



Association Between Disease Severity and Calcium Concentration in Critically Ill Patients Admitted to Intensive Care Unit

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Received 2017 July 04; Revised 2018 January 23; Accepted 2018 February 18.

Abstract

Background: Hypocalcemia is very common in critically ill patients admitted to ICU. However, its clinical importance and relation to patient's outcome during early days of ICU admission is questionable. Based on the mentioned problem, it seems that calcium assessment is highly important in these patients. The present study aimed at evaluating the relationship between different calcium concentrations (total/ionized/corrected) and disease severity in critically ill patients.

Methods: A total of 100 patients admitted to intensive care units of Imam Reza and Shohada hospitals during Feb 2014 and Apr 2016 were enrolled in this prospective trial. Concentrations of total, corrected, and ionized calcium and their relationship with APACHE score and disease severity were noted during the study.

Results: There was a strong and inverse correlation between disease severity and ionized calcium concentration ($P < 0.001$, $r = -0.697$). There was a medium and significant inverse correlation between disease severity and total calcium concentration ($P < 0.001$, $r = -0.368$). Weak and direct significant correlation was observed between disease severity and corrected calcium concentration ($P = 0.02$, $r = 0.232$).

Conclusions: A significant correlation was found between total and ionized calcium, but there was not any significant correlation between corrected and ionized calcium. Hypocalcemia is a predictor of disease severity and mortality. We recommend measuring ionized calcium concentration for patients admitted to ICU.

Keywords: Serum Calcium, Hospital Mortality, Critically Ill Patients, Disease Severity

1. Background

Calcium is one of the most important electrolytes of human body and regulators of cell events, such as signaling, hormone secretion, glycogen metabolism, and cell mitosis. Extracellular calcium not only is a source for intracellular calcium but also has an important role in the maintenance and stability of cell wall and clot formation (1). The wide range in the concentration of total calcium may be related to changes in albumin concentration or any change in hydration in patients. As serum total calcium level can change without any change in ionized calcium level, measurement of serum total calcium concentration can lead to wrong interpretation of results (2). Total calcium concentration is changed in patients with hypo- or hyper-albuminemia and myeloma multiple, but ionized

calcium is constant (3). It has been reported that critically ill patients are susceptible to become hypocalcaemic (4-6). Since hypocalcaemia is asymptomatic in these patients, its deficiency is not detected on time in most cases (7, 8). On the other hand, calcium indicators including total, ionized, and corrected calcium are influenced by different factors; therefore, it is not clear which of them is appropriate for assessing calcium status in ICU patients (9). Moreover, the findings of previous studies conducted about the relationship between hypocalcemia and adverse outcomes in ICU patients are controversial (5, 10-12). In most studies, only one indicator of calcium status and its correlation with ICU outcomes were investigated. Besides, most of these patients have comorbidities like kidney, liver, endocrine, and acid/base disorders which can lead to changes

in ionized calcium concentration. Albeit, the most routine way of calcium assessment is measuring serum total calcium concentration, but even corrected calcium level cannot be a correct estimation of ionized calcium level in critically ill patients. Despite this, calcium supplementation is administered in ICU patients based on total and corrected calcium results.

Considering the important role of calcium in the human body, the high prevalence of hypocalcaemia in ICU patients, and the low number of studies assessing the correlation between all calcium indicators (total, ionized, and corrected calcium) with ICU outcomes, we decided to determine the relationship between total, corrected, and ionized calcium concentrations and disease severity in critically ill patients.

2. Objectives

The present study aimed at evaluating the relationship between different calcium concentrations (total/ionized/corrected) and disease severity in critically ill patients.

3. Methods

Convenience sampling method was used in this study. After obtaining approval from the research committee of Tabriz University of Medical Sciences, all patients who were admitted to intensive care units of Imam Reza and Shohada hospitals (2 University-affiliated hospitals that are referral centers of northwest of Iran) from Feb 2014 to Apr 2016 were enrolled in this study. Patients with previous history of end stage renal disease, dialysis, and those who needed anticoagulation with citrate were excluded from the study. Those who received blood products, calcium, vitamin D, furosemide, or therapeutic doses of heparin within the 24 hours before laboratory measurements were also excluded from the study. Additional exclusion criteria consisted of patients with pancreatitis, hyperphosphatemia ($P > 6$ mg/dL), hyperbilirubinemia (> 3.5 mg/dL), and hypomagnesemia (< 1.5 mg/dL).

The blood was obtained from an indwelling arterial catheter at 6 a.m. while patients were supine in bed. Each patient was contributed only once to the data pool.

Total serum calcium concentration was measured colorimetrically, whereas the serum ionized calcium concentration was measured using an ion-selective electrode method. Corrected calcium was estimated based on albumin concentration and following formula:

Corrected calcium = total calcium concentration + 0.8 (patient albumin-Normal albumin).

Most patients were evaluated after resuscitation within 2 days of initiation of nutritional support and within 5 days after admission to surgical ICU. Patients' demographic characteristics, APACHE II scores, albumin, calcium, magnesium, and phosphorus were noted. Blood pH was assessed based on arterial blood gas analysis.

3.1. Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS, Version 11.5, Chicago, IL). The normality of data was assessed by Kolmogorov-Smirnov test. Quantitative variables were expressed as mean \pm SD and qualitative variables as percent. We used Pearson correlation coefficient test to show the relationship between quantitative variables, especially total and ionized calcium. Independent t test was used to compare the variables between study groups. P value less than 0.05 was considered statistically significant.

4. Results

A total of 100 patients were enrolled in this prospective study. The mean age of the patients was 56 ± 14 years for males and 59 ± 18 years for females, and the difference was not statistically significant ($P = 0.31$). There was not a statistically significant difference between the mean age of survivors and non-survivors ($P = 0.51$). Mean albumin level in survivors was 2.4 ± 0.36 g/dL and was 3.19 ± 0.43 g/dL in non-survivors, which was significantly different ($P < 0.001$). Mean levels of total, ionized, and corrected calcium concentration, phosphorus, albumin, GFR, pH, and APACHE score in the 2 genders are displayed in [Table 1](#). There was no difference in these parameters between the 2 genders; i.e., sex did not have any effect on ionized, total, and corrected calcium concentrations of patients.

[Table 2](#) displays the mentioned parameters in the 2 groups of survivors and non-survivors; and there was a significant difference between these groups.

Correlation of different calcium parameters and disease severity are demonstrated in [Table 3](#). There was a statistically significant and inverse strong correlation between disease severity and ionized calcium concentration ($P < 0.001$, $r = -0.697$). There was a medium and a statistically significant inverse relationship between disease severity and total calcium concentration ($P < 0.001$, $r = -0.368$). However, there was a weak and direct statistical relationship between disease severity and corrected calcium in patients admitted to intensive care unit ($P = 0.02$, $r = 0.232$). Disease severity had a significant and inverse correlation with phosphorus ($P < 0.001$, $r = -0.5$), GFR ($P < 0.001$, $r = -0.567$), pH ($P = 0.009$, $r = -0.259$), and albumin ($P <$

Table 1. Patients' Characteristics Stratified by Gender

Variables	Men	Women	P Value ^a
Total Calcium, mg/dL	7.87 ± 0.46	7.79 ± 0.39	0.43
Ionized Calcium, mg/dL	1.08 ± 0.11	1.10 ± 0.10	0.37
Corrected Calcium, mg/dL	8.55 ± 0.31	8.45 ± 0.33	0.15
Phosphorus, mg/dL	3.51 ± 0.44	3.41 ± 0.56	0.34
Albumin, gr/dL	3.04 ± 0.48	3.09 ± 0.51	0.97
GFR, mL/min	62.71 ± 19.88	69.60 ± 15.94	0.08
pH	7.35 ± 0.09	7.34 ± 0.06	0.58
APACHE	22.2 ± 4.9	20.8 ± 4.7	0.08

^aP, independent test.**Table 2.** Comparison of Patients' Data in Two Groups of Survivors and Non-Survivors

Variable	Survivors	Nonsurvivors	P Value ^a
Total Calcium, mg/dL	7.88 ± 0.43	7.49 ± 0.37	0.003
Ionized Calcium, mg/dL	1.11 ± 0.1	0.94 ± 0.7	< 0.001
Corrected Calcium, mg/dL	8.50 ± 0.31	8.70 ± 0.33	0.04
Phosphorus, mg/dL	3.54 ± 0.43	3.04 ± 0.66	0.001
Albumin, gr/dL	3.15 ± 0.63	2.83 ± 0.35	< 0.001
GFR, mL/min	67.66 ± 17.29	45.41 ± 19.14	< 0.001
PH	7.36 ± 0.73	7.28 ± 0.96	0.001
APACHE	20.2 ± 4	29.5 ± 5	< 0.001

^aP, independent t test.

0.001, $r = -0.588$), and a non-significant direct correlation with age ($P = 0.448$, $r = 0.07$). There was also a significant and direct correlation between ionized calcium with GFR ($P < 0.001$, $r = 0.471$) and phosphorus ($P < 0.001$, $r = 0.519$).

5. Discussion

Several mechanisms have been shown for hypocalcemia in critically ill patients, such as proinflammatory biomarkers (8), end organ resistance to PTH, extra and intra cellular redistribution of calcium ion, suppression of PTH secretion, and catecholamine release in critically ill patients (9). The results of this study revealed a significant inverse association between total, ionized, and corrected calcium concentrations with disease severity. The highest correlation was observed between ionized calcium and disease severity of ICU patients.

Our results were not consistent with previous studies which have reported no significant correlation between mortality and calcium concentration (5, 13). Zivin et al. in their small cohort failed to show any correlation between

mortality and calcium concentration (5). Slomp et al. showed that 30-day mortality was not independently predicted by hypocalcemia and it is more likely that hypocalcemia is a sign of disease severity (13). This difference may be due to the fact that our patients had higher incidence of kidney dysfunction and higher APACHE score in admission and they were surgical ICU patients compared to medically ill patients; all these factors were accompanied with lower calcium levels and higher mortality rate.

Dey et al. noted that hypocalcaemia may be related to adverse outcome in ICU patients. In another study by Zhang et al. (14), it was found that mild and moderate hypocalcaemia increased the risk of death, which is similar to our findings (15). The mechanism by which low serum calcium concentration leads to poor outcome in critically ill patients can be described as follows:

Firstly, as hypocalcemia causes decline in myocardial contractility, it is associated with congestive heart failure in hypocalcemic patients. Secondly, hypocalcemia can be associated with increased risk of rapid renal dysfunction,

Table 3. Correlation of Different Calcium Parameters and Disease Severity

Variables	Total Calcium	Ionized Calcium	Corrected Calcium	APACHE
Total calcium	-	P < 0.001, r ^a = 0.416	P < 0.001, r ^a = 0.457	P < 0.001, r ^a = -0.368
Ionized calcium	P < 0.001, r ^a = 0.416	-	P = 0.189	P < 0.001 r ^a = -0.697
Corrected calcium	P < 0.001, r ^a = 0.457	P = 0.189	-	P = 0.02, r ^a = 0.232

^a r, Pearson correlation.

which may result in renal replacement therapy. Thirdly, considering the important role of calcium in the body, its serum levels are precisely regulated and is in close relationship with levels of phosphorus, magnesium, and vitamin D; so, any impairment in homeostasis of serum calcium is accompanied with altered concentration of the mentioned factors. All these issues can contribute to worse outcome of critically ill patients.

Constantine et al. found that serum calcium levels significantly correlated with disease severity in patients with dengue (16). Steel et al. assessed the clinical course of hypocalcemia in critical illness and concluded that hypocalcemia was normalized within the first 4 days after ICU admission; moreover, failure in calcium level optimization could be associated with increased mortality (11). They also found that corrected calcium level is not a good indicator of ionized calcium level in critically ill patients, which is similar to our results. Consistent with the present study, 3 other studies performed on trauma patients and emergency departments showed a strong association between initial hypocalcemia and mortality in critically ill patients (17-19). As some studies suggested that calcium supplementation could have negative effects on mortality, we excluded patients receiving calcium supplementation to eliminate the impact of intervention on calcium concentration like previously performed studies (17, 18). They indicated that non-survivors had lower ionized calcium levels compared to survivors, which this is similar to our results. Gauci et al. evaluated pitfalls of measuring total blood calcium levels in patients with chronic renal failure (20). They found that the risk for underestimating ionized calcium was independently increased by a low total CO₂ concentration when either non-corrected or albumin-corrected calcium was used and by a low albumin concentration only when non-corrected total calcium was used. The risk for overestimating ionized calcium was increased by a low albumin concentration only when albumin-corrected calcium was used. In conclusion, albumin-corrected total calcium does not predict ionized calcium better than non-corrected total calcium. Moreover, both total and albumin-corrected calcium concentrations poorly predict hypo- or hypercalcemia in patients

with CKD.

Calvi et al. recommended that ionized calcium measurement should be performed in critically ill patients as a standard method, especially in situations like continuous venovenous hemofiltration (1).

The most common reasons for this difference can be due to the low number of patients with severe hypocalcemia in those trials and different cut-off points for defining hypocalcemia in studies. The explanation for lack of accuracy for corrected calcium for estimation of ionized calcium can include changes in pH affecting calcium albumin binding and alteration in blood concentration of citrate, phosphate, and fatty acids (7, 13).

As a result, we propose that measurement of ionized calcium rather than adjusted calcium be performed to define hypocalcemia wherever available. Only if ionized calcium cannot be measured, adjusted calcium should be calculated with the formula published by Stomp providing the best area under the curve (13). The fact that abnormal phosphorus and albumin levels are independently associated with ionized hypocalcemia, with a strong trend for higher phosphate, suggests that these biochemical derangements be specifically considered in the assessment of hypocalcemic patients.

The strength of this study was that most of the patients were surgical ones; so, the population was almost homogeneous. Limitation of this study was that our population consisted of surgical ICU patients and our study was conducted in just 2 centers; so, generalization of these results to other population of critically ill patients (i.e., patients of medical ICUs) should be performed with caution. Therefore, we suggest conducting future multi-center studies with larger sample size.

5.1. Conclusion

We found a significant correlation between ionized calcium and total calcium concentration. Nonetheless, there was not any significant correlation between ionized calcium and corrected calcium levels. Our results suggest that abnormalities of ionized calcium concentrations are likely a marker of illness severity and mortality and physicians should assay ionized calcium in critically ill patients.

Acknowledgments

The authors are grateful for the financial support of research vice-chancellor, Tabriz University of Medical Sciences. Special thanks to Mr. Shahrokh Teshnedel, Mr. Qorbanali Tarinezhad, and ICU staff of Imam Reza and Shohada hospitals for their cooperation during study.

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