

Time to stop debating about the everlasting story: Some issues concerning serum total calcium and ionized calcium

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To the Editor: We appreciate the interesting and attentive article titled “Predictive accuracy of serum total calcium for both critically high and critically low ionized calcium in critical illness,” written by Hu *et al.*^[1] The use of serum total calcium and its corrected value in predicting critical ionized calcium concentration in critical illness is controversial. Hence, the authors retrospectively searched the Medical Information for Intensive Care III database to determine whether the level of total calcium, either corrected for albumin or not, could predict critically high and low ionized calcium. The authors concluded that both uncorrected and corrected total calcium levels are unreliable indexes for predicting the critical values of ionized calcium in critical illness. It is fully believed that this article will provide a profound presentation of and supplement to the everlasting story of calcium state estimation by total calcium. To completely understand the story between total calcium and ionized calcium and comprehensively interpret the results regarding calcium in this manuscript, some issues should first be prioritized.

Why is total calcium more frequently measured in clinical settings? It is well accepted and recognized that ionized calcium, which accounts for approximately 50% of calcium circulating in the serum or plasma, is the biologically important fraction. Consequently, the measurement of ionized calcium should be more frequently performed than that of total calcium in theory. However, in reality, the opposite is true, to some extent. The earliest published method for determining ionized calcium dates back to the 1930s. However, currently, as recommended by the International Federation of Clinical Chemistry and Laboratory Medicine, the only reliable method for measuring ionized calcium in the laboratory is with a potentiometer and a direct ion-selective electrode, which are usually included with blood gas analyzers but not large chemistry auto-analyzers. In contrast,

several modern methods have been successfully used to detect total calcium, such as spectrophotometry of dye-calcium complexes, which have paved the way to auto-analyze total calcium along with other blood chemistry testing items. Aside from method availability and lack of automated analysis, there are some other previously validated and cited reasons for not measuring ionized calcium, such as standardization, analytical performance, and manual sample handling in particular.^[2]

Is solely measuring total calcium rational in clinical practice? In patients without serum protein or pH abnormalities, the levels of total calcium are highly correlated with ionized calcium concentrations. Hence, in routine clinical practice, total calcium often serves as an alternative and legitimate measure to quantify physiologically relevant calcium, which indirectly influences the status of ionized calcium. However, the correlation between ionized calcium and total calcium can worsen in a variety of conditions: low albumin concentrations, abnormal pH, myeloma-related paraprotein, and so on. Many assays have been proposed to adjust or correct the level of total calcium.^[3] The abovementioned study clearly concludes that although total calcium is positively corrected with ionized calcium, the correlation coefficient was only 0.51, which indicates that in intensive care unit settings, serum total calcium cannot represent the concentration of ionized calcium well. Furthermore, the authors demonstrated that the area under curves of both corrected and uncorrected serum total calcium for predicting critically low ionized calcium values were 0.69 and 0.70, respectively, with no significant difference. In another study published recently,^[4] the agreement rates between total calcium and paired ionized calcium and between corrected total calcium and paired ionized calcium were analyzed. They concluded that improper use of uncorrected and corrected total calcium measurements would lead to a misclassification of calcium status.

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What should we do in our clinical practice? From the clinician side, ionized calcium tests should be ordered more frequently as long as the corresponding laboratories can provide measurements of ionized calcium. To the best of our knowledge, most blood gas analyzers can yield results on ionized calcium along with pH, oxygen saturation, and so on, which would be of great use, especially in cases of suspected critically low calcium. From the laboratory technician side, the reporting of corrected total calcium values in patients who have albumin <40 g/L and total calcium <1.62 mmol/L (the threshold of critically low value of total calcium) is encouraged if measurement of ionized calcium is not available.^[5] From the top or clinical guidance makers side, the utility of ionized calcium measurements should be emphasized.

The interpretation of serum total calcium in patients with abnormal protein levels is not a new concept. It is time to stop debating about this story; however, it will not end unless ionized calcium testing instead becomes the first choice for determining the real calcium state with progress in appropriate sample handling, including a change in laboratory processing.

Conflicts of interest

None.

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