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Prognostic value of hypocalcemia in COVID-19

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Abstract

Background: Preliminary data suggest that hypocalcemia is common among patients with coronavirus 2019 (COVID-19) admitted to the hospital.

Objective: To examine the prognostic value of hypocalcemia in the setting of COVID-19.

Methods: Literature search (Pubmed) until September 15, 2020. Search terms include hypocalcemia, COVID-19, mortality, complications. Retrospective studies are reviewed due to lack of randomized trials.

Results: Hypocalcemia is the most common electrolyte abnormality in patients with COVID-19 admitted to the hospital after hyponatremia. Prevalence of hypocalcemia among hospitalized patients with COVID-19 ranges from 9.5% to 78% depending on the definition of hypocalcemia and patients' characteristics. In most cases, hypocalcemia is mild to moderate biochemically. Hypocalcemia is a risk factor for hospitalization of patients with COVID-19. In already hospitalized patients, hypocalcemia is significantly associated with increase severity of COVID-19 and its complications including multi-organ failure, intensive care unit (ICU) admission, need for mechanical ventilation, acute respiratory distress syndrome (ARDS), and death. Hypocalcemia is significantly correlated with inflammatory markers of COVID-19. Causes of hypocalcemia in COVID-19 patients are unclear, but vitamin D deficiency may be a contributing factor.

Conclusions: Hypocalcemia is common in hospitalized patients with COVID-19 and carries unfavorable outcomes. Further studies are needed to examine causes of hypocalcemia in COVID-19 and to see whether normalization of circulating calcium levels improve prognosis.

Introduction

COVID-19 is caused by a newly discovered coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Shortly after many patients with COVID-19 were admitted to the hospital, few retrospective studies reported a high frequency of hypocalcemia (Table 1) [1-8]. The frequency of hypocalcemia in patients with COVID-19 admitted to the hospital ranges from 9.5 to 78% depending on its definition and patients' characteristics [1-8]. In one single Chinese cohort of 304 patients admitted to the hospital, only 22 patients (7%) had hypocalcemia [9]. In the latter study, definition of hypocalcemia was not mentioned, and calcium values most likely were an outlier. In the report of Liu *et al.* [3], only 3 of 107 patients had severe hypocalcemia defined as ionized serum calcium of < 1.9 mmol/L. In one series of 408 patients with COVID-19 admitted to the hospital, hyponatremia was the most common electrolyte abnormality occurring in 35.8% of patients followed by hypocalcemia occurring in 9.5% of patients [7].

Mechanisms of hypocalcemia in COVID-19

Causes of hypocalcemia in general are hypoparathyroidism, vitamin D deficiency, hypomagnesemia, and chronic kidney disease [10]. Hypoparathyroidism can be easily demonstrated by the finding of low or inappropriately normal plasma parathyroid hormone (PTH) levels in the face of hypocalcemia. Unfortunately, no studies assessed PTH values in patients with COVID-19 and hypocalcemia. Sun *et al.* [2] were the only investigators that measured PTH levels in a small subgroup of 26 patients among their cohort of 241 patients admitted with COVID-19. However, these 26 patients were not hypocalcemic. Likewise, vitamin D serum levels were measured in these 26 patients and were found to be low in all patients (Table 1) [2]. It is not known whether hypocalcemia plays a role in infection with the SARS-CoV-2. In fact, calcium ion was shown to be essential in fusion of coronavirus and its entry into host cells [11,12]. Therefore, it is tempting to speculate that "consumption" of circulating calcium for the sake of virus entry into host cells might contribute to hypocalcemia. Clearly, this hypothesis requires clarification by further investigations. It is also likely that hypocalcemia in hospitalized patients with COVID-19 and its association with more severe COVID-19 may be a marker of severe illness. Indeed, it was shown that hypocalcemia was common in patients with critical disease admitted to the ICU and was associated with poor prognosis [13].

Impact of hypocalcemia on hospitalization

In the series of 531 patients with COVID-19 reported by Di Filippo *et al.* [4], 424 (79.8%) patients were admitted to the hospital. The authors found that serum calcium levels were significantly lower in patients requiring hospitalization than patients who were managed as outpatients. 1,13 and 1.16 mmol/L, respectively (P<0.001) [4]. Moreover, by multivariate analysis, hypocalcemia emerged as independent risk factor for hospitalization, but not for death [4]. Furthermore, in the study of Wu *et al.* [5], hypocalcemia was independent risk factor for long-term hospitalization (defined as hospitalization longer than 14

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days); odds ratio 3.3, 95% CI, 1.4-7.9). Likewise, in their case series from Turkey, Tezcan *et al.* [7] reported that hypocalcemia was associated with more prolonged hospitalization, with odds ratio (OR) of 1.08 (95% CI 1.04-1.12; P <0.001).

Impact of hypocalcemia on severity of COVID-19

Sun *et al.* [2] found that COVID-19 patients with hypocalcemia (total serum calcium <2.0 mmol/L) developed the following complications: 32.6% had multiple organ dysfunction, 14.0% had septic shock, and 16.3% had cardiac injury, whereas none of patients with normal serum calcium (> 2.2 mmol/L) developed any of these complications. Moreover, in the hypocalcemic group of patients, 34.9% had ARDS compared with only 1.6% in the normocalcemic group [2]. In their pooled analysis of 2 small Chinese studies, Lippi *et al.* [6] found significantly lower serum calcium levels in patients with severe COVID-19 compared with non-severe disease, weighted mean difference being 0.2 mmol/L, 95% CI -0.25 to -0.20). In the latter study, severe COVID-19 was defined as patients requiring mechanical ventilation, vital life support or ICU admission [2]. In the series of 408 patients reported by Tezcan *et al.* [7], these researchers found that hypocalcemia was associated with approximately 5-fold increase risk of ICU admission and need for mechanical ventilation (Table 1).

Table 1. Retrospective studies that evaluate hypocalcemia in COVID-19

Study	Cappellini et al. [1]	Sun et al. [2]	Liu et al. [3]	De Filippo et al. [4]	Wu et al. [5]	Lippi et al. [6]	Tescan et al. [7]	Khamis et al. [8]
Patients' characteristics	N=585, 34% women, median age 66 years. 420 patients positive for COVID-19	N=241, 53% women, median age 65 years	N=107, 51% women, median age 68 years	N=531, 32% women, median age 59 years, 424 (79.8%) patients were hospitalized	N=125, 47% women, median age 55 years	N=140 pooled from 2 studies.	N=408, 54% women, mean age (± SD) 54±16 years	N=63, 15% women, mean age (± SD) 48 ± 16
Type of measured serum Ca	Total and ionized Ca	Total Ca, not albumin-corrected	Total Ca corrected for serum albumin	Ionized Ca	Total Ca, not corrected for albumin	Total Ca, not corrected for albumin	Total Ca not corrected for albumin	Total Ca corrected for albumin
Definition of hypocalcemia	NR	Total Ca ≤ 2.2 mmol/L (n=43)	Albumin-corrected Ca < 2.15 mmol/L	Ionized Ca < 1.18 mmol/L	Total Ca < 2.2 mmol/L	NR	Total calcium <2.1 mmol/L	Albumin-corrected Ca ≤ 2.15 mmol/L
Proportions of patients with hypocalcemia	NR	74.7%	62%	78.6%	64.8%	NR	9.5%	48%
Results (all serum Ca are in mmol/L)	Total Ca (median, 95% CI)=2.14 (2.13-2.15) in COVID-19 vs 2.27 (2.25-2.29) in non-COVID-19. Ionized Ca 1.12 (1.12-1.13) in COVID-19 vs 1.17 (1.16-1.19), P <0.0001 for both comparisons.	Significantly higher mortality and multiorgan failure in patients with hypocalcemia	Patients with poor outcomes (defined as death, admission to intensive care or mechanical ventilation) had lower median Ca compared with patients with favorable outcome, 2.01 and 2.10, respectively (P< 0.001)	Hospitalized patients had lower calcium than non-hospitalized patients, 1.13 and 1.16, respectively, P <0.001. In multivariate analysis, hypocalcemia was independent risk factor for hospitalization (P < 0.001), but not for death.	Hypocalcemia was independent risk factor for long-term hospitalization > 14 days (odds ratio 3.3, 95% CI, 1.4-7.9; P=0.007)	Significantly lower calcium in patients with severe vs non-severe COVID-19. Weighted mean difference -0.2 mmol/L (95% CI, -0.25 to -0.20)	Hypocalcemia associated with ICU admission OR 5.1, (95% CI, 2.3-11.5), mechanical ventilation OR 5.2 (95% CI 2.1-12.5), mortality OR 5.1 (95% CI 2.1-12.8), and duration of hospitalization OR 1.08 (95% CI 1.04-1.12)	15% of patients with hypocalcemia died vs. none in patients with normal Ca (P=0.047).
Median parathyroid hormone (PTH) (normal range 15-65 pg/ml)	NR	Measured in 26 patients: 55.3 pg/ml	NR	NR	NR	NR	NR	NR
Median 25 OH Vitamin D (normal range 30-80 ng/ml)	NR	Measured in 26 patients 10.2 ng/ml. All 26 patients had low 25 OH vitamin D levels: *IQR 8.2-12.6) ng/ml.	NR	NR	NR	NR	NR	NR
Significant association of hypocalcemia with inflammatory markers	NR	C-reactive protein, D-dimer (negative correlation), lymphocyte count (positive correlation)	Hypocalcemic patients had higher C-reactive protein, D-dimer, pro-calcitonin, interleukin-6, and leukocyte count vs normocalcemic patients	Negative correlation of serum Ca with C-reactive protein, lactate dehydrogenase (LDH)	NR	NR	NR	NR

Normal total serum calcium: 2.15- 2.50 mmol/L. To convert to mg/dl, multiply by 4.
Normal range of serum ionized calcium was not reported in the studies. In general, range of ionized calcium: 1.2-1.4 mmol/L.
SD: Standard deviation
NR: Not reported.
*IQR: Inter-quartile range

Impact of hypocalcemia on mortality in COVID-19

Sun *et al.* [2] reported 23.3% mortality rate in patients with COVID-19 and hypocalcemia having median total calcium 1.96 mmol/L [inter-quartile range (IQR) 1.90-2.00] compared to no mortality among patients with normal serum calcium values. In agreement with these results, Liu *et al.* [3] found that COVID-19 patients with poor outcomes (defined as death, admission to ICU or need for mechanical ventilation) had lower serum calcium concentrations compared with patients with favorable outcome, 2.01 and 2.10 mmol/L, respectively ($P < 0.001$). In the study of Tezcan *et al.* [7], hypocalcemia was associated with significant increase risk of death (OR 5.14, 95% CI 2.0-12.2; $P<0.001$). Furthermore, in the series of Khamis *et al.* [8], 15% of patients with hypocalcemia died compared with none among patients with normal serum calcium ($P=0.047$) (Table1).

Relationship of hypocalcemia to inflammatory markers in COVID-19

Multiple studies have shown significant association between hypocalcemia and inflammatory markers that reflect severity of COVID-19. Thus, there was significant negative correlation between hypocalcemia and plasma levels of C-reactive protein [2,4], lactic dehydrogenase (LDH) [4] and D-dimer (Table 1) [2,4]. In addition, patients with hypocalcemia had higher circulating interleukin-6 and pro-calcitonin compared with normocalcemic patients [3].

Potential complications of hypocalcemia in hospitalized patients with COVID-19

In most patients with COVID-10 reported in the literature, hypocalcemia was mild to moderate biochemically [1-8]. To the best of the authors' knowledge, so far, no cases of hospitalized COVID-19 patients experienced neurological symptoms of hypocalcemia such as tetany or seizures. Meanwhile, it is known that hypocalcemia is associated with prolongation of QT interval, which is proportional to the degree of hypocalcemia and may cause life threatening torsade de pointes [14]. Interestingly, in one study, 48.5% (50 of 103) patients with COVID-19 with prolonged QT interval had electrolyte abnormalities [15]. Thus, in these patients, hypomagnesemia was recorded in 30.1% of patients and hypokalemia in 27% [15]. Unfortunately, calcium levels were not reported [15].

Conclusions and current needs

Hypocalcemia commonly occurs in hospitalized patients with COVID-19 and carries unfavorable prognosis. Etiology of hypocalcemia in patients with COVID-19 is still unclear but is likely multifactorial. Further studies are urgently needed to examine causes of hypocalcemia in hospitalized patients with COVID-19. Measurement of ionized serum calcium should be done because it is more accurate than albumin-corrected calcium in critically ill patients [16]. In addition, plasma levels of PTH, magnesium, and 25-hydroxy vitamin D levels should be measured in all patients with hypocalcemia to clarify the etiology of hypocalcemia. Randomized trials are required to see whether correction of hypocalcemia would lead to improvement of outcomes.

Conflict of interest

The authors do not have any conflict of interest to declare.

References

1. Cappellini F, Brivio R, Casati M, Cavallero A, Contro E, et al. (2020) Low levels of total and ionized calcium in blood of COVID-19 patients. *Clin Chem Lab Med* 58: e171-e173. [Crossref]
2. Sun J, Zhang W, Zou L, Liu Y, Li JJ, et al. (2020) Serum calcium as a biomarker of clinical severity and prognosis in patients with coronavirus disease 2019. *Aging* 12: 11287-11295. [Crossref]
3. Liu J, Han P, Wu J, Gong J, Tian D (2020) Prevalence and predictive value of hypocalcemia in severe COVID-19 patients. *J Inf Pub Health* 13: 1224-1228. [Crossref]
4. Di Filippo L, Formenti AM, Rovere-Querini P, Carlucci M, Conte C, et al. (2020) Hypocalcemia is highly prevalent and predicts hospitalization in patients with COVID-19. *Endocrine* 68: 475-478. [Crossref]
5. Wu Y, Hou B, Liu J, Chen Y, Zhong P (2020) Risk factors associated with long-term hospitalization in patients with COVID-19: a single-centered, retrospective study. *Frontiers Med* 7: 315. [Crossref]
6. Lippi G, South AM, Henry BM (2020) Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). *Ann Clin Biochem* 57: 262-265. [Crossref]
7. Tezcan ME, Dogan Gokce G, Sen N, Zorlutuna Kaymak N, Ozer RS (2020) Baseline electrolyte abnormalities would be related to poor prognosis in hospitalized COVID-19 patients. *New Microbes New Infect*. [Crossref]
8. Khamis F, Al-Zakwani I, Al Naamani H, Al Lawati S, Pandak N, et al. (2020) Clinical characteristics and outcomes of the first 63 adult patients hospitalized with COVID-19: An experience from Oman. *J Infect Public Health* 13: 906-913. [Crossref]
9. Lu L, Xiong W, Liu D, Liu J, Yang D, et al. (2020) New onset acute symptomatic seizures and risk factors in coronavirus disease 2019. A retrospective multicenter study. *Epilipsia*. [Crossref]
10. Bove-Fenderson E, Mannstadt M (2018) Hypocalcemic disorders. *Best Pract Res Clin Endocrinol Metab* 32: 639-656. [Crossref]
11. Millet JK, Whitaker GR (2018) Physiological and molecular triggers for SARS-CoV membrane fusion and entry into host cells. *Virology* 517: 3-8. [Crossref]
12. Strauss MR, Tang AL, Lai AL, Flegel A, Bidon M, et al. (2020) Ca2+ ions promote fusion of Middle East respiratory syndrome coronavirus with host cells and increase infectivity. *J Virol* 94: e00426-20. [Crossref]
13. Sanaie S, Mahmoodpoor A, Hamishekar H, Shadvar K, Salimi N, et al. (2018) Association between disease severity and calcium concentration in critically ill patients admitted to intensive care unit. *Anesth Pain Med* 8: e57583. [Crossref]
14. Chabra ST, Mehta S, Chabra S, Singla M, Aslam N, et al. (2018) Hypocalcemia presenting as life threatening torsades de pointes with prolongation of QTc interval. *Int J Clin Biochem* 33: 235-238. [Crossref]
15. Jain S, Workman V, Ganeshan R, Obasare ER, Burr A, et al. (2020) Enhanced electrocardiographic monitoring of patients with coronavirus disease 2019. *Heat Rhythm* 17:1417-1422. [Crossref]
16. Hu ZD, Huang YL, Wang MY, Hu GJ, Han YQ (2018) Predictive accuracy of serum total calcium for both critically high and critically low ionized calcium in critical illness. *J Clin Lab Anal* 32: e22589. [Crossref]