AUTHOR'S REPLY

Pitfalls in the use of HbA_{1c} as a diagnostic test

Samuel Dagogo-Jack

In their correspondence (A conundrum addressed: The prognostic value of HbA_{1c}. *Nat. Rev. Endocrinol.* **7**, doi:10.1038/nrendo.2010.126-c1), Selvin and Brancati raise four issues regarding my Perspectives article (Pitfalls in the use of HbA_{1c} as a diagnostic test: the ethnic conundrum. *Nat. Rev. Endocrinol.* **6**, 589–593 (2010))[1] on the diagnostic use of HbA_{1c}.

First, they question the clinical significance of genetic contribution to the variation in HbA_{1c} levels. In addition to the paper by Snieder *et al.*,[2] several reports document differential genetic influences on HbA_{1c} and fasting glucose values that would make it clinically precarious to use HbA_{1c} alone for the diagnosis of diabetes mellitus or prediabetes.[3–7] Among patients with type 1 diabetes mellitus enrolled in the Diabetes Control and Complications Trial, genome-wide association studies identified a major locus (near *SORCS1*) that was associated with both HbA_{1c} and glucose ($P = 7 \times 10^{-10}$ for the association with HbA_{1c}, $P = 2 \times 10^{-5}$ for the association with mean glucose).[3]

Studies in nondiabetic individuals provide a less perturbed internal environment for assessing independent genetic contributions to the variations in HbA_{1c} and fasting glucose values.[4–7] Such studies have indicated that heritable factors[4] and genetic loci[5–7] for HbA_{1c} exist that are not necessarily shared by fasting and nonfasting blood glucose values. The clinical significance of the nonoverlapping genetic loci for HbA_{1c} and blood glucose may be moot in a given patient receiving treatment for established diabetes mellitus. However, the genetic contribution to the discordance between HbA_{1c} and mean blood glucose can be clinically significant if HbA_{1c} is used as the sole diagnostic test for diabetes mellitus or prediabetes.[1,8] The use of HbA_{1c} as the primary criterion for diagnosis assumes a degree of universal concordance between HbA_{1c} and mean blood glucose values that is unsupported by current evidence.

Second, Selvin and Brancati suggest that the effects of age and ethnicity on the relationship between HbA_{1c} and blood glucose values could be owing to inadequate sampling of postprandial glucose levels and differences in dietary practices among older individuals and those from ethnic minorities—an interesting suggestion. However, dietary practices in the US overlap to such a degree[9] that it is doubtful whether any systematic differences can account for the ethnic disparities in HbA_{1c}.

Third, the standardization of HbA_{1c} methodology does represent progress in the right direction. Unfortunately, such standardization does not obviate the genetic or many of the biological concerns about the diagnostic use of HbA_{1c}.[1] Finally, without question, the collection of multiple glucose data points would increase the validity of HbA_{1c} comparisons. In this regard, data from continuous glucose monitoring also showed wide variability in HbA_{1c}–glucose correlation among individuals.[10]

To be clear, I do not dispute the role of HbA_{1c} as a 'gold' standard for monitoring glycemic control and predicting microvascular events among patients with diabetes mellitus. However, the sole or preferential use of HbA_{1c} for diagnosis is fraught with biological and demographic pitfalls that create genuine clinical concern[1,8] regarding underdiagnosis or overdiagnosis of a substantial number of individuals. In recognition of these issues, clinicians should utilize direct glucose measurement to validate abnormal HbA_{1c} results when screening patients for diabetes mellitus or prediabetes.

Division of Endocrinology, Diabetes & Metabolism, University of Tennessee Health Science Center, 920 Madison Avenue, Suite 300A, Memphis, TN 38163, USA.
sdj@uthsc.edu

doi:10.1038/nrendo.2010.126-c2

Competing interests
The author declares no competing interests.

1. Dagogo-Jack S. Pitfalls in the use of HbA_{1c} as a diagnostic test: the ethnic conundrum. *Nat. Rev. Endocrinol.* **6**, 589–593 (2010).
2. Snieder, H. *et al.* HbA_{1c} levels are genetically determined even in type 1 diabetes: evidence from healthy and diabetic twins. *Diabetes* **50**, 2858–2863 (2001).
3. Paterson, A. D. *et al.* A genome-wide association study identifies a novel major locus for glycemic control in type 1 diabetes, as measured by both A1c and glucose. *Diabetes* **59**, 539–549 (2010).
4. Simonis-Bik, A. M. *et al.* The heritability of HbA1c and fasting blood glucose in different measurement settings. *Twin Res. Hum. Genet.* **11**, 597–602 (2008).
5. Soranzo, N. *et al.* Common variants at ten genomic loci influence hemoglobin A1C levels via glycemic and non-glycemic pathways. *Diabetes* doi:10.2337/db10–0502.
6. Paré, G. *et al.* Novel association of HK1 with glycated hemoglobin in a non-diabetic population: a genome-wide evaluation of 14,618 participants in the Women's Genome Health Study. *PLoS Genetics* **4**, e1000312 (2008).
7. Bonnefond, A. *et al.* A genetic variant in HK1 is associated with pro-anemic state and HbA1c but not other glycemic control related traits. *Diabetes* **58**, 2687–2697 (2009).
8. Olson, D. E. *et al.* Screening for diabetes and pre-diabetes with proposed A1C-based diagnostic criteria. *Diabetes Care* **33**, 2184–2189 (2010).
9. Kant, A. K. Graubard, B. I. & Kumanyika, S. K. Trends in black-white differentials in dietary intakes of, U. S. adults, 1971–2002. *Am. J. Prev. Med.* **32**, 264–272 (2007).
10. Diabetes Research in Children Network (DirecNet) Study Group. Relationship of A1C to glucose concentrations in children with type 1 diabetes: assessments by high-frequency glucose determinations by sensors. *Diabetes Care* **31**, 381–385 (2008).