Things We Do for No Reason™: Calculating a "Corrected Calcium" Level

Colin M Kenny, DO[1]*, Caroline E Murphy, MD[1], Dacia S Boyce, MD[1], Deptmer M Ashley, MD[1], Jay Jahanmir, MD[2]

[1]*Division of Internal Medicine and Department of Medicine, Tripler Army Medical Center, Honolulu, Hawaii;* [2]*Division of Nephrology, Department of Medicine, Tripler Army Medical Center, Honolulu, Hawaii.*

Inspired by the ABIM Foundation's Choosing Wisely® campaign, the "Things We Do for No Reason™" (TWDFNR) series reviews practices that have become common parts of hospital care but may provide little value to our patients. Practices reviewed in the TWDFNR series do not represent clear-cut conclusions or clinical practice standards but are meant as a starting place for research and active discussions among hospitalists and patients. We invite you to be part of that discussion.

CLINICAL SCENARIO

A hospitalist admits a 75-year-old man for evaluation of acute pyelonephritis; the patient's medical history is significant for chronic kidney disease and nephrotic syndrome. The patient endorses moderate flank pain upon palpation. Initial serum laboratory studies reveal an albumin level of 1.5 g/dL and a calcium level of 10.0 mg/dL. A repeat serum calcium assessment produces similar results. The hospitalist corrects calcium for albumin concentration by applying the most common formula (Payne's formula), which results in a corrected calcium value of 12 mg/dL. The hospitalist then starts the patient on intravenous (IV) fluids to treat hypercalcemia and obtains serum 25-hydroxyvitamin D and parathyroid hormone levels.

BACKGROUND

Our skeletons bind, with phosphate, nearly 99% of the body's calcium, the most abundant mineral in our body. The remaining 1% of calcium (approximately 9-10.5 mg/dL) circulates in the blood. Approximately 40% of serum calcium is bound to albumin, with a smaller percentage bound to lactate and citrate. The remaining 4.5 to 5.5 mg/dL circulates unbound as free (ie, ionized) calcium (iCa).[1] Calcium has many fundamental intra- and extracellular functions. Physiologic calcium homeostasis is maintained by parathyroid hormone and vitamin D.[2] The amount of circulating iCa, rather than total plasma calcium, determines the many biologic effects of plasma calcium.

In the hospital setting, clinicians commonly encounter patients with derangements in calcium homeostasis.[3] True hypercalcemia or hypocalcemia has significant clinical manifestations, including generalized fatigue, nephrolithiasis, cardiac arrhythmias, and, potentially, death. Thus, clinical practice requires correct and accurate assessment of serum calcium levels.[1]

WHY YOU MIGHT THINK CALCULATING A "CORRECTED CALCIUM" LEVEL IS HELPFUL

Although measuring biologically active calcium (ie, iCa) is the gold standard for assessing calcium levels, laboratories struggle to obtain a direct, accurate measurement of iCa due to the special handling and time constraints required to process samples.[4] As a result, metabolic laboratory panels typically report the more easily measured total calcium, the sum of iCa and bound calcium.[5] Changes in albumin levels, however, do not affect iCa levels. Since calcium has less available albumin for binding, hypoalbuminemia should theoretically decrease the amount of bound calcium and lead to a decreased reported total calcium. Therefore, a patient's total calcium level may appear low even though their iCa is normal, which can lead to an incorrect diagnosis of hypocalcemia or overestimate of the extent of existing hypocalcemia. Moreover, these lower reported calcium levels can falsely report normocalcemia in patients with hypercalcemia or underestimate the extent of the patient's hypercalcemia.

For years physicians have attempted to account for the underestimate in total calcium due to hypoalbuminemia by calculating a "corrected" calcium. The correction formulas use total calcium and serum albumin to estimate the expected iCa. Refinements to the original formula, developed by Payne et al in 1973, have resulted in the most commonly utilized formula today: corrected calcium = (0.8 x [normal albumin − patient's albumin]) + serum calcium.[6,7] Many commonly used clinical-decision resources recommend correcting serum calcium concentrations in patients with hypoalbuminemia.[6]

WHY CALCULATING A CORRECTED CALCIUM FOR ALBUMIN IS UNNECESSARY

While calculating corrected calcium should theoretically provide a more accurate estimate of physiologically active iCa in patients with hypoalbuminemia,[4] the commonly used correction equations become less accurate as hypoalbuminemia worsens.[8] Payne et al derived the original formula from 200 patients using a single laboratory; however, subsequent retrospective studies have not supported the use of albumin-corrected calcium calculations to estimate the iCa.[4,9-11] For example, although Payne's corrected calcium equations assume a constant relationship between albumin and calcium binding throughout all serum-albumin concentrations, studies have shown that as albumin falls, more calcium ions bind to each available gram of albumin. Payne's assumption results in an overestimation of the total serum calcium after correction as compared to the iCa.[8] In comparison, uncorrected total

serum calcium assays more accurately reflect both the change in albumin binding that occurs with alterations in albumin concentration and the unchanged free calcium ions. Studies demonstrate superior correlation between iCa and uncorrected total calcium.[4,9-11]

Several large retrospective studies revealed the poor in vivo accuracy of equations used to correct calcium for albumin. In one study, Uppsala University Sweden researchers reviewed the laboratory records of more than 20,000 hospitalized patients from 2005 to 2013.[9] This group compared seven corrected calcium formulas to direct measurements of iCa. All of the correction equations correlated poorly with iCa based on their intraclass correlation (ICC), a descriptive statistic for units that have been sorted into groups. (ICC describes how strongly the units in each group correlate or resemble each other—eg, the closer an ICC is to 1, the stronger the correlation is between each unit in the group.) ICC for the correcting equations ranged from 0.45-0.81. The formulas used to calculate corrected calcium levels performed especially poorly in patients with hypoalbuminemia. In this same patient population, the total serum calcium correlated well with directly assessed iCa, with an ICC of 0.85 (95% CI, 0.84-0.86). Moreover, the uncorrected total calcium classified the patient's calcium level correctly in 82% of cases.

A second study of 5,500 patients in Australia comparing total and adjusted calcium with iCa similarly demonstrated that corrected calcium inaccurately predicts calcium status.[10] Findings from this study showed that corrected calcium values correlated with iCa in only 55% to 65% of samples, but uncorrected total calcium correlated with iCa in 70% to 80% of samples. Notably, in patients with renal failure and/or serum albumin concentrations <3 g/dL, formulas used to correct calcium overestimated calcium levels when compared to directly assessed iCa. Correction formulas performed on serum albumin concentrations >3 g/dL correlated better with iCa (65%-77%), effectively negating the utility of the correction formulas.

Another large retrospective observational study from Norway reviewed laboratory data from more than 6,500 hospitalized and clinic patients.[11] In this study, researchers calculated corrected calcium using several different albumin-adjusted formulas and compared results to laboratory-assessed iCa. As compared to corrected calcium, uncorrected total calcium more accurately determined clinically relevant free calcium.

Finally, a Canadian research group analyzed time-matched calcium, albumin, and iCa samples from 678 patients.[4] They calculated each patient's corrected calcium values using Payne's formula. Results of this study showed that corrected calcium predicted iCa outcomes less reliably than uncorrected total calcium (ICC, 0.73 for corrected calcium vs 0.78 for uncorrected calcium).

Utilizing corrected calcium formulas in patients with hypoalbuminemia can overestimate serum calcium, resulting in false-positive findings and an incorrect diagnosis of hypercalcemia or normocalcemia.[12] Incorrectly diagnosing hypercalcemia by using correction formulas prompts management that can lead to iatrogenic harm. Hypoalbuminemia is often associated with hepatic or renal disease. In this patient population, standard treatment of hypercalcemia with volume resuscitation (typically 2 to 4 L) and potentially IV loop diuretics will cause clinically significant volume overload and could worsen renal dysfunction.[13] Notably, some of the correction formulas utilized in the studies discussed here performed well in hypercalcemic patients, particularly in those with preserved renal function (estimated glomerular filtration rate ≥60 mL/min/1.73 m²).

Importantly, correction formulas can mask true hypocalcemia or the true severity of hypocalcemia. Applying correction formulas in patients with clinically significant hypocalcemia and hypoalbuminemia can make hospitalists believe that the calcium levels are normal or not as clinically significant as they first seemed. This can lead to the withholding of appropriate treatment.[12]

WHAT YOU SHOULD DO INSTEAD

Based on the available literature, uncorrected total calcium values more accurately assess biologically active calcium. If a more certain calcium value will affect clinical outcomes, clinicians should obtain a direct measurement of iCa.[4,9-11] Therefore, clinicians should assess iCa irrespective of the uncorrected serum calcium level in patients who are critically ill or who have known hypoparathyroidism or other derangements in iCa.[14] Since iCa levels also fluctuate with pH, samples must be processed quickly and kept cool to slow blood cell metabolism, which alters pH levels.[4] Using bedside point-of-care blood gas analyzers to obtain iCa removes a large logistical obstacle to obtaining an accurate iCa. Serum electrolyte interpretation with a properly calibrated point-of-care analyzer correlates well with a traditional laboratory analyzer.[15]

RECOMMENDATIONS

- Use serum calcium testing routinely to evaluate calcium homeostasis.
- Do not use corrected calcium equations to estimate total calcium.
- If a more accurate measurement of calcium will change medical management, obtain a direct iCa.
- Obtain a direct iCa measurement in critically ill patents and in patients with known hypoparathyroidism, hyperparathyroidism, or other derangements in calcium homeostasis.
- Do not order a serum albumin test to assess calcium levels.

CONCLUSION

Returning to our clinical scenario, this patient did not have true hypercalcemia and experienced unnecessary evaluation and treatment. Multiple retrospective clinical trials do not support the practice of using corrected calcium equations to correct for serum albumin derangements.[4,9-11] Hospitalists should therefore avoid the temptation to calculate a corrected calcium level in patients with hypoalbuminemia. For patients with clinically significant total serum hypocalcemia or hypercalcemia, they should consider obtaining an iCa assay to better determine the true physiologic impact.

Do you think this is a low-value practice? Is this truly a "Thing We Do for No Reason™"? Share what you do in your practice and join in the conversation online by retweeting it on Twitter (#TWDFNR) and liking it on Facebook. We invite you to propose ideas for other "Things We Do for No Reason™" topics by emailing TWDFNR@hospitalmedicine.org

---

References

1. Peacock M. Calcium metabolism in health and disease. *Clin J Am Soc Nephrol.* 2010;5 Suppl 1:S23-S30. https://doi.org/10.2215/cjn.05910809
2. Brown EM. Extracellular Ca2+ sensing, regulation of parathyroid cell function, and role of Ca2+ and other ions as extracellular (first) messengers. *Physiol Rev.* 1991;71(2):371-411. https://doi.org/10.1152/physrev.1991.71.2.371
3. Aishah AB, Foo YN. A retrospective study of serum calcium levels in a hospital population in Malaysia. *Med J Malaysia.* 1995;50(3):246-249.
4. Steen O, Clase C, Don-Wauchope A. Corrected calcium formula in routine clinical use does not accurately reflect ionized calcium in hospital patients. *Can J Gen Int Med.* 2016;11(3):14-21. https://doi.org/10.22374/cjgim.v11i3.150
5. Payne RB, Little AJ, Williams RB, Milner JR. Interpretation of serum calcium in patients with abnormal serum proteins. *Br Med J.* 1973;4(5893):643-646. https://doi.org/10.1136/bmj.4.5893.643
6. Shane E. Diagnostic approach to hypercalcemia. UpToDate website. Updated August 31, 2020. Accessed April 8, 2021. https://www.uptodate.com/contents/diagnostic-approach-to-hypercalcemia
7. Ladenson JH, Lewis JW, Boyd JC. Failure of total calcium corrected for protein, albumin, and pH to correctly assess free calcium status. *J Clin Endocrinol Metab.* 1978;46(6):986-993. https://doi.org/10.1210/jcem-46-6-986
8. Besarab A, Caro JF. Increased absolute calcium binding to albumin in hypoalbuminaemia. *J Clin Pathol.* 1981;34(12):1368-1374. https://doi.org/10.1136/jcp.34.12.1368
9. Ridefelt P, Helmersson-Karlqvist J. Albumin adjustment of total calcium does not improve the estimation of calcium status. *Scand J Clin Lab Invest.* 2017;77(6):442-447. https://doi.org/10.1080/00365513.2017.1336568
10. Smith JD, Wilson S, Schneider HG. Misclassification of calcium status based on albumin-adjusted calcium: studies in a tertiary hospital setting. *Clin Chem.* 2018;64(12):1713-1722. https://doi.org/10.1373/clinchem.2018.291377
11. Lian IA, Åsberg A. Should total calcium be adjusted for albumin? A retrospective observational study of laboratory data from central Norway. *BMJ Open.* 2018;8(4):e017703. https://doi.org/10.1136/bmjopen-2017-017703
12. Bowers GN Jr, Brassard C, Sena SF. Measurement of ionized calcium in serum with ion-selective electrodes: a mature technology that can meet the daily service needs. *Clin Chem.* 1986;32(8)1437-1447.
13. Myburgh JA. Fluid resuscitation in acute medicine: what is the current situation? *J Intern Med.* 2015;277(1):58-68. https://doi.org/10.1111/joim.12326
14. Aberegg SK. Ionized calcium in the ICU: should it be measured and corrected? *Chest.* 2016;149(3):846-855. https://doi.org/10.1016/j.chest.2015.12.001
15. Mirzazadeh M, Morovat A, James T, Smith I, Kirby J, Shine B. Point-of-care testing of electrolytes and calcium using blood gas analysers: it is time we trusted the results. *Emerg Med J.* 2016;33(3):181-186. https://doi.org/10.1136/emermed-2015-204669