Increasing evidence suggests that post prandial state is a contributing factor for the development of atherosclerotic macrovascular disease. Post prandial hyperglycaemia [PPH] significantly contributes towards overall glycaemic control as reflected by Haemoglobin A1c [HbA1c]. Impaired glycaemic control as indicated by raised HbA1c is associated with chronic vascular complications of diabetes such as micro vascular and microvascular diseases and maintenance of HbA1c in normal or near normal range leads to significant reduction of micro vascular complications. Post prandial blood glucose depends on several factors such as amount and the type of food consumed, delay and deficiency of insulin secretion, and excess of post prandial glucagon secretion. There are various ways to asses PPH, and conventionally it is assessed by measurement of plasma glucose two hours after beginning of a meal. However mere single point value at 2 hours after meal does not convey the full implications of PPH. Furthermore, HbA1c does not fully reflect the implications of PPH. Acute glycaemic excursions, which cause detrimental effect on vasculature through severe oxidative stress, are not picked up by HbA1c estimation.

For a long time, PPH\ post glucose challenge hyperglycaemia has been more strongly associated with macro vascular disease as compared to fasting hyperglycaemia as brought out by several observational studies. However, whether PPH was a marker of vascular disease or a risk factor for the same was not very clear, particularly since PPH was also associated with post prandial hypertriglyceridemia. Recently it has been documented that both hyperglycaemia and hypertriglyceridemia independently induce endothelial dysfunction through oxidative stress. Stop NIDDM study which was a primary prevention study to prevent onset of diabetes in those with impaired glucose tolerance, also had secondary end points which included study of relative risk reduction of fresh myocardial infarction, cardio vascular mortality and new onset hypertension. In this study, an alpha glucosidase inhibitor, acarbose, was compared with the placebo for relative risk reduction of new onset diabetes and above mentioned cardio vascular complications. In this study, efficacy of acarbose in prevention of diabetes, which was a primary end point, as well as relative risk reduction for myocardial infarction, cardio vascular death and new onset hypertension, which were secondary end points, was proved. Thus, the role of reduction in post prandial blood glucose in reduction of macro vascular disease was proved. [Acarbose was given to those having impaired glucose tolerance.

**MECHANISM INVOLVED:**

Acute increase in blood glucose levels as it occurs in post prandial state in diabetes directly affects most of the other cardio vascular risk factors. It has been shown that in patients with type 2 diabetes, LDL oxidation rapidly increases in post prandial state in tandem with post prandial glycemic excursion. Endothelial function is impaired in diabetes. Hyperglycaemic spikes induce endothelial dysfunction both in normal as well as in patients with diabetes. This effect is probably mediated through reduced production or bioavailability of nitric oxide. Post prandial hyperglycaemia causes overproduction of thrombin and abnormalities in various other factors associated with coagulation as such as shortening of fibrinogen half life. Increase in circulating levels of adhesion molecules as well as various markers of inflammation such as interleukin-6, TNF-α has been demonstrated in during the hyperglycaemic spikes. Several indirect and direct evidences support the concept that acute hyperglycaemia works through the production of oxidative and nitrosative stress.

**TARGETS FOR POST PRANDIAL GLYCEMIC GOALS:**

Two hours post meal plasma glucose should not exceed 140 mg% as long as hypoglycaemia is avoided. It is important to note that there is a tendency to monitor post lunch blood glucose by ordering lab tests and to assume that post breakfast and post dinner blood glucose values would be identical. In reality, often these values differ significantly. Post breakfast plasma glucose is often higher than post lunch value, even in those who take a lighter breakfast. Similarly, many eat heavier dinner as compared to lunch and thus end up having higher post dinner plasma glucose value. Thus it is important to encourage the patient to do frequent self monitoring with glucometer and test at all the post prandial times in rotation. Even in those who are not self monitoring, high HbA1c in spite of good control over
fasting and post lunch plasma glucose should lead to the suspicion of poor post prandial control at other post prandial periods.

MANAGEMENT OF POST PRANDIAL HYPERGLYCAEMIA IN A DIABETIC PATIENT;

Multi pronged approach should be followed. Meal planning should include adjustment of total calories consumed as per weight and daily physical activity, consuming total daily food quantity in the form of small frequent meals and avoidance of simple carbohydrates such as sugar. Appropriate physical activity should be encouraged. These simple non pharmacological measures go a long way in reducing the post prandial excursions however most of the patients will require additional pharmacological therapy to attain satisfactory glycaemic control including control of PPH.

PHARMACOLOGICAL TREATMENT:

We will take an overview of anti diabetic agents with specific pharmacokinetic and or pharmacodynamic properties making them more suitable for management PPH and then see how to incorporate them in individual patient’s plan depending upon his specific requirement.

Meglitinides: [repaglinide and nateglinide]

Mechanism of action and limitations of these agents resemble those of sulphonylureas [SU]. Thus they are of no use in type 1 diabetics and type 2 diabetics with severe reduction in beta cell mass. Rapid absorption from the GI tract leads to better post prandial control as compared to SU’s. Thus they are more suitable for post prandial blood glucose control. On the flip side, they are eliminated more rapidly than SU’s and thus they are weaker than SU’s for fasting blood glucose control and need to be given before each meal.

Place of meglitnanes in therapy;

1. Type 2 diabetics with predominantly post prandial hyperglycaemia. These agents are more suitable than SU’s in elderly and those who have mild renal impairment as these situations increase the chances of hypoglycaemias. Shorter half life makes meglitinides less pone to hypoglycaemias, particularly, severe, prolonged ad recurrent episodes.

2. As add on to metformin or glitazones in those type 2 diabetics with good fasting glucose control but inadequate post prandial control.

Alpha Glucosidase Inhibitors; [AGI- Acarbose, Miglitol, Voglibose]

These agent act on the small intestine and slow down the digestion of complex carbohydrates in to glucose by inhibiting alpha glucosidase enzymes in small intestinal mucosal brush border. Thus conversion of ingested complex carbohydrates to glucose occurs over longer period in a phased out manner leading to more gradual absorption of glucose in to the circulation and blunting of post prandial peaks. Mechanism of action of AGI is complimentary to all other anti diabetic agents including insulin and thus they can be co prescribed with all of them as per the situation in an individual patient. The effect on fasting plasma glucose is lesser.

Place of AGI’s in therapy:

1. As solo agents in those having isolated post prandial hyperglycaemia.

2. As add on agents along with any mainline anti diabetic agent, if post prandial blood glucose control is inadequate. AGI’s can be co prescribed with all mainline oral anti diabetic agents

AGI’s can be combined with basal insulin if required.

Incretin Mimetics: Exenatide is a synthetic substance resembling GLP1 in structure and is resistant to the action of DPP4 inhibitors. It shares the properties of GLP1 such as:

It stimulates post prandial insulin release from viable pancreatic beta cells in glucose dependant manner.

It inhibits inappropriate post prandial glucagon release from pancreatic alpha cells.

It delays gastric emptying.

It suppresses appetite.

All these actions lead to reduction of blood glucose with more pronounced effect on post prandial blood glucose as compared to fasting blood glucose.

Exenatide is suitable for type 2 diabetics with some viable beta cells particularly if they have predominantly post prandial hyperglycaemia. It can be combined with oral anti diabetic agents such as SU’s and metformin. It is injected subcutaneously twice a day. Since its use leads to significant weight reduction in a majority of the patients, it is particularly suitable for overweight patients.

DPP4 inhibitors: [sitagliptin and vildagliptin ]

These are orally active agents which act by inhibiting DPP4, an enzyme which is secreted in small intestine in close proximity to cells secreting incretins such as GLP1 and GIP. DPP4 splits m incretins immediately after their secretion in small intestine. Thus inhibition of DPP4 leads to increase in plasma levels of natural incretins by 2 to 4 folds, which ultimately lead to blood glucose reduction with more pronounced effect on post prandial blood glucose by the mechanisms described above.

Place of DPP4 inhibitors in the therapy: High cost is the main limitation of these agents, otherwise they are ideal for replacing SU’s as they are not associated with two major drawbacks of SU’s, namely weight gain and hypoglycaemias.

Rapid acting insulin analogues: [ Lispro,Aspart and Glulisine ]

Traditionally short acting insulin has been used for achieving post prandial glucose control. However its main drawbacks include slower absorption from injection site and slower elimination from the circulation. Thus sometimes inadequate post prandial
control and late post prandial hypoglycaemia result. Rapid acting insulin analogues were specifically developed to address these deficiencies of short acting human insulin. They are absorbed in circulation faster than short acting insulin and thus their use leads to better post prandial blood glucose levels and lesser episodes of late post prandial hypoglycaemia. Thus rapid acting insulin analogues can be considered in those on short acting insulin with inadequate post prandial blood glucose control or in those who develop late post prandial hypoglycaemia. It should be noted that good control over fasting and pre meal blood glucose values leads to better post prandial control. Thus, one should not reduce the emphasis on fasting blood glucose control.

CONCLUSIONS:

Even though there are some loose ends still to be tied up, there is significant accumulated evidence suggesting the role of post prandial hyperglycaemia in causation of atherosclerotic macro vascular disease, which is a major cause of mortality in patients with diabetes, particularly type 2 diabetes. Thus all the major associations have come out with specific guidelines regarding the post prandial glycaemic goals. While managing patients with diabetes, the clinicians should plan the strategies so as to reach both the glycaemic goals, i.e. HbA1c <7% and 2 hours post prandial blood glucose < 140 mg%. Judicious use of appropriate mainline anti diabetic agents will lead to attainment of both the glycaemic goals in the majority. Whenever indicated agents specifically suited for post prandial glycaemic control should be introduced in the therapy.

REFERENCES: