The Glycemic Pentad: Role Of Insulin Analogues

**Corresponding Author:**
Dr. Sanjay Kalra,  
Endocrinologist, Bharti Research Institute of Diabetes and Endocrinology, 132001 - India

**Submitting Author:**
Dr. Sanjay Kalra,  
Endocrinologist, Bharti Research Institute of Diabetes and Endocrinology, 132001 - India

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The Glycemic Pentad: Role Of Insulin Analogues

Author(s): Kalra S , Kalra B

Introduction

Achieving glycemic control is the main aim of diabetes care, and near euglycemic levels are targeted to minimize the risk of developing chronic complications of the condition. Large trials have demonstrated the benefits of glycemic control in both type 1 and type 2 diabetes (1,2). Good glycemic control means effective targeting of fasting plasma glucose (FPG), postprandial plasma glucose (PPPG) and glycated hemoglobin (HbA1c), together known as the glucose triad (3). In spite of adequate control of the triad, however, diabetic complications do occur, and recent trials have shown an increase in mortality inspite of good HbA1c (4).

This has led to the emergence of a fourth aspect of glycemic control, i.e., glycemic variability, which needs to be minimized for effective diabetes care (3). This is included in the concept of the glycemic tetrad. A fifth angle, however, which has emerged recently, is quality of life. Just as it is important to target glucose levels, it is necessary to ensure good quality of life with any anti-diabetic medication (5).

These concepts can be unified as a ‘The Glycemic Pentad,’ and need to be kept in mind while planning any diabetes management strategy. This article reviews current information regarding the role, utility and importance of modern insulin analogues with respect to all angles of the Glycemic Pentad.

Table 1: The Glycemic Pentad

<table>
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<th>Fasting Plasma Glucose</th>
<th>Postprandial Plasma Glucose</th>
<th>HbA1c</th>
<th>Glycemic Variability</th>
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| Fasting hyperglycemia is mediated by excessive hepatic insulin resistance, normal muscle insulin sensitivity, a decrease in first phase (0-10 min) insulin secretory response to intravenous glucose, a reduced early phase (0-30 min) response to oral glucose, and normal late --phase (60-120 min) insulin response to oral glucose(3). High FPG has been shown to increase the risk of retinopathy, microalbuminuria, renal failure, as well as cardiovascular death, heart failure, coronary artery disease, stroke, and all cause mortality (6-9). Variability of FPG (measured as variation coefficient (CV) of FPG) is an independent risk factor for proliferative retinopathy, and is inversely related to survival of patients with type 2 diabetes (10,11). FPG of 110 mg% has been shown to increase the risk of cardiovascular events by 1.33 (1.06-1.67) with respect to an FPG of 75 mg% (12). An effective anti-diabetes regime, therefore, should target FPG, while reducing the variability of FPG as well. While choosing of an oral drug or insulin, one should take these factors into account. Post Prandial Plasma Glucose: Postprandial hyperglycemia is linked with normal or slightly reduced hepatic insulin sensitivity, severe muscle insulin resistance, defective early phase insulin secretion in response to oral glucose, and a severe deficit in late --phase insulin response to glucose load (3). Many epidemiological and interventional studies have shown an independent link between high PPG and cardiovascular disease, retinopathy, neuropathy, and nephropathy (13,14). The role of PPG as an independent risk factor is less clear for microvascular complications than macrovascular ones (3). A 2 hour glucose level of 140 mg% is associated with a relative risk of cardiovascular events of 1.58 (12). The importance of controlling post-prandial hyperglycemia, thus, can not be ignored, and modern diabetes management should focus on this as well. HbA1c is the stable adduct of glucose at the N-terminal amino group of the β-chain of HbA1c, formed by a post --translational modification which forms an unstable Schiff base, and later, a stable ketoamine. Total glycohemoglobin refers to HbA1c as well as products of glycation at certain lysine residues on the Hb a and β--chains (15,16). HbA1c is the gold standard for assessment of glycemic control. Many trials have shown the correlation between reduction in HbA1c and reduction of micro- as well as macro vascular complications (1,2). The UK Prospective Diabetes Study (UKPDS) in type 2 diabetes, and the Diabetes Complications and Control Trial (DCCT) in type 1 diabetes patients, have shown reduction in risk of chronic complications with improvement in HbA1c (1,2). HbA1c correlates with the average glycemia over the preceding 8-12 weeks. Hence, all anti --hyperglycemic drugs, new or old, are measured by their ability to reduce HbA1c, and this is often taken as a measure of quality of life.
efficacy. However, variability is noted in individual mean glucose concentrations for a given HbA1c. At the same time, the mean glycemic value (MGV) is determined not only by the various FPG and PPG values, but also by glycemic swings. To give a simple example, a person with PG values of 100 and 200 will have an MGV of 150 while another individual with PG values of 50 and 250 will also have an MGV of 150. Taking HbA1c alone as a therapeutic target, therefore, is not enough.

Variability

The limitations of HbA1c and point glucose estimation as markers for glycemic control has led to the emergence of glycemic variability as a fourth target for therapy. The acceptance of variability as an endpoint for treatment has spawned the term ‘glycemic tetrad’ (3). Authors of the DCCT have hypothesized that mean HbA1c is not the most complete expression of degree of glycemia. Complication risk might be linked to glycemic excursions, which generate reactive oxygen species (ROS) and lead to oxidative stress. Apoptosis is markedly increased and the production of protein kinase C enhanced in human umbilical vein endothelial cells exposed to periodic hyperglycemia (17), and cells cultured in a medium with glycemic fluctuations produce larger amounts of markers of oxidative stress (18).

In vivo studies have revealed direct relationship between mean amplitude of glycemic excursion (MAGE) and urinary excretion of 8-iso- PGF2a, a marker of oxidative stress (19). Glycemic swings have shown to be more harmful to the endothelium, measured by flow-mediated dilation, than stable hyperglycemia (20). A retrospective analysis of DCCT data has demonstrated that glycemic variability is linked to development of microvascular complications (21).

This body of evidence, therefore, means that variability of action, or predictiveness, should be an important consideration when deciding the pros and cons of a particular therapy (3). One should search, therefore, for a therapy with minimal intra-and inter-individual variability.

Quality Of Life

Quality of life forms the fifth angle of the Glycemic Pentad, along with FPG, PPG, HbA1c variability. Any diabetes medication should be assessed with regards not only to physician-reported outcomes, such as blood glucose or HbA1c, but also by patient–reported outcomes (PROs).

Patient reported outcomes are gaining ground as a therapeutic target in diabetes and other chronic disease, as they reflect the patient’s opinion about disease state or health status. PROs include various measures, including quality of life (QoL), as well as indices related to treatment satisfaction, mental health, social life, and diabetes management and well being. A recent tool is the MIND Youth Questionnaire (MK-Q) (5). Which is used to assess psychosocial health in pediatric diabetes. Other tools include the Diab Met Sat questionnaire (22). The Diab Met Sat questionnaire has 21 items which can be assessed as an overall score or as three subscales: burden (11 items), symptoms (5 items) and efficacy (5 items) and efficacy (5 items).

Modern Insulins And The Glycemic Pentad

Traditional anti-diabetic therapy, including oral drugs and the older insulins had some shortcomings, including the risk of hypoglycemia, high intra-individual and inter individual variability, high index of intrusion (e.g. having to take a tablet or injection 30 minutes before meals), poor quality of life, and poor satisfaction with medical therapy.(23) The poor acceptance of traditional insulins was in part because of their unphysiological action profile, which did not match with food absorption patterns, and therefore, led to unacceptable post-meal hyperglycemia, and pre-meal hypoglycemia.

The risk of hypoglycemia and the glycemic swings to the variability of control achieved with these drugs. Modern insulins, or insulin analogues, such as insulin detemir, aspart and lispro, have a more physiological time-action profile, and less variability. These attributes, combined with good efficacy, safety and tolerability, ensure better quality of life with these drugs. The freedom and flexibility of time of administration means a lower index of intrusion into the patient’s lifestyle.

Modern Insulins And Variability

Insulin analogues have been shown to be associated with lower risks of hypoglycemia, lower levels of postprandial glucose excursions, better patient adherence, greater quality of life, and higher satisfaction with treatment. The long-acting basal analog insulin detemir has the additional advantage of producing less weight gain, which has been considered until now an almost inevitable consequence of insulin replacement.(23) In a study, nine healthy male volunteers received subcutaneous injections of soluble insulin (0.2 U/kg) in the abdominal region on each of the four study days. Another 10 volunteers received an injection of insulin aspart four times. Glucose infusion rates necessary to neutralize the blood glucose-lowering effect of the administered insulin were registered during euglycemic glucose clamps (blood glucose 5.0 mmol/l; basal intravenous insulin infusion 0.15 mU x kg(-1) x
min(-1) over the subsequent 600 min. In comparison to soluble insulin, subcutaneous injections of insulin aspart led to a more rapid onset of action and a shorter duration of action. Subcutaneous injection of the insulin preparations resulted in intraindividual CVs of the summary measures between 10 and 30% (soluble insulin vs. insulin aspart: maximal metabolic activity 15+/−7 vs. 16+/−10%, time to maximal metabolic activity 14+/−10 vs. 11+/−6%; NS between the preparations [means +/- SD]). The decline to half-maximal activity after maximal activity showed a lower intraindividual CV with insulin aspart (19+/−9 vs. 11+/−5%; P = 0.018). The interindividual CVs were higher than the intraindividual CVs (26 vs. 28, 23 vs. 19, and 26 vs. 17%). Generally, the pharmacodynamic variability was higher than the pharmacokinetic variability. For the pharmacokinetic measures, the intra- and interindividual variability in t(max) was lower for insulin aspart than for soluble insulin. (24)

In another treatment study, glucose excursions evaluated from 24-hour glucose profiles showed less variability with insulin aspart compared with human insulin.(25)

Similar results have been noted for insulin detemir, which exhibits much lower variability, and is more predictive in its action, than glargine or NPH.(26)

Modern Insulins And Quality Of Life

Analysis of a cohort of Indian patients enrolled in the improve study, receiving biphasic aspart, showed higher patient satisfaction, with a mean overall score of 79.03 at final visit vs. 52.33 at baseline visit. Overall number of extremely satisfied patients increased from 5.4 % to 26%.

Improvement was noted in all subscales, with symptoms score improving from 58.12 to 77.82, burden score improving from 49.77 to 77.56, and efficacy score from 48.98 to 81.79.(27)

Conclusion(s)

All aspects of the Glycemic Pentad, including quality of life and glycemic variability, should be kept in mind while prescribing therapy to a person with diabetes. Modern insulins, or insulin analogues, combine efficacy with safety and tolerability. This makes them superior to, and better accepted, as management strategies, as compared to traditional insulin preparations.

The favourable data related to variability and quality of life encourages use of modern insulins for management of hyperglycemia.

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