Clin Chem Lab Med 2018; 56(8): e188–e189 DE GRUYTER

Letter to the Editor

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Interference of glucose and total protein on Jaffe-based creatinine methods: mind the covolume

https://doi.org/10.1515/cclm-2018-0192
Received February 20, 2018; accepted March 1, 2018; previously published online April 9, 2018

Keywords: covolume; creatinine; glucose; interference; Jaffe method; total protein.

To the Editor,

Den Elzen et al. [1] reported on the interference of glucose and total protein in the Jaffe creatinine assays. Although this interference is well known (it was already noticed as early as 1886 by Jaffe himself) [2], we believe that the issue is more complex than depicted by den Elzen et al. [1].

It is generally accepted that plasma proteins constitute the largest source of analytical error in the Jaffe-based methods. The so-called protein error produces a positive difference of ~27 μmol/L creatinine compared with reference methods [3]. However, when reducing the protein concentration in plasma, the covolume of the solutes is affected as well as density of plasma proteins is 1.3 kg/L and plasma proteins constitute more than 80% of the volume of solutes present in human plasma. In hypoproteinemia, the space lost by absence of plasma proteins is restored by extracellular water, containing the extracellular concentration of creatinine. In Jaffe-based creatinine assays, the apparent loss of protein due to the pseudochromogen effect (±0.36 μmol creatinine/g protein) is partially counteracted by volume displacement. The net effect of this compensation will depend on the plasma creatinine concentration.

Since the distribution volume of creatinine corresponds to the total body water, even an ideal creatinine assay will measure an apparent increase in plasma creatinine due to the increased water content of the plasma in case of hypoproteinemia. As eGFR formulas are based on exponential functions, a water shift of 2.5% in a Caucasian women aged 55 years with a creatinine concentration of 93 μmol/L would result in an apparent increase of creatinine concentration with 2.33 μmol/L, yielding a 3.3% decrease in eGFR. Thus, it is remarkable that this predictable effect on creatinine and eGFR has not been noticed by den Elzen et al. [1].

When dealing with extreme increases or reductions of plasma protein concentrations, attention should be paid to this covolume effect. In the real world, extreme values of protein concentrations are mainly observed in intensive care ward patients. In these patients, however, eGFR measurements are often unreliable because of the instability of the patient [4]. In case of hypoproteinemia, edema will occur, which strongly affects the distribution of creatinine in the various body compartments, making eGFR calculation unreliable. Similarly, in case of extreme hyperglycemia, marked osmotic diuresis will occur, which will largely affect the total body water and hence disturb creatinine kinetics. In this case, an analytical correct creatinine result does not warrant a reliable eGFR value. The National Kidney Foundation argues against the use of eGFR formulas when renal function is not stable or in patients with serious comorbid conditions or malnutrition (which is clearly the case in life-threatening hyperglycemia and pronounced edema). The physiological limitations of creatinine as a filtration marker have to be respected. All estimates of GFR based on serum creatinine will be less accurate for critically ill patients. Thus, in clinical practice, one should be aware that in conditions associated with extreme concentrations of pseudochromogens (e.g. glucose, total protein), calculation of eGFR remains risky. It should be noted that eGFR formulas [5] have been developed for assessing chronic kidney disease in the general population and not for adjusting drug doses in intensive care wards. As in the critically ill, complete laboratory data sets are available, mathematical correction formulas for compensating analytical errors [6] can be applied confirmatory tests with exogenous measured GFR or measured creatinine clearance should be performed for people in whom estimates based on serum/plasma creatinine alone may be inaccurate [4].

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Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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