# Over what albumin concentration range are adjusted calcium equations valid?

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Calcium is the fifth most abundant element in the organism. This essential element is primarily available to the body through dietary intake. In the body, the vast majority of calcium (>99%) is stored in bones, and thus plays a major role in bone mineralization. In plasma, calcium (<1% of the body's calcium) is found either in free ionized form or bound (mainly to albumin), but only ionized calcium (Ica) is active and plays a major role, especially in intra- and extracellular signalling pathways, in nerve impulse transmission and muscle contraction (1). Thus, calcium is involved in numerous physiological functions, and is therefore commonly measured in clinical practice. Indeed, dyscalcemia can lead to serious clinical consequences. In clinical practice, the total calcium (Tca) is mostly measure, representing both free and bound calcium. To estimate the active form by Tca, corrected calcium (Cca) could be determined. Hence, many adjusted calcium equations have been developed using albumin levels such as Payne, the most used in practice, Clase or Jain formulas, etc. (2-4). However, the literature suggests some limits about this adjustment, regardless of albumin levels.

Indeed, Ladenson *et al.* (5) compared different adjusted calcium equations in a population of 375 hospitalized patients and 53 controls. In this study, Tca and Ica were measured, and Cca was calculated according to 13 formulas. The aim was to evaluate the effectiveness of the calcium correction formulas. Finally, this study showed that Cca does not significantly improve calcium true state (determined by Ica) than Tca, which means that uncorrected calcium would sometimes give a better indication of calcium status than Cca (5). Moreover, Dickerson *et al.* (6) evaluated adjusted calcium equations from literature (22 formulas). They showed that seven formulas estimated Ica and 15 estimated corrected Tca. On 100 patients admitted to the trauma intensive care unit who were referred to the Nutrition Support Service, they showed a low sensitivity of these formulas for both hypocalcemia and hypercalcemia (25% and 15% respectively) (6). Additionally, Mateu-de Antonio (7) evaluated 11 formulas in two cohorts of 269 and 146 hospitalized patients, showing a poor predictive value for hypocalcemia (26% for Payne formula).

Recently, a retrospective study performed by Pekar *et al.* (8) on 5,055 patients found that Cca tends to overestimate calcium status, and more particularly in case of low albumin levels or blood pH disorders. In this study, for the patients with normal levels of albumin, the global agreement rate for the Cca was between 64% and 65% according to the formulas (between 63% and 66% for Tca) suggesting no significant improvement of Cca compared to Tca (8). Also, a study performed by Smith *et al.* (9) retrospectively on 5,553 patients and prospectively on 440 patients concludes that the Cca tends to overestimate calcium, with a more pronounced effect in patients with low albumin or renal impairment. Hence, these last two studies show that the correction formulas are even more inefficient in case of hypoalbuminemia.

Overall, numerous factors influence the binding of calcium to albumin, and the pH seems to be a major determinant, explaining why adjusted calcium equations have some limitations. Moreover, adjusted equations suppose a constant link between albumin and calcium, regardless of albumin level. However, in case of hypoalbumin state, the calcium affinity for albumin increase (10). Thus, the use of Cca can lead to patients' mismanagement. The formulas to correct Tca using pH would be of limited interest. Indeed, the measure of pH determination and Ica measurement require same strict pre-analytical conditions and can be performed under the same blood-gas analyzers (11). Ideally, measurement of Ica should be preferred in whole blood collected anaerobically into blood gas syringes, to determine the calcium status of patients.

Because Ica is not yet measured routinely, a formula to predict hypocalcemia using the anion gap (AG) has been proposed by Yap *et al.* (12). Authors evaluated their formula on a set of patients from intensive care unit, Ica measurement had been performed simultaneously with Tca measurement, either by venous blood gas (VBG cohort) or by arterial blood gas (ABG cohort); 182 patients with hypocalcemia (Ica <1.1 mmol/L) were selected: 96 in the VBG cohort and 86 in the ABG cohort. To estimate Ica from Tca, 2 correction formulas were evaluated, using, in addition to the albumin level, the AG or its components (sodium, chloride, total carbon dioxide). The Cca was also calculated (correction only by albumin level). Finally, the correction with AG or its components were better than Cca, indeed albumin correction does not involve important variation of the complexed fraction of Tca. The inverse correlation between AG and Ica suggests that AG might be a good indicator of the complexed fraction (12).

To conclude, albumin-adjusted calcium equations should no longer be used routinely, regardless of albumin level. Moreover, if calcium affinity to albumin is dependent on the pH, the use of pH adjusted calcium equations would be of limited interest because all blood gas analyzers can directly measure Ica. Ica assay is to be preferred and should be used routinely: representing the active form of calcium, Ica it is the best reflection of calcium status. Hence, it allows to avoid misclassifications of patients. Calcium correction equations lead to higher discordance rate than Tca uncorrected, we also suggest to use Tca in situations in which the measurement of the Ica is impossible, especially when it is impossible to collect a blood gas. New formulas are under development, considering the AG or its components, but are not yet used routinely.

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