Optimal Glycaemic Management: Is Reaching HbA1c Target Enough?

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Editor

For two decades, glycated haemoglobin (HbA1c) has been regarded as the gold standard for therapeutic target in diabetes management. It was first introduced as a measure of long-term blood glucose control in the early 1980s. The results from the Diabetes Control and Complications Trial (DCCT) studies in 1993 gave great emphasis to the role of HbA1c as a surrogate marker for the subsequent development of vascular complications. Indeed, different guidelines had set out similar figures for achieving HbA1c targets (6.5% or 7.0%). However, is HbA1c the most important or useful predictor for cardiovascular disease in diabetes management?

Postprandial Glucose vs HbA1c

Reduction in HbA1c is more beneficial in reducing microvascular than macrovascular complications in type 2 diabetes. In the United Kingdom Prospective Study (UKPDS), the difference in HbA1c achieved between the intensive treatment group and the conventional treatment group was ~1% (7.0% vs 7.9%) over a period of 9 years for type 2 diabetic patients. This improvement in glycaemic control resulted in significant improvements in microvascular complications but not in macrovascular complications such as myocardial infarction. In the UKPDS study, the most important predictor for myocardial infarction was LDL-c followed by HDL-c, with HbA1c coming third in the order.

In a recent retrospective study of a very large GP database from the United Kingdom involving ~48,000 people with type 2 diabetes showed a U-shape distribution of HbA1c in predicting all-cause mortality. The 10% of patients with the lowest Hba1c values (<6.7%) had a higher death rate than all but the highest top 10% who had a Hba1c of >9.9%. Thus it would appear that too high or too low an HbA1c is harmful in people with type 2 diabetes. To add weight to this discussion, there is strong evidence from both Caucasian and Chinese populations that many individuals (not previously known to have dysglycaemia) who suffered from acute coronary syndrome had fairly normal HbA1c and it was the postprandial glucose (PPG) that was high (in those with impaired glucose tolerance) but not in macrovascular complications such as myocardial infarction.

What HbA1c does not take into account is the glycaemic variability. For instance, an individual with acceptable HbA1c may have significant glycaemic variability (see figure 1). There is now cumulative evidence to indicate that glycaemic variability is an independent risk factor for complications in type 1 and type 2
diabetes. At the level of basic science, glucose variability is detrimental to cellular health. An experimental study showed that there was more apoptosis (cell death) when human endothelial cells were cultivated in fluctuating glucose concentrations than those in solutions with chronic hyperglycaemia. It is very likely that an increased magnitude of glucose variability generates reactive oxygen species in complications-prone cells as a result of hyperglycaemia-variability generates reactive oxygen species in complications-prone cells as a result of hyperglycaemia. This could be a major complications-prone cells as a result of hyperglycaemia-variability generates reactive oxygen species in complications-prone cells as a result of hyperglycaemia. This could be a major mechanism to explain glucose-mediated vascular damage. In addition, increased post-prandial glucose increased LDL oxidation, an important process in atherogenesis. A clinical trial had also confirmed that acute glucose fluctuations exerted a more specific triggering effect on oxidative stress than chronic sustained hyperglycaemia. Optimal glycaemic control should include minimising glucose variability in reducing vascular complications in the management of diabetes.

Role of Continuous Glucose Monitoring
Given the importance of PPG and glucose variability, modern management in diabetes should include the assessment of glucose variability. Currently diabetes management software is available that synthesises data uploaded from blood glucose meters and to calculate the standard deviation of blood glucose values to ascertain the quality of diabetes control. It will also allow physicians to fine tune anti-diabetic oral therapies or insulin therapy leading to minimal glycaemic variability and to reach HbA1c target. This is particularly beneficial to patients on multiple insulin injections to minimise severe hypoglycaemic episodes yet achieving quality glycaemic control.

References