Review Article

Management of diabetes mellitus in developing countries: The relevance of postprandial hyperglycaemia

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SUMMARY

The prevalence of diabetes mellitus is rising globally and its complications present an immense public health burden to all health economies world-wide. The objective of this review article is to present the relevance of postprandial hyperglycaemia in the management of diabetes, which should guide clinicians in developing countries. It will discuss the definition, epidemiology, pathophysiology, complications and treatment strategies for postprandial hyperglycaemia. Sources of Data/Study selection: The data search used in this review covered studies published from 1965-2008 obtained from recent international conferences, World Health reports, prevalence studies, hospital- based studies, registry reports, hospital statistics, government estimates, United Nations Resolution on diabetes, International Diabetes Federation Declarations and clinical practice guidelines. *Data Extraction:* The MEDLINE database, the internet (e-medicine, medscape resource centre), World Health and International Diabetes Federation Monographs were used for data extraction. The global explosion of diabetes as a pandemic is well recognized as well as preventive measures and effective treatments. This current knowledge however is under-utilized because in practice only about a third of people living with diabetes achieve optimum targets for glycaemic control. Hyperglycaemia is the central disorder in diabetes mellitus. It has been shown in several studies that the development of complications of diabetes is directly due to prolonged exposure of the body cells to glucose. There is a lot of emphasis on monitoring and treatment of fasting hyperglycaemia in diabetics. Drugs which target postprandial hyperglycaemia are not widely in use in developing countries. It is hoped that this review will emphasize the need to use these drugs to the benefit of our patients.

KEY WORDS: Diabetes mellitus, Postprandial, Hyperglycaemia, Advances, Pharmacologic therapy.

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INTRODUCTION

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.[1] It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular/macrovascular complications and diminished quality of life.

The prevalence of diabetes mellitus is becoming an epidemic globally. It currently affects 246 million

people worldwide, and without action, by 2025 this total is expected to increase to 380 million people.[2]

In Nigeria, the national prevalence of diabetes is 2.2% with higher prevalence in the urban than in rural communities.[3] The American Diabetes Association recommends Fasting Plasma Glucose (FPG) target of 3.9-7.2mmol/l, a HbA1c target of <7.0% and peak postprandial glucose levels less than 180mg/dl (10.0mmol/l).[4] The International Diabetes Federation recommends a target of <5.5mmol/l for FPG, <7.8mmol/l for 2hr PPG and <6.5% for HbA1c.[5] These targets are usually challenging for both the physician and the patient. In the United States, Saddine et al report that One in five diabetic persons (20%) still have poor glycaemic control despite improvement in the diabetes process of care in the last decade.[6] Glycaemic control remains poor in resource-poor countries such as Nigeria. In a study by Onunu in Benin, a town in southern Nigeria, 32.4% of the patients had poor glycaemic control.[7]

Postprandial hyperglycaemia: Recent studies indicate that elevated postprandial plasma glucose levels are an independent and clinically significant risk for cardiovascular disease in non-diabetic and diabetic individuals and is associated with a two-fold increase in cardiovascular risk.[8] Postprandial glucose (PPG) is usually measured two hours after a meal as it approximates the peak value in diabetic patients.[9] Post-challenge or post-load glucose refers to blood glucose level two hours after a glucose load (usually 75g) and is significantly correlated with post-meal glucose.[10] In a study by Avignon et al[10], a four point plasma glucose assessment was made and the values correlated with HbA1c levels. It was found that post-lunch (2.00pm) and extended post-lunch (5.00pm) values correlated significantly with HbA1c but that pre-breakfast and pre-lunch did not. These values also demonstrated better sensitivity, specificity and positive predictive value in predicting poor glycaemic control.

The relative contributions of FPG and 2hours PPG to HbA1c also varies with the level of HbA1c. When HbA1c is between 7.3% and 8.4% the impact of FPG and PPG are the same. As HbA1c levels decline, PPG becomes the main contributor to overall blood glucose control.[11] This suggests that targeting FPG is more beneficial when HbA1c levels are very high, while targeting PPG is more effective at lower HbA1c levels. This is in line with the ADA recommendations which say that preprandial glucose should be targeted first. Only when preprandial glucose is at goal, but HbA1c is not, is PPG targeted i.e. "fix the fasting first".[4]

Pathophysiology of postprandial hyperglycaemia: The PPG profile is determined by carbohydrate absorption, insulin and glucagon secretion, and their coordinated effects on glucose metabolism in the liver and peripheral tissues.[9] In people without diabetes, peak PPG occurs about one hour after a meal and generally does not exceed 140mg/dl. It returns to normal levels in two to three hours.[9] People with impaired glucose tolerance (IGT) or diabetes have poor automatic control of blood glucose after a meal. As a result, they often experience extended periods of elevated post-meal glucose levels.[5] A number of factors contribute to this, like insufficient secretion of insulin, decreased sensitivity to the action of insulin, an inability to suppress glucose output from the liver and deficiencies in other digestion-related hormones.[5] Excessive postprandial glucose excursions in diabetics are attributed to an abnormal first phase insulin response.[12] This is an early sign of beta cell dysfunction. This first phase insulin response should occur postprandially and promotes peripheral utilization of the glucose load and also suppresses hepatic glucose production. Patients with Type-2 diabetes also have an abnormal temporal pattern of insulin secretion, secreting more insulin basally than postprandially unlike in non-diabetic subjects in whom equal amounts are secreted basally and postprandially. The rapid insulin pulses in non-diabetic subjects are also abnormal in diabetics, being shorter and irregular in nature.[13]

Glucagon-like peptide-1 (GLP-1) is a gut hormone which is released postprandially. It acts by stimulating both insulin release and insulin gene expression. It also stimulates pancreatic beta-cell growth. It is responsible for the incretin effect which is the augmentation of insulin secretion following oral glucose.[14] This it does in concert with another hormone: Glucose-dependent insulinotropic peptide (GIP). In patients with Type-2 DM, there is a reduced secretion of GLP-1 resulting in a reduction in this incretin effect.[14] Deficiencies in these incretin hormones in people with Type-2 diabetes contribute to postprandial hyperglycaemia. There is also a deficiency in Amylin: A gluco regulatory peptide that is also co-secreted with insulin by the pancreatic â–cells.[15] A recent study showed that over 84% of people with Type-2 diabetes experience significantly elevated post-meal glucose.[16]

Postprandial hyperglycaemia and cardiovascular risk: Postprandial glucose has been seen to be a key player in the incidence of cardiovascular complica-

tions in diabetes. Temelkova et al reported that carotid-intima thickening is correlated with postprandial glucose levels and particularly with the glycaemic spikes during the OGTT.[17] A similar earlier study showed that postprandial plasma glucose is an independent risk factor for increased carotid intima-media thickness in non-diabetic individuals.[17] Hence postprandial glucose plays a significant role in the development of atherosclerosis. Various pathogenetic mechanisms are involved. Hyperglycaemia plays a direct role in vascular tone and endothelial damage. Acute hyperglycaemia produces hypertension by inducing endothelial dysfunction.[18] It has also been shown that in diabetic individuals' postprandial hyperglycaemia causes an overproduction of thrombin and this is strictly dependent on the level of blood glucose attained.[19]

Some large epidemiological studies viz the Hoorn study[20], the DECODE study[21] and the Funagata study[22] have clearly shown that the serum glucose level 2 hours after oral challenge with glucose is a powerful predictor of cardiovascular risk. The DECODE study concluded that 2hour blood glucose is a better predictor of deaths from all causes and cardiovascular disease than Fasting blood glucose.[21] The Funagata study showed that impaired glucose tolerance and not impaired fasting glycaemia predicted cardiovascular mortality in diabetic patients.[22]

In 2001, the American Diabetic Association issued a consensus statement on postprandial glucose: "In summary, there are insufficient data to determine accurately the relative contribution of the FPG and PPG to HbA1c. It appears that FPG is somewhat better than PPG in predicting HbA1c especially in Type-2 diabetes".[9] This provoked a lot of controversy and some authors have written reviews and commentaries either in favor of or against postprandial glucose monitoring, targeting and treatment.[23,24] In their recent standards of care for diabetes mellitus the ADA have added a postprandial glucose target of 180mg/dl (10mmol/l) as this corresponds to a HbA1c of <7.0%.[4]

Treatment of Postprandial hyperglycaemia: Dietary intervention is mainly the intake of food with a low glycaemic index and diets rich in minimally-processed, high-fiber plant-based foods. These positively impact postprandial dysmetabolism.[25]

Several pharmacological therapies specifically target post-meal glucose. These include the α-glucosidase inhibitors, glinides (rapid-acting insulin secretagogues) and insulins (rapid-acting insulin analogues, biphasic [premixed] insulins, inhaled insulin, human regular insulin).[5]

In addition, new classes of therapies for managing post meal plasma glucose in people with diabetes (amylin analogs, glucagons-like peptide-1 [GLP-1] derivatives, dipeptidy 1 peptidase 4 [DPP-4] inhibitors) have shown significant benefits in reducing post-meal plasma glucose excursions and lowering HbA1c.[26]

Acarbose, the typical alpha-glucosidase inhibitor acts specifically at the level of postprandial glucose excursions. It inhibits the enzyme: alpha-glucoidase, which breaks down disaccharides thus delaying carbohydrate absorption from the gut. In a meta-analysis it was found to reduce cardiovascular events by 35%.[27] In patients with impaired glucose tolerance it lowers the incidence of newly diagnosed diabetes by 36.4%.[27]

Nateglinide, an insulin secretagogue was found to reverse the impairment of early insulin response after a glucose load which resulted in postprandial hyperglycaemia.[12] It has a similar action to sulphonylureas.

The International Diabetes Federation in 2007 published guidelines for the management of post-meal glucose.[5] They concluded that there is a strong association between post-meal and post-challenge glycaemia and cardiovascular risk and outcomes in people with normal glucose tolerance, IGT and diabetes, as well as an association between hyperglycaemia and oxidative stress, inflammation, carotid intima-thickening and endothelial dysfunction all of which are known markers of cardiovascular disease. They recommended that the goal of glycaemic therapy should be to achieve glycaemic status as near to normal as safely possible in all three measures of glycaemic control namely: HbA1c, fasting and post-meal glucose. Their recommendation is that people with diabetes should keep post-meal blood glucose below 7.8mmol/l (140mg/dl) during the two hours after a meal.[5]

Advances in the Pharmacologic Management of Postprandial glycaemia: The beginning of the 21st century witnessed multiple advances in the pharmacologic management of Type-2 diabetes. Large scale intervention studies highlight pharmacologic limitations in safely achieving normoglycemia in diabetes. Attaining a balance of tight postprandial control while maintaining normal homeostatic mechanisms to prevent hypoglycemia is difficult with our traditional therapies. There is need for novel physiologic-based therapies that effectively normalize both fasting and postprandial glucose, limit hypoglycemia and weight gain.

Insulin and sulfonylureas are highly effective glucose-lowering agents. However, they continuously promote insulin action to lower glucose and are not discriminating enough to cease action when blood glucose declines to unsafe levels.

Thiazolidinediones are potent insulin sensitizers targeting a key pathogenic defect in Type-2 diabetes: insulin resistance. They effectively lower fasting and postprandial glucose levels and are not associated with significant hypoglycemia, but they are associated with weight gain and edema, with concerns of increase in congestive heart failure.[28]

Incretin mimetics: Incretins are hormones produced by the gastrointestinal tract in response to nutrient entry, which then stimulate insulin secretion in a glucose-dependent manner. The first incretin Glucose insulinotropic peptide (GIP) was characterized and purified in the 1970s.[29] This mechanism of action targets postprandial glucose control and limits the potential for enhanced insulin secretion in the absence of hyperglycemia, thereby limiting the risk for hypoglycemia.[29]

Incretin mimetics also slow gastric emptying and promote satiety resulting in diminished calorie intake and subsequent weight loss. Exenatide and Liraglutide are commercially available incretin mimetics.

Incretin Enhancers – Dipeptidyl Peptidase-4 Inhibitor: The first oral DPP-4 inhibitor, sitagliptin, was approved by the FDA in October 2006 as monotherapy or adjunctive therapy in the treatment of Type-2 diabetes. DPP-4 inhibitors are incretin enhancers that increase the secretion of endogenous active incretin hormones.[30]

As with GLP-1 analogs, insulin secretion is enhanced in a glucose-dependent manner, limiting the potential for hypoglycemia. Consistent with its mechanism of action, DPP-4 inhibitors lower both fasting and postprandial glucose levels.

In a meta-analys, DPP-4 inhibitors lowered HbA1c to a mean of -0.74% compared with placebo.[30] Without any effects on gastric emptying or satiety, DPP-4 inhibitors are weight-neutral and do not cause significant nausea or vomiting.[31] In clinical studies, an increased incidence of nasopharyngitis, urinary tract infection, and headache has been seen with DPP-4 inhibitors.[30]

Amylin Agonists: Amylin is a peptide hormone that is co-secreted with insulin from the pancreatic ß-cell and is thus deficient in diabetics.[15] It inhibits glucagon secretion, delays gastric emptying, and acts as a satiety agent. Amylin replacement could therefore possibly improve glycemic control in some people with diabetes.

However, human amylin exhibits physicochemical properties predisposing the peptide hormone to aggregate and form amyloid fibers, which may play a part in ß-cell destruction in Type-2 diabetes.[32] This obviously makes it unsuitable for pharmacological use. A stable analog, pramlintide, which has actions and pharmacokinetic and pharmacodynamic properties similar to the native peptide, has been developed.[33] Several large-scale phase III studies involving more than 3,000 diabetic individuals have demonstrated a beneficial effect of amylin replacement on the HbA1c level in both Type-1 and Type-2 diabetes without an increased number of hypoglycaemic events and weight gain.[33,34] In fact a significant and sustained weight reduction for one year has been observed in Type-2 diabetic patients.[35]

Pramlintide has been shown primarily to reduce prandial glucose excursions, which plays a role in the development of cardiovascular complications. However, it would be important to further characterize responders to amylin analogs Vs nonresponders, in terms of both reduction in HbA1c and weight loss, in order to delineate the group of patients who will benefit from treatment.

CONCLUSION

Hyperglycaemia is the central disorder in diabetes mellitus. It has been shown in several studies that the development of complications of diabetes is directly due to prolonged exposure of the body cells to glucose. There is a lot of emphasis on monitoring and treatment of fasting hyperglycaemia in diabetics. The treatment of postprandial hyperglycaemia in diabetics will address the problem of those with normal fasting plasma glucose levels yet sub-optimal HbA1c levels.

Drugs which target postprandial hyperglycaemia are not widely in use in developing countries. It is hoped that this review has emphasized the need to use these drugs to the benefit of our patients.

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