. These
were treated with low glycemic diet and acarbose 50 mg thrice daily which was reduced to a maintenance dose of 25 mg thrice daily. An average decline of 4.7 mmol/L was reported in post-prandial blood sugar (PPBS) in 85% of cases. Thus the low glycemic diet apparently promotes the decline in PPBS in larger number of cases with lower dosage of acarbose.46

Diet rich in high GI carbohydrates produce postprandial hyperglycemia and associated CVD. Low carbohydrate diet accompanied with pharmacological intervention reduces post-meal glucose levels.

**Recommendations**

- For individuals with IGT or type 2 diabetes, lifestyle modification should form the basis of PPHG management strategy. (Level D)
- Medical nutrition therapy (MNT), physical activity and weight reduction are the cornerstones of non-pharmacologic therapy in patients with type 2 diabetes. (Level D)
- MNT should include the following
  - Diabetic patient must ingest 45-65% of their total caloric intake in the form of carbohydrates, with a minimum of 130 g/day for adults. (Level D)
  - Increase intake of low glycemic index foods such as hand pounded brown rice. (Level D)
  - Substitution of saturated fat for unsaturated fat (for instance, cold water fish, olive oil, etc). (Level D)
  - Increase intake of soluble and insoluble fiber consumption, and consumption of fruit and vegetables instead of refined carbohydrates. (Level D)
  - Modification of the popular and staple food items to provide adequate calories, proteins, fiber etc. (Level D)
  - Encourage intake of pulses such as Bengal gram (Cicer aritinum) or channa dal, urad, moong, masur, matar because of the presence of complex carbohydrates, having in general relatively low GI and containing substantial protein, fiber and calorie content. (Level D)
  - Pulses need to be acceptably cooked in the form of chapattis or parathas which the patients are habituated to take during principal meals instead of wheat and rice preparations. (Level D)
- Patients should be encouraged to increase physical activity. (Level D)
- Patients should be instructed, supported, and motivated to make the necessary changes to successfully implement an appropriate lifestyle intervention. (Level D)

**IV. Pharmacotherapy**

Drugs targeting post-meal hyperglycemia are essential to control the post prandial glucose level. These drugs may be used in combination or as a monotherapy.47 Repaglinide and glyburide are known to have different efficacy on postprandial hyperglycemia, on carotid intima-media thickness (CIMT).

Therapies which are available for managing PPG include alpha-glucosidase inhibitor (AGI), Glinides, short-acting sulfonylureas (SU), rapidly acting human insulins or insulin analogues and biphasic (pre-mixed) insulins or analogues, dipeptidyl peptidase-4 (DPP4) inhibitors, and glucagon-like peptide (GLP-1) derivatives.

**Oral Antidiabetic Drugs (OADs) and Control of PPHG**

i. **Metformin**: Effect of metformin was studied against prandial secretagogue repaglinide in non-obese T2DM patients. Metformin reduced postprandial levels of glycemia, triglycerides and free fatty acids (FFA) similarly compared to repaglinide. Furthermore, metformin reduced fasting and postprandial cholesterololemia and insulinaemia compared with repaglinide.48

Metformin can play an important role in non-obese patients with T2DM targeting fasting and postprandial glucose and lipid metabolism.

ii. **Sulfonylureas (SUs) and glinides**: Use of traditional secretagogue SUs is associated with unwanted hypoglycemia in diabetic patients especially in elderly. Hypoglycemia occurs due to lengthy plasma half-lives, prolonged drug-receptor interactions, and active metabolites or due to insufficient renal clearance. Repaglinide belongs to meglitinide group, while nateglinide is an amino acid derivative of phenylalanine. They stimulate a rapid but short-lived (for 1-2 hours) release of insulin from pancreatic β-cells. Sulfonylureas and glinides are effective in the stages of type 2 diabetes when β-cell mass is still sufficient to secrete appropriate amounts of insulin. Due to their short-lived secretagogue property they do not produce hypoglycemia.

Glinides have a much shorter action of only a few hours compared with sulfonylureas because of their pharmacokinetic properties. Hypoglycemia occurs with the glinides, but some studies report a lower incidence of
Table 2: Reduction of HbA1c and PPBG in long-term studies with acarbose in combination with oral hypoglycemic agents (OA), sulphonylureas (SU) or metformin (MF)

<table>
<thead>
<tr>
<th>Study</th>
<th>Combination</th>
<th>N</th>
<th>HbA1c Reduction</th>
<th>p-value</th>
<th>PPBG Reduction (mg/dl)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halimi et al77</td>
<td>MF</td>
<td>152</td>
<td>0.90</td>
<td>&lt;0.0001</td>
<td>45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lindstrom et al53</td>
<td>OA</td>
<td>72</td>
<td>0.90</td>
<td>&lt;0.002</td>
<td>48.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Holman et al78</td>
<td>MF/SU/Insulin</td>
<td>1,946</td>
<td>0.50</td>
<td>&lt;0.001</td>
<td></td>
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</tbody>
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hypoglycemia compared with sulfonylurea therapy.49

These agents secrete less insulin several hours after the meal. When taken at mealtimes, they attenuate post-meal plasma glucose excursions and decrease the risk of post-meal hypoglycemia.

iii. Alpha-Glucosidase Inhibitor (AGI): AGIs delay the absorption of carbohydrates from the gastrointestinal tract, thereby limiting post-meal plasma glucose excursions. Specifically, they inhibit α-glucosidases located in the brush border of the proximal small intestine that breaks down disaccharides and more complex carbohydrates. Acarbose, miglitol and voglibose are commercially available AGIs.

AGIs have favorable effect on PPG, FBG and HbA1c which reflect the overall improvement in glucose control of the patients AGIs could be used effectively to control PPHG and provide additional benefits. Evidences exist in favour of two of the AGIs: Acarbose and Voglibose to support their benefits in PPG control.

Acarbose

The Cochrane Library lists 143 published placebo-controlled trials that have evaluated the efficacy of acarbose on HbA1c, fasting and postprandial blood glucose. In this meta-analysis, acarbose specifically reduced postprandial hyperglycemia with an average reduction of HbA1c by 0.8%50 of 0.12 mg/dl from baseline in acarbose plus metformin group while metformin alone reported a reduction of decrease of 27.76 ± 22.91 mg/dl in PPBG.51

Miglitol

Miglitol is a first pseudomonosaccharide alpha-glucosidase inhibitor. It effectively lowers postprandial peak plasma glucose levels thus improves glycemic control. In a systemic review conducted by Scott et al, it was shown that miglitol significantly reduce post prandial glucose levels. In a study, it was observed that miglitol and sitagliptin treatment resulted in similar glycemic control.52 Another study provided the evidence of beneficial effect of miglitol on endothelial function established by postprandial RHI improvement (p=0.007) as a result of control of PPHG. Significant inverse correlation was found between the postprandial change in RHI and postprandial fasting-to-60-minutes surge in glucose (r = −0.382, p = 0.009).53

Voglibose

1780 patients with impaired glucose tolerance were randomly assigned to oral voglibose 0.2 mg thrice daily or placebo in a multicentre, double-blind, parallel group trial. Patients treated with voglibose had a lower risk of progression to type 2 diabetes than placebo (50 of 897 vs 106 of 881; hazard ratio 0.595, 95% CI 0.433-0.818; p=0.0014). More people in the voglibose group achieved normoglycemia than those in the placebo group (599 of 897 vs 454 of 881; 1.539, 1.357-1.746; p=0.0001).54

Of all three clinically used AGIs, acarbose produced the HbA1c by almost 1.76% while metformin alone reduced it by around 1.06%. FBG was decreased by 45.30 ± 15.30 mg/dl from baseline in acarbose plus metformin group while metformin alone reported a reduction of decrease of 27.76 ± 22.91 mg/dl in PPBG.51
Exenatide can be advantageous in controlled studies and long-term clinical investigations. Indian diet has a more carbohydrate load thereby increasing the odds of post-meal glucose and lipid excursions. So the roles of AGIs that inhibit carbohydrate absorption from gut become even more crucial in Indian settings.

iv. GLP-1-based Therapy

GLP-1 is an incretin hormone secreted from the gut that lowers glucose through its ability to stimulate insulin secretion, inhibit glucagon secretion, decelerate gastric emptying and induce satiety. Patients with type 2 diabetes have diminished ability of insulin secretion in response to meal which is called as the incretin effect. This defect can be attenuated by the administration of exogenous GLP-1 analogues or GLP-1 receptor agonists. GLP-1 derivatives diminish post-meal glucose excursions with a low risk of hypoglycemic episodes. GLP-1 receptor agonists are peptides that use GLP-1 action and can be used as an injectable therapy in type 2 diabetes. Exenatide and liraglutide are currently commercially available GLP-1 analogues.

Exenatide

Exenatide has been effective in lowering A1C in patients failing oral therapy with metformin and/or sulfonylurea. There may be enhancement of post-prandial glucose control and some diminution of fasting glucose control with shorter acting GLP - 1 receptor agonist (exenatide twice daily) compared to longer-acting agonist (exenatide once weekly, liraglutide). Exenatide can be advantageous for patients where hypoglycemic episodes and insulin therapy associated increase in body weight is not desirable.

Liraglutide

In the LEAD trials, treatment with liraglutide was associated with substantial improvements in glycemic control and low risk of hypoglycemia. Liraglutide was also shown to be effective at reducing postprandial glucose (PPG); consistent reductions were observed in peak PPG (across all three meals) in the LEAD-1-5 studies). In addition liraglutide significantly improved β-cell function, reduced systolic blood pressure and induced weight loss. Overall, liraglutide was well tolerated.

GLP-1 analogues control postmeal hyperglycemia by stimulating insulin secretion in response to meals. They are not associated with risk of hypoglycemia or insulin associated increase in body weight.

v. DPP-4 inhibitor

DPP-4 inhibitors act by inhibiting the DPP-4 enzyme which degrades GLP-1, thereby increasing the active form of the hormone. This in turn stimulates glucose-dependent insulin secretion and suppresses glucagon release. DPP-4 inhibitors decrease post-meal glucose and improve HbA1c without causing hypoglycemia. Currently, linagliptin, saxagliptin, sitagliptin and vildagliptin are commercially available DPP-4 inhibitors in India. DPP-4 inhibitors are effective in early stages of type 2 diabetes, either as monotherapy or in combination with metformin or other oral agents for type 2 diabetes. They do not change the body weight and have no intrinsic risk for hypoglycemic episodes.

Sitagliptin

Efficacy and safety of sitagliptin as an add-on to metformin therapy in patients with moderately severe type 2 diabetes mellitus was studied in a randomized controlled trial. Sitagliptin was administered as 100 mg once daily dose for 18 weeks. The combination significantly reduced HbA1c, FPG, and 2-h PPG, compared with placebo. HbA1c was reduced by 1.0% in the combination group. 22.1% patients in the treatment group achieved HbA1c levels of lesser than 7.0% compared to only 3.3% in placebo. No change in body weight, neither hypoglycemic nor gastrointestinal episodes were reported.

Saxagliptin

In a similar 24-week safety and efficacy study, saxagliptin was used as 2.5, 5, or 10 mg once daily in combination with metformin. Combination therapy significantly decreased HbA1c, FPG and PPG. PPG AUC was reduced by 8,891, 9,586, and 8,137 from baseline, with three doses respectively. Metformin alone demonstrated a mean change of -3,291 mg.min/dl). β-Cell function and postprandial C-peptide, insulin, and glucagon AUCs improved in all saxagliptin treatment groups at week 24. Effects on body weight and incidences of hypoglycemia with saxagliptin were comparable to placebo group.

Objective: This 24-week trial assessed the efficacy and safety of saxagliptin as add-on therapy in patients with type 2 diabetes with inadequate glycemic control with metformin alone.

Research Design and Methods: This was a randomized, double-blind, placebo-controlled study of saxagliptin (2.5, 5, or 10 mg once daily).

Linagliptin
To assess the effect of linagliptin on PPG, 67 patients were treated with linagliptin and were compared against placebo group. A meal tolerance test was performed 30 minutes after study drug dosing administration. After 24 weeks, treatment group showed a placebo adjusted mean change of -3.2 mmol/l in 2-h postprandial glucose from baseline\(^2\) randomized, parallel group, phase III study compared linagliptin treatment (5 mg once daily, \(n = 336\)).

**Vildagliptin**

Vildagliptin has been examined when used in monotherapy (50 mg once daily) for 52 weeks in subjects with type 2 diabetes with mild hyperglycemia (HbA1c 6.2–7.2%). When adjusted for placebo, vildagliptin reduced HbA1c by 0.3%. The study was followed by a 52-week extension period in 131 patients. Following the 2-year period in these patients, HbA1c was reduced by 0.5% by the use of vildagliptin. Finally, in subjects with impaired glucose tolerance (IGT), treated for 12 weeks with vildagliptin at 50 mg once daily (\(n = 90\)) versus placebo (\(n = 89\)), vildagliptin improved glycemia as was evident by the reduced prandial glycemia following a test meal.\(^3\) A subgroup analysis by Bosi et. al in 2009 demonstrated a HbA1c reduction of 1.1% (\(p<0.01\) vs. placebo) from a baseline HbA1c of 8.7% with vildagliptin 50mg BID\(^4\) randomized, double-blind, active-controlled study. Treatment-naive patients with T2DM who had a glycated haemoglobin (HbA1c DPP-4 inhibitors when used in combination with metformin exhibit better post-meal glycemic control without causing hypoglycemic episodes, body weight gain or gastrointestinal complications.

**vi. Insulin**

The goal of insulin therapy in both type 1 and type 2 DM is to mimic endogenous insulin as closely as possible thereby reaching the target HbA1c levels. Insulin therapy also aims to avoid the common side effects of antidiabetic therapies like hypoglycemia and gain in body weight. Genetically engineered human insulin is a new class of therapeutic agents known as insulin analogues. More than 300 short, moderate or long-acting analogues have been studied but few are used clinically. Evidences suggest that those analogues provide several benefits over traditional human insulin including improved physiologic profile, reduced risk of hypoglycemia and less weight gain. Analogues support physiological insulin profile more effectively than does the conventional insulin therapy.\(^5\)

**Rapid-acting Insulin Analogues**

The fast-acting insulin analogues were developed to mimic the physiological insulin response after a meal with a better action profile than regular human insulin and can also be used for prandial insulin therapy.\(^6\) The new insulin analogues aim to eliminate these limitations. Five insulin analogues are commercially available and approved for individuals with type 1 diabetes: three rapid-acting (insulin lispro, insulin aspart and insulin glulisine) and two rapid-acting insulin analogues, insulin Lispro and insulin Aspart, are already in the market, while a third one, insulin Glulisine, has recently obtained approval from the FDA. Rapid-acting insulin analogues closely match normal insulin patterns. Rapid acting analogues have faster absorption after subcutaneous administration and reach a peak concentration about 1 h after injection. There are various advantages of using Rapid-acting Insulin analogues for PPG control.

- Faster onset of action
- Higher peak insulin concentration around high PPG values
- Mimic physiologic insulin profile (1st and 2nd Phase)
- Improved PPG control
- Improved HbA1c
- Lower weight gain
- Lower risk of late hypoglycemia

The rapid-acting insulin analogues should be injected 5 to 15 minutes before a meal. However, in infants or in older adults with dementia who both have unpredictable eating patterns, rapid-acting analogues can be administered after the meal without excessive deterioration of glycemic control.

**Insulin Aspart**

Effect of an immediately pre-meal injection of insulin Aspart on postprandial glucose was studied against human insulin injected immediately or 30 minutes before a test meal in insulin-treated type 2 diabetic patients. Patients treated with Aspart demonstrated a significantly improved postprandial glucose control and a significantly smaller postprandial blood glucose excursion (899 ± 609 (SD) mmol/l min) versus (1102 ± 497 mmol/l min) in patients treated with human insulin. Immediate pre-meal administration of insulin Aspart resulted in improved postprandial glucose control compared to regular human insulin injected immediately before the meal, with no concerns about safety.\(^7\) Double dummy crossover design, patients attended three study days where the following insulin injections in...
Feinglos et al showed that using Insulin lispro improves insulin lispro compared with regular human insulin, in IDDM patients. Anderson et al. found that mealtime therapy with lispro reduced postprandial hyperglycemia compared with regular human insulin therapy, and that it may decrease the rate of mild hypoglycemic episodes in patients with type 2 diabetes. An insulin analog recently developed particularly formealtime therapy, has a fast absorption rate and a short duration of action. We compared insulin lispro and regular human insulin in the mealtime treatment of 1,068 patients with IDDM. The study was a 6-month randomized multinational (17 countries). Feinglos et al showed that using insulin lispro in combination with a sulfonylurea at mealtime, not only reduced 2-h postprandial glucose excursions, but also reduced both fasting glucose and A1C levels. 2-hour PPG was reduced from 18.6 to 14.2 mmol/l in combination group compared with sulfonylureas alone. FPG levels were decreased from 10.9 to 8.5 mmol/l, and HbA1c values were reduced from 9.0 to 7.1%. Subjects in the lispro group also benefited from significantly decreased total cholesterol levels and improved HDL cholesterol concentrations.

Insulin Glulisine

Compared with regular human insulin, glulisine has a more rapid onset of action and shorter duration of effect, affording greater flexibility in the timing and content of meals. In a single-dose, randomized, study, subjects received subcutaneous injections of either insulin glulisine or human insulin pre meal. Postprandial baseline-subtracted maximum blood glucose excursion was reported in glulisine as 65 mg/dl compared with 89 mg/dl in human insulin. Postprandial baseline-subtracted maximum blood glucose concentration was 180 vs. 209 mg/dl.

v. Combination therapy

Many oral agents successfully lower both FPG and PPG levels but may lose their effectiveness over time. Thus combinations of agents with complementary mechanisms of action may provide better control of FPG and PPG levels. These combinations include agents that specifically target PPG including AGIs, short-acting insulinotropic agents, amylin analogues, GLP-1 analogues, DPP-4 inhibitors, and rapid-acting insulin analogues.

Proposed Recommendations

- In view of its myriad benefits and its relatively benign side effect profile, metformin remains the first-line therapy for most cases of type 2 diabetes irrespective of its effect on PPHG. (Level A)
- All antidiabetic drug regimens should include metformin unless specifically contraindicated. (Level A)
- Glinide use is now limited to the treatment of PPHG if sulfonylureas are contraindicated and in patients who cannot afford or are not otherwise candidates for the newer agents.
- AGIs can be used as first-line drug in early type 2 diabetes, as well as in combination with nearly all established oral antidiabetic and insulin. (Level A)

vi. PPG management in pregnancy

In diabetic pregnant women those require insulin; controlling PPG has resulted in better glycemic control than controlling FPG. Controlling postprandial blood glucose values further reduces chances of neonatal hypoglycemia, macrosomia, and cesarean delivery. A 2 hours post-meal blood glucose monitoring is suggested by Seshiah et al, although different studies advocate varied intervals of 1 hour, 1.5 hours and 2 hours. Indian guidelines further recommend that management of GDM should encompass MNT, OHDs and insulin.

In a study that compared preprandial and postprandial monitoring of glycemic control in women with gestational diabetes, 33 women those who had PPG control indicated by lower Hba1c levels, gave birth to babies with lower weights, lower risk of neonatal hypoglycemia, and were less
Better glycemic control in pregnant women with GDM was shown to assist in achieving better PPG levels. The ADA recommends walking for 10 minutes after each meal to improve PPG control significantly in such patients. Evidences suggest that strict postprandial glycemic control in patients with GDM correlates with lower risk of macrosomia, neonatal hypoglycemia, neonatal hypocalcemia and with reduced chances to undergo cesarean surgery. Strict control in third trimester has the most potent effect on fetal body weight. Furthermore, physical activity also helps to reduce PPG levels.

**Proposed Recommendation**

- PPG rather than FPG should be used to guide management in pregnant women with GDM, requiring insulin therapy. (Level D)
- Post-meal monitoring should be performed 2 hours after meal intake. (Level D)
- All GDM patients should receive nutritional counseling. (Level D)
- Metformin alone or with supplementation with insulin is preferred. (Level D).
- Premix insulin (30/70) to be initiated at 4 units before breakfast and to be increased by 2 units till 10 units. (Level D)
- Rapid acting insulin analogues should be considered if PPG is still uncontrolled. (Level D)

**Conclusion**

PPG is an independent risk factor of cardiovascular complications in diabetes patients and a better predictor of glycemic control than the FPG. Patients who are seemingly well controlled with diet, exercise, and medical therapy, even those with normal FPG and HbA1C could have uncontrolled PPHG. The combination of improved detection and monitoring of PPG along with effective medications may help to establish optimal glycemic control thereby reducing diabetic complications. SMBG provides information on glucose excursions in response to daily events, meals, medications, exercise, and illness hence it may complement information provided by HbA1C. To realize the full potential of SMBG, patients must be educated on how and when to monitor and what steps to take in response to high or low blood sugar levels. Severe hypoglycemia is a challenge in primary care settings. It can however be managed in most patients with type 2 diabetes through strategically used therapeutic options, in combination with appropriate blood glucose monitoring regimens and comprehensive patient education. Therefore, the ideal treatment for patients with type 2 diabetes should include a combination of agents that lower basal plasma glucose levels and agents that control meal-related glucose excursions. The success in maintaining the glycemic and perhaps, the lipid excursion must be acknowledged as the therapy target. Most available treatments reduce fasting glycemia, but have a lesser effect on the postprandial glucose excursions. The availability of new agents directed at the postprandial state as the aforementioned ones, leads to the possibility of better long-term management of patients with type 2 diabetes, aiding in the prevention of the high morbidity-mortality associated to diabetes, especially cardiovascular disease.

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