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Impact of low serum calcium at hospital admission on SARS-CoV-2 infection outcome



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ABSTRACT

Background: Calcium is an essential ion for pathogen survival and virulence and is involved in the regulation of the inflammatory response. Hypocalcemia is a common laboratory finding in critically ill patients. Data regarding levels of calcium in SARS-CoV-2 infection is scarce. Patients with SARS-CoV-2 infection who present with hypocalcemia could have a worse outcome.

Methods: We performed a retrospective analysis of hospitalized patients with SARS-CoV-2 infection and included all patients who had any serum calcium measurement in the first 72 h since hospital admission. The main objective was to investigate the relation of low serum calcium with adverse outcome, measured by the requirement of high oxygen support – defined as high flow nasal cannula oxygen, non-invasive mechanical ventilation and/or invasive ventilation – intensive care unit admission or death.

Results: A total of 316 patients were included in the study. Median age was 65 years (IQR 55–74); 65% were men. Hypocalcemia within 72 h since hospital admission was present in 63% of patients. A higher number of patients in the hypocalcemia group required high oxygen support during hospitalization (49% vs 32%; $p = 0,01$) and were admitted to the ICU (42% vs 26%; $p = 0,005$). No differences in mortality were observed between groups.

Conclusions: Hypocalcemia is frequent in hospitalized patients with SARS-CoV-2 infection and can identify patients who will have a worse outcome. More studies are needed to understand the role of calcium metabolism in SARS-CoV-2 infection and to address the clinical implications and therapeutic interventions it might have.

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Introduction

Severe Acute Respiratory Syndrome Coronavirus 2, named SARS-CoV-2, was isolated in January 2020 after an outbreak of respiratory infections originated in December 2019 in the city of Wuhan, China (Zhu et al., 2020). The virus spread rapidly, first to neighboring countries and weeks afterward throughout the world, causing a worldwide pandemic.

Clinical characteristics of SARS-CoV-2 infected patients have already been reported and several laboratory parameters have been identified as prognostic markers (Wang et al., 2020; Zhou et al., 2020; Ji et al., 2020).

Calcium is an important ion involved in different cellular processes and it has been recognized as critical for pathogen survival and virulence. Moreover, calcium metabolism is known to regulate the inflammatory response in critically ill patients (Steele et al., 2013).

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Patients with SARS-CoV-2 infection who present with hypocalcemia could present a more severe clinical syndrome.

Methods

From 1st March until 15th May 2020, 2400 patients needed hospital admission due to COVID-19 in our center.

Clinical and laboratory information of hospitalized patients with a SARS-CoV-2 infection is retrospectively being collected and managed using REDCap electronic data capture tools hosted at Hospital Clínic (Harris et al., 2009).

We performed a retrospective analysis of the database and included all patients who had at least one calcium determination in the first 72 h since hospital admission.

Calcium was measured in milligrams per deciliter and corrected for proteins measured in the same blood test (Corrected serum calcium = serum calcium/0.6 + (total proteins/18.5)). The study was approved by the local ethics committee.

Epidemiological and clinical data, laboratory findings, chest X ray results and patient outcomes were reviewed.

The main objective of the study was to investigate the relation of low serum calcium levels in the first 72 h since hospital admission with adverse outcome, defined by the need for high oxygen support, ICU admission or death during hospitalization.

We also performed a multivariate logistic analysis in order to assess if low serum calcium at admission was an independent risk factor for ICU admission or death.

Statistical analysis

All continuous variables are expressed in medians and interquartile ranges. Categorical variables are expressed as an absolute value and relative frequencies. Means of continuous variables were compared with student t test, and binary variables were compared with the Chi-Squared test, between low (hypocalcemia) and normal calcium level patients. Univariate logistic regression was performed to assess the association of clinically meaningful variables in the significant primary endpoint outcomes. p-Values under 0.05 were considered statistically significant. Variables with pre-specified significance in the univariate model were then included in a multivariable logistic regression model in order to analyze if calcium level was an independent

factor for ICU admission. All statistical analysis was performed with IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL USA) and Stata 14 (StataCorp LP, College Station, TX, USA).

Definitions

Confirmed SARS-CoV-2 infection was diagnosed when a positive reverse-transcription polymerase chain reaction (RT-PCR) test in the nasopharyngeal swab was obtained in a clinical context. Probable SARS-CoV-2 infection was considered with a negative, indeterminate or absent RT-PCR test result but there was a high suspicion of SARS-CoV-2 infection by clinical symptoms and radiologic and laboratory findings.

Hypocalcemia was considered if, corrected for proteins, serum calcium was lower than 8.5 mg/dL.

High Oxygen Support was considered when a patient had required high flow nasal cannula oxygen (HFNC), non-invasive mechanical ventilation (NIMV) or invasive mechanical ventilation (IMV) at any time point during hospitalization.

Results

At the time of database export 552 registries were introduced in the online database. Of them, 316 patients had at least one measurement of calcium in the first 72 h since hospital admission and were included in the study.

Of the 316 patients included, 206 (65%) were men and median age was 65 years (IQR, 55–74). Baseline characteristics are described in Table 1. Diagnosis of SARS-CoV-2 infection with RT-PCR confirmation was established in 262 patients (83%); swab was negative or indeterminate in 8 and was not performed in the remaining 46 (14%). However, in all these cases, a probable SARS-CoV-2 infection was diagnosed by compatible analytical, radiological and laboratory findings.

The most frequent laboratory test findings at admission were elevation in lactate dehydrogenase (85%), ferritin (74%), D-dimer (63%) and low count of lymphocytes (62%). Electrolyte imbalances were also observed: hyponatremia, hypokalemia and hypomagnesemia appeared in 17, 18 and 19% respectively (Table 2). The most frequently altered electrolyte was calcium. The percentage of patients with calcium lower than 8,5 mg/dL was 63%.

Table 1

Baseline characteristics of the whole cohort and according to calcium levels.

	Cohort n = 316	Low calcium n = 198	Normal calcium n = 118	p
Age, median (IQR)	65 (55–74)	65 (52–74)	65 (57–75)	0,12
Sex (female), n (%)	110 (35)	62 (31)	48 (41)	0,09
Comorbidities, n (%)	265 (84)	173 (87)	92 (78)	0,02
Hypertension, n (%)	162 (51)	97 (49)	65 (55)	0,29
Diabetes, n (%)	52 (16)	31 (16)	21 (18)	0,62
Cardiopathy, n (%)	63 (20)	38 (19)	25 (21)	0,66
Pulmonary disease, n (%)	26 (8)	20 (10)	6 (5)	0,12
Dyslipidemia, n (%)	88 (28)	51 (25)	37 (31)	0,28
Neoplasia, n (%)	21 (7)	15 (7)	6 (5)	0,39
Limitation ALS, n (%)	60 (19)	35 (18)	25 (21)	0,44
Days of symptoms at admission, median (IQR)	7 (4–10)	7 (4–8)	7 (4–10)	0,04
SpO ₂ /FiO ₂ < 357, n (%)	99 (31)	64 (32)	35 (30)	0,69
Fever, n (%)	276 (87)	171 (86)	105 (89)	0,58
Sore throat, n (%)	18 (6)	13 (6)	5 (4)	0,36
Cough, n (%)	222 (70)	146 (73)	76 (64)	0,04
Dyspnea, n (%)	182 (58)	113 (57)	69 (58)	0,81
Vomits, n (%)	18 (6)	10 (5)	8 (6)	0,52
Diarrhea, n (%)	82 (26)	48 (24)	34 (29)	0,39
Myalgias, n (%)	72 (23)	45 (23)	27 (23)	0,98

Abbreviations: IQR: interquartile range; ALS: advanced life support; SpO₂/FiO₂: oxygen saturation by pulse oximeter/oxygen inspiration fraction (a SpO₂/FiO₂ < 357 corresponds to Pa/FiO₂ < 300).

Bold value P < 0,05 statistically significant.

Forty-four percent of all patients required high oxygen support at any time during hospitalization. One hundred and fourteen patients (36%) were admitted to the intensive care unit. Fifty-five patients out of these 114 patients (48%) were admitted in the first 24 h since hospital admission. Death occurred in 58 (18%) patients in the whole cohort. Death in patients admitted to the ICU occurred in 25 out of 114 patients (22%) (Table 3).

Patients with hypocalcemia had any underlying condition, as a global measure, more frequently than patients with normal calcium (87% vs 78%; $p = 0.02$). There were not any other significant differences in baseline characteristics or symptoms at presentation, with the exception of cough (73% vs 64%; $p = 0.04$) (Table 1). In relation to laboratory findings, patients with hypocalcemia had a significantly lower lymphocyte count (700/mL [500–900] vs 800/mL [600–1215]; $p = 0.008$) and higher LDH levels (356 UI/L [277–464] vs 301 UI/L [234–396]; $p = 0.04$). Sodium levels below 135 mEq/L were more common in hypocalcemia patients (22% vs 8%; $p = 0.003$), however no differences in the other electrolytes, potassium and magnesium, were observed (Table 2). Pearson correlations for the studied laboratory parameters and calcium confirmed a significant positive association with lymphocytes ($r = 0.129$; $p < 0.05$) and sodium ($r = 0.229$; $p < 0.01$) and a negative association with LDH ($r = -0.144$; $p < 0.05$). No other correlations were observed.

High oxygen support requirement during hospitalization was available in 245 patients of the cohort. It was administered in 49% of patients in the hypocalcemia group versus 32% of patients in the normal calcium group ($p = 0.017$). Eighty-three (42%) patients in the hypocalcemia group vs 31 (26%) in the normal calcium group were admitted to the ICU ($p < 0.005$). Forty-three (22%) in the hypocalcemia group vs 12 (10%) in the normal calcium group were admitted to the ICU within 24 h since hospital admission ($p = 0.21$). No differences in deaths were observed (Table 3).

Due to the fact that no differences in mortality between groups were observed, we only evaluated if calcium was an independent risk factor for ICU admission. In the univariate analysis,

hypocalcemia was correlated with ICU admission, with an OR = 1.95 (IC95% 1.18–3.20. $P = 0.009$) (Supplementary Table 1). However, it was not an independent predictor for ICU admission after adjusting for other significant variables in the multivariate model OR = 1.53 (IC95% 0.83–2.81) (Supplementary Table 2).

Discussion

Here we describe a total of 316 hospitalized patients with SARS-CoV2 infection with focus on the relation of hypocalcemia with the need of high oxygen support, ICU admission and death.

Baseline characteristics of patients were in accordance with previous clinical series (Wang et al., 2020; Guan et al., 2020; Lagi et al., 2020; Goyal et al., 2020).

Low serum calcium at admission was frequent in our study and similar to what has been reported in other viral infections (Borgherini et al., 2007; Dahanayaka et al., 2017; van Griensven et al., 2016; Zhang et al., 2014), including a study of an outbreak in 2002 of SARS in 144 patients in Toronto, Canada (Booth et al., 2003). By the present date, there are only three published studies reporting calcium alterations in SARS-CoV-2 infection. The first one is a Chinese epidemiological retrospective clinical series describing clinical characteristics of 91 hospitalized COVID-19 patients that observed a relation between low levels of calcium and more severe disease (Qian et al., 2020). Two Italian studies focused on levels of calcium. The first one compared calcium levels in patients with SARS-CoV2 infection vs. not infected admitted to the emergency department and found that COVID-19 patients had lower concentrations of calcium with respect to non-COVID-19 patients (Cappellini et al., 2020), however, prevalence was not reported in this brief study. The second one included 531 patients admitted to the emergency department. Hypocalcemia (defined in the study as ionized calcium < 1.18 mmol/L; normal range 1.16–1.31 mmol/L) was observed in 82% of COVID-19 patients and was reported to be a risk factor for ICU admission and death in the univariate but not in the multivariate analysis (Di Filippo et al.,

Table 2
Laboratory parameters in the whole cohort and according to calcium levels.

	Cohort n = 316	Low calcium n = 198	Normal calcium n = 118	p
Leukocytes ($\times 10^6/L$) median (IQR)	6000 (4520–8135)	5855 (4537–7782)	6255 (4450–9225)	0,85
>11 000 n (%)	40 (13)	22 (11)	18 (15)	0,28
Lymphocytes ($\times 10^6/L$)	800 (550–1060)	700 (500–900)	800 (600–1215)	0,008
<900	194 (61)	128 (64)	66 (56)	0,11
Platelets ($\times 10^9/L$)	185 (138–237)	176 (136–224)	208 (143–257)	0,85
<150 000	96 (30)	63 (32)	33 (28)	0,57
CRP (mg/dL)	9 (4,7–17,8)	9,7 (4,7–18)	8,4 (4,5–16)	0,55
>10	142 (45)	92 (46)	50 (42)	0,6
AST (U/L)	42 (30–69)	42 (33–73)	37 (26–67)	0,96
>40	156 (49)	103 (52)	53 (45)	0,23
ALT (U/L)	34 (20–63)	34 (20–64)	34 (18–63)	0,46
>40	128 (40)	80 (40)	48 (41)	0,97
LDH (U/L)	339 (264–441)	356 (277–464)	301 (234–396)	0,04
>234	243 (77)	163 (82)	80 (68)	0,000
Creatinine (mg/dL)	0,93 (0,78–1,17)	0,93 (0,79–1,19)	0,93 (0,72–1,16)	0,46
>1,3	59 (19)	39 (20)	20 (17)	0,61
Na (mEq/L)	138 (135–140)	137 (135–139)	138 (136–141)	0,001
<135	53 (17)	43 (22)	10 (8)	0,003
K (mEq/L)	3,9 (3,6–4,2)	3,8 (3,5–4,1)	3,8 (3,6–4,2)	0,3
<3,5	55 (18)	40 (20)	15 (13)	0,1
Mg (mEq/L)	2 (1,8–2,1)	2 (1,8–2,1)	1,9 (1,8–2,1)	0,8
<1,8	55 (17)	33 (17)	22 (19)	0,69
Ferritin (ng/mL) ^a	861 (384–1558)	802 (367–1498)	854 (370k1541)	0,9
>400	122/165 ^a (74)	77/105 (73)	45/60 (75)	0,81
D Dimer (ng/mL) ^a	750 (400–1200)	800 (400–1325)	700 (400–1400)	0,09
>800	112/266 ^a (42)	70/165 (42)	42/101 (41)	0,89

Abbreviations: CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; Na: sodium; K: potassium; Mg: magnesium.

Bold value $P < 0,05$ statistically significative.

^a Ferritin measured in 165/316 patients. D Dimer measured in 266/316 patients.

Table 3
Outcome in the whole cohort and according to calcium levels.

	Cohort n = 316	Low calcium n = 198	Normal calcium n = 118	p
<i>Outcome</i>				
High oxygen support ^a , n (%)	107/245 (44)	82/167 (49)	25/78 (32)	0,01
ICU admission, n (%)	114 (36)	83 (42)	31 (26)	0,005
ICU admission 24 h, n (%)	55 (17)	43 (22)	12 (10)	0,21
Death, n (%)	58 (18)	37 (19)	21 (18)	0,84

Bold value $P < 0,05$ statistically significative.

^a Data available in 245/316 patients.

2020). Serum calcium lower than 8.5 mg/dL in our study was also a risk factor for need of high oxygen support and ICU admission but not for death. Low levels of calcium seem to be associated with other laboratory features (higher LDH, lower lymphocytes count) that have been repeatedly reported to be independent risk factors for SARS-CoV-2 progression in hospitalized patients (Ji et al., 2020).

Calcium is essential for virus life cycle and virulence. The calcium pump SCAP1 has been identified as a protein used by many viruses. It regulates the intracellular calcium concentration required by proteases involved in virus maturation (Hoffmann et al., 2017). In addition to this, the SARS-CoV-2 envelope E-protein is a viroporin that forms calcium permeable channels and alters calcium homeostasis within cells boosting the activation of the NLRP3 inflammasome, which leads to the overproduction of IL-1 β (Nieto-Torres et al., 2015).

Due to the fact that calcium homeostasis is tightly regulated by hormonal processes, the above-mentioned mechanisms would not totally explain the magnitude of the low serum calcium levels observed in SARS-CoV-2 infection and in other viruses. A possible relation of hypocalcemia and inflammation may therefore exist. According to some studies in animal models, cytokines, concretely IL-1 β , can upregulate the expression of the calcium sensing receptor (CaSR), a membrane protein that can sense changes in calcium concentration (Canaff and Hendy, 2005). CaSR upregulation reduces the set point for circulating calcium suppression of PTH secretion. Thus, a lower circulating calcium concentration, even concentrations in the hypocalcemic range, would be sufficient to reduce PTH secretion and, as a consequence, to decrease serum calcium (Klein, 2018).

Taking into account that calcium is an inflammation mediator, some authors have supported the theory that hypocalcemia can act as a regulator of inflammation (Klein et al., 2016).

This mechanism would explain the observed relationship between low levels of calcium and more severe SARS-CoV-2 infection with worse prognosis, and it could then be possible that patients with higher levels of inflammatory cytokines would present with lower serum calcium concentration. Unfortunately, we did not measure interleukin levels in our study, thus, we could not demonstrate the relationship between low levels of calcium with a higher degree of inflammation.

Irrespective of the mechanism responsible for hypocalcemia, it appears that low levels of calcium are frequent in hospitalized patients with SARS-CoV-2 infection and could have important clinical implications, such as cardiovascular, neurological, musculoskeletal and psychiatric adverse events. However, at the present moment, international COVID-19 management guidelines do not consider measurement and supplementation of calcium in hospitalized patients with SARS-CoV-2 infection.

The main limitations of our work are the limited number of patients due to the retrospective characteristics of the study and the difficulty to establish an independent relationship of calcium with worse outcome or death due to several confounding factors.

In conclusion, hypocalcemia is frequent in hospitalized patients with SARS-CoV-2 infection and can identify patients with worse prognosis and urgent need of intensive care. Further research is needed in order to understand the role of calcium metabolism in the physiopathology of viral infections.

Article's main point

In our study 63% of hospitalized patients with SARS-CoV-2 infection presented low serum calcium levels at admission. Hypocalcemia was related to adverse outcome in terms of requirement of high oxygen support and Intensive Care Unit admission.

Conflicts of interest

All of authors declare not having any conflict of interest.

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Ethical approval

Study was approved by the local ethics committee with date 15th May 2020.

Authors' contributions

BT conceived the idea, designed the study, performed data collection, analysis and interpretation and wrote the paper.

PA performed data collection, analysis and interpretation.

AGC, AI, MC, CC and FM performed data collection and interpretation.

MG and ADH provided revisions of scientific content of manuscript.

AS performed data interpretation and provided scientific content to manuscript.

All authors provided revisions to preliminary draft and approved the final version of the manuscript.

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Appendix A. Supplementary data

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