Review Article

Can ionized calcium-estimating equations replace albumin-corrected calcium?—a narrative review

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Background and Objective: An accurate appraisal of ionized calcium status is important for clinical management and prognosis in many domains of medicine, such as critical care and renal disease. The direct measurement of ionized calcium is still relatively costly and not entirely routine, especially in low-resource areas, but the popular indirect method, which infers ionized calcium status from the value of total calcium (T_{Ca}) corrected for albumin, has fared poorly in validation studies. There is a need for a validated indirect method of screening for patients at risk of abnormal ionized calcium based on routine data to serve as a guide for direct testing. The aim of this article is to review some of the newer models that estimate ionized calcium from additional routinely obtained biochemical data besides T_{Ca} and albumin and that have undergone successful external validation.

Methods: Literature in English reporting or validating models of either albumin-corrected calcium or ionized calcium from 1935 to 14 February 2022 were retrieved from PubMed and Google Scholar using these search terms: corrected calcium; adjusted calcium; calcium equation; ionized calcium; hypocalcemia; hypercalcemia. Validated models of ionized calcium status were identified and synthesized into a narrative overview.

Key Content and Findings: We identified several recently published models of ionized calcium that were derived in cohorts of inpatients, critical care patients, or renal patients, and that showed better discrimination for ionized hypocalcemia and hypercalcemia compared with albumin-corrected calcium in validation studies. While these models continue to use T_{Ca} and albumin as inputs, they have in common the use of other independent variables drawn from routine data, such as phosphate or the components of the anion gap, that appear to further account for the complexation of calcium by small anions.

Conclusions: New ionized calcium models have been derived that can help clinicians and laboratories better screen more seriously ill patients for ionized calcium testing. The generalizability of these models to less seriously ill patients merits further investigation.

Keywords: Ionized calcium; anion gap; phosphate; corrected calcium

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Introduction

Serum total calcium (T_{Ca}) is made up of three fractions of calcium ions in equilibrium with each other (1,2). The physiologically active fraction (~50%) consists of solvated calcium ions and is commonly referred to as the ionized calcium (I_{Ca}) fraction. Its concentration is regulated, with a typical reference range of 1.15–1.29 mmol/L, although its chemical activity is only about 30% of its concentration (3). The second fraction (~40%) is bound to protein, mainly albumin. Binding of calcium to albumin is reduced by hydrogen, magnesium, and chloride ions, but increased by free fatty acids (4-7). The remaining fraction (~10%) is complexed by small anions such as bicarbonate (the least calcium-avid but most abundant such anion), phosphate, lactate, and citrate (most avid but with a typical serum concentration of only 0.12 mmol/L) (1,8). I_{Ca} has been shown to be of prognostic value in critical care, COVID-19, and even the general population (9-11). Since direct I_{Ca} measurement is relatively costly and laborious, and has stringent sampling requirements, it is still not an entirely routine test, especially in developing countries (12-14). There is a need for an indirect method of screening for patients at risk of abnormal I_{Ca} based on routine data to serve as a guide for direct testing. This review compares the traditional albumin-corrected calcium method, which was derived without I_{Ca} testing, with newer regression models of measured I_{Ca} that utilize routine data in addition to T_{Ca} and albumin as independent variables, with a focus on models that have undergone successful external validation. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-22-16/rc).

Methods

We searched the PubMed and Google Scholar databases through February 14, 2022 using these terms: corrected calcium; adjusted calcium; calcium equation; ionized calcium; hypocalcemia; hypercalcemia. We selected articles published in English that either reported new models to estimate I_{Ca} status or tested the external validity of previously published models. We further examined the references of the resulting articles to identify additional relevant publications. Using these sources, we traced the history of (I) published albumin-corrected calcium models and of (II) models of pH-unadjusted I_{Ca} that rely solely on routine biochemical data (not, for example, on pH or lactate) as independent variables. We reviewed how well these two classes of models align with the underlying biochemistry of I_{Ca}, how well they performed on internal and external validation, and what the limitations to their clinical application are (*Table 1*).

Discussion

Corrected calcium

It is well-known that the concentrations of T_{Ca} and albumin co-vary (15). This trend has been quantified by the slope of the linear regression of T_{Ca} on albumin (T_{Ca} = slope × albumin + intercept) in a multitude of studies. Possibly the earliest example is the study by Gutman and Gutman in 1937, which found the relationship to be T_{Ca} (mmol/L) = 0.0207 × albumin (g/L) + 1.747 [T_{Ca} (mg/dL) = 0.83 × albumin (g/dL) + 7.0] in a mixed cohort including normal subjects, and patients with various disorders including nephrotic syndrome, cirrhosis, lymphogranuloma inguinale, and miscellaneous hyperproteinemic conditions (16). Ultimately, this linear relationship inspired a method to produce a value of T_{Ca} corrected for altered albumin concentrations (cT_{Ca}). Popularized in the 1970s, it uses the slope of the regression of T_{Ca} on albumin to "correct" measured T_{Ca} to the hypothetical value it would have if albumin concentration were at the population mean of healthy subjects (15). Using this method, cT_{Ca} is calculated as: measured T_{Ca} + slope × (reference albumin – current albumin). One might conceive of cT_{Ca} as the T_{Ca} value that would result if a hypoalbuminemic plasma sample were subjected to ultrafiltration, concentrating its albumin to the reference value while removing plasma water and its associated non-colloidal solutes (with an "opposite" maneuver for a hyperalbuminemic sample). Notwithstanding the equilibrium among the three calcium fractions, the cT_{Ca} method ascribes the change in T_{Ca} concentration entirely to the albumin-bound fraction, and explicitly assumes that the I_{Ca} concentration remains constant (2,16). The resultant cT_{Ca} value is then simply compared to the reference range of T_{Ca}. Many different estimates of the slope have been published (generally unaccompanied by a 95% CI), although a consensus value of 0.02 mmol/L calcium per g/L of albumin (0.8 mg/dL per g/dL) is most commonly used (15).

Limitations of corrected calcium

The cT_{Ca} method was developed in the era before

Table 1 The search strategy summary

Items	Specification
Date of Search (specified to date, month and year)	Searches performed up to 14 Feb 2022
Databases and other sources searched	Electronic searches of PubMed and Google Scholar, and hand searches of references of retrieved literature
Search terms used (including MeSH and free text search terms and filters)	Corrected calcium; adjusted calcium; calcium equation; ionized calcium; hypocalcemia; hypercalcemia
Timeframe	Models published between 1935 and 14 Feb 2022
Inclusion and exclusion criteria (study type, language restrictions, etc.)	Articles that were not written in English or that reported models of I_{Ca} that used non-routine data (e.g., pH, lactate) or pH-adjusted I_{Ca} were excluded
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Conducted by PG, with consensus by both authors

measurements of I_{Ca} were readily available, and remains popular in spite of its poor diagnostic performance, often no better than that of T_{Ca}, in later external validation studies performed after the I_{Ca} electrode became more clinically available (14,17-21). The various factors that contribute to the method's poor performance can be classified as follows.

Biochemical

The cT_{Ca} equation doesn't account for variation in I_{Ca} resulting from variation in pH, magnesium, free fatty acids, and complexing small anions. The method also assumes that I_{Ca} remains constant when albumin varies, when, in fact, I_{Ca} and albumin have been found to co-vary (22). That direct correlation might be partly causal, resulting from the Donnan effect, and partly due to confounding by disease-severity, which might progressively but independently decrease both albumin and I_{Ca}, the latter, perhaps, by disrupting the physiologic regulation of I_{Ca} or by increasing the anion-complexed fraction as small anions such as lactate and phosphate accumulate.

Statistical

Even if a regression model included all known explanatory variables and accurately estimated group means, its application to individual subjects can be limited by substantial imprecision, often quantified as a 95% prediction interval (PI) (23). A minimal estimate of the cT_{Ca} equation's imprecision might be obtained by cumulating the random analytic error of its two inputs. To illustrate this, consider a patient having a T_{Ca} measurement of 2.45 mmol/L (9.8 mg/dL) with a coefficient of variation (CV) of 1.3% and reference interval of 2.10–2.54 mmol/L (8.4–10.2 mg/dL), and a concomitant albumin measurement of 34 g/L with a CV of 1.8% [CV values taken from a recent study by the authors (24)]. Calculating cT_{Ca}, with a slope 0.02 and a population mean albumin of 40 g/L, yields a point prediction of 2.57 mmol/L (10.3 mg/dL), suggesting borderline hypercalcemia. However, the combined, weighted standard deviation of the cT_{Ca} prediction is 0.034 mmol/L {i.e., the square root of $[(0.013\times2.45)^2+0.02^2\times(0.018\times34)^2]$} with a resultant 95% imprecision range of ±0.067 mmol/L (±0.27 mg/dL). Imprecision of this size is large enough to lead to a significant rate of misclassification of patients having cT_{Ca} values near the boundaries of the reference range. Moreover, this doesn't include the other sources of imprecision, such as uncertainty of the estimate of the slope, and biological variation. Bias can be an important limitation for cT_{Ca} too. It typically stems from the temporal and geographic differences in calcium and albumin assays, and even the use of entirely different assays for albumin (bromocresol purple yields lower albumin values than does bromocresol green) (25-27). Bias is often correctible by local model recalibration (27).

Epidemiologic

Another likely source of the poor generalizability of cT_{Ca} equations to seriously ill patients is that such patients were underrepresented in the cohorts used to derive the equations (27,28).

Table 2 Models of measured I_{Ca} that adjust T_{Ca} for specific anions or the anion gap

First author	Model	Population	Validation	Web support
Obi[a] (30)	$Ca_{Corrected} = 1.35 \times T_{Ca} - 0.0162 \times Alb - 0.1158 \times P + 0.0749$	Hemodialysis	Geographic	
Ramirez-Sandoval (31)	$I_{Ca} = 0.44 \times T_{Ca} - 0.00666 \times Alb - 0.0425 \times P - 0.003 \times tCO_2 + 0.539$	Inpatients		Yes[b]
Sakaguchi (34)	$I_{Ca} = 0.337 \times T_{Ca} - 0.0027 \times Alb - 0.006 \times Na + 0.006 \times Cl - 0.001 \times tCO_2 + 0.835$	CKD		
Sakaguchi (34)	$I_{Ca} = 0.289 \times T_{Ca} - 0.005 \times Na + 0.005 \times Cl + 0.005 \times tCO_2 + 0.665$	Hemodialysis		
Yap (24)	Probability that I_{Ca} is <1.10 mmol/L = $1/[1 + \exp(12.417 \times T_{Ca} - 0.0721 \times Alb - 0.174 \times Na + 0.294 \times Cl + 0.177 \times tCO_2 - 32.272)]$	Critical care	Internal	Yes[c]
Yap (24)	$I_{Ca} = 0.365 \times T_{Ca} - 0.0034 \times Alb - 0.0042 \times Na + 0.0073 \times Cl + 0.0047 \times tCO_2 + 0.219$	Critical care	External (35)	Yes[c]

[a], the "corrected calcium" model presented in reference (30) is, in fact, a model of the z-scores of measured I_{Ca} values, which were mapped into the distribution of T_{Ca}. The units are mmol/L; [b], smartphone app is available at: https://play.google.com/store/apps/details?id=com.uioinc.truecalcium; [c], Web calculator and smartphone app are available at: https://qxmd.com/calculate/calculator_704/predicting-ionized-hypocalcemia-in-critical-care. I_{Ca}, ionized calcium (mmol/L); T_{Ca}, total calcium (mmol/L); P, phosphate (mmol/L); Alb, albumin (g/L); tCO_2, total CO_2; CKD, chronic kidney disease (not end-stage).

Estimating I_{Ca}: anions get a vote

Could a linear model of I_{Ca} based solely on T_{Ca} and albumin perform better than cT_{Ca}? To examine this question, we took an unpublished model derived during our recent study of I_{Ca} in critical care (24) [$I_{Ca} = 0.353 \times T_{Ca} - 0.0045 \times$ albumin + 0.568 (in conventional units: $I_{Ca} = 0.088 \times T_{Ca} - 0.045 \times$ albumin + 0.568)] and tested its discrimination for ionized hypocalcemia in the same study's validation cohort. The model's ROC curve area (AUC) was 0.82, similar to what we had found for cT_{Ca} (0.81) (24). Thus, I_{Ca} models based on linear combinations of albumin and T_{Ca} alone are unlikely to significantly outperform cT_{Ca}, suggesting the need for either additional explanatory variables or non-linear terms. A great many equations that estimate I_{Ca} from non-linear combinations of T_{Ca} and albumin (or total protein) were published since 1935, when the pioneering model of McLean and Hastings appeared (2). Unfortunately, as was the case for cT_{Ca}, their poor diagnostic performance was disclosed in later validation studies (17,18,29).

The inclusion of certain anions in I_{Ca}-estimating models as predictors—specifically phosphate (30,31) or chloride (17,32,33)—to account for small anion complexation appears to be a promising strategy, especially in the renal and inpatient settings (*Table 2* and Table S1). Adjusted for T_{Ca} and albumin, an increase in phosphate, a calcium-chelator (36,37), decreases the estimate of I_{Ca} (30,31) while an increase in chloride increases estimated I_{Ca} (32,33). The basis for the latter association might be confounding, with higher chloride simply acting as a marker of the lack of complexing anions and/or the presence of hyperchloremic acidosis, or it might even be causal, reflecting the direct interaction of chloride with albumin (6).

Three of these newer anion-based models underwent validation. The inpatient canine I_{Ca} model of Danner *et al.* was validated both internally, in a large cohort (32), and externally, in a small, retrospective cohort drawn from three centers using multiple different chemistry analyzers (38). A similar inpatient feline model was derived and internally and externally validated by Hodgson *et al.* (33). Each model includes ten predictors treated as splines, with the three most important predictors being T_{Ca}, chloride and albumin. With slight exception, the discrimination of these models for ionized hypocalcemia and hypercalcemia tended to match or exceed those of T_{Ca} and cT_{Ca}. Since these models are complex, the authors made a web-based calculator available for user-support (39). It provides both the point prediction of I_{Ca} and the 95% PI (canine model: ±0.14 mmol/L; feline model: ±0.11 mmol/L), which together define a range that permits the user to intuitively assess the probability of abnormal I_{Ca} (23). The model of Obi *et al.* (30), derived in dialysis patients, was validated for the diagnosis of ionized hypercalcemia in a contemporary but geographically distant

dialysis cohort, albeit using the exact same laboratory, while its discrimination for hypocalcemia was not assessed.

In 1989, Nordin *et al.* reported a simple and practical way to account for anion complexation. They deduced that the fraction of calcium complexed by small anions should vary directly with the anion gap, a previously overlooked relationship, and derived a non-linear model that estimated I_{Ca} from T_{Ca}, albumin, total protein, and the anion gap in a large outpatient cohort of post-menopausal women (40). They also confirmed model's calibration in a group of inpatients (40), but its diagnostic performance for hypocalcemia and hypercalcemia was poor in a later external validation study (18). There was an apparent lull in the use of this approach until approximately three decades later when Sakaguchi *et al.* and our group each described new models that adjusted T_{Ca} for the anion gap (34) or its components (24). The models by Sakaguchi *et al.*, which estimate I_{Ca} in non-dialysis renal patients and dialysis patients, respectively, have not been validated (*Table 2*) (34). In a large critical care cohort, our group derived a pair of linear models of I_{Ca} and a pair of logistic models of hypocalcemia (I_{Ca} <1.10 mmol/L), with one member of each pair using the anion gap as a predictor and the other using the anion gap's ionic components as three independent predictors ("ion models") (24). Each of the four equations was much better than cT_{Ca} or T_{Ca} for detecting hypocalcemia on ROC analysis in the study's internal validation cohort (AUC values: 0.89 for each anion gap-based model; 0.92 for each ion model; 0.81 for cT_{Ca}; 0.78 for T_{Ca}). Moreover, the ion models (*Table 2*) were significantly better than the anion gap models (0.92 *vs.* 0.89, P<0.01). The point predictions of the linear ion model were associated with a mean 95% PI of ±0.115 mmol/L. We recently externally validated our linear ion model for detecting hypocalcemia in a small cohort of inpatients with COVID-19 and renal failure at a different center using a different chemistry analyzer (35). The model had good discrimination and calibration. The performance of our equations for hypercalcemia has not been formally tested.

Applications and limitations of new I_{Ca}-estimating equations

Most of the limitations cited above in regard to the cT_{Ca} equations apply to I_{Ca} models too. As is true of all models, the agreement between predictions of an I_{Ca} model and observed values needs to be examined in each new laboratory environment and, if bias is detected, minor local model recalibration may be needed (27). The I_{Ca} models' reliance on additional analytes (Na, Cl, tCO_2, phosphate) compared to cT_{Ca} makes them more susceptible to test artifacts, and may reduce their ability to be requested retroactively [e.g., when the measurement of tCO_2 is requested to be added on to a serum sample that has been exposed to air for more than an hour, the resultant value tends to be spuriously low (41)]. Similarly, by their use of extra analytes, they cumulate more analytic and biologic imprecision. Consequently, even if a linear model's point prediction of I_{Ca} is accurate on average, it needs to be used together with its 95% PI when applied to an individual subject. Given this uncertainty, the main application of the models will be to more efficiently identify patients for direct I_{Ca} measurement. However, we can foresee circumstances in which the output of an I_{Ca} model might be used to directly inform treatment decisions in those medical domains where decisions that affect I_{Ca} are often made without recourse to direct I_{Ca} testing. Consider, for example, a hypothetical hemodialysis outpatient with a high-normal I_{Ca} point prediction of 1.28 mmol/L with a 95% PI of 1.16–1.40 mmol/L for whom parathormone-lowering therapy is being entertained for severe secondary hyperparathyroidism. Despite the uncertainty about the actual I_{Ca} value, the data favor the prescription of a calcimimetic drug, which tends to lower I_{Ca}, over active vitamin D therapy, which does the opposite.

Based on their level of validation, the canine model of Danner *et al.* (32) and the feline model of Hodgson *et al.* (33) appear to be useful tools for screening for ionized hypocalcemia and hypercalcemia. In human medicine, the models of Yap *et al.* for critical care patients (24) and the model of Obi *et al.* for hemodialysis patients (30) appear to be the most promising, having undergone successful but limited validation for ionized hypocalcemia (24,35) and hypercalcemia (30) respectively, but their discrimination needs to be tested for both hypocalcemia and hypercalcemia and their calibration confirmed on a broader range of analytic platforms. Moreover, further validation is necessary before they can be generalized to other patient groups, such as less seriously ill patients in whom more frequent appraisal of I_{Ca} would be desirable (14) but in whom variation in small anion-complexation may be of lesser importance compared with the models' respective derivation cohorts (27,28). Examples of such groups include patients with primary parathyroid disorders, cancer, myeloma, and the full spectrum of renal disease (chronic kidney disease, transplant, end-stage on peritoneal or hemodialysis) (14), and even

perhaps the general population (11). The performance of I_{Ca} models also requires specific confirmation in critically ill patients receiving anticoagulation with citrate, an especially avid calcium-chelating anion. Since these newer models can be challenging to memorize, model predictions could be reported in routine metabolic panels, similar to the way the anion gap, estimated glomerular filtration rate, and other forms of laboratory-based decision support are provided. Alternatively, in accord with recommended guidelines for predictive models (42), web-based calculators or smartphone apps could be provided, as a number of the studies cited above have done (*Table 2*) (24,31-33).

Conclusions

In domains in which small anion complexation is important (critical care, inpatients, renal failure), models of I_{Ca} have been derived based on the further adjustment of T_{Ca} for phosphate or the components of the anion gap. Unlike cT_{Ca}, they have undergone successful validation and can be used as clinical tools to identify patients for I_{Ca} testing.

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Footnote

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Supplementary

Table S1 Models of measured I_{Ca} that adjust T_{Ca} for specific anions or the anion gap (conventional units)

First author	Model	Population	Validation	Web support
Obi[a] (30)	$Ca_{Corrected} = 1.35 \times T_{Ca} - 0.65 \times Alb - 0.15 \times P + 0.3$	Hemodialysis	Geographic	
Ramirez-Sandoval (31)	$I_{Ca} = 0.44 \times T_{Ca} - 0.267 \times Alb - 0.055 \times P - 0.012 \times tCO_2 + 2.16$	Inpatients		Yes[b]
Sakaguchi (34)	$I_{Ca} = 0.084 \times T_{Ca} - 0.027 \times Alb - 0.006 \times Na + 0.006 \times Cl - 0.001 \times tCO_2 + 0.835$	CKD		
Sakaguchi (34)	$I_{Ca} = 0.072 \times T_{Ca} - 0.005 \times Na + 0.005 \times Cl + 0.005 \times tCO_2 + 0.665$	Hemodialysis		
Yap (24)	Probability that I_{Ca} is <1.10 mmol/L = $1/[1+\exp(3.098 \times T_{Ca} - 0.721 \times Alb - 0.174 \times Na + 0.294 \times Cl + 0.177 \times tCO_2 - 32.272)]$	Critical care	Internal	Yes[c]
Yap (24)	$I_{Ca} = 0.091 \times T_{Ca} - 0.034 \times Alb - 0.0042 \times Na + 0.0073 \times Cl + 0.0047 \times tCO_2 + 0.219$	Critical care	External (35)	Yes[c]

[a], the "corrected calcium" model presented in reference (30) is, in fact, a model of the z-scores of measured I_{Ca} values, which were mapped into the distribution of T_{Ca}. The units are mg/dL; [b], smartphone app is available at: https://play.google.com/store/apps/details?id=com.uioinc.truecalcium; [c], Web calculator and smartphone app are available at: https://qxmd.com/calculate/calculator_704/predicting-ionized-hypocalcemia-in-critical-care. I_{Ca}, ionized calcium (mmol/L); T_{Ca}, total calcium (mg/dL); P, phosphate (mg/dL); Alb, albumin (g/dL); tCO_2, total CO_2; CKD, chronic kidney disease (not end-stage).

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