Capturing glucose variability in patients with diabetes

DAVID LAIGHT

Measurement of glycated haemoglobin (HbA1c) as a marker of glycaemic control has become a cornerstone in the management of diabetes, while also predicting cardiovascular risk. However, this does not fully capture fluctuations in glucose levels – glucose variability – which has recently emerged as a significant independent risk factor. This article considers clinical approaches to capturing glucose variability that may help improve glycaemic control in diabetes in the future.

Figure 1. Flash glucose monitoring using the FreeStyle Libre system can help routinely track glucose variability by continuously recording changing glucose levels in the interstitial fluid.

However, intensively managing this aspect of glycaemic control is therapeutically limited by the risk of iatrogenic hypoglycaemia, which is itself thought to be another source of cardiovascular risk. In addition, long-standing type 2 diabetic patients at high cardiovascular risk subjected to intensive (compared to standard) HbA1c reduction experienced higher mortality in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.1,2

A more multidimensional definition of glycaemic control

The circulating level of HbA1c, reflecting haemoglobin exposure to glucose over the previous two to three months, has essentially become synonymous with glycaemic control.3,4 Its indication of the average circulating glucose level over this time period facilitates communica-
tion about hyperglycaemia to patients and clinicians. The pre-eminence of HbA1c as a ‘gold-standard’ glycaemic marker and therapeutic target in diabetes was further endorsed in 2011 when the World Health Organization (WHO), welcomed by Diabetes UK, recommended its use as an alternative diagnostic criterion for diabetes (with the exception of certain patient groups). This is, of course, alongside the WHO- and Diabetes UK-supported criteria based on elevated fasting, random and post-oral glucose challenge glycaemia (see Table 1). However, glycaemic control is now considered to be more far-reaching than hyperglycaemia and HbA1c alone, incorporating short- to medium-term glucose variability as well as hypoglycaemia, neither of which is well reflected, if at all, in circulating levels of glycated haemoglobin as a marker of average glycemia.

A more multidimensional definition of glycaemic control may sound academic, but actually potentially translates to a clinically significant benefit. This is because it may lead to novel therapeutic targets for the optimisation of dysglycaemia management, which may not be addressed by all current antihyperglycaemic agents. Hence, the availability of alternative glycaemic control endpoints, such as reduced glucose variability, could prove a game changer in the refinement of diabetic therapy. This conceptual advance is especially welcome, given that the clinical utility of chasing down HbA1c on the arduous path towards euglycaemia in diabetes provides diminishing therapeutic returns.

Intensive glycaemic control fixed on HbA1c lowering may also create problems, not only owing to the risk of side-effects such as iatrogenic severe hypoglycaemia, but also relating to increased treatment burden and costs. Furthermore, there is evidence to suggest that the full cardiovascular benefits afforded by certain antihyperglycaemic therapies for type 2 diabetes, such as glucagon-like peptide-1 (GLP-1) agonists and sodium-glucose co-transporter 2 (SGLT2) inhibitors (gliflozins) may not be completely accounted for by their Hba1c-lowering effects. Taken together, this now suggests that circulating glycated haemoglobin not only fails to fully represent the totality of glycaemic control, but also fails to adequately predict cardiovascular risk in diabetes. Furthermore, HbA1c measurement/interpretation is subject to confounding by a host of factors, including the presence of blood abnormalities, end-stage renal disease and pregnancy.

Clinical importance of measuring and managing glucose variability
Glucose variability, or the degree, frequency and duration of glucose excursions over time, is rooted in circulating glucose fluctuations, which is not inherently conveyed by a mean or median glucose level or indeed HbA1c level. In contrast, data variability or dispersion is typically summarised by the use of standard deviation (SD), co-efficient of variation (CV; where SD is expressed as a ratio of the mean) or interquartile range (for non-parametric data), and these metrics can be readily applied to describe glucose variability. Although, in the face of a lack of clinical consensus on either describing or reporting glucose variability and no ‘gold-standard’ measurement, many metrics may be suggested and applied (see Table 2).

Mealtimes, of course, provide a prime source of such glucose excursions (influenced by meal glycaemic index and load), along with antihyperglycaemic therapy, especially insulin. In addition, glucose variability will also be influenced by hormonal function, stress and illness, as well as behavioural interventions such as physical exercise. These glucose fluctuations will likely incorporate incidences of hyper- and hypoglycaemia, as well as glucose concentrations in between, including those within the normal range. While this implies that glucose variability cannot be completely separated from traditional indicators of glycaemic control, it would equally suggest that clinically managing variability might be the key to addressing multiple aspects of glycaemic control simultaneously. Incretin-based antidiabetic therapies (eg GLP-1 agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors) have shown potential in this regard by reducing glucose variability parameters in type 2 diabetes, in part due to their ability to reduce postprandial glucose excursions.

Increased glucose variability has now been recognised as a significant, independent risk factor for poor patient outcomes in a number of clinical scenarios (including hospital, critical care and general surgery settings), as well as in the context of diabetes and microvascular and macrovascular complications. Perhaps more surprisingly, glucose variability has also been demonstrated to be associated with cardiovascular and

| Table 1. Summary of the WHO diagnostic criteria for diabetes, in association with diabetes symptoms
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes symptoms (eg polyuria, polydipsia and unexplained weight loss for type 1)</strong> plus:</td>
</tr>
<tr>
<td>- a random venous plasma glucose concentration ≥11.1mmol/L or</td>
</tr>
<tr>
<td>- a fasting plasma glucose concentration ≥7.0mmol/L (whole blood ≥6.1mmol/L) or</td>
</tr>
<tr>
<td>- plasma glucose concentration ≥11.1mmol/L two hours after 75g anhydrous glucose in an oral glucose tolerance test</td>
</tr>
<tr>
<td>- If there are no symptoms, diagnosis requires confirmation with at least one additional glucose test result on another day (fasting, random sample or two-hour post glucose load) with a value in the diabetic range</td>
</tr>
<tr>
<td>- A laboratory venous HbA1c of 48mmol/mol (6.5%) is recommended as the cut-off point for diagnosing diabetes; however, a value of less than that does not exclude diabetes diagnosed using glucose tests and it is not appropriate for diagnosis in all clinical situations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Some suggested measurements of clinical glucose fluctuations (glucose variability)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Standard deviation (SD)</td>
</tr>
<tr>
<td>- Co-efficient of variation (CV)</td>
</tr>
<tr>
<td>- Interquartile range (IQR)</td>
</tr>
<tr>
<td>- Mean amplitude of glucose excursions (MAGE)</td>
</tr>
<tr>
<td>- Glycaemic lability index (LI)</td>
</tr>
<tr>
<td>- Mean of daily difference (MODD)</td>
</tr>
<tr>
<td>- Continuous overlapping net glycaemic action (CONGA)</td>
</tr>
<tr>
<td>- High blood glucose index (HBGI)</td>
</tr>
<tr>
<td>- Low blood glucose index (LBGI)</td>
</tr>
</tbody>
</table>

prescriber.co.uk
mortality risk in a general population of healthy individuals without diabetes.\textsuperscript{22} Raised oxidative stress, pathological cell signalling and atherosclerotic plaque instability are just some of the suggested harmful pathways resulting from glucose fluctuations.\textsuperscript{13,17}

In fact, minimising glucose variability as part of diabetes management has been suggested to be at least as therapeutically important as addressing sustained hyperglycaemia or dyslipidaemia.\textsuperscript{6} That this might be achievable without reducing mean circulating glucose levels, now points to a novel way of tightening glycaemic control independent of additional HbA1c lowering and the attendant risk of hypoglycaemia. Indeed, under a proposed new treatment model aimed at minimising glucose variability, reducing hyperglycaemia (including fasting and postprandial circulating glucose levels) and avoiding hypoglycaemia,\textsuperscript{10,23,24} moderate HbA1c reduction targets are likely to be sufficient as part of overall diabetes management.\textsuperscript{8}

The role of continuous glucose monitoring

While a change in HbA1c over time has itself been used to capture glucose variability in the longer term,\textsuperscript{25} other surrogate circulating markers of glycaemia are better suited to track more acute fluctuations in average glucose level, by virtue of their short-term glycaemic reporting characteristics (over days to weeks, rather than months). Such markers include glycated serum proteins such as fructosamine and glycated albumin, and 1,5-anhydroglucitol (a dietary polyol, levels of which are inversely related to hyperglycaemia leading to glycosuria).\textsuperscript{12,26}

However, the advent of continuous glucose monitoring (CGM) and related technologies (most commonly based on interstitial fluid [ISF] sampling with a subcutaneous implantable glucose sensor), in particular flash glucose monitoring using the FreeStyle Libre system (see Figure 1), has now perhaps provided the ideal technological platform for routinely tracking glucose variability based on acutely fluctuating circulating glucose levels.\textsuperscript{27-31} This may be achieved either retrospectively (with historical data recorded for later inspection by a healthcare professional) or in real time; although ISF glucose lags behind circulating levels by some minutes.

Currently, the most commonly employed method for self-monitoring of blood glucose (SMBG) is fingerprick capillary glucose testing with a blood glucose meter. This remains an accurate and affordable method of intermittently assessing glycaemia on demand,\textsuperscript{4} and is obligatory during insulin therapy and important for oral medications prone to cause hypoglycaemia. However, this will not fully capture glucose variability or pick up all hypoglycaemic episodes (especially nocturnal episodes), owing to infrequency of testing. SMBG is also inconvenient for patients long-term. In contrast, CGM can provide data that enables calculation of glucose variability, report hypo- and hyperglycaemia, and also record glucose exposure (mean glucose level) and the time spent in the target glucose range. Hence, CGM may be seen as an adjunct (or in some cases a viable alternative) to intermittent SMBG that adds value to glucose measurements.

Given that the rate and direction of change in glycaemia is readily discernible with frequent, real-time sampling, personal CGM can automatically alert patients to actual or predicted significant glucose excursions. At present, according to NICE guidance, the recommended use of CGM only concerns the management of hypoglycaemia and related

---

**Table 3.** Clinical summary of the relevance of managing glucose variability in improving glycaemic control

- The concept of glycaemic control now extends beyond a typical focus on hyperglycaemia, based on average circulating glucose levels and HbA1c, to include more dynamic measurement of glucose fluctuations over time (glucose variability) and episodes of hypoglycaemia
- Many measurements of glucose variability have been proposed, in the current absence of a standardised clinical approach or consensus
- Personal, real-time continuous glucose monitoring (CGM) offers a valuable tool in the measurement, and ultimately the management, of glucose variability in diabetic dysglycaemia by tracking acute glucose fluctuations and providing alerts in respect of extreme glucose excursions
- NICE guidance on the use of CGM is currently restricted to managing hypoglycaemia in type 1 diabetes
- Minimising glucose variability, either by behavioural modification or using certain antihyperglycaemic drugs, may potentially be a legitimate treatment aim in patients with diabetes, together with lowering HbA1c and avoiding hypoglycaemia
- All three domains of glycaemic control (hyperglycaemia, glucose variability and hypoglycaemia) have been linked with the progression of cardiovascular disease in diabetes
- Glycaemic control can provide multiple targets for clinical interventions aimed at preventing diabetic complications
- If glucose variability can be effectively managed, this will automatically address all three domains of glycaemic control
- Incretin-based antidiabetic medications are associated with improvements in glucose variability in diabetic patients, along with cardiovascular benefits that cannot simply be accounted for by reduction in HbA1c
- Therapeutically addressing glucose variability, with the aid of novel technologies like CGM, may mean that only moderate HbA1c treatment targets are required in the overall management of glycaemic control and prevention of cardiovascular complications in diabetes
- Achieving better glycaemic control independently of lowering HbA1c further may be especially beneficial in diabetic patient groups most vulnerable to hypoglycaemia and its consequences, eg the elderly
issues in type 1 diabetes (such as the fear of hypoglycaemia and lack of hypoglycaemia awareness). However, in addition to this valuable clinical utility, the wider application of CGM, together with a fresh appreciation of the role of glucose variability in glycaemic control, may have much to contribute to the prevention of complications in both type 1 and type 2 diabetes (see Table 3).

Conclusion
The concept of glycaemic control is shifting from a traditional focus on hyperglycaemia (dominated by HbA1c measurement) to a broader view of absolute glucose levels (both high and low) and how these fluctuate (ie glucose variability). Furthermore, the measurement and targeted management of glucose variability, eg with the help of CGM and the use of incretin-based therapies, in diabetic patients appears to have great potential in the overall management of glycaemic control, independent of lowering HbA1c. This may be of particular benefit in older diabetic patients, who are at greater risk from iatrogenic hypoglycaemia and its consequences.

References

Declaration of interests
None to declare.

David Laight is a Principal Lecturer in Pharmacology at the University of Portsmouth