COMMENTS AND RESPONSES

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

Response to Cohen et al.

I have read with interest the article by Cohen et al. (1) in *Diabetes Care*. In this article, the authors reported a significant effect of heredity on the A1C values in twin subjects. This hereditary effect was attributed to "genes that preferentially affect erythrocyte lifespan or glucose and/or nonenzymatic glycation or deglycation in the intracellular rather than extra cellular compartment."

I would appreciate the authors' comments regarding another possibility. In their research, Cohen et al. used a nonspecific method for estimating A1C. The method used was that used in the Diabetes Complications and Control Trial (DCCT), Bio Rex 70 ion exchange chromatography. This method does not measure the irreversible derivitization of glucose to globin proteins in hemoglobin at the NH_2-terminal end of the β-chains, i.e., fructosylation at that site, which is the true definition of A1C. The results obtained are merely an index of a change in charge at that site.

With this methodology, I, as well as others, have pointed out that on average, ~40% of what is being reported as A1C in individuals without diabetes is not glucose derivatized at that site (2,3). This has now been confirmed using a highly specific mass spectroscopy method (4).

The nonglucose derivatives that are being reported as A1C using the ion-exchange method have not been identified clearly. Thus, the use of nonspecific methods to quantify the A1C fraction can potentially confound the interpretation of mechanistic studies.

Because of the nonspecificity of the A1C method used, I would be interested in the authors' comments regarding whether a variance in binding of nonglucose-derived adducts to the globin proteins in hemoglobin could also contribute to the inherited differences observed in A1C.

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