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Hypocalcemia in COVID-19: Prevalence, clinical significance and therapeutic implications

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Abstract
COVID-19 extra-pulmonary features include several endocrine manifestations and these are becoming strongly clinically relevant in patients affected influencing disease severity and outcomes.
At the beginning of COVID-19 pandemic no population data on calcium levels in patients affected were available and in April 2020 a first case of severe acute hypocalcemia in an Italian patient with SARS-CoV-2 infection was reported. Subsequently, several studies reported hypocalcemia as a highly prevalent biochemical abnormality in COVID-19 patients with a marked negative influence on disease severity, biochemical inflammation and thrombotic markers, and mortality. Also a high prevalence of vertebral fractures with worse respiratory impairment in patients affected and a widespread vitamin D deficiency have been frequently observed, suggesting an emerging "Osteo-Metabolic Phenotype" in COVID-19.
To date, several potential pathophysiological factors have been hypothesized to play a role in determining hypocalcemia in COVID-19 including calcium dependent viral mechanisms of action, high prevalence of hypovitaminosis D in general population, chronic and acute malnutrition during critical illness and high levels of unbound and unsaturated fatty acids in inflammatory responses.
Since hypocalcemia is a frequent biochemical finding in hospitalized COVID-19 patients possibly predicting worse outcomes and leading to acute cardiovascular and neurological complications if severe, it is reasonable to assess, monitor and, if indicated, replace calcium at first patient hospital evaluation and during hospitalization.

Keywords Hypocalcemia · COVID-19 · SARS-CoV-2 · Calcium · Vitamin D · Bone

1 Introduction

Clinical manifestations of Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), are mainly characterized by an asymptomatic/mild-to-severe respiratory disease with predominantly pulmonary involvement [1, 2].

During progressive pandemic spread, several studies have shown that also COVID-19 extra-respiratory features, including the "endocrine phenotype", are becoming strongly relevant clinical manifestations in patients affected influencing disease severity and outcomes [3–7].

Concomitant history or newly diagnosed diabetes mellitus and abnormalities of glucose metabolism, including worsened hyperglycemia and euglycemic ketosis, rapidly emerged as one of the most relevant medical conditions negatively influencing COVID-19 [8, 9]. Similar results were reported in obese patients, especially in those with marked visceral adiposity [10, 11].

Vitamin D (VD) is involved in immunocompetence both regarding innate and adaptive immunity, and a strong and strict association between hypovitaminosis D and fat mass excess and diabetes mellitus is widely recognized [6, 12, 13]. Several mechanisms have been hypothesized to explain these associations including lower dietary intake of VD, lesser outdoor physical activity with poorer skin exposure to sunlight, impaired hydroxylation in adipose tissue, VD accumulation in fat, and an impaired hepatic and renal metabolism of VD in diabetic patients [12, 13]. Therefore,

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since a high prevalence of VD deficiency in COVID-19 patients was reported by several studies and possibly influencing viral infection and disease manifestations, VD might represent the main key regulator in the COVID-19 endocrine phenotype [4].

Moreover, not only VD deficiency has been reported as a typical COVID-19 patients feature but also a high prevalence of vertebral fractures, worsening respiratory impairment in patients affected, and a widespread hypocalcemia with negative impacts on disease severity have been frequently observed, suggesting an emerging "osteo-metabolic phenotype" in COVID-19 [15, 16].

Aim of this paper is to review the main evidences regarding calcium metabolism in COVID-19, starting from first detections of lower calcium levels in patients affected, then reporting hypocalcemia influence on COVID-19 manifestations, successively exploring the possible main pathophysiological mechanisms and clinical-therapeutic implications of hypocalcemia in COVID-19 patients.

2 Prevalence of hypocalcemia in COVID-19

At the beginning of COVID-19 pandemic in 2019, several studies, especially conducted in China, investigated the clinical and laboratory characteristics of COVID-19 patients, including inflammatory and organ injury biomarkers [1, 2]. However, no population data on calcium levels in these studies were available.

In April 2020, during the first pandemic spread in Europe, a case of severe acute hypocalcemia in an Italian previously thyroidectomized patient with SARS-CoV-2 infection was reported [17]. Therefore, COVID-19 was suggested for the first-time as the possible precipitating cause of a subclinical post-surgical hypoparathyroidism.

Interestingly, previous studies, conducted in 2003 and 2016 and focused on SARS and Ebola past epidemic emergencies, reported hypocalcemia as a highly prevalent biochemical abnormality in patients affected [18, 19]. In fact, Booth et al. described the clinical features and short-term outcomes of 144 patients with SARS hospitalized in the greater Toronto area in 2003 [18]. Laboratory indices were evaluated at hospital admission and during hospitalization, and these included total calcium evaluation. Hypocalcemia was defined as a total calcium level corrected for serum albumin below 8.8 mg/dL (reference values 8.8–10.5 mg/dL). Median calcium value detected at hospital admission was 8.52 mg/dL and hypocalcemia was found in 53/89 (60%) patients. During hospitalization electrolyte and biochemical abnormalities found on admission tended to worsen. Median calcium value detected during hospitalization, recording the most abnormal value, was 8.1 mg/dL and hypocalcemia was found in 71/101 (70%) patients. Furthermore, Uyeki et al. described the clinical characteristics of 27 patients affected by Ebola Virus (EBV) who received care in the United States and Europe from August 2014 through December 2015 [19]. Laboratory indices were evaluated at hospital admission and during hospitalization, and these included total calcium evaluation. Hypocalcemia was defined as a total calcium level below 8 mmol/L. Hypocalcemia was found in 10/16 (62%) patients at hospital admission and in 15/20 (75%) during hospitalization.

Based on the seminal clinical observation above reported of severe acute hypocalcemia in a COVID-19 patient [17] and on the previous available reports of hypocalcemia as a frequent finding in SARS and EBV infection, in order to identify the existence and prevalence of low calcium levels in COVID-19 patients we conducted the first retrospective cohort study at IRCCS San Raffaele Hospital, a tertiary health-care hospital in Milan, Italy, one of the mostly involved European centers by the pandemic spread. We evaluated ionized calcium levels of adult patients with COVID-19 admitted to our Emergency Department (ED) excluding those with comorbidities and concomitant therapies influencing calcium metabolism [16]. Ionized calcium levels were expressed both as actually measured levels (AC) and as adjusted mathematically to a standardized pH of 7.4. levels (SC) to avoid influence of sample handling, and hypocalcemia was defined as calcium level below 1.18 mmol/L. A total of 531 patients were included in the study and hypocalcemia was found in 462 patients (82%) with AC levels, in 414 (78.6%) patients with SC levels.

Several following studies conducted worldwide confirmed these data reporting an unexpected and very high prevalence of hypocalcemia, reported, to date in literature, ranging from 62.6% to 87.2%, depending on the hypocalcemia definition used.

Most of the available studies evaluated total serum calcium levels, adjusted or not for albumin levels, defining hypocalcemia as levels below either 2.2 mmol/L (8.8 mg/dL) or 2.15 mmol/L (8.6 mg/dL) or 2.12 mmol/L (8.5 mg/dL), reporting a hypocalcemia prevalence ranging from 62.6% to 74.7% (20–30). Other studies evaluating ionized serum calcium levels reported a hypocalcemia prevalence higher than 80% [15, 16, 30, 31].

Interestingly, Cappellini et al. reported lower total and ionized calcium levels in patients positive for nasopharyngeal swabs SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction (RT-qPCR) test as compared to those admitted in ED with same clinical signs and symptoms and negative to RTqPCR test [30]. However, no clinical, biochemical, and disease severity parameters were reported for these patients making difficult an adequate case–control comparison.

Therefore, in order to understand if hypocalcemia may be a distinctive specific feature of COVID-19 and not only

influenced by patient clinical disease severity and concomitant inflammatory illness, we compared ionized calcium levels in patients admitted to our ED during the same period for acute respiratory illness related (CoV) or not (nCoV) to SARS-CoV-2 infection matched for age, gender, and presence of concomitant comorbidities, all factors known to influence COVID-19 patients outcomes, on one case-one control basis [32]. Despite the same baseline clinical characteristics and inflammatory parameters of the two groups, we found lower calcium levels in CoV patients compared to nCoV with a doubled rate of hypocalcemia [32].

A recent study, collecting data from venous blood gas analysis of patients admitted to ED for respiratory illness, showed significantly lower ionized calcium levels in patients tested positive for SARS-CoV-2 than in negative patients [31]. Furthermore, two retrospective case–control studies found lower total calcium levels in COVID-19 patients as compared to outpatient age and sex-matched population-based controls [21, 24].

3 Clinical significance of hypocalcemia in COVID-19 patients

3.1 Hypocalcemia and disease severity

The clinical spectrum of COVID-19 manifestations widely ranges from asymptomatic to severe forms. Mild manifestations with favourable prognosis are present in most patients [33, 34]. However, particularly in elderly male patients with several comorbidities, SARS-CoV-2 infection may be complicated by acute respiratory distress syndrome (ARDS) requiring hospitalization, assisted ventilation and intensive care unit (ICU) admission, with high mortality risk [33, 34].

Identifying early predictors of clinical severity in COVID-19 may be helpful in the effort to adequately manage disease complications and improving outcomes in high risk affected patients.

Hypocalcemia, detected at initial and first evaluation upon admission in ED, has been identified in univariate and multivariate analyses as an independent risk factor highly associated with risk of hospitalization and long-term hospitalization [16, 28].

Sun et al. reported lower calcium levels in multivariate analyses, together with older age, C-Reactive Protein (CRP) and Interleukin 6 (IL-6) levels, as an independent risk factor for COVID-19 poor outcomes, including needs for mechanical ventilation (MV), intensive care unit (ICU) admission or death for any cause [25].

Moreover, also multiple organ dysfunction syndrome (MODS), ARDS, acute kidney injury, septic shock, high oxygen support, needs for MV and continuous renal replacement therapy were reported more frequently in hypocalcemic patients compared to normocalcemic [27–29].

Recently, Zhao et al., in order to early identify mild and severe COVID-19 patients, selected six disease features to obtain the best performance in discriminating the two groups using a linear kernel support vector machine with mean accuracy of 91.38%, sensitivity of 0.90 and specificity of 0.94. Interestingly, calcium levels were included in those six features besides interleukin-6, high-sensitivity cardiac troponin I, procalcitonin, high-sensitivity C-reactive protein and chest distress [35].

3.2 Hypocalcemia and inflammatory response

Severe COVID-19 patients are characterized by a hyperinflammatory response with high levels of inflammatory and organ injury biomarkers, typically including C-Reactive Protein (CRP), lactate dehydrogenase (LDH), interleukin 6 (IL-6), procalcitonin (PCT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), D-dimer, and immune dysfunction markers such as lymphopenia and neutrophilia [1, 2, 33].

Interestingly, hypocalcemia and lower calcium levels were found strongly correlated with a more pronounced inflammatory response in COVID-19 patients. In fact, we firstly showed a negative association of calcium levels with LDH and CRP levels [16]. Moreover, hypocalcemic patients were characterized by higher LDH and CRP levels as compared to normocalcemic patients.

Furthermore, other following studies confirmed and extended our initial findings showing strong negative correlations between calcium levels and CRP, PCT, IL-6 and D-dimer, while a positive correlation with lymphocyte count was also reported [23, 25, 36].

3.3 Hypocalcemia and coagulopathy

COVID-19 extra-pulmonary manifestations include systemic and diffuse hematologic and thrombotic complications [37]. Symptomatic acute pulmonary embolism, deep-vein thrombosis, ischemic stroke, myocardial infarction or systemic arterial embolism were reported in up to 30% of patients [3].

Calcium ion plays a fundamental role in coagulation, platelet adhesion, contractility of myocardial and smooth muscle cells. It is required by clotting factors II, VII, IX and X, as well as proteins C and S for activation at the damaged endothelium [38]. In addition, calcium plays a role in stabilizing fibrinogen and platelets in the developing thrombus [38]. Moreover, acute coagulopathy is reported independently correlated with hypocalcemia and patients with severe prothrombotic status invariably present lower calcium levels [39].

D-dimer is a fibrin degradation product that increase during blood clot fibrinolysis resulting a useful marker of coagulopathy and it is typically increased in severe COVID-19 predicting worse outcomes [1, 2].

Confirming a possible strict relationship between hypocalcemia and coagulopathy, D-dimer levels and prothrombin activity were reported higher in hypocalcemic compared to normocalcemic COVID-19 patients [23, 25, 27] and a strongly negative correlation was found between serum calcium and D-dimer levels [23, 25], although, to date, no comparative data on thrombotic events in hypocalcemic and normocalcemic patients are reported.

3.4 Hypocalcemia and mortality

The rapid spread of COVID-19 pandemic caused a dramatic pressure on healthcare systems worldwide overloading hospitals resulting globally, on March 16th 2021, in 119,960,700 confirmed cases and 2,656,822 (> 100.000 only in Italy deaths), reported to WHO [40].

Higher risk of mortality is reported especially in male patients [41] with older age and/or affected by concomitant comorbidities, such as cardiovascular diseases, diabetes mellitus, obesity and active cancers [42–44].

Due to its strict relationship with inflammatory response and disease severity, also hypocalcemia has been associated with an increased risk of mortality. Hypocalcemia and lower calcium levels, at hospital admission, were significantly related to a higher risk of in-hospital short-term and 28-day mortality in several different study cohorts [16, 20, 22, 25, 26]. Moreover, low calcium negative impact was recently confirmed by Ko et al. in their artificial intelligence model of COVID-19 severity based on routine blood sample at hospital admission (EDRnet, ensemble learning model based on deep neural network and random forest models) [45]. In fact, inclusion of calcium in this model, provided a high sensitivity (100%), specificity (91%), and accuracy (92%) in predicting in-hospital mortality [45].

4 Pathophysiology

Several authors contributed to a better understanding of hypocalcemia in COVID-19 underlying diverse possible pathophysiological mechanisms and clinical determinants with related relevant implications in the management of patients affected.

In view of the dimensions of the observed phenomenon, it is likely that multiple mechanisms could underlie a so widespread finding in COVID-19 patients, a quite heterogenous population with different degree of severity, clinical background and disease outcomes [46].

To date, several potential factors have been hypothesized to play a role in determining hypocalcemia in COVID-19. Among them, we will shortly review calcium dependent viral mechanisms of action, high prevalence of hypovitaminosis D in general population, chronic and acute malnutrition during critical illness and high levels of unbound and unsaturated fatty acids (UFA) in inflammatory responses.

4.1 Calcium and virus interactions

Calcium ion (Ca2+) is one of the most ubiquitous molecules involved as signaling messenger in almost every aspect of cellular processes [47]. Ca2+ signaling regulates cellular processes modulating the activity of several calcium-sensitive components, including membrane receptors, ion pumps, transmembrane channels, intra and extra-cellular enzymes and nuclear transcriptional factors [48]. Ca2+ has been involved in almost every step of viral life-cycles, regulating virion structure formation, virus cell entry, viral gene expression, post-translational processing of viral proteins and virion maturation and release [47].

Structural characterization of SARS-CoV viral fusion peptides (FPs), the specific region of envelope S-glycoproteins that directly interact with target host cell membranes, revealed a calcium-dependent mechanism of action. Positive Ca2+ ions are able to bind, by electrostatic interactions, the conserved negatively charged and hydrophobic residues in both the FP1 and FP2 domains forming an extended FP1-FP2 "platform" to enhance membrane fusion [49].

Confirming that SARS-CoV infection could be highly dependent by the calcium action, EDTA, an extracellular calcium chelating agent, BAPTA-AM, an intracellular endosomal calcium chelator, and amiodarone, a drug that blocks endosomal/lysosomal calcium channels, are able to inhibit SARS-CoV infectivity and entry *in vitro* and *in vivo* assays [50, 51].

Extracellular and intracellular Ca2+ enhances also Middle East Respiratory syndrome coronavirus (MERS-CoV) particles infectivity and chelation of intracellular Ca2+ with BAPTA-AM and EGTA resulted in a marked infectivity drop [52].

The role of Ca2+ for viral fusion was explored also for other enveloped viruses such as Rubella virus (RuV) [53], Ebola virus (EBOV) [54, 55], human immunodeficiency virus type I (HIV-1) [56] and influenza A virus [50].

How this heavily calcium-dependent SARS-CoV-2 mechanism of action may affect serum calcium levels is yet unknown. However, it can be hypothesized that disruption in calcium homeostasis in patients with severe infection and high viral load may cause calcium depletion from blood circulation.

4.2 Hypovitaminosis D

At the beginning of COVID-19 spread in Europe, especially in the northern regions of Italy, Giustina and Formenti first reported on the risks related to the highly prevalent chronic lack of VD in Italian population, with a strong potentially negative combined impact on immune responses and calcium metabolism leading to increased vulnerability to COVID-19 in the Country [57].

In fact, since then high prevalence of VD deficiency in COVID-19 patients was reported by several studies [20–27]. Being VD involved in immunocompetence both regarding innate and adaptive immunity, [58] recent studies hypothesized that VD deficiency may predispose to SARS-CoV-2 infection and lower levels of VD could be linked to increased COVID-19 severity and worse outcome risks, although not all researchers confirmed these findings [21, 59–64].

Sun et al. reported in 26 COVID-19 patients a median 25-hydroxy-VD level of 10.20 (IQR 8.20–12.65) ng/mL, all affected by hypovitaminosis D [25]. The median serum calcium level in these 26 patients was 2.13 (IQR 2.03–2.16) mmol/L, and correlation analyses showed a positive association between calcium and VD levels. As a matter of facts, chronic hypovitaminosis D is known to alter calcium metabolism, reducing the absorption of calcium and phosphorus from the intestinal tract, and COVID-19 may predispose and exacerbate hypocalcemia occurrence in patients affected, particularly in those with hypovitaminosis D and severe infection.

4.3 Unbound and unsaturated fatty acids

Unbound and unsaturated fatty acids (UFAs) are generated by adipose lipolysis. They are typically found in high levels in the blood in critical illnesses such as severe lipotoxic acute pancreatitis [65, 66]. Several studies have shown a proinflammatory role of UFAs promoting cytokine storm, multisystem organ failure and acute lung injury [66, 67].

In support of the concept of UFAs production and their proinflammatory role in critical illness, elevated levels of UFAs were reported also in COVID-19 patients showing a positive association with disease inflammatory markers and severity [68, 69].

In patients affected by severe acute pancreatitis circulating UFAs can bind calcium ions and albumin, by ionic electrostatic interactions, causing and triggering calcium saponification, hypocalcemia and hypoalbuminemia [70, 71]. Sigh et al. hypothesized that a similar mechanism could occur also in COVID-19 patients, with increased levels of UFAs contributing to the genesis hypocalcemia, particularly in severe patients [72].

4.4 Undernourishment and malnutrition

In April 2020 a statement from the European Society of Endocrinology identified COVID-19 patients at high risk of undernourishment and malnutrition, mostly due to hyperinflammatory responses with release of great amount of cytokines, mechanical ventilation requirement and prolonged hospital stay with immobilization [4].

A recent editorial summarized data derived from three studies on overall 589 patients focused on weight loss and cachexia in COVID-19 [73–76]. Weight loss $\geq 5\%$ (that defines cachexia) was reported in the 37% of patients (range 29–52%). Forty-two percent of hospitalized patients was found at high risk of malnutrition, detected with Mini Nutritional Assessment score, and the 28% was considered malnourished. This negative nutritional balance, in addition to a widespread chronic hypovitaminosis D, could predispose to hypocalcemia occurrence in COVID-19 patients, especially during hospital stay.

5 Clinical-therapeutic implications of hypocalcemia in COVID-19

In view of the central role of calcium ion in virus life cycle, infection and replication, and of the negative influence on disease outcomes of hypocalcemia and hypovitaminosis D, a medical treatment specifically involved in this pathophysiological setting could be hypothesized to play a role in COVID-19 patients and in general population, in order to reduce SARS-CoV-2 infection risk and poor disease outcomes.

Treatment with Ca2 + channel blockers (CCBs), particularly the L-type CCBs diltiazem hydrochloride and verapamil, and with amiodarone, a multi-ion channel inhibitor, resulted in a significant decrease of infection rate in a dose-dependent mechanism in cell cultures of Ebola Virus, Influenza A virus (IAV) and Porcine deltacoronavirus (PDCoV), viruses with known calcium dependent mechanisms of infection [77–79].

A recent study reported that a panel of nine clinically approved CCBs inhibited the post-entry replication events of SARS-CoV-2 *in vitro*, while no effects were observed for the two other major types of antihypertensive drugs, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) [80]. Moreover, the authors reported on a retrospective clinical evaluation of 96 hospitalized COVID-19 patients with hypertension as the only comorbidity that treatment with CCB amlodipine besylate was associated with a decreased case fatality rate [77]. Furthermore, a retrospective multicenter cohort study including 3686 hypertensive COVID-19 patients showed a lower mortality risk in patients treated with CCBs compared

to those treated with other antihypertensive drugs and non-treated patients [81]. Conversely, a recent meta-analysis comprising 39 cohort studies and 14 case–control studies, including a total of 2,100,587 participants, observed no association between prior usage of antihypertensive medications including ACEIs/ARBs, CCBs, β-blockers, or diuretics and the risk and severity of COVID-19 [82].

Since UFAs possible influence on calcium levels and proinflammatory response in COVID-19 patients, El-Kurdi et al. suggested that calcium and albumin supplementation, by promoting UFAs bind and neutralization, may reduce lipotoxicity, mitochondrial dysfunction and multiorgans injury improving disease outcomes, as previously reported in severe pancreatitis patients [68].

VD treatment effectiveness in patients with acute respiratory infectious diseases and COVID-19 is still matter of debate [83–85]. In fact, Yamshchikov et al. in a systematic review of randomized controlled trials investigated the efficacy of VD in the prevention and treatment of infectious diseases reported that the strongest evidence was in reducing the risk of acute respiratory illness and influenza [86]. Moreover, Martineau et al. in a systematic review and meta-analysis of 25 trials, including over 11,000 patients, showed that VD supplementation reduced the risk of acute respiratory infections, particularly in VD deficient patients treated with daily or weekly doses but not with bolus doses [87]. Finally, a most recent meta-analysis of 42 randomised controlled trials, including 47,262 subjects, showed a VD protective effect against risk for acute respiratory infection for trials in which VD supplements were given daily but not for trials where VD was given weekly or monthly to 3-monthly [88].

Based on the above results, the scientific community suggested the possibility of a protective role of VD in prevention of SARS-CoV-2 infection and/or treatment of COVID-19 patients. However, to date, only few peer-reviewed observational studies and small randomized open label clinical trials of uncertain quality were performed, showing conflicting results [89–95]. In fact, Entrenas-Castillo et al. published a preliminary pilot study in Spain including 76 COVID-19 patients [93]. The study is based on the COVIDIOL trial protocol, a randomized double blinded controlled trial, on hospitalized patients randomized to hydroxychloroquine and azithromycin alone (N = 26) or with calcifediol. Calcifediol group received 0.532 mg of calcifediol on admission, 0.266 mg on days 3 and 7, and then weekly. Despite the baseline characteristics being similar between the two groups, the authors reported that only one out of the 50 patients receiving calcifediol required ICU admission while 50% of those in control group required ICU admission. A randomized placebo-controlled trial, conducted in India, included VD deficient asymptomatic or mildly symptomatic COVID-19 patients randomized to receive 60,000 IU/d of cholecalciferol (N = 16) or placebo for 7 days (N = 24) [94]. At the 14th day follow up, 20.8% of the participants in the placebo group became SARS-CoV-2 negative compared to the 62.5% in the intervention group. Finally, a very recently published multicenter double-blind randomized placebo-controlled trial, conducted in Brazil, randomized 240 hospitalized patients with moderate-to-severe COVID-19 to receive either a single oral dose of VD3 of 200,000 IU (N = 120) or placebo (N = 120) [95]. In this study, VD supplementation did not reduce length of hospital stay and did not improve COVID-19 related outcomes such as need for mechanical ventilation, ICU admission and mortality compared to placebo [95]. On the other hand, interestingly, Formenti et al. reported that osteoporotic women treated with VD did not seem to be at increased risk of severe COVID-19 despite treatment with anti-osteoporotic drugs potentially predisposing to both respiratory infections and hypocalcemia [96].

Besides possibly protecting from vulnerability to SARS-Cov-2 due its immunomodulatory actions, it can be hypothesized that VD supplementation in patients at high risk for COVID-19 living in largely VD deficient areas may also protect them from developing hypocalcemia [46]. This may be clinically relevant since hypocalcemia apparently predicts poor outcomes. Moreover, although not frequent we demonstrated that hypocalcemia may be severe [16, 17] and limiting the risks of severe acute hypocalcemia may protect from its related cardiovascular and neurological sequelaes potentially fatal in hospitalized patients with severe COVID-19 who are per se at risk of developing such complications [3].

Finally, since hypocalcemia is a frequent finding in hospitalized COVID-19 patients possibly predicting poor outcome and leading to acute complications if severe we think reasonable to measure in COVID-19 patients calcium levels on hospital admission, to monitor them thereafter during hospitalization and to provide adequate replacement treatment in those with moderate to severe hypocalcemia.

6 Conclusions

COVID-19 endocrine phenotype is becoming increasingly relevant in patients affected by SARS-CoV-2 infection. Among the endocrine features found in these patients, an emerging key role for an “Osteo-Metabolic phenotype” in COVID-19 was suggested potentially influencing infectious risk, inflammatory response and patients outcome.

As discussed in this review, hypocalcemia may represent a significant component of this novel phenotype. In fact, data in COVID-19 suggest a possible role of calcium levels as useful laboratory marker of disease aggressiveness that can be easily evaluated also in emergency situations helping

clinicians in recognizing severe COVID-19 patients. Therefore, assessing, monitoring and, if indicated, replacing calcium may be reasonable at first patient hospital evaluation and during hospitalization. Finally, VD replacement may be considered in high risk VD deficient patients [14] since it could have among other possible benefits a protective role from the occurrence of hypocalcemia in patients with COVID-19.

Declarations

Conflict of interest The authors have nothing to disclose and conflicts of interest.

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