LUPINE PUBLISHERS

Archives of Diabetes & Obesity

DOI: 10.32474/ADO.2018.01.000124

ISSN: 2638-5910

Mini Review

Management of Postprandial Blood Glucose in Diabetes Mellitus

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Received: December 15, 2018 **Published:** December 19, 2018

Abstract

Patients with type-2 diabetes have more than half the day in the post meal state. Elevation in post meal plasma glucose is due to loss of first phase insulin secretion, decreased insulin sensitivity in peripheral tissues and consequent decreased suppression of hepatic glucose output after meals due to insulin deficiency. Elevated or exaggerated post meal response is directly responsible for endothelial dysfunction and pro-atherogenic states. Post-meal hyperglycemia is a prominent early defect in type-2 diabetes patients.

Keywords: Post prandial blood glucose; Insulin resistance; HbA1c level; Hyperglycemia; Drugs reducing PPBS

Introduction

80% of total caloric intake is carbohydrate rich in our country. The higher glucose load in the diets is responsible for an exaggerated prandial glycemic response. This in turn leads to a higher lipaemic peak which has a direct correlation with cardiovascular disease. Even before diagnosis of clinical diabetes, these metabolic abnormalities are first evident as elevation in post-meal plasma glucose. HbA1c levels reflect overall glycemic exposure and are determined by both fasting and PPG exposure. In a study patient who achieved fasting plasma glucose levels of < 100 mg/dl, 64% achieved HbA1c level of <7% and of patients who achieved PPG levels < 140 mg/dl, 94% achieved an HbA1c < 7%. In diabetic patients with HbA1c levels between 6.8 to 8.9, PPG contributed to almost 70% of the HbA1c level.

Effect of Post Prandial Blood Glucose

Post prandial blood glucose has been linked to diabetic complications like cardiovascular problems. Achieving diet control in diabetic patients remains a significant challenge in our country. The value of good glycemic control by intensified insulin therapy in type 1 diabetes patients has been established by DCCT trial. Subsequent studies like UKPDS and Kumamoto confirm that the extent of benefit of tight control in type 2 patients also. In one study almost half the patients have post prandial values more than 70 mg over fasting values. 1/3 of patients had glucose excursion over 100 mg/dl. Elevated post prandial blood glucose with normal fasting blood glucose can cause complications like retinopathy. Some of the micro and macro vascular complications are seen even before the diagnosis of DM clinically. The Rancho Bernardo study [1] suggests that isolated post challenge hyperglycemia increase the risk of fatal CVD. Plasma glucose value more than 140 mg% at 2 hours after an OGTT defines postprandial hyperglycemia (PPHG). It includes all cases of IGT. Post prandial glucose reduction is seen with metformin, alpha glucosidase inhibitors, pioglitazone and DPP-4 inhibitors.

Causes of High Postprandial Blood Glucose are

a. Unusually high intake of carbohydrate diet.

b. OHA or insulin when given at pre-lunch or pre-breakfast time is not able to bring post lunch blood sugar but is controlling fasting blood glucose. Any attempt to increase the dose of medication in such situation results in 5.00 pm hypo glycaemia (Evening Hypo glycaemia) hence is not the preferred mode of treatment.

c. In Type 2 DM meal stimulated insulin secretion seems to be lost. This occurs even before overt DM develops. Normally after IV

Glucose, insulin peaks within 10 minutes and second phase peaks after 20 minutes. In DM insulin in 1st phase is absent, and second stage secretion is blunted and delayed. Fasting hyper glycaemia occurs when a loss of approximately 75% in beta cells occur.

d. Due to β-cell dysfunction there is altered insulin pulsatility both in timing and amplitude, low insulin and high glucagon levels increase hepatic glucose output.

e. Insulin resistance aggravates the non-suppressibility of hepatic glucose output and also reduces peripheral glucose uptake.

f. There is defect in glut-2 and glut-4 transporter system

g. Kidney has a role in postprandial hyperglycemia

Patho phytologic mechanism of tissue damage due to post-meal hyperglycemia

Hyperglycemia Induced Mitochondrial Production Leads to

a. Increased flux in polyol pathway

b. Increased intracellular formation of advanced glycation end-products

c. Protein kinase C activation

d. Increased flux through hexosamine pathway

How to Recognize Post-Meal Hyperglycemia?

a. Self-monitoring blood glucose is ideal for deducting and monitoring post-meal glucose profile

b. Continuous monitoring of blood glucose profile adds to identification of post-meal surges in apparently well controlled diabetes

c. Fructosamine and 1, 5 – anhydroglucitol measure short-term glucose exposure. They accurately reflect post-meal blood glucose value.

Glucose monitoring in type2 diabetes mellitus seems to be more complex than previously thought, because fasting glucose is a rather poor index of glucose levels throughout the day. HbA1c seems to provide poor information on postprandial glucose levels and it provides no information on glucose excursions with meals. Post-meal is one of the earliest defects in diabetes and is the predominant contributor to HbA1C at values below 8.4%

PPBG Elevations and DM

Glucose is a potent inducer of oxidative stress and induces free radical oxidation of low-density lipoprotein. This leads to increased vessel wall atherogenesis. Increased PPBG produces dyslipidemia, activates prothrombotic activity and reduces insulin sensitivity. All these factors lead to chronic complications of DM. In gestational diabetes normalizing postprandial glucose levels are associated with a better outcome of pregnancy. [2] There is epidemiologic evidence to show that postprandial hypoglycemia correlated directly with incidence of retinopathy, nephropathy, cerebro-vascular accidents and their outcome. The Decode study shows that meal time glucose spikes are independent risk factors for cardiovascular mortality. White Hall study [3] the mortality doubled in those with postprandial levels between 96 mg/dL and 146 mg/dL compared to those with <96 mg/dL. In the Islington Diabetes Survey [4] the prevalence of major CVD increased from 9% in those with normal glucose tolerance to 19% in those with IGT (Table 1) [5-19].

Table 1: Relationship of postprandial hyperglycemia to chronic complications of diabetes.

S. No.	Study	Findings
1	National Health and Nutrition Examination Survey [5]	2 Hr. PPBS >194 mg/dL - 3-fold increase in retinopathy, despite normal FBS
2	Honolulu Heart Study [6]	CAD twice high in PPBS between 157-189 mg/dL. Sudden death doubled with PP glucose >151 mg/dL
3	Italian General Practitioners Study Group [7]	Increase FBS/Increase PPBS - related to increased incidence of diabetic neuropathy
4	Whitehall Study [3]	Plasma glucose level >196 mg/dL, 2 hours after meals 2-fold increase in mortality from CAD
5	Islington Diabetic Survey [4]	Major CAD (MI/Major ECG changes) 17% increase with 2-hour postprandial blood glucose between 120-180 mg/dL. Only 9% when PPBS was <120 mg/dL
6	Oslo Study [8]	Predictor of stroke in diabetes patients. Risk increased by 13% for each 18 mg/dL elevation in PBS
7	Hoorn Study [9]	Increased risk of peripheral vascular disease in elderly patients with diabetes mellitus or IGT
8	Paris Prospective Study [10]	Postprandial hyperinsulinemia is a predictor of CAD
9	Helsinki Policemen Study (1985) - 9 1/2-year follow-up [11]	CAD events correlated with ½ hour postprandial hyperinsulinemia
10	Diabetic Early Pregnancy Study [12]	High birth weight of newborn correlated well with mother's 3rd trimester postprandial elevated glucose level

11	Diabetic Intervention Study [13]	Postprandial blood sugar and not FBS was independent risk factor for MI and cardiac death
12	Bedford Survey [14]	Protection from CAD lost when elevated postprandial blood sugar occurred
13	Rotterdam Study [15]	Increased postprandial blood sugar and intellectual functions deteriorated - impaired cognitive function
14	DECODE* [16]	2-hr. blood glucose levels following 75 gm OGTT better predictor of all cause and cardiovascular deaths than FBG
15	Chicago Heart Association [17]	Increased risk of CVD mortality with higher PPG levels
16	Temelkova Kurktschiev, et al. [18]	2-hr blood glucose level and spikes more strongly associated with CIMT (carotid intima medial thickness) than FPG or HbA1c
17	Campanian post-prandial hyperglycaemia study [19]	Reduction in post-meal but not FPG, associated with reduction in CIMT

*DECODE- Diabetes epidemiology collaborative analysis of diagnostic criteria in Europe.

Management [20]

A drug should reduce rate of glucose entry, improve meal related insulin level and inhibit glucagon effect in order to be effective in controlling PPG.

a. Reduce carbohydrate intake at lunch. Diets with a low glycaemic index are beneficial like legumes, pasta and most fruits. Diets with high GI viz. potatoes, white and brown bread, rice are to be minimized. Sugars which are slowly digested and absorbed are less glycemic by nature viz. fructose and lactose.

b. Incretin Mimetics (Exenatide), GLP1 analogue (liraglutide), DPP-4 (sitagliptin and vildagliptin) and Amylin analogues can be used [21].

c. α-glucosidase inhibitors [21] is a complex oligosaccharide which acts on alpha-glucosidase in the brush border of the small intestine by competitively inhibiting α-glucosidase. This inhibition delays digestion of complex carbohydrates in the upper GI and retards absorption of glucose and blunts postprandial hyperglycemia. Voglibose is approximately 20-30 folds more potent inhibitor of small intestinal disaccharides as compared with Acarbose. It has less gastric side effects. Reduces oxidative stress generation and reduces PPG and lipids in obese type-2 diabetes. Side effects are flatulence, abdominal distension, borborgymi and diarrhoea. The drug lowers insulin raises in post prandial hyper glycaemia, no weight gain occurs with the therapy and there are no hypoglycemic episodes when given as monotherapy. Available as 50mgm tablets, maximum is 100mgm/day. If hypo glycaemia develops in combination therapy, glucose should be used and not sucrose or table sugar.

d. Insulin analogue and short-acting regular insulin are useful. Lispro [22] insulin is an insulin analogue, has proline from position B28 to B29, thus Lispro hexamers dissociate more readily than regular human insulin hexamers into monomers. It is indicated for reduction of pre-prandial and post-prandial blood sugar. As it is a short acting insulin and it has to be used in conjunction with longer acting human insulin. It can- be taken with meals. It has rapid onset action and shorter duration of action than regular human insulin. If a person is taking 30/70 mixture of injection Human Mix tard insulin it can be changed to 50/50 i.e. containing equal parts of short acting and intermediate acting insulin.

e. Long acting basal insulin (Glargine) can also be used in order to bring fasting hyperglycemia and once fasting hyperglycemia is controlled, postprandial hyperglycemia may also be controlled to some extent.

f. Metformin 0.5 gm twice before meals can be tried to increase insulin sensitivity. Maximum dose of 3 gm can be tried if there is no GI intolerance.

g. Nateglinide and Repaglinide are non sulphonylurea drugs when taken before meals effectively reduce post meal hyper glycaemia. They are short acting anti-diabetic drugs.

Conclusion

Persistent post prandial hyper glycaemia in a diabetic is not desirable. It will lead to long term macro-vascular and micro vascular complications. Every effort should be made to bring it down to normal acceptable level. Current modalities of therapy to bring down prandial hyper glycaemia are briefly reviewed.

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DOI: 10.32474/ADO.2018.01.000124