Clin Chem Lab Med 2008;46(5):727–728 © 2008 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2008.143

Letter to the Editor

Standardization of carbohydrate-deficient transferrin: reply to the letter by Tagliaro and Bortolotti

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Keywords: carbohydrate-deficient transferrin (CDT); disialotransferrin; standardization.

The first publication of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) working group on carbohydrate-deficient transferrin (CDT) standardization (WG-CDT) was devoted to defining the analyte and proposing a candidate reference method (1). Ongoing activities are to investigate the analyte and validate the reference method, and to work out procedures for the production of reference materials. Further recommendations will focus on the methods used in routine analysis of CDT. Accordingly, the criticism given in the letter by Tagliaro and Bortolotti largely deals with the future issues of the CDT standardization work.

In the first publication of the WG-CDT (1), we concluded that ''the definition of disialotransferrin as the primary target molecule for CDT measurement and the single analyte for CDT standardization, and the recommendation of HPLC as the analytical principle for an interim reference method until a mass spectrometric method becomes available, represent the first steps toward standardization of CDT measurements''. Tagliaro and Bortolotti argue for including asialotransferrin in addition to disialotransferrin in the calculation of CDT, in order to increase the specificity. However, as stated above, the WG proposed disialotransferrin as the primary (not sole!) target molecule for CDT *measurement*, but did not rule out inclusion of asialotransferrin in CDT (as with the immunoassays). The rationale for this statement, and also for choosing disialotransferrin as the single analyte for CDT *standardization*, is that disialotransferrin represents the major glycoform measured with the (current) analytical methods for CDT and standardization is hard to perform for a mixture of two analytes. Furthermore, because asialotransferrin is only detected following heavy drinking and always accompanies an already elevated disialotransferrin level, individual measurement of asialotransferrin will yield a low diagnostic sensitivity. Should specificity be preferred over sensitivity (e.g., in forensic toxicology), an alternative to the addition of asialotransferrin suggested by Tagliaro and Bortolotti would be to raise the cutoff for disialotransferrin. However, we will postpone any recommendations about the benefits of routinely measuring disialotransferrin alone or the sum of asialo- plus disialotransferrin until sufficient evidence on their relative performance is available.

For reasons given previously (1), the WG-CDT considers HPLC the best currently available candidate for an interim reference method. The second concern by Tagliaro and Bortolotti relates to potential problems with the chromatographic separation between disialo- and trisialotransferrin by HPLC. We fully agree that a good peak resolution is very important, but the reference they cite to highlight the risk for underestimation of peak area at poor resolution refers to the use of valley-valley integration in a capillary electrophoresis method. The HPLC candidate reference method uses baseline integration, especially because the results obtained in this way are less sensitive to variations in peak resolution (2).

Finally, Tagliaro and Bortolotti advocate forensic toxicology expertise in the WG-CDT, which they believe is missing. However, some of the WG members have a strong background in forensic drug and alcohol testing with continued education, are members of the major international forensic toxicology organizations, and are also actively involved in external quality assurance activities in this field. The concept of screening and confirmation is well known to

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the WG-CDT, but this is meant for combining a high sensitivity/low specificity ''preliminary'' method (e.g., immunoassays) with a high specificity verification method. It is evident that physico-chemical methods, such as HPLC, combine high sensitivity with high specificity and usually do not require another confirmation method. We thank Tagliaro and Bortolotti for their critical comments leading us to clarify these issues.

References

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