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LETTER TO THE EDITOR

Creatininium reference intervals for corrected methods

The Jaffé methods for creatininium usually show false, too high results especially at low and reference interval levels. These deviations have been shown in several cases when Jaffé methods have been compared with more specific methods such as the ID-GCMS, HPLC and enzymatic methods. The deviation is caused by non-creatininium chromogens present in all plasma/serum samples. Proteins and substances with a ketone group are known interferents.

Using a method-specific correction of all Jaffé results can decrease the deviations in the Jaffé method results from specific method results. To gain good concordance, a negative correction term has to be used for the Jaffé method results usually in combination with a correction factor above 1 (one). The correction formula could be calculated by simple linear regression analysis if results are available from both methods using the same patient samples.

An even more convenient method of correcting the Jaffé methods has been proposed by the main provider of quality assurance programs for clinical chemistry in Sweden, Equalis. A creatininium-free serum has been produced. The serum was prepared by adding creatininium deaminase to a normal serum pool. The resulting serum contains no creatininium but normal concentrations of the interferents. Laboratories using Jaffé methods are proposed to correct their low-point calibrations to get 0 (zero) μmol/L with the creatininium-free serum. The routine low-point calibrator, often water, can still be used but a negative correction term should be introduced in the instrument calculation program. The level of the patient results at the high-point calibrator level should be maintained.

Equalis simulated a situation where the laboratories using Jaffé methods use creatininium-free serum to correct their low-point calibration. Swedish laboratories were provided with a creatininium-free serum, a normal-level and a high-level serum pool and also asked to report their high-point calibrator set value for creatininium. The results of the creatininium-free serum are presented in Table I.

The uncorrected results from 51 laboratories using Jaffé methods, including 11

TABLE I. Results of creatininium-free serum in 78 Swedish laboratories September 2003.

		Min.	Max.	Mean	Manufacturer's recommended correction
Method groups	N			(μmol/L)	
Roche, enzymatic	26	0	5	2	–
Ortho, Vitros	12	<4	14	10*	−8
All Jaffé methods	40	3	30	18	–

* One result <4 μmol/L not included.

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with a Jaffé-correlated dry chemistry method, were corrected according to the formula below.

$$\begin{bmatrix}\text{Corrected}\\ \text{result}\end{bmatrix} = \left[\begin{pmatrix}\text{Uncorrected}\\ \text{result}\end{pmatrix} - \begin{pmatrix}\text{Creatininium} - \text{free}\\ \text{serum result}\end{pmatrix}\right] \times \frac{\begin{bmatrix}\text{High point calibrator}\\ \text{set value}\end{bmatrix}}{\left[\begin{pmatrix}\text{High point calibrator}\\ \text{set value}\end{pmatrix} - \begin{pmatrix}\text{Creatininium} - \text{free}\\ \text{serumresult}\end{pmatrix}\right]}$$

After correction, the results from all creatininium methods showed better agreement for a normal-level serum pool. Uncorrected results from 26 laboratories using enzymatic methods were included in the comparison. For the normal-level serum pool the total inter-laboratory variation was improved from approximately 9.7 to 6.1 CV% and the mean value was decreased from 74 to 66 μmol/L. The variation of the high-level serum pool was not affected (CV% ~ 4).

If the above principles are used in the Nordic Reference Interval Project (NORIP), this will change the originally proposed reference intervals. In Table 3 of the article in Klinisk Biokemi i Norden about NORIP, reference intervals calculated for the three main method groups are shown: Enzymatic, Jaffé and Vitros. The calculations for creatininium were made as for all other non-enzymes by a simple correction factor for all results from each laboratory to reach the correct CAL level.

This letter, instead, proposes using a correction term first before using a correction factor. To do this calculation, the originally proposed limit values were first calculated back to unfactorized values. Then the same formula as that in the Swedish simulation was used to calculate the new reference limits shown in Table II. In the latter calculation, the mean value (18 μmol/L) of the creatininium-free serum for the Jaffé methods from the Swedish simulation was used. For the high-point calibrator set value, the set value for the Scandinavian Society of Clinical Chemistry (NFKK) reference material X was used.

The new reference limits for the Vitros methods have been calculated after first correcting the results in accordance with a new document from Ortho. This document states that multiplying measured values by 1.02 and then subtracting 8.1 μmol/L should give results traceable to reference method values.

In Table II "Change" represents the change from the originally calculated NORIP reference limits for the method group. The concordance between the limits for the different method groups is improved compared to the original limits. The widths of the different intervals are also very similar. Even though the changes are small, it seems reasonable to change the common low limit for women and the common high limit for men.

When the Nordic laboratories are going to implement the NORIP reference interval, they

TABLE II. NORIP reference limits for corrected methods.

Reference intervals for creatininium	Women		Men	
	Low limit	High limit	Low limit	High limit
Enzymatic method	46	92	60	105
Change	0	0	0	0
Corrected Jaffé methods	47	88	62	106
Change	−5	4	−2	8
Corrected Ortho, Vitros	48	82	63	105
Change	−2	1	−1	3
Original NORIP	50	90	60	100
Corrected NORIP	**45**	90	60	**105**

NORIP = Nordic Reference Interval Project.

should first check their bias with the NFKK reference material X. This material is an unmodified human serum pool with normal levels of all components. Most laboratories using Jaffé creatininium methods will have problems retrieving the set value for X. By first correcting their low-point calibration according to the principles above, it is more likely that they will succeed.

Note that the new reference limits proposed in this letter are only valid for laboratories using the enzymatic method, corrected Jaffé method or corrected Vitros method. One could say that it is only possible to use a common reference interval if the used methods are corrected to show good agreement over the whole reference interval.

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