The Role and Quality of Hb A_{1c}: A Continuing Evolution

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Since glycohemoglobin was first described in the red cells of diabetes patients in 1968 (1), the test has evolved to become an essential tool for prognosis, monitoring, treatment, and diagnosis of diabetes mellitus. An increasing clinical focus together with the development of diabetes management guidelines based on glycated hemoglobin (Hb A_{1c}) necessitated a standardization of the method initially achieved in schemes such as the National Glycohemoglobin Standardization Program (NGSP) (2) and later refined by the IFCC (3).

Now that we know the reference values we should be aiming for, the IFCC task force has investigated approaches for setting the analytical quality targets for Hb A_{1c} (4) so that we can know how close to those reference values we need to be; the task force’s report is published in this issue of Clinical Chemistry (4). The task force has acknowledged the importance of the Stockholm hierarchy, in which clinical outcome studies are the preferred method of defining analytical quality (5). In Milan during November 2014, the European Federation of Laboratory Medicine revisited the Stockholm consensus and retained clinical decision making at the forefront of the rationales for defining analytical quality, ahead of biological variation and state-of-the-art approaches (6).

Hb A_{1c} is ideally placed for using clinical rationales to define quality specification, because we know so much about diabetes outcomes in relation to Hb A_{1c}, and we correspondingly have agreed-on clinical protocols to manage diabetes. The IFCC task force authors have borrowed the excellent example of the UK National Institute for Health and Care Excellence (NICE) guidelines for the management of type 2 diabetes that focus on a change in Hb A_{1c} of ±5 mmol/mol (0.46%) to define the total allowable error (TAE) according to clinical decision making.

The IFCC Task Force found that the clinically defined TAE of ±5 mmol/mol (0.46%) was achievable by 77% of laboratories participating in proficiency testing, whereas only 48% of laboratories were able to achieve the minimum biological variability goal of ±3.4 mmol/mol (0.31%).

The underlying principle of using biological variability as the basis for analytical quality specifications is that measurement noise should not mask the underlying variations we are trying to detect. The simplest Cotlove criterion, that the imprecision of analysis (CV_A) should be less than half the intraindividual biological variation (CV_i) (7), has been refined to include minimal (CV_A < 0.75CV_i), desirable (CV_A < 0.5CV_i), and optimal (CV_A < 0.25CV_i) criteria. The critical step in these definitions is to define CV_i, which is easier said than done: not only does Hb A_{1c} CV_i vary from study to study, as highlighted in the IFCC task force article, but the variability of Hb A_{1c} itself seems to vary, from the stable situation of health (CV_i ~ 1.0%) to the increasing instability of type 2 diabetes (CV_i 4.3%) and type 1 diabetes (CV_i = 8.8%) (8). It is important to acknowledge that the higher Hb A_{1c} in each of these states is a reflection not only of higher average glucose concentrations but also the higher Hb A_{1c} variability of blood glucose values due to increasing insulin resistance and deficiency (9). The task force chose to use the single CV_i value of 1.85% from the Westgard QC Ricos database (10) while acknowledging that different quality targets could be obtained using different values for CV_i.

The variations in CV_i across varying states of health and types 1 and 2 diabetes have corresponding implications for clinical decision making using Hb A_{1c}. The clinical challenge of controlling type 2 diabetes, even in the NICE guidelines (6), depends on the clinical context, as the target value is 48 mmol/mol (6.5%) in type 2 diabetes treated with a single oral hypoglycemic medication and 58 mmol/mol (7.5%) in a type 2 patient treated with more medication or insulin (similar to type 1 diabetic treatment). Therefore, not only does the biological variability of Hb A_{1c} change in various clinical conditions, but the clinical decisions themselves vary according to the patient category. In an adolescent with poorly controlled type 1 diabetes and Hb A_{1c} of >86 mmol/mol (10.0%), the clinical challenge may be to improve control and reach a Hb A_{1c} value <64 mmol/mol (8.0%). These large differences can be measured with confidence using relatively imprecise assays, which is why point-of-care technologies are well suited to clinics that manage...
such difficult patients. Conversely, with the increasing focus on the distinction between health and prediabetes that uses Hb A1c cutoff values around 39 mmol/mol (5.7%), a clinician may want to be able to distinguish small changes in the direction of diabetes [Hb A1c 48 mmol/mol (6.5%)], particularly considering that cardiovascular risk rises exponentially between these limits (11). There is some suggestion that an early Hb A1c might become useful in distinguishing gestational diabetes at even lower Hb A1c thresholds (12); however, even an assay with a TEA of ±5 mmol/mol (0.46%) may not reliably distinguish Hb A1c values around 39 mmol/mol (5.7%).

The improvements in Hb A1c standardization and the test’s increasing importance, not only in diabetes but in delineating prediabetes, will continue to drive further improvements in analytical quality, including both aspects of Hb A1c analytical quality: accuracy and imprecision.

The analytical proficiency testing criteria for Hb A1c in the College of American Pathologists survey decreased by 50% between 2007 and 2012. In the Royal College of Pathologists of Australasia Quality Assurance Program survey, the TAE has also decreased to be ±4 mmol/L (0.37%) at Hb A1c of 45 mmol/mol (6.7%). Some recently released methods—including the revolutionary enzymatic digestion and detection method of Abbott Capillarys (13) and the capillary electrophoresis method of Sebia Capillaries (14)—and improvements in ion exchange chromatography are all capable of achieving CVA values <2.2% (1.5% NGSP). If we look closely at Fig. 4 of the IFCC task force article (4), we can see that as long as bias is kept <2 mmol/mol (0.18% NGSP), an imprecision of CVA <2.2% (1.5% NGSP) will meet defined goals for biological variation.

The task force has applied σ metrics to the NICE clinically defined TEA of ±5 mmol/mol (0.46%) for the management of type 2 diabetes and shown that this goal can be achieved by most laboratories today. However, we still need to be cognizant that improved understanding of the clinical changes in other clinical scenarios fundamentally shapes the way we manage our patients (15). As we become more interested in lower Hb A1c levels that signal disease and smaller fluctuations that indicate a change in disease state, we will require further improvements in our methods, but these fundamental aims have driven clinical chemistry ever since its beginnings. Integral to understanding analytical improvements is understanding their clinical purpose and being aware of the limitations of our existing methods.

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References