COMMENTS AND RESPONSES

Evidence for Independent Heritability of the Glycation Gap (Glycosylation Gap) Fraction of HbA_{1c} in Nondiabetic Twins

Response to Nuttall

We appreciate Dr. Nuttall (1) drawing our attention back to the considerations raised by his previous work (2). In essence, the suggestion is that one of the sources of variability in A1C, when determined by a charge-based methodology like anion-exchange high-performance liquid chromotography, is that there are other modifications or variants to hemoglobin that could cause the same alterations in charge as glycation and that these are more common than is generally recognized. This leads to the question whether such alterations could explain the finding of heritability in our study (3) and in its predecessor (4). The simple answer is that this possibility remains in the differential diagnosis of our findings: we can neither implicate this specifically, nor can we exclude it. When we go the next step to address what molecular form could account for the finding, there is no good answer. Hemoglobinopathies have an exceedingly low prevalence in the population studied and are not plausible; they should have been detectable with the method used (5). Carbamylation, aspirin, or ascorbic acid–induced modification similarly are implausible to form a pattern in identical twins not found in nonidentical twins in a large enough fraction of the population to explain our result. Any other molecular species that could account for the result would be a novel finding and of broad general interest.

We would point out that our original demonstration of A1C heritability in twins was not limited to the nondiabetic range of glycemic control (4). We also anticipate that studies in progress on in vivo rates of A1C synthesis in people with and without diabetes will shed further light on the extent to which these findings can be explained by nonglucose confounders (6).

As we await the results of the International Federation of Clinical Chemists/American Diabetes Association/International Diabetes Federation studies on GHb standardization, this is a reminder that there inevitably will be limitations to whatever method we select for measurement of long-term glucose exposure. Genetic and environmental/chemical limitations have been the factors detected thus far. Current interest in the use of mass spectrometry–based methods may help to overcome these limitations. The purpose of the glycation gap is to provide a more general means of detecting such confounding of measures of glycemic control and to develop the means by which clinical decision making about glycemic management can proceed in the face of it. With the use of the glycation gap, we anticipate that physiologic confounding of these measures will be increasingly recognized. We therefore anticipate that the glycation gap approach will become an increasingly useful tool regardless of which methodology for GHb determination wins out.

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