Addressing the Glucose Triad for Comprehensive Glycemic Control

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INTRODUCTION
Type 2 diabetes mellitus (T2DM) has reached pandemic levels in India. It is characterized by worsening metabolic control as the disease progresses incessantly in spite of all known treatments, causing micro- and macrovascular complications, leading to severe morbidity and mortality. Since the publication of the seminal UK Prospective Diabetes Study (UKPDS) in the late 1990s, controlling blood glucose as measured by glycosylated hemoglobin (HbA1c) has been the cornerstone for the management of T2DM. This in turn is a function of the values of fasting plasma glucose (FPG) and postprandial plasma glucose (PPPG), an integrator of fasting and prandial glycemic disorders. This relationship between HbA1c, FPG and PPPG, therefore, play a central role in the metabolic changes central to T2DM and this troika is known as the glucose triad (Figure 1).

Early and sustained control of glycemia remains important in the management of T2DM. Recent publications suggest that simply driving down HbA1c levels may not be enough to prevent complications of diabetes and seems to suggest that there are other factors which play a role in glucose control may need to be addressed. The contribution of postprandial glucose levels to overall glycemic control and the role of postprandial glucose targets in disease management are currently debated. There has also been some interest in the concept of glucose variability. There seems now to be a paradigm shift to include awareness of the components of the glucose triad, the existence of glucose variability and their potential influence on the choice of pharmacological treatment both at diagnosis and through the course of the disease and it is being progressively accepted that treatment should address all these areas.

THE IMPORTANCE OF LOWERING HbA1c
The UKPDS established that HbA1c is the best prognosticator for T2DM and its complications. Since its publication in the late 1990s, clinicians worldwide were driven by the concept of "lower the better". However, the publication of three trials in quick succession: The Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Veterans’ Affair Diabetes Trial (VADT) trials, raised concerns about stringent control of HbA1c, indicating that it could be harmful to some patients. Indeed the ACCORD trial was stopped midway when it was found that there was an increase in mortality for patients who were treated to a target HbA1c of less than 6%. What it also showed was that patients who suffered from severe hypoglycemia had an increased risk of death even if they were not in the intensive control arm of the study. The ADVANCE and VADT studies failed to show any improvement in cardiovascular mortality or morbidity in spite of good glycemic control. To add to this, a retrospective cohort study of databases maintained by UK general practitioners published in 2010, (albeit with multiple shortcomings) suggested that the optimal HbA1c was 7.5%, lesser or higher being equally harmful.

The mortality and morbidity from T2DM continues unabated and is worsening. The conundrum, however, now is that if driving down HbA1c is not of benefit, what is? There has been much interest in the last few years in the concepts of daily glycemic variability and postprandial glucose excursions contributing to the HbA1c levels and indeed to the pathology of dysglycemia-induced complications. Though till date there has been no convincing evidence to indict any of the two parameters, the debate on these two areas particularly that of targeting PPPG levels, has reached an interesting stage.

POSTPRANDIAL GLUCOSE EXCURSIONS AND GLYCEMIC VARIABILITY
Type 2 diabetes mellitus is a progressive disease which is initially characterized by glycemic excursions higher than 140 mg/dL. In
fact, in the initial stages of T2DM, HbA1c levels are usually well-controlled along with normal FPG levels. As the disease progresses, fasting hyperglycemia appears to be quickly followed by night-time hyperglycemia as well.

The initial defect of postprandial hyperglycemia is due to the loss of first phase insulin response, which is the release of insulin 5 minutes after food intake. This response is responsible for reducing hepatic gluconeogenesis and sensitizing the liver and muscle to glucose uptake.6

With the progress of T2DM, resistance to insulin action in peripheral tissues is coupled with progressive deterioration in beta-cell function leading to reduced insulin secretion and action. Increased FPG levels in T2DM are largely attributable to reduced hepatic sensitivity to insulin leading to overproduction of glucose by the liver during the overnight fast. The causes of raised PPPG are not so clear cut and well-defined being dependent on multiple variables. They are dependent on the glucose load at the meal, the premeal glucose levels, the insulin response and sensitivity of the individual and of course the incretin secretion from the gut. The incretin hormones, glucagon-like peptide (GLP)-1 and gastric inhibitory polypeptide are released by the intestine in response to ingestion of carbohydrate. These hormones enhance insulin secretion, reduce glucagon production, suppress hepatic glucose production and decrease gastric emptying and have a greater effect on PPPG than FPG levels. Patients with T2DM have reduced levels of the incretin hormones. 

Though different in the way FPG and PPPG levels are regulated, both FPG and PPPG contribute to the HbA1c levels in T2DM. At higher levels of HbA1c, the FPG contributes more to the HbA1c levels while when HbA1c levels are around less than or equal to 8%, the contribution is more from PPPG.11

Epidemiological studies have suggested that elevated PPPG is associated with complications of T2DM.15 The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM)13 Trial, suggested that control of PPPG in patients with impaired glucose tolerance, using acarbose, improves cardiovascular outcomes. This has been replicated in a meta-analysis on acarbose in T2DM.14 However, this has not been replicated in two large studies: Hyperglycemia and its effect after acute myocardial infarction on cardiovascular outcomes in patients with Type 2 Diabetes (HEART2D)15 Study and the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR).16 In fact the NAVIGATOR trial showed no benefit of using Nateglinide to reduce PPPG, and indeed suggested deleterious consequences.

However, much the debate may persist about the pros and cons of treating PPPG, one point has been highlighted and impressed by the publication of UKPDS “legacy” effect,17 ACCORD, VADT and ADVANCE studies. Whether it is fasting or postprandial hyperglycemia, the targets should be set early in the course of the disease and treatment must be aggressive at the onset of disease, because aggressive treatment of hyperglycemia later on in the disease is bound to lead to unhealthy consequences.

It is also important to note that glucose spikes may contribute to overall glycemic control. As Figure 2 shows that for even a well-controlled individual, there may be huge spikes of blood glucose particularly post meals or otherwise too. Some recent data suggests that this may be an independent risk factor for both micro- and macrovascular complications of T2DM, though this remains a matter for further research and debate.18

It is, surmised, that glycemic variability, postprandial hyperglycemia and chronic dysglycemia, worsen oxidative stress in T2DM, leading to release of superoxide radicals—this is considered to be the cause of diabetic complications at a molecular level.19,20 It is, therefore, no surprise that current evidence and debate seems to be looking at treatment modalities that target all these areas. In other words, it is increasingly being felt that the best bet for managing T2DM would be to address the Glucose Triad of FPG, PPPG and HbA1c.

Figure 2: Individual 24-hour recordings from a continuous glucose monitoring system in four patients with type 2 diabetes on insulin therapy and a mean HbA1c of 6.7%. Source: Ceriello A. The glucose triad and its role in comprehensive glycemic control: current status, future management. Int J Clin Pract. 2010;64(12):1705-11
MANAGING THE GLUCOSE TRIAD

The current evidence for managing hyperglycemia would suggest that the best way of managing T2DM would be to set stringent goals for HbA1c, fasting and postprandial glucose levels, while avoiding hypoglycemia. The 2012 American Diabetes Association (ADA) guidelines have taken all the evidence and have made recommendations which are aimed at addressing the glucose triad while ensuring that the “one size fits all” philosophy is not applied to the management of T2DM.

The recommendations of the ADA addressing the glucose triad advises that the goal HbA1c levels should be less than 7.0%, with FPG levels between 70 mg/dL and 130 mg/dL and PPPG levels less than 180 mg/dL, 1–2 hours after a meal. The recommendations advise that initial premeal plasma glucose levels should be targeted to control HbA1c and if in spite of controlling premeal plasma glucose levels, HbA1c remains outside of target range, prandial glucose levels should be monitored and addressed. However, it lays down a few caveats which are highly practical and applicable in view of the recent evidence:

- In advanced age or if life expectancy is short and in presence of other comorbidities these levels must be relaxed
- If the duration of diabetes is prolonged and if micro- and macrovascular complications are well-established and advanced the target levels should be set much lower
- Hypoglycemia must be avoided at all costs and in people with hypoglycemia unawareness, lax glycemic control is warranted
- However, if the person is young with recent onset diabetes and no comorbidities or complications the recommendations suggest that stringent goals be set for such individuals.

Whatever be the HbA1c goals, literature suggests that it cannot be achieved without addressing both FPG and PPPG levels. This should be done through lifestyle modification, drugs and when needed insulin therapy.

Lifestyle modification plays a big role in the management of T2DM. Particularly in obese T2DM, weight loss through low fat, low carbohydrate and high fiber diet is recommended. Diabetics are advised to take foods which have a low glycemic index, in other words, low carbohydrate meals containing carbohydrates which are slowly digested and absorbed preventing rise and spikes of PPPG. The importance of exercise cannot be over emphasized as it improves insulin sensitivity and glucose utilization which would help in reducing both FPG and PPPG.

Metformin has been universally accepted as the first-line pharmacological therapy worldwide. It reduces hepatic glucoseogenesis, improves insulin sensitivity and reduces intestinal glucose absorption. It causes a reduction of HbA1c of ~ 1% when compared to placebo over 3 months in a dose of 1,500 mg per day. It mainly reduces FPG and has little effect on PPPG, but it is weight neutral and does not cause hypoglycemia. This, in addition to it being the only proven drug to reduce cardiovascular morbidity and mortality, makes it the choice of all august bodies worldwide for the treatment of T2DM.

Thiazolidinediones (TZDs), pioglitazone and rosiglitazone, were put on the same pedestal as metformin as being almost a replacement for metformin from its ability to reduce HbA1c by 1-1.25%, yet not cause any hypoglycemia and act favorably on lipid levels. However, recent evidence has highlighted the risks associated with TZD use including worsening cardiovascular mortality, risk of bladder cancer and osteoporosis, which has well-nigh put this group of drugs on the back burner of the diabetes pharmacotherapy armamentarium.

Sulfonylureas are tried and tested drugs which when taken in the morning reduce PPPG and have a lasting effect on FPG thereof. It causes a HbA1c reduction of 1.5%, but is associated with hypoglycemia and a recent meta-analysis has suggested that with the exception of Gliclazide all other sulfonylureas are unsafe from cardiovascular point of view. However, its low cost and ability to address each component of the glucose triad efficaciously keeps it still one of the best drugs for the comprehensive glycemic control.

Alpha glucosidase inhibitors (AGI) reduce HbA1c levels by ~ 1% when used in supramaximal doses (for e.g. 200 mg of acarbose). They are difficult to tolerate in such doses causing severe gastrointestinal upset. In doses which are tolerated AGI produce small reductions of HbA1c impacting PPPG having almost no effect on FPG.

The newer incretin mimetics though expensive have been a revelation in targeting various aspects of the glucose triad. There are two types of Incretin mimetics: (1) the orally used Dipeptidyl peptidase (DPP)-IV inhibitors and (2) the injectable and more expensive GLP-1 analogues. These drugs work on the incretin axis increasing insulin secretion and reducing glucagon secretion from the pancreatic islets. They do not cause hypoglycemia and the injectable GLP-1 analogs cause significant weight loss. However, they are “new kids on the block” and their long-term safety remains yet to be tested.

The DPP IV Inhibitors, reduce HbA1c by 0.7-0.9%, have a significant effect of reducing FPG by ~ 20 mg/dL and PPPG by ~ 50 mg/dL. In Indian subjects, their efficacy seems even more showing reduction of HbA1c by 1.2% at 24 weeks with FPG reduction of 31 mg/dL. The GLP-1 analogs cause a HbA1c reduction of 1-1.6% when used as monotherapy. They reduce FPG by ~ 20 mg/dL and PPPG by ~ 40 mg/dL. These effects are compounded when used along with other agents like Metformin.

The DPP IV Inhibitors and GLP-1 analogs therefore, appear to be an ideal choice of drug to address the glucose triad.

An ideal approach to the treatment of a patient with newly diagnosed type 2 diabetes might be to start with the combination of metformin and a DPP-4 inhibitor. This combination effectively targets the two key pathophysiological features of type 2 diabetes: (1) loss of first phase insulin secretion and (2) insulin resistance. Clearly this might also be the ideal way to address the vagaries of the glucose triad. In addition, best evidence suggests that this combination would also make the patient least susceptible to glycemic variability.

CONCLUSION

The Glucose triad comprising the dynamics between HbA1c, FPG and PPPG, has been drawing a lot of interest of late, as recent evidence suggests that lowering HbA1c as much as possible might not be a panacea to treating the hyperglycemia of T2DM and in fact might be detrimental. The implications of PPPG excursions and glycemic variability are drawing a lot of debate. However, best practice still remains to reduce and control all the three arms of the glucose triad without avoiding hypoglycemia at all costs. The best option at this point seems to be to implement lifestyle changes and introduce pharmacotherapy in the form of metformin and DPP IV inhibitors early on in the life history of T2DM. It is felt that this combination would best address the glucose triad, avoid hypoglycemia and probably prevent or postpone long-term complications of this disease.

REFERENCES

Chapter 36  Addressing the Glucose Triad for Comprehensive Glycemic Control


