Poor Performance of Albumin or Protein-Adjusted Plasma Calcium to Diagnose Dyscalcemia in Hospitalized Patients: A Confirmatory Study in a General Internal Medicine Department

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Abstract

Background

Hypo- and hypercalcemia are common and some causes require urgent diagnosis and treatment. Measurement of ionized calcium is the reference test to diagnose calcium disorders but total calcium adjusted for protein or albumin concentration is more often used.

Patients and methods

Patients hospitalised in a general internal medicine department from September 2013 to December 2015 who had a total plasma calcium concentration and a serum albumin or protein concentration measured within 24h of a ionized calcium blood measurement were included. Total calcium was adjusted for protein or albumin concentration using widely used formulas and compared to ionized calcium as the gold standard.

Results

Among 210 included patients, 46 (22%) had hypocalcemia, 124 (59%) normocalcemia and 40 (19%) hypercalcemia according to ionized calcium concentration. Total calcium had 50% sensitivity and 95 % specificity to diagnose hypocalcemia and a 93% sensitivity and 89 % specificity to diagnose hypercalcemia. Adjusting total calcium for protein or albumin concentrations did not increase and sometimes decreased diagnostic accuracy.

Discussion and conclusions

Total calcium, with or without albumin/protein adjustment, is poorly sensitive to screen for hypocalcemia. Unadjusted total calcium is as sensitive as protein- or albumin-adjusted total calcium to screen for hypercalcemia. These data argue against the use of albumin- or protein-adjusted calcium. Ionized calcium measurement should be performed to confirm dyscalcemia in patients with abnormal total calcium concentration and to rule out hypocalcemia in patients with total calcium concentration in the lower range of normal values.

Keywords:

Hypocalcemia; hypercalcemia; calcium; sensitivity and specificity

Introduction

Plasma calcium exists in three different molecular states: ionized (or free calcium) (~50%), calcium bound to plasma proteins (mainly albumin, ~40%) and calcium complexed to small size anions (mainly bicarbonates, ~10%) [1]. Ionized calcium is the biologically active form that is regulated.

Hypo- and hypercalcemia are common and may be the first manifestation of serious diseases. The accurate identification of abnormal plasma calcium concentrations is therefore important and relies on ionized calcium measurement. However, direct measurement of ionized calcium is subject to preanalytical pitfalls if not performed rapidly and in anaerobic conditions. Total calcium measurement is therefore routinely performed as a first diagnostic step [2]. Formulas have been proposed to take abnormal albumin or protein concentrations into account and adjust total calcium concentration accordingly. Although the Association for Clinical Biochemistry and Laboratory Medicine has called the accuracy of these generic formulas into question [1], their use is still recommended by international clinical guidelines [3–6] and official student textbooks.

Previous studies have already focused on the diagnostic accuracy of unadjusted and protein- or albumin-adjusted calcium concentrations in specific populations, with conflicting results [7–19]. The goal of the present study was to evaluate the diagnostic accuracy of total and adjusted plasma calcium concentrations compared to ionized calcium values in a general internal medicine department.

Patients and Methods

Design

This is a retrospective diagnostic study from data prospectively collected during routine patient care. French law does not require written patient consent for monocentric retrospective studies using patient data collected during routine care and analysed anonymously. Patients are informed on their consultation and hospitalization reports that their data are collected into a data warehouse for research purposes and they can freely opt out this process. The report complies with the RECORD and STARD statements [20,21].

Patients

Eligible patients were adults with at least one measurement of ionized blood calcium concentration during their stay in a 59-bed general internal medicine department between 01/09/2013 and 31/12/2015. Patients with a measurement of total calcium concentration and a measurement of albumin or protein concentration within 24h from an ionized calcium concentration measurement were included in the study.

Biochemical measurements and normal values

Blood samples for ionized calcium measurement were collected in appropriately filled and sealed heparinized tubes (lithium heparin); specimen were thoroughly mixed, kept on ice and analyzed within 3 hours without centrifugation. Ionized calcium and pH were measured on total blood by an ion-selective electrode (ABL 825, Radiometer, Neuilly sur Marne, France). Normal range for ionized blood calcium was 1.14 to 1.31 mmol/L.

Blood samples for total calcium measurement were collected in heparinized tube (lithium heparin) and analyzed within 6 hours of collection. Total plasma calcium, serum protein and serum albumin concentrations were determined with an Architect ci 8200 analyzer (Abbott Diagnostics, Rungis, France). Normal concentrations ranged from 2.20 to 2.55 mmol/L for total calcium concentration, 60 to 83 g/L for serum protein concentration, and 33 to 40.3 g/L, for albumin concentration.

Formulas for adjusted plasma calcium concentration

Serum albumin and protein concentrations were used to adjust total calcium according to published formulas derived from patient data and not from theoretical considerations [9,11,22–25] (Table 1).

Statistical analyzes

When a patient had more than one ionized calcium measurement coupled with total calcium and proteins or albumin measurements within the appropriate time frame, only the first one (or the first one with both proteins and albumin measurements) was analyzed.

The relationships between total, protein- and albumin-adjusted calcium concentrations, and ionized calcium concentration were determined with modified Bland and Altman plots and logistic regression. To this end, these variables were first standardized into z-scores using the means and the standard deviations inferred from the upper and lower limits of normal ranges regarded as the 97.5 and 2.5 percentiles of a normal distribution. Ionized calcium concentration was taken as the diagnostic gold standard. Sensitivity, specificity, positive and negative likelihood ratios (PLR and NLR), and diagnostic odds ratio (DOR) were computed for total calcium and adjusted calcium concentrations.

Results obtained with the two most widely used formulas for protein- and albumin-adjusted calcium concentrations (Parfitt and Payne formulas) and with the linear transformations best fitting our data are reported in the main text. Other results are reported in the appendix. Sensitivities and specificities of total calcium and adjusted calcium concentrations were compared for the diagnosis of hypocalcemia and hypercalcemia. Due to four comparisons per adjustment formula, differences were considered statistically significant for $p < 0.01$ (Bonferroni correction). Analyses were performed with Stata 16.2 (StataCorp, College Station, TX).

Results

Patients

Among 283 patients with at least one measurement of ionized calcium concentration, 73 (26%) missed a total calcium and protein or albumin measurement in the appropriate time frame and were excluded. Among 210 included patients, 46 (22%) had hypocalcemia, 124 (59%) normocalcemia and 40 (19%) hypercalcemia according to ionized calcium concentration (Figure 1). Main characteristics of included patients are summarized in Table 2.

Relation between ionized calcium and total or adjusted calcium

Modified Bland and Altman plots (Figure 2) show that that unadjusted, protein-adjusted and albumin-adjusted calcium concentrations overestimate ionized calcium concentrations (mean differences > 0), but protein- and albumin-adjusted calcium concentrations overestimate it more than unadjusted total calcium concentrations. This bias is more pronounced with lower ionized calcium concentrations (descending regression line) and especially in patients with hypocalcemia. Unadjusted total calcium concentration is therefore a more accurate proxy for ionized calcium than protein-adjusted and albumin adjusted calcium concentrations.

As expected, the difference between standardized total calcium and standardized ionized calcium depends on protein and albumin concentrations. The linear adjustment formulas that best fit with our data are the following:
- Albumin-adjusted calcium [mmol/L] = total calcium [mmol/L] + 0.008 x (26.9 – serum albumin [g/L])
- Protein-adjusted calcium [mmol/L] = total calcium [mmol/L] + 0.007 x (60.1 – serum protein [g/L])

Diagnosis of hypocalcemia (Table 3)
Total calcium concentration has a good specificity (94% [95% confidence interval (CI): 89, 97]) but a poor sensitivity (52% [95% CI: 37, 67]) to diagnose hypocalcemia. Low total calcium concentration indicates hypocalcemia with a good level of confidence (PLR 8.6 [95% CI: 4.4, 17]) but normal total plasma calcium concentration does not discard hypocalcemia (NLR 0.51 [95% CI: 0.38, 0.69]).

Adjusting for albumin concentration using the Payne formula significantly improves specificity ($p = 0.008$) but significantly decreases sensitivity ($p = 0.001$). Adjusting for protein concentration using the Parfitt formula does not significantly improve specificity ($p = 0.55$) but significantly decreases sensitivity ($p = 0.001$). The sensitivity and specificity of both best linear fit formulas do not significantly differ from those of unadjusted total calcium.

The highest total calcium observed in a patient with true hypocalcemia (1.10 mmol/L) was 2.50 mmol/L. In this patient, total proteins were 71 g/L and protein-adjusted calcium 2.52 mmol/L, albumin 33 g/L and albumin-adjusted calcium 2.67 mmol/L.

Diagnosis of hypercalcemia (Table 4)
Total calcium has a good sensitivity (93% [95% CI: 80-98]) and a fair specificity (89% [95% CI: 83-93]) to diagnose hypercalcemia. High total calcium concentration indicates hypercalcemia (PLR 8.3 [95% CI: 5.4-13]) and normal total plasma calcium concentration discards hypercalcemia (NLR 0.08 [95% CI: 0.03, 0.25]) with a good level of confidence.

Adjusting calcium for protein or albumin concentrations does not significantly increase sensitivity but significantly decreases specificity ($p < 0.001$ for both formulas). The sensitivity

and specificity of both best linear fit formulas do not significantly differ from unadjusted total calcium concentrations.

Discussion

Our study shows that measurement of total plasma calcium performs relatively well to diagnose hyper- but not hypocalcemia, due to the lack of sensitivity in the latter case. Adjustement formulas using serum albumin or protein concentrations, including those taylored to our data, do not improve the accuracy of total plasma calcium to diagnose hypocalcemia and even deteriorate its accuracy to diagnose hypercalcemia.

This is a retrospective study using data collected during routine clinical care with a number of patients with hyper- or hypocalcemia sufficient to draw conclusions with appropriate statistical power. However, the maximum interval of 24h between ionized and total calcium and either albumin or protein is long and the studied variable might change due to underlying disease and treatments, even if patients hospitalized outside intesive care units are relatively stable. A shorter interval would have lost many patients because ionized calcium measurement is typically prescribed for the next day in patients with an abnormal total calcium. Moreover, our laboratory routinely uses protein as the standard for total calcium adjustment and albumin was measured in only about two out of three patients. We did not measure ionized blood calcium concentration in all hospitalized patients and did not follow a standardized work-up for dyscalcemia. The diagnostic accuracy of total or adjusted plasma calcium could partly depend on the cause of dyscalcemia, most notably through globulin concentrations and the acid-base status. However, our sample reflects the population of hospitalized patients in whom a measurement of ionized calcium concentration is prescribed and for whom the question of using total or adjusted plasma calcium concentration is relevant.

Albumin-adjustment of total calcium did not improve the agreement with ionized calcium in three large studies using paired samples of a mix of hospitalized patients [16,18,19] and even worsened it in a fourth similar study [17]. Albumin-adjustment was especially misleading in case of hypoalbuminemia [18,19]. These studies argue against the use of albumin-adjusted calcium. However, they did not report sensitivity, specificity and likelihood ratios of total and

albumin-adjusted calcium for hypo- and hypercalcemia, which are the meaningful statistics from a clinical point of view. Moreover, these studies included heterogeneous case-mixes of intensive and acute care inpatients from diverse medical and surgical departments [18,19], or even case-mixes of in- and outpatients [16,17]. By contrast our sample is representative of a general internal medicine department.

One previous study has assessed the diagnostic performance of total and albumin-adjusted calcium in a sample of acutely but not critically ill hospitalized patients [15]: total calcium had a 61% sensitivity and a 92% specificity for hypocalcemia, and a 69% sensitivity and a 95% specificity for hypercalcemia; albumin-adjusted calcium (Payne formula) had a 95% sensitivity and a 76% specificity for hypocalcemia, and a 20% sensitivity and a 99% specificity for hypercalcemia. These results are largely consistent with those we got in our more selected sample of internal medicine in-patients.

The diagnostic performance of total and albumin-adjusted calcium has been studied in stable patients with chronic kidney disease [10,12]. Total calcium was poorly sensitive (40-50%) but fairly specific (~90%) to detect hypocalcemia, and very poorly sensitive (20-30%) but highly specific (99-100%) to detect hypercalcemia. Albumin-adjusted calcium did not perform better. Albumin-adjusted calcium was also a poor surrogate for ionized calcium in stable elderly subjects [14]. These results are also consistent with ours.

Our results concur with previous ones against the use of albumin- or protein-adjusted calcium concentration formulas. Ionized calcium concentration is easily measured, the main limitation being the need to rapidly analyse the sample (< 3 hours at room temperature). It should be performed to confirm dyscalcemia and precisely evaluate its severity in patients with abnormal total calcium concentration, and to rule out hypocalcemia in patients with total calcium concentration in the lower range of normal values.

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Declarations of interest

None

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Figure legends

Figure 1. Patient flow-chart

Figure 2. Differences between total or adjusted calcium concentration and ionized calcium concentrations according to ionized calcium concentration.

A. Total calcium concentration

B. Protein-adjusted calcium concentration (Parfitt formula)

C. Albumin-adjusted calcium concentration (Payne formula)

Table 1. Formulas for protein- or albumin-adjusted total calcium concentration

Protein-adjusted calcium concentration	
Parfitt 1974 [24]	Adjusted total calcium = total calcium / [0.55 + (proteins / 160)]
Payne 1973 [23]	Adjusted total calcium = total calcium + 0.017 x (73.4 - proteins)
Pfitzenmeyer 2007 [9]	Adjusted total calcium = 0.592 - 0.00449 x proteins + 0.410 x total calcium
Albumin-adjusted calcium concentration	
Payne 1973 [23]	Adjusted total calcium = total calcium + 0.025 x (40 - albumin)
Orrell 1971 [22]	Adjusted total calcium = total calcium + 0.0176 x (34 - albumin)
Rustad 2004 [25]	Adjusted total calcium = total calcium + 0.02 x (41.3 - albumin)
James 2008 [11]	Adjusted total calcium = total calcium + 0.012 x (39.9 - albumin)

Total calcium, ionized calcium and adjusted total calcium concentrations in mmol/L; serum proteins and serum albumin concentrations in g/L.

Table 2. Characteristics of included patients (number and percentages or median and quartiles)

	Number (percentage) or median [interquartile range]
Females	137/210 (65%)
Age (years)	77 [62, 86]
Ionized calcium concentration (mmol/L)	1.20 [1.15, 1.29]
Total calcium concentration (mmol/L)	2.41 [2.25, 2.57]
Phosphatemia (mmol/L)	1.07 [0.88, 1.22]
Estimated GFR (CKD-EPI, mL/min/1.73m²)	69 [44, 86]
Venous pH	7.34 [7.30, 7.38]
Plasma protein concentration (g/L)	67 [61, 71]
Plasma protein concentration < 60g/L	42/210 (20%)
Plasma albumin concentration (g/L)	32 [28, 36]
Albumin concentration < 33g/L	78/139 (56%)

GFR: glomerular filtration rate

Table 3. Diagnostic accuracy of total and adjusted calcium concentrations to diagnose hypocalcemia [95% confidence interval]

	Sensitivity	**Specificity**	**NLR**	**PLR**	**DOR**
Total calcium	52% [37, 67]	94% [89, 97]	0.51 [0.38, 0.69]	8.6 [4.4, 17]	17 [7.2, 39]
Albumin-adjusted (Payne 1973) [23]	14% [4, 32]	100% [97, 100]	0.86 [0.75, 1.0]	-	- [4.4, -]
Albumin-adjusted (best linear fit)	59% [39, 77]	89% [82, 94]	0.46 [0.30, 0.72]	5.4 [2.9, 9.9]	12 [4.5, 30]
Protein-adjusted (Parfitt 1974) [24]	28% [16, 44]	96% [91, 98]	0.75 [0.62, 0.90]	6.6 [2.8, 16]	8.8 [3.4, 23]
Protein-adjusted (best linear fit)	67% [52, 81]	91% [85, 95]	0.36 [0.24, 0.55]	7.4 [4.4, 12]	21 [9.2, 46]

NLR: Negative Likehood Ratio; PLR: Positive Likehood Ratio; DOR: Diagnostic Odds Ratio

Table 4. Diagnostic accuracy of total and adjusted calcium concentrations to diagnose hypercalcemia [95% confidence interval]

	Sensitivity	**Specificity**	**NL**	**PLR**	**DOR**
Total calcium	93% [80, 98]	89% [83, 93]	0.08 [0.03, 0.25]	8.3 [5.4, 13]	98 [29, 327]
Albumin-adjusted (Payne 1973) [23]	97% [83, 100]	63% [54, 72]	0.05 [0.01, 0.36]	2.6 [2.0, 3.4]	50 [8.3, -]
Albumin-adjusted (best linear fit)	83% [65, 94]	91% [84, 96]	0.18 [0.08, 0.41]	9.1 [4.9, 17]	50 [16, 154]
Protein-adjusted (Parfitt 1974) [24]	98% [87, 100]	78% [71, 84]	0.03 [0.00, 0.22]	4.5 [3.4, 6.0]	140 [23, -]
Protein-adjusted (best linear fit)	90% [76, 97]	92% [87, 96]	0.11 [0.04, 0.27]	12 [6.9, 20]	109 [34, 338]

NLR: Negative Likehood Ratio; PLR: Positive Likehood Ratio; DOR: Diagnostic Odds Ratio

Appendix

Table A1. Diagnostic accuracy of other formulas to diagnose hypocalcemia [95% confidence interval]

	Sensitivity	**Specificity**	**NLR**	**PLR**	**DOR**
Protein-adjusted total calcium					
Payne 1973 [23]	20% [9, 34]	96% [91, 98]	0.84 [0.73, 0.97]	4.6 [1.8, 12]	5.5 [2.0, 15]
Pfitzenmeyer 2007 [9]	20% [9, 34]	98% [95, 100]	0.82 [0.71, 0.95]	11 [3.0, 38]	13 [3.6, -]
Albumin-adjusted total calcium					
Orrell 1971 [22]	38% [21, 58]	94% [87, 97]	0.66 [0.50, 0.88]	6.0 [2.5, 14]	9.0 [3.2, 26]
Rustad 2004 [25]	21% [8, 40]	100% [97, 100]	0.79 [0.66, 0.96]	- [-, -]	- [7.1, -]
James 2008 [11]	31% [15, 51]	99% [95, 100]	0.70 [0.54, 0.89]	34 [4.5, 259]	49 [7.5, -]

NLR: Negative Likehood Ratio; PLR: Positive Likehood Ratio; DOR: Diagnostic Odds Ratio

Table A2. Diagnostic accuracy of other formulas to diagnose hypercalcemia [95% confidence interval]

	Sensitivity	**Specificity**	**NLR**	**PLR**	**DOR**
Protein-adjusted total calcium					
Payne 1973 [23]	98% [87, 100]	73% [66, 80]	0.03 [0, 0.24]	3.6 [2.8, 4.6]	105 [18, -]
Pfitzenmeyer 2007 [9]	98% [87, 100]	79% [73, 85]	0.03 [0, 0.22]	4.7 [3.5, 6.4]	150 [25, -]
Albumin-adjusted total calcium					
Orrell 1971 [22]	93% [78, 99]	84% [76, 91]	0.08 [0.02, 0.30]	6.0 [3.8, 9.4]	76 [18, -]
Rustad 2004 [25]	100% [88, 100]	66% [56, 75]	0 [-, -]	3.0 [2.0, 3.8]	- [15, -]
James 2008 [11]	100% [88, 100]	76% [67, 84]	0 [-, -]	4.2 [3.0, 5.9]	- [24, -]

NLR: Negative Likehood Ratio; PLR: Positive Likehood Ratio; DOR: Diagnostic Odds Ratio