

Correcting the Myth of Calcium Correction

By [Dr. Janet Simons](#) on June 26, 2019

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What gap I have noticed

Calcium levels are commonly ordered in both primary and acute care in patients with a variety of signs and symptoms. Hypocalcemia (total calcium concentrations generally below 2.0 mmol/L or ionized calcium below 1.15 mmol/l) is usually related to dietary deficiencies or disorders of the parathyroid axis, such as in patients with previous surgery or autoimmune destruction of the parathyroid gland. Hypercalcemia (above 2.5 mmol/L total calcium or 1.3 mmol/L ionized) in primary care is commonly associated with dehydration, primary hyperparathyroidism, and malignancy such as multiple myeloma. When hypercalcemia is severe, generally defined as total calcium above 3.5 mmol/L or ionized calcium above 2.0 mmol/L, therapy should be initiated immediately. Values of calcium below this threshold but above 3.0 mmol/L total calcium or 1.75 mmol/L ionized are considered moderate hypercalcemia and patients with calcium values in this range may not need immediate therapy but should be monitored closely. Precise values of normal ranges and cut offs may vary between laboratories.



It remains common practice to apply the Payne formula (usually expressed as albumin-adjusted calcium (mmol/L) = total calcium (mmol/L) + 0.02 [40 – albumin (g/L)]) (1) to adjust total calcium. This correction is intended to enhance the ability of the total calcium concentration to serve as a marker of the physiologically relevant parameter, ionized calcium, in

patients with hypoalbuminemia.

Since the original Payne paper, clinical use of this correction formula has spread such that many clinicians routinely apply this 'correction' to all total calcium measurements. This observation is supported by data available from Vancouver Coastal Health and Providence Health Care laboratories. In 2018, total serum calcium and albumin were ordered together **72%** of the time, suggesting that many clinicians believe that serum albumin measurement is required in order to interpret total calcium concentrations.

There are a number of problems with the Payne formula. This formula was derived in 200 patients whom Payne considered to be **unlikely to have abnormalities of ionized calcium**, however 20% of the patients had **hyperproteinemia secondary to multiple myeloma**. Payne et al relied upon results from a single laboratory which used methodologies for the measurement of albumin and total calcium which are different from methods in routine use today. The formula was designed to transform the calcium results in those patients who had hypoalbuminemia so that the distribution of results would match the distribution of calcium results in the patients with normal serum albumin concentrations. There was no validation of the formula using ionized calcium, which was not measured.

What data addresses this gap

There is considerable evidence (2-12) that application of the Payne formula tends to misclassify the calcium status of patients and performs less well than simply evaluating uncorrected total calcium. Payne himself recently wrote a letter to the editor (13) in which he acknowledged that his original formula is not universally applicable, requiring modification for the specific albumin assay in use by a laboratory, and that any albumin-based adjustment will likely overestimate calcium in patients with renal failure. In renal failure, the albumin concentration is underestimated when

uremia induced carbamylation of albumin reduces its detection by the assay (14). Attempts to derive a new formula (10-12) to improve upon the performance of the Payne formula have failed to find a correction which performs significantly better than unadjusted total calcium.

The physiological basis for the albumin adjustment is the theory that when albumin is reduced, the amount of calcium bound to albumin is also reduced, such that the total serum calcium may be low despite a normal ionized calcium concentration. However, this physiologic basis is belied by evidence that in hypoalbuminaemic states, the binding constant between albumin and calcium changes, and more calcium binds to each available gram of albumin (15). Formulae such as the Payne formula which assume a constant relationship between albumin concentration and the fraction of calcium which is bound to albumin are thus expected to overestimate ionized calcium in patients with low albumin. Several studies have borne out this tendency of correction formulae to overestimate ionized calcium.

Steen et al (2) found that in patients with albumin <30 g/L, 75% of patients classified as normocalcemic using the Payne formula in fact had hypocalcemia based on ionized calcium levels. Another study (3) found that adjusted calcium values derived by applying the Payne formula agreed with ionized calcium levels in only 55-65% of patients. In contrast, unadjusted total calcium correctly categorized 70-80% of patients. Agreement between adjusted calcium and ionized calcium was even worse for patients with renal impairment ($\text{eGFR} < 60 \text{ mL/min/1.73m}^2$). The adjustment significantly overestimated calcium concentrations in these patients. A similar trend has been documented in critically ill patients in both the medical and surgical ICU settings (4-6).

The poor performance of the calcium correction has also been observed in the hypoalbuminemic geriatric population (7).

Again, the correction impairs the sensitivity of the corrected result to detect true hypocalcemia. The more severe the hypoalbuminemia, the poorer the performance of the adjustment formula. This has also been demonstrated in stable hemodialysis patients (8-9).

Other studies (10-11) have sought to derive new formulae for the purpose of correcting calcium for albumin concentration. James et al (10) considered many possible formulae but ultimately concluded that if any adjustment is to be made to calcium to account for hypoalbuminemia, the adjustment formula must be locally derived.

Many of the studies above were done in hospital inpatients. Less data is available in outpatients, as ionized calcium is more difficult to measure in this population due to the requirement that specimens for ionized calcium be analyzed promptly after collection (16). However, a study which examined results from both inpatients and outpatients of a hospital and excluded critically ill patients (12) confirmed that unadjusted total calcium performs better than any of the available correction formulae (including those put forth by Payne and James) in ROC analysis compared to the ionized calcium gold standard.

What I recommend (practice tips)

Formulae to adjust total calcium for the albumin concentration should be abandoned. The use of these formulae overestimates ionized calcium in patients with hypoalbuminemia, causing false negatives for hypocalcemia and false positives for hypercalcemia. Measurement of ionized calcium is now relatively inexpensive and is available in most hospitals and many outpatient settings.

1. Measurement of ionized calcium is recommended over total calcium when calcium homeostasis is in question.
2. If calcium is ordered as a 'screening' test without

specific clinical suspicion for a disorder of calcium homeostasis, it is reasonable to assess unadjusted total calcium. If this level is abnormal, confirmation with ionized calcium may be sought prior to further workup or therapy.

3. Where ionized calcium is not available, total calcium should be assessed without the application of any correction formula.
4. Order serum albumin only if clinically indicated for reasons other than adjusting total calcium.

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