



COMMENT ON LEWIS ET AL.

Management of Hemoglobin Variants Detected Incidentally in HbA_{1c} Testing: A Common Problem Currently Lacking a Standard Approach. Diabetes Care 2017;40:e8–e9

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Randie R. Little and Curt L. Rohlfing

We read with concern the article by Lewis et al. (1) regarding HbA_{1c} analysis in the Vitamin D and Type 2 Diabetes (D2d) Study. Although the article focused on reporting the presence of hemoglobin (Hb) variants after incidental detection of variants by HbA_{1c} high-performance liquid chromatography (HPLC) methods, there was also clear mention of a lack of interference from HbS and HbC with the HbA_{1c} assay used for the study—the Tosoh G8 HPLC. Unfortunately, although the authors claim that there is no interference of these common Hb variants with the Tosoh G8 method, there is clear evidence to the contrary. Our study (2) clearly showed a statistically and clinically significant bias in results from this method with all four common Hb variants (HbAS, AC, AD, AE). This variant interference study was published in early 2016, but the actual sample analysis occurred in early 2015 and the interference may have begun as early as 2014. The NGSP website (3) indicates that this bias is “clinically significant” (defined as $\geq \pm 7\%$ at 6% and/or 9% HbA_{1c}). The Tosoh G8 showed an actual bias of almost 0.8% HbA_{1c} at the 9% HbA_{1c} level. The recommendation by the NGSP and others is to use a method that does not show interference in order to report an accurate result. This is important in routine clinical care, but it is also essential for important clinical studies

such as D2d where 2.2% of participants had an Hb variant.

For some methods, variant interference is an issue that is consistent with the method and does not change over time unless major changes are made to the method. However, with ion exchange HPLC methods, subtle changes in software or reagents can cause changes in the way each variant is eluted off the column and can thus affect the degree of variant interference. Even small statistically significant interferences that are not clinically significant can impact research studies and clinical trials. For example, a recent article (4) concluded that individuals with sickle cell trait (HbAS) had significantly lower HbA_{1c} for any given fasting or postprandial glucose concentration. This conclusion is likely in error given that the HbA_{1c} methods used for the study, although not showing clinically significant interference during the time period in which the samples were analyzed, did show statistically significant biases comparable to the differences reported by the authors. Therefore, the conclusion that HbA_{1c} results in individuals with sickle cell trait are lower than those in subjects without sickle cell trait may be incorrect.

HbA_{1c} measurement has improved tremendously over the years. With improvement in method precision, we are now able to detect small interferences

due to Hb variants. These interferences might not always be significant in clinical settings but could still affect clinical studies. More importantly, as in the case of the Tosoh G8, interferences for some methods can change over time and these changes can result in clinically significant interference. Even though Tosoh has been able to alleviate these interferences by changing their software, this new software version is still not available in the U.S. Laboratories and physicians need to be aware of HbA_{1c} method interferences so that accurate results can be reported for patient care and clinical studies.

Duality of Interest. No conflicts of interest relevant to this article were reported.

References

1. Lewis MR, Macauley RC, Sheehan PR, et al.; D2d Research Group. Management of hemoglobin variants detected incidentally in HbA_{1c} testing: a common problem currently lacking a standard approach. *Diabetes Care* 2017;40:e8–e9
2. Rohlfing C, Hanson S, Weykamp C, et al. Effects of hemoglobin C, D, E and S traits on measurements of hemoglobin A_{1c} by twelve methods. *Clin Chim Acta* 2016;455:80–83
3. NGSP. HbA_{1c} assay interferences [Internet], 2016. Available from <http://www.ngsp.org/interf.asp>. Accessed 10 April 2017
4. Lacy ME, Wellenius GA, Sumner AE, et al. Association of sickle cell trait with hemoglobin A_{1c} in African Americans. *JAMA* 2017;317:507–515