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COMMENTARY

The rise and fall of HbA_{1c} as a risk marker for diabetes complications

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Abstract It is still unclear whether short-term, within-day, variability in glycaemic control is contributory to the development of diabetes micro- or macrovascular complications. However, consistent and compelling data are emerging that longer term fluctuations in glucose, as evidenced by increases in HbA_{1c} variability, do indeed add to the mean HbA_{1c} value in predicting the risk of microvascular disease. Until now, studies have found this to be the case mainly in type 1 diabetes, but in this issue of *Diabetologia* (DOI: 10.1007/s00125-012-2572-7) an analysis of the Tsukuba Kawai Diabetes Registry in Japan has found that HbA_{1c} variability also predicts the risk of nephropathy in type 2 diabetic patients. These observations raise the possibility that reducing rises and falls in HbA_{1c} may help avoid hyperglycaemia-related vascular disease without running the same risk of hypoglycaemia that a strategy focusing purely on lower HbA_{1c} might incur.

Keywords Complications · Glycaemia · HbA_{1c} · Microvascular · Variability

The title of this commentary does not chart any demise of HbA_{1c} as an essential test in the management of diabetic patients. Instead, it highlights the important role that fluctuations in HbA_{1c} may have in the development of long-term complications. In this issue of *Diabetologia*, an analysis of the Tsukuba Kawai Diabetes Registry in Japan adds to the accumulating evidence that clinic visit-to-visit variability in HbA_{1c} increases the risk of nephropathy in patients with diabetes, over and above the risk that would already be predicted by their mean HbA_{1c} [1]. Adding to data from previous studies, the authors have found this to be the case in patients with type 2, rather than just type 1, diabetes. In doing so, it may point towards there being benefit in developing strategies to reduce these long-term fluctuations in glycaemia in both groups of patients.

The term ‘glucose variability’ can itself have varied definitions. Most people would associate this with the within-day fluctuations in an individual’s glucose level as it rises and falls, partly as a consequence of meals. However, it can also relate to swings in glycaemia over longer periods of time, such as the day-to-day or week-to-week changes in the mean glucose concentration of a daily profile. Beyond that, glycaemic variability can be expressed as the change in HbA_{1c} from one clinic visit to the next.

The distinction between these definitions is of relevance because definitively showing an association between increasing short-term glycaemic variability and an additional risk of micro-or macrovascular complications has so far proved to be elusive. Retrospective data analyses of the Diabetes Control and Complications Trial (DCCT) have shown little signal that within-day variability is important in the development of microvascular complications [2–4]. However, this study was not originally designed to address this question.

Although postprandial hyperglycaemia (a subset of glucose variability) is generally regarded as a risk marker for cardiovascular disease [5], the only prospective study to specifically assess whether reducing within-day glycaemia might influence cardiovascular events has been unable show any benefit [6].

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By comparison, showing an association between HbA_{1c} variability and microvascular complication risk has proved far less difficult. In 2008, a retrospective analysis of the DCCT dataset showed that HbA_{1c} variability, in contrast to glucose variability in the same study, added to the risk of nephropathy and retinopathy independently of mean HbA_{1c} in both treatment groups of type 1 diabetic patients [7]. In 2009, a Finnish longitudinal, observational study only examined nephropathy as a microvascular complication but showed similar findings in their free-living population of 2,107 type 1 patients [8]. Moreover, HbA_{1c} variability was also predictive of cardiovascular events. More recently, the same association of HbA_{1c} variability with nephropathy was also found in a group of 1,232 adolescent patients with type 1 diabetes [9].

In the current Tsukuba Kawai Diabetes Registry study [1], Sugawara et al have found that HbA_{1c} variability is now linked to the development of microalbuminuria in patients with type 2 diabetes. The patients, who were intially normoalbuminuric, were followed for a mean period of 4.3 years, but for the first year following registration had their mean HbA_{1c} and HbA_{1c} variability (expressed as standard deviation) established. In many healthcare systems there would be too few HbA_{1c} measurements in the space of a year to establish a reliable estimate of variability, but in Japan this test was undertaken a median of 11 times. A raised urinary albumin/creatinine ratio was subsequently found in 24% of patients, and both mean HbA_{1c} and HbA_{1c} variability were found to be independently associated with its development. However, this study was not without its limitations, perhaps the most important being its lack of account for antihypertensive treatments, including ACE inhibitors, and for different glucose-lowering agents, including insulin.

The magnitude of the effect that HbA_{1c} variability has on nephropathy risk in all of these studies is not unsubstantial [1, 7–9]. The range of mean HbA_{1c} and HbA_{1c} SD was different in each, but the influence of HbA_{1c} variability was consistently at least as much as that of mean HbA_{1c}.

The possible reasons as to why HbA_{1c} variability might be important to complication risk are as speculative as they are numerous. Both clinical and laboratory evidence demonstrate that periods of sustained hyperglycaemia are ‘remembered’ and so place patients at higher subsequent long-term risk of complications [10, 11]. In this regard, the detrimental effect of HbA_{1c} variability may be mediated through the same mechanism underlying the ‘metabolic memory’ phenomenon [12].

A second possible explanation relates to the fact that microvascular complication risk rises exponentially, rather than linearly, as HbA_{1c} rises [13, 14]. Thus, although the time spent above and below the mean value may be the same for a patient with a more variable HbA_{1c} as for one with a comparatively stable HbA_{1c}, the patient with the more variable HbA_{1c} will have a higher average risk because of the greater increase in the risk of complications associated with periods at the upper end of their HbA_{1c} range. This will more than cancel out any reduction in risk afforded by the equal amount of time spent far below their mean.

Another possible reason for the link between HbA_{1c} fluctuations and complication risk is the consistent observation that improving glycaemic control can lead to a short-term ‘early’ worsening in retinopathy before a subsequent net improvement in the long term [15]. If a patient has cycles of glycaemic improvement followed by worsening then it is possible that there is insufficient time for them to acquire the long term benefits before they have another cycle of fluctuant glycaemia. However, this is not consistent with the fact that early worsening of nephropathy after glycaemic improvement is not well recognised.

It is also possible that HbA_{1c} is simply more sensitive at detecting the effect of glucose changes than traditional daily glucose profiles, or that patients with variable HbA_{1c} are those in whom the rest of their diabetes management is suboptimal [8].

What is the next step? From a research perspective, HbA_{1c} has been the standard means of assessing glycaemia in trials and in diabetes registers for over 30 years, so it should be relatively simple to establish the reproducibility, or otherwise, of this finding in many clinical situations. If proven, the next challenge will be to establish whether reducing HbA_{1c} variability, independently of mean HbA_{1c}, can reduce the risk of micro- or macrovascular complications. If successful, the attractiveness of this approach is that it may allow patients to help avoid hyperglycaemia-related vascular disease without running the same risk of hypoglycaemia that a strategy focusing purely on lower HbA_{1c} might incur.

For now, it seems that the findings such as those from the Tsukuba Kawai Diabetes Registry study might at least provide another reason for minimising the delays known to occur before glycaemic treatments in type 2 diabetic patients are intensified [16]. Rather than just delaying an improvement in glycaemia, any delay in intensification might also worsen HbA_{1c} variability, compounding the risk of complications when another agent is eventually introduced.

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Contribution statement The author was responsible for the conception and design of the commentary and for writing, revising and approving the version to be published.

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