Adjusted calcium equation: a step forward

Calcium is one of the most frequently requested biochemical tests. It is widely accepted that total serum calcium concentrations are unreliable markers of the physiologically important ionised calcium fraction in serum, hence, calculated by adjusting calcium to albumin concentration using an equation.

This issue of the *Journal of Laboratory and Precision Medicine* sees the publication of a series of papers on the broad theme of calcium albumin adjustment in laboratory medicine. This series is made up of four reviews each with a different focus. Jassam and O'kane questioned whether standardisation of adjusted calcium measurement is possible (1). The authors reviewed the available literature to identify the source of variation in adjusted calcium and listed the factors contributing to the variability of adjusted calcium measurement. The source of variation divided broadly in to three categories; variation intrinsic to the original assumption of adjustment of calcium to albumin, variation yielded from the use of various analytical methods used to measure calcium and albumin and population and case mix impact on variation in the regression equations. The impact of each factor on the variability of adjusted calcium measurement has been weighed. In concordance with previous reports (2-4), the authors emphasised that albumin methods remain as the largest contributing factor to variability of adjusted calcium measurement. Therefore, they support calls of other research groups in that the road map for harmonisation starts with improving the standardization of albumin methods, Bromocresol and Green (BCG) and Bromocresol Purple (BCP). Until then, the use of a single albumin method is recommended (5-7). Due to the non-specificity and poorer analytical performance of the BCG method, the BCP albumin method use has been promoted as a preferable choice for using to adjust calcium to albumin (5).

One of the first adjusted calcium equations and probably the most famous equation originated in the UK in 1973. Roberts and Thomas colleagues have given, for the first time, an insight into 50 years of the UK experience with standardisation of the adjusted calcium equation (8). The authors have given a historical view about the first adjusted calcium equation. Then reviewed the impact of a number of UK-based initiatives aimed to harmonise the adjusted calcium equation via standardisation of the method of derivation (data collection, sifting, calculation and reporting) by the Association of Clinical Biochemistry (ACB). Undoubtedly, the recent guidelines [2015] from the ACB made a clear improvement with regards to the use of a locally derived equation, highlighting the success of the current harmonisation initiatives.

There is a growing assumption among physicians and patients that test results from different laboratories are equivalent and hence can be interpreted by the same reference interval. This concept has driven several professional efforts to harmonise reference intervals at least for assays with an established standardised calibration system such as calcium.

One of the reviews in this series also covered global efforts for harmonisation of the calcium reference interval and what has been achieved until now (1). Reference interval is amongst many other variables influencing adjusted calcium concentration. Two reviews in this series remind us that (1,8), we cannot talk about adjusted calcium in isolation of the calcium reference interval for two reasons. The first is because reference intervals inform the classification of hypo/hyper calcaemia and essentially the aim of the harmonisation is the correct classification of calcium status. The second is because the adjusted calcium equation is normalised to the mid-point of the calcium reference interval. While Jassam and O'Kane showed that calcium reference intervals vary significantly with analytical platform and population, the Roberts and Thomas reminded us that the UK approach to harmonisation of adjusted calcium equation which has been predicated on a pragmatically defined reference interval of 2.2–2.60 mmol/L, can be misleading. Payne used a cut of 2.4 mmol/L because this was the mid-point of a local reference range of 2.2–2.6 mmol/L. They emphasized that an adjustment equation set to a mean calcium of 2.4 mmol/L, which is significantly different from the mid-point of a local calcium reference range, is an invalid approach and misclassification of calcium status is an inevitable outcome. Finally, the review shows that the road of harmonisation does not end here. Further UK audits on the frequency and how a local adjustment equation is being validated are required. Both reviews have recommended further studies especially in medical domains where the adjustments equation showed clear shortcomings. Gernez and Grzych attempted to answer a question about "over what albumin concentration range are adjusted equations valid". The authors reviewed selected comparative studies of adjusted calcium against ionised calcium (iCa). They found that in the normal albumin concentration range, the agreement between adjusted calcium and iCa at best is 65% and this is the same as with total calcium. This relationship is worse over the low albumin concentrations, concluding that adjusted calcium equations should no longer be routinely used regardless of albumin concentration (9).

Adjusted calcium remains popular despite its poor diagnostic performance. The shortcomings of the adjusted calcium

meant the search for a practical alternative and a non-expensive approach continues. While adjusted calcium essentially is an estimation of the biologically active "ionised calcium". Yap and Goldwasser reviewed another indirect approach called "estimated ionised Calcium" estimated iCa" measurement (10).

The concept of estimated iCa is not a new one, this was pioneered by McLean and Hastings in 1935 (11). This approach went silent since then but was only resurrected in the last decade. Data shows that the linear estimated iCa model based on the combination of calcium and albumin only is unlikely to outperform adjusted calcium. This model, however, lends itself to the inclusion of other biochemicals of special clinical significance in specific patient groups (e.g., phosphate, chloride in renal patients or critically ill patients) hence generating new equations. These new equations appear promising but require further validation. We are aware that promising findings are not sufficient to make the clinical use, unless validated and supported by positive clinical outcomes.

Yap and Goldwasser remind us that the limitations of the estimated iCa are the same as that of adjusted calcium. In fact, the more variables included in the estimated iCa equation, the wider the uncertainty interval would be which may disadvantage the new equations. However, the estimated iCa model may complement adjusted calcium in patient groups where adjusted calcium demonstrated shortfalls e.g., renal medicine.

In summary, this series presents views of adjusted calcium current practice in light of standardisation, present an effective harmonisation example of adjusted calcium equation, and literature scanning for new concepts that may improve adjusted calcium measurement solely or in combination with new approaches. Finally, this series addresses areas in clinical practice, which may require attention and leadership from professional bodies to improve adjusted calcium measurement and reporting.

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