Postprandial Hyperglycaemia — The Real Challenge in Diabetes

L Rajmohan*, V Mohan**, TR Ramanujam***

The term "postprandial" is broadly defined as the period following a meal. The duration of this period depends on the composition of the meal. The postprandial period for a meal high in glucose would be around 2-3 hours whereas for a meal high in fats, it would be close to 8 hours. Most of the period in a person's life is spent in the postprandial state. Hence the postprandial period should logically be more important to assess the metabolic control of diabetes than the fasting state. However, most studies have focussed on fasting plasma glucose for assessment of metabolic control. More recently there has been a shift to postprandial hyperglycaemia and this article will try to review the importance of assessing postprandial hyperglycaemia.

During the postprandial period in normal individuals, glucose levels rarely rise above 140 mg/dl (7.8 mmol/L). However with increasing degrees of impairment of glucose tolerance, there is a progressive rise in postprandial glucose levels. However fasting glucose levels in these individuals are often below 126 mg/dl which is the current glycemic threshold for the diagnosis of diabetes. It is estimated that 40% of all patients with type 2 diabetes with 2 hr post glucose value > 200 mg/dl have fasting glucose levels below 126 mg/dl. It therefore appears that type 2 diabetes begins largely as a postprandial disease. There are therefore suggestions that we should refer to this early phase of diabetes as "Postprandial Diabetes".

Control of postprandial blood glucose is a challenging task in clinical practice in India. This was brought out in a large multicentric study conducted in India to understand the extent of postprandial hyperglycaemia.

The two hour glucose excursions in the centres ranged from 70 mg% to 90 mg% indicating that controlling postprandial hyperglycaemia is a significant problem in Indian patients.

The postprandial state: Mechanisms of glucose intolerance

The appearance of glucose from the gut does not differ between glucose intolerant and healthy control subjects. Rates of postprandial glycoegenolysis also do not differ between diabetic and non-diabetic individuals. However the rate of gluconeogenesis following a meal are higher in diabetic than in non-diabetic individuals. It has been estimated that the diabetic liver may release up to 25 gm of glucose during the postprandial period. This might be due to lack of postprandial suppression of glucagon, which was demonstrated in a recent study.

There is also a defect in insulin secretion in the postprandial state. It has been shown that there is a blunted and delayed postprandial insulin profile in individuals with NIDDM. This also might contribute to postprandial hyperglycaemia. The gut plays an important role in glucose homeostasis by modulating beta cell function via secretion of gastrointestinal hormones (the incretin effect). This has been shown to be altered in individuals with NIDDM and has led to some promising new developments in therapy of NIDDM - the glucagon like peptide or GLP-1.

Postprandial hyperglycaemia and HbA1c levels

Postprandial glucose levels contribute as much as 25% of glycosylated haemoglobin levels (HbA1c) in type 2 diabetic patients. Arigno et al measured plasma glucose levels pre-breakfast, pre-lunch, and 2 hr and 5 hr post lunch in type 2 diabetic patients and correlated the results with HbA1c levels. Multiple linear regression analysis indicated that only the 2 hr and 5 hr post lunch plasma glucose levels correlated significantly and independently with HbA1c.

Postprandial hyperglycaemia and gestational diabetes

The best evidence for the benefit of postprandial blood glucose monitoring and glycemic control comes from a recent study by Veciana et al. The study in-
involved two groups of patients with gestational diabetes, one monitored pre-prandially and the other group postprandially. Control of glucose levels based on postprandial levels produced a 3% decrease in HbA1c while in the preprandial group, the reduction was only 0.6%. Moreover, the group monitored post-prandially had significantly smaller babies, compared to the group monitored pre-prandially who tended to have macrosomic babies.

Mechanisms of injury by postprandial hyperglycaemia

Excessive postprandial glucose levels could lead to increased protein glycation. Protein glycation in turn leads to atherosclerosis through various mechanisms like glycated low-density lipoprotein (LDL) which is more susceptible to oxidation and also by stimulating platelet aggregation. Excessive postprandial glucose levels in diabetic patients are accompanied by an increased release into the circulation of D-dimers and prothrombin fragments which activate thrombin formation and consequently fibrinolysis.11

It is hypothesised that hyperglycaemia activates protein kinase C in endothelial cells. This leads to increased expression of intracellular adhesion molecules like ICAM-1. ICAM-1 and reduces the release of vasodilatory substances like prostacyclins. In addition, hyperglycaemia favours the release by the endothelium of vasoconstrictive agents like endothel and platelet derived growth factor (PDGF).

Postprandial hyperglycaemia as a risk factor for atherosclerosis

Recent evidence suggests that the development of atherosclerosis often precedes a diagnosis of NIDDM. It is possible that postprandial changes precipitate atherosclerosis before fasting plasma glucose concentrations are affected.12 Evidence that postprandial glycemic fluctuations are important in the progression of atherosclerosis comes from the Helsinki Policeman study.13 This study involving 3267 men, showed that the 5 year incidence of cardiovascular death was significantly associated with 1 hr postprandial glucose levels.

The question of whether fasting and postprandial blood glucose levels are independent predictors of risk for atherosclerotic disease and total mortality in patients with diabetes was addressed in the Diabetes Intervention Study (DIS) conducted in Germany.14 Multivariate analysis shows that blood pressure, triglycerides and postprandial blood glucose but not fasting blood glucose were risk factors for myocardial infarction.

Individuals with IGT also have increased postprandial glucose levels and an increased risk of atherosclerosis. Evidence for this comes from epidemiological studies, such as the Da Qing study, which reported a 10 fold higher incidence of ECG abnormalities in individuals with IGT, compared with a control population.15 In subjects with IGT, fasting plasma glucose values are normal by definition and this again supports the concept that postprandial hyperglycaemia precedes fasting hyperglycaemia in conferring susceptibility to CAD in a given population.

Even among the non-diabetic individuals, postprandial plasma glucose is an independent risk factor for atherosclerosis. This was shown in a study from Germany which showed that the top quintiles of 2 hr postprandial plasma glucose were associated with increased carotid intimal-medial thickness in non-diabetic individuals.16

Implications of postprandial hyperglycaemia for therapy

Prevention of postprandial hyperglycaemia is important, as it is implicated in the development of various metabolic abnormalities and macrovascular complications associated with diabetes.2 Moreover, postprandial hyperglycaemia itself is implicated in the development of type 2 diabetes.17 Even modest postprandial hyperglycaemia desensitizes the B cells to glucose and causes B cell dysfunction. Over time, this could lead to decreased insulin secretion, further promoting fasting hyperglycaemia.

Therapy of postprandial hyperglycaemia

Normalising postprandial blood glucose levels is more difficult than normalising fasting hyperglycaemia. Recently, several drugs with differing pharmacodynamic profiles have been developed which target postprandial glucose. These include insulin lispro, amylin analogues, alpha glucosidase inhibitors and meglitinide analogues.

1. Insulin lispro has a more rapid onset and shorter duration of action than regular human insulins. Clinical trials reveal that insulin lispro improved control of postprandial glucose with lower amplitude of glucose excursions.18 Moreover, the rate of hypoglycaemia was less with insulin lispro.

2. Amylin analogues: Pramlintide is a new drug useful in controlling postprandial glucose levels. Mechanism of action involves regulation of gas-
Table 1: Comparative profile of agents available for managing postprandial hyperglycaemia

<table>
<thead>
<tr>
<th>Potency</th>
<th>Insulin Lispro</th>
<th>Premilinide</th>
<th>α glucosidase inhibitors</th>
<th>Repaglinide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperinsulinemia</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Gastrointestinal adverse effects</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
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Dietic empting, limiting rate of delivery of nutrients to the absorbing surface of the gut and suppression of postprandial glucagon secretion.19

3. Alpha glucosidase inhibitors such as acarbose, miglitol and voglibose reduce postprandial glucose primarily by interfering with the carbohydrate digesting enzymes and delaying glucose absorption.20,21 These drugs have also been shown to reduce postprandial hypertriglyceridemia.22 Optimum effect of this drug is seen when it is administered with the first mouthful.

4. Repaglinide: This is a short acting insulinotropically agent which when given before meals, stimulates endogenous insulin secretion and lowers postprandial hyperglycaemic excursions.

Table 1 compares the efficacy and disadvantages of various agents available for managing postprandial hyperglycaemia.

Besides these new therapeutic agents for the control of postprandial hyperglycaemia, lifestyle modifications also may help to reduce postprandial hyperglycaemia. Modifications include a diet that is rich in fibre and increasing complex carbohydrates with restriction of simple carbohydrates, spacing of the breakfast into two small meals rather than a single heavier one. All these measures would also help to prevent the postprandial surge of glucose. Regular physical exercise also helps to lower the postprandial glucose levels by improving insulin sensitivity.

References


