



# The osteo-metabolic phenotype of COVID-19: an update

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## Abstract

**Context** In the multifaceted COVID-19 clinical scenario characterized by a multi-system disorder with negative implications not only on respiratory function but also on cardiac, hematological, neurological and endocrine-metabolic systems, a distinctive osteo-metabolic phenotype with an independent influence on disease severity and recovery of patients affected was early reported.

**Aim** To summarize and update the main evidences regarding the distinct components of this phenotype in acute and Long COVID-19, reinforcing its clinical relevance and discussing the main pathophysiological and clinical-therapeutic implications of the most recent reported findings.

**Results** This emerging phenotype is characterized by a widespread acute hypocalcemia and hypovitaminosis D with an impaired compensatory parathyroid hormone response, and a high prevalence of skeletal complications such as vertebral fractures. The clinical relevance of this osteo-metabolic phenotype on acute COVID-19 is well characterized, and novel seminal evidences are progressively highlighting its importance also in predicting patient's long-term outcomes and Long COVID-19 occurrence.

**Conclusions** These findings reinforced the central role of a multidisciplinary team, including endocrinologists, in evaluating these patients for a proactive search of each aspect of the osteo-metabolic phenotype components since they may represent suitable therapeutic targets to prevent SARS-CoV-2 infection, poor COVID-19 outcomes, Long COVID-19 occurrence and even possibly better responses to COVID-19 vaccination.

**Keywords** Osteo-metabolic phenotype · Vertebral fractures · COVID-19 · Hypocalcemia · Long-COVID · Vitamin D

## Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a long-lasting pandemic with a dramatic impact worldwide. During the early pandemic spread, several emerging findings have progressively defined COVID-19 as a multi-system disorder and not only as a respiratory disease, with negative implications on cardiac, hematological, neurological, gastrointestinal and, not surprisingly, also on endocrine and metabolic system [1–5]. Diabetes mellitus and obesity were early identified as frequent

comorbidities and independent risk factors for severe COVID-19 [6]. Thyroid and pituitary disorders were reported as disease complications possibly due to the inflammatory-(auto)immune dysfunctions and/or direct viral damage since the ubiquitous tissue presence of the angiotensin-converting enzyme 2 (ACE2), the main recognized receptor for SARS-CoV-2 entry [7–9]. In this multifaceted COVID-19 endocrine scenario, a distinctive osteo-metabolic phenotype with an independent influence on disease severity and recovery of patients affected, was early reported [10]. This phenotype is characterized by a widespread acute hypocalcemia, hypovitaminosis D with an impaired compensatory parathyroid hormone (PTH) response, and high prevalence of skeletal complications such as vertebral fractures (VFs).

Aim of this review is to summarize and update the main evidences regarding the distinct components of the osteo-metabolic phenotype in COVID-19, discussing main pathophysiological and clinical-therapeutic implications of the most recent reported findings and understanding if this

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finding in patients with acute COVID-19 predicting poor clinical outcomes, we find reasonable to measure in these patients calcium levels at hospital admission, and to monitor them during hospitalization. In particular, severe and acute hypocalcemia can represent a life-threatening emergency with possible negative cardiovascular and neurological complications potentially fatal in hospitalized patients with severe COVID-19 who are per se at risk of developing such complications [32]. Therefore, despite the absence of specific guidelines [33], it can be considered to provide an adequate replacement treatment in those with moderate to severe or symptomatic hypocalcemia according to published recommendations for treatment of hypoparathyroidism [34] which based on the severity of hypocalcemia range from oral calcium and Vitamin D3 or active Vitamin D (VD) supplements to intravenous calcium gluconate.

Finally, in COVID-19 survivors, more than 3 months after negative test for SARS-CoV-2, a non-significant difference in calcium levels was observed compared to healthy matched for age and sex subjects, possibly confirming the casual relationship between COVID-19 and hypocalcemia, and its transient nature once the patient recovered from the acute viral syndrome [35]. These data does not entirely support a routine estimation of serum calcium in all post-COVID-19 patients [36]. However, it appears reasonable to assess calcium and VD levels in the follow-up of patients with symptomatic hypocalcemia during the acute disease and eventually consider to supplement VD in those with persistently altered biochemical results.

## Hypovitaminosis D

A tight link between VD and COVID-19 was hypothesized from the early pandemic spreading due to the VD well known involvement in immune response and immunocompetence both regarding innate and adaptive immunity [37, 38]. VD is known to have antimicrobial roles and antiviral mechanisms of actions, and to regulate the adaptive immune response promoting a shift from proinflammatory to tolerogenic state downregulating the immune responses mediated by T-helper-1 lymphocytes cells, inhibiting the production of pro-inflammatory cytokines and promoting regulatory T cells maturation [39, 40].

Due to its important immune-modulating role and its widespread deficiency particularly in European Mediterranean Countries (which were heavily impacted by the pandemic), hypovitaminosis D was early reported as a possible risk factor for SARS-CoV-2 infection, severe COVID-19 and worse clinical outcomes. These only-observational findings were confirmed by several large systematic reviews and meta-analyses involving nearly 2 million adults, strongly suggesting the negative impact of hypovitaminosis D in COVID-19 patients [41–44].

In the light of the known pathophysiological role of VD and hypovitaminosis D underlying the main conditions and comorbidities related to severe COVID-19, such as older age [45], male sex [46, 47], diabetes mellitus [6, 48, 49], visceral adiposity/overweight/obesity [50, 51], and hypocalcemia, VD deficiency was suggested to represent the possible common denominator of the endocrine phenotype of COVID-19 [52], as confirmed also by the observational data reporting high prevalence of low VD levels particularly in older, male, diabetic and overweight patients [53, 54]. Given these data, VD was suggested to have a primary role in the prevention of infection and severe disease and reaching an adequate VD level especially in the population at high risk of both hypovitaminosis D and COVID-19 was recommended as a preventive measure [55, 56]. The effect of VD supplementation in general population and in COVID-19 patients was evaluated by several observational studies and randomized controlled trials, with different treatment strategies, reporting initially contrasting results. However, recent systematic reviews and meta-analyses concluded that VD supplementation was strongly effective in reducing rates of viral test positivity and COVID-19 severity [57–60].

Besides the above reported role of hypovitaminosis D in acute COVID-19, its function in patients' recovery after acute infection and in the pathophysiology of the Long-COVID or Post-acute COVID-19 syndrome characterized especially by neuromuscular, respiratory, and nutritional disorders [61, 62] is still poorly evaluated. VD is known to play key-roles in several metabolic pathways involved in musculoskeletal health [51], and, in previous studies, VD supplementation was proven to provide a muscle recovery benefit after intense physical and damaging stress [63–65]. VD levels were also reported to predict and influence illness duration and time until recovery after acute severe pneumonia [66]. To date, the VD role in Long-COVID occurrence was investigated by only few small studies. A recent pilot-study that included elderly patients after acute COVID-19 reported the efficacy of a six-weeks 2.000 IU/day cholecalciferol therapy vs placebo in reducing creatinine kinase values and in showing a positive improvement trend in the general and physical health status [67]. In two other recent studies, no associations between VD levels and the post-COVID symptoms were observed [68, 69].

Nevertheless, it is widely recommended that an appropriate nutritional status evaluation and a personalized dietary management, including VD supplementation, may represent one the best strategy to facilitate COVID-19 survivors' recovery [70].

Finally, based on the VD immunomodulatory effects, a possible role of hypovitaminosis D in regulating the anti-SARS-CoV-2 vaccination response and the possible VD deficiency-related vaccine side effects [71], should be

investigated, although recent findings on anti-COVID vaccination and previous studies on other vaccinations reported contrasting results [72–76].

### Impaired compensatory PTH response and hypoparathyroidism

Among the pathophysiological mechanisms underlying hypocalcemia occurrence in COVID-19, in addition to the high prevalence of VD deficiency, a not-adequate compensatory PTH response was recently proposed. VD is a crucial hormone for calcium homeostasis increasing its intestinal absorption and, in subjects with hypovitaminosis D, the increase in PTH (secondary hyperparathyroidism) generally maintains eucalcemia [77].

Severe acute hypocalcemia cases in COVID-19 patients due to the worsening of previous controlled postsurgical and/or primary hypoparathyroidism have been reported [11, 78], suggesting that hypocalcemia in COVID-19 could occur due the acute combination of low VD levels not adequately compensated by PTH response.

Interestingly, a recent study reported that hypocalcemia occurred prevalently in a context of a marked hypovitaminosis D not adequately compensated by secondary hyperparathyroidism, since, despite most of patients presented with quite severe VD deficiency and hypocalcemia, only one-fifth of them had secondary hyperparathyroidism [31]. Other observational studies seem to confirm this evidence: in fact, PTH median levels of 44.2 pg/mL were reported in 162 COVID-19 patients with VD levels below 20 ng/mL [79] and secondary hyperparathyroidism occurred in only 43.3% of 97 COVID-19 patients characterized by a median VD level of 21 ng/mL [80].

The mechanism underlying this impaired PTH response to hypovitaminosis D and hypocalcemia in COVID-19 is yet to be understood. Parathyroid gland function may be impaired during systemic inflammatory response with increased circulating cytokines [81]. In addition, respiratory alkalosis, typically observed in COVID-19, was reported to increase the PTH resistance at renal receptor level, resulting in hypocalcemia without increase in PTH levels [82]. Moreover, previous autptic studies conducted during SARS epidemic identified viral RNA and antigenic materials in parathyroid gland cells, and expression of ACE2 receptors in parathyroid glands cells has been, although not consistently, reported [83, 84]. Therefore, SARS-CoV-2 may potentially directly affect the parathyroid glands by binding the ACE2 receptors. Supporting this hypothesis, in the literature also three case reports of new-onset primary hypoparathyroidism due to SARS-CoV-2 infection have been reported [85–87]. Finally, both hypermagnesemia and severe hypomagnesemia were reported in COVID-19 patients [88, 89]. Since altered

magnesium levels may suppress PTH secretion it can be hypothesized that they may play a role in the determinism of functional hypoparathyroidism [90].

### Skeletal complications and vertebral fractures

Morphometric VFs are one of the most relevant clinical manifestations of osteoporosis and skeletal fragility and have been recently reported to be highly prevalent in COVID-19 patients [91]. In the literature, VFs are associated with decreased survival, reduction of respiratory function and impaired quality of life in the general population [91, 92].

In a previous study, COVID-19 patients presenting with VFs required noninvasive mechanical ventilation more frequently and their mortality rate was almost doubled compared to non-fractured patients [84]. Following studies conducted on different patient cohorts partly confirmed these data showing a high prevalence of VFs in COVID-19 patients and a negative influence of lower bone mineral density (BMD) on patient outcomes [93–95].

In fact, in hospitalized COVID-19 patients, several concomitant factors may lead to an increased fracture risk [96–99], such as advanced age and comorbidities including diabetes, cardiovascular diseases and hypertension [100].

Moreover, as reported above, hospitalized COVID-19 patients frequently show hypovitaminosis D, which is known to be associated with lower BMD and increased fractures risk [77]. However, in the available studies on VFs in COVID-19, VD levels were not so far reported.

VFs and decreased BMD are known to increase risk of pneumonia and to impair respiratory function leading to a restrictive pulmonary dysfunction in general population [101–103]. A very recent study, assessing the clinical impact of VFs in COVID-19 survivors on their medium term follow-up respiratory recovery, reported that patients with VFs, detected at hospital admission, had impaired respiratory function compared to those without VFs showing worse spirometric parameters and higher rate of pulmonary function tests abnormalities at six-month follow-up, despite patients in both groups presenting similar acute infectious lung involvement at hospital admission [104]. Therefore, VFs appear to also influence the medium-term impaired respiratory function of COVID-19 survivors which, in turn, may significantly influence their recovery and contribute to Long-COVID occurrence.

These findings suggest that VFs assessment at baseline may help in identifying patients at higher risk of worse clinical outcomes and those needing a more intensive respiratory follow-up. Moreover, patients showing persistent respiratory impairment without evidence of pulmonary



disease may benefit from a VFs assessment to prevent the vicious circle of further fractures and respiratory deterioration. Therefore, as anti-osteoporotic treatments, including denosumab, do not only appear to cause an increased predisposition to COVID-19 [105] but even seem to reduce disease risk [106, 107], they should be continued during the pandemic and vaccination campaigns to avoid an increased fracture risk, detrimental in the context of COVID-19 [108].

## Conclusions

In conclusion, in the context of the endocrine and metabolic complications of COVID-19, recent literature confirmed the existence, strengthening its clinical relevance, of a distinct osteo-metabolic phenotype which we originally and seminally reported. Specifically, it has recently emerged that high rate of acute hypocalcemia likely occurs in the context of a widespread hypovitaminosis D and of a not adequate compensatory PTH response possibly due also to a direct involvement of the parathyroids in SARS-CoV-2 infection. Moreover, high prevalence of VFs was recently highlighted not only as predictor of poor outcome in acute COVID-19 but also of inadequate respiratory recovery in COVID-19 survivors. The clinical relevance of the osteo-metabolic phenotype on short- and long-term outcomes of the disease confirms the important role of the endocrinologist in the COVID-19 multidisciplinary team [109] for proactive search of the different contributing components since they may all represent suitable therapeutic targets to prevent SARS-CoV-2 infection, poor COVID-19 outcomes, Long-COVID occurrence and even possibly better responses to COVID-19 vaccination.

**Author contributions** All authors contributed equally.

## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.

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