Managing glycaemic variability: Clinical approach
Sanjay Kalra¹, Sunil Kota²

Abstract
The benefits of glycaemic control in prevention of microvascular complications both in type 1 and type 2 diabetes are established by several randomized clinical trials. Though variable glycated haemoglobin (HbA1C) is an established cause of increased microvascular complications, its link with macrovascular events or increased cardiovascular events is still not proved despite several indirect evidences. One more useful tool in the name of glycaemic variability is a possible explanation to justify the relation between hyperglycaemia and increased cardiovascular risk in diabetic patients. According to some schools of thought, glycaemic variability along with fasting blood glucose, postprandial blood glucose, HbA1C, and risk of hypoglycaemia can be grouped as glycaemic pentad, which is an important factor in diabetes management. Glycaemic variability is a reflection of postprandial spikes in blood glucose and hypoglycaemic events, both of which are blamed for increased cardiovascular events in type 2 diabetics. Hence prevention of future cardiovascular events can be done by minimizing glycaemic variability. This article focuses on its various causes, its adverse impacts and briefly discusses various newer treatment options to reduce glycaemic variability.

Keywords: Cardiovascular events, glycaemic variability, hypoglycaemia, insulin analogues, type 1 diabetes, type 2 diabetes

Negative impact of variability
Glycaemic variability (GV) is a common occurrence in diabetes practice.¹ Though accurate definitions of GV are a matter of debate, physicians frequently encounter persons with highly variable glycemic patterns.² While some individuals may experience extreme fluctuations in glucose levels during a particular day, others report different glucose readings from day to day. Such GV becomes a challenge for good diabetes care, as it may be associated with impaired quality of life, (symptomatic) hypoglycaemic episodes, inability to titrate doses of glucose-lowering drugs, and unwanted long term outcomes.²,³ Significant GV increases the need for more frequent glucose monitoring and health provider contact, thus increasing diabetes-related expenditure. It is not surprising that GV reduces both patient satisfaction and diabetes care provider satisfaction leading to suboptimal relationships and team work.

Identification of cause
This brief communication is oriented for primary care physicians who encounter GV in persons with diabetes. It does not discuss the methods of measuring GV. Rather, it emphasizes simple aspects of diabetes care delivery which can help minimize GV in clinical practice. This practical and pragmatic approach presents the common cause of GV in a 3x3x3 rubric, facilitating easy understanding and usage (Table 1).

Fictitious variability
The first step, prior to evaluating causes of GV, is to exclude fictitious GV. The technique of self monitoring of blood glucose (SMBG) must be audited. This audit must include an assessment of the instrument being used, the ancillary supplies including sticks, and technique of pricking oneself, using the instrument, reading and recording the glucose values.⁴ All these must be in order. Laboratory based venous glucose estimation may be needed to corroborate GV. Ambulatory glucose monitoring (flash) and continuous glucose monitoring systems (CGMS) provide accurate means of confirming GV.⁵,⁶

Lifestyle variability
Once GV is confirmed, the first cause of GV to be excluded should be variability in lifestyle.² History taking may reveal variation in the pattern, composition or quality of food intake, timing, duration or intensity of physical activity/exercise, and/ or sleep pattern, psychological stress or physical and social environment. All these may lead to fluctuations in glycaemic levels.

Pharmacological variability
The second broad etiology of GV pertains to choice of
drug regimens, drug preparations and drug delivery techniques. It may be possible that the chosen drug regimen, preparation or delivery device is not appropriate for the patient’s glucophenotype or biomedical status. Examples include prescribing a basal insulin regimen to a person with predominant hyperglycaemia, and using human insulins (with higher coefficients of variability) rather than analogue insulins (which have lower coefficients of variation).

Even within a particular class of insulins, all analogues are not similar. The diabetes care provider should be aware of the pharmacokinetic and pharmacodynamic properties of each insulin preparation, while making an informed choice. The same holds true for oral drugs which are available in instant release and modified/sustained release, e.g.; metformin and gliclazide.

### Biomedical causes of variability

If lifestyle and drug related cause are ruled out, focus shifts to biomedical etiologies of GV. For ease of understanding, we classify these in three groups: gastrointestinal, neuroendocrine and drug kinetics related. Gastrointestinal causes of GV include disorders of motility and absorption, which may cause variable change in the absorption of nutrients, and lead to a nutrient-insulin mismatch.

Neuroendocrine reasons include disorders of the autonomic nervous system (leading to hypoglycaemia unawareness), pancreas (glucagon deficiency/due to destruction of islets of Langerhans, and exocrine enzyme deficiency, due to destruction of exocrine pancreas) and other glands which secrete counter-regulatory hormones (e.g.; cyclical Cushing’s, pheochromocytoma, changes in thyroid function while using thyrotropic medication).

A third category of biomedical causes is drug-drug interactions when new drugs are introduced in the prescription to treat undercurrent illness. Common examples include anti-fungal drugs (fluconazole, ketoconazole), anti-tubercular drugs (rifampin), cardio

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Table: causes of glycaemic variability.

<table>
<thead>
<tr>
<th>DOMAIN</th>
<th>VARIABILITY IN</th>
<th>SPECIFIC ISSUES EXAMPLES</th>
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</thead>
<tbody>
<tr>
<td>Lifestyle related</td>
<td>Diet</td>
<td>• Pattern of diet&lt;br&gt;• Composition of diet&lt;br&gt;• Quality of diet</td>
</tr>
<tr>
<td></td>
<td>Physical activity</td>
<td>• Timing of exercise&lt;br&gt;• Duration of exercise&lt;br&gt;• Intensity of exercise</td>
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<td></td>
<td>Stress management</td>
<td>• Sleep cycle&lt;br&gt;• Psychological stress&lt;br&gt;• Ambient environment</td>
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<tr>
<td>Pharmaceutical delivery related</td>
<td>Choice of regimen</td>
<td>• Premixed vs basal bolus&lt;br&gt;• High mix vs low mix&lt;br&gt;• Human insulin vs analogue insulin</td>
</tr>
<tr>
<td></td>
<td>Choice of preparation</td>
<td>• Traditional sulfonylureas vs modern sulfonylureas&lt;br&gt;• Long acting insulin vs. ultra long acting insulin&lt;br&gt;• Immediate release vs sustained / modified release tablets</td>
</tr>
<tr>
<td></td>
<td>Drug delivery</td>
<td>• Injection in lipo hypertrophy vs healthy subcutaneous tissue vs intramuscular tissue&lt;br&gt;• Injection in exercising vs non-exercising; hypo-perfused vs normal; externally heated vs cold limb&lt;br&gt;• Correct tablet/injection-meal time gap</td>
</tr>
<tr>
<td>Biomedical</td>
<td>Gastrointestinal</td>
<td>• Diabetic gastro paresis&lt;br&gt;• Malabsorption&lt;br&gt;• Diarrhoea (diabetic or infective)</td>
</tr>
<tr>
<td></td>
<td>Neuroendocrine</td>
<td>• Hypoglycaemia unawareness&lt;br&gt;• Pancreatic diabetes(exocrine deficiency / glucagon deficiency)&lt;br&gt;• Counter-regulatory hormone dysfunction, e.g.; cyclical Cushing’s pheochromocytoma, variation in thyroid function while on thyrotropic medication</td>
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<td>Drug kinetics</td>
<td>• Drugs increasing metabolism of glucose lowering drugs, e.g., rifampin increases breakdown of sulfonylureas&lt;br&gt;• Drug decreasing metabolism of glucose lowering drugs, e.g., fluconazole inhibits breakdown of pioglitazone and sulfonylureas&lt;br&gt;• Medical conditions causing variation in drug metabolism and excretion, e.g., renal and hepatic impairment</td>
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tropic drugs (amiodarone) and anti-seizure drugs (phenobarbital).\textsuperscript{9,10}

**Tackling glycaemic variability**

Lifestyle modification with measures aiming at weight loss is a welcome step. Antidiabetic modalities which address postprandial hyperglycaemia better with lesser chances of hypoglycaemia and which provide 24 hour glucose control are better suited to reduce the occurrence of glycaemic variability. The traditional choices of drugs are metformin, thiazolidinediones and meglitinides. Modern diabetes management options including newer sulfonylureas, incretin based therapies (DPP-4 inhibitors and GLP-1 analogues), SGLT-2 inhibitors, analogue basal and prandial insulins, and modern insulin pumps address the issue of GV effectively.\textsuperscript{2,11}

**Summary**

In addition to standard glycaemic parameters like blood glucose and glycated haemoglobin, glycaemic variability is a potential target parameter for optimum glycaemic control. By minimization of glycaemic variability, there is an improvement in outcomes for both micro and to some extent macrovascular diabetic complications. This applies to all varieties of diabetes including Type 1 diabetes, type 2 diabetes, gestational diabetes, and probably non diabetic critically ill patients. Newer antidiabetic medications like incretin mimetics, SGLT-2 inhibitors, newer basal and prandial insulins, Continuous subcutaneous insulin infusion can significantly reduce GV.

**References**