REVIEW

Hypovitaminosis D and the endocrine phenotype of COVID-19

Andrea Giustina [iD][1]

Abstract

Background Vitamin D and its deficiency have recently been suspected to be involved in increased susceptibility and negative outcomes of COVID-19. This assumption was based on the well known immunomodulatory actions of vitamin D and on the consistent finding of low levels of 25 hydroxyvitamin D (25OHD) in hospitalized patients with COVID-19. Moreover, several studies reported a correlation between 25OHD levels and different clinical outcomes of the disease.
Aim Aim of the current review was to approach the topic of vitamin D and COVID-19 from a different perspective summarizing the data which led to the evidence of the existence of an endocrine phenotype of COVID-19.
Conclusions This review analyzed in the light of the current knowledge the possibility that several endocrine manifestations of COVID-19 could be holistically interpreted in the context of an inadequate vitamin D status.

Keywords Vitamin D · Hypocalcemia · Vertebral fractures · Diabetes mellitus · Obesity · COVID-19

Introduction

COVID-19 has been immediately defined as an often severe respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) but with time important extrapulmonary involvement highly contributing to the lethality of the resulting syndrome has been described [1]. Despite the origin and first outbreak of the infection being apparently in China, Mediterranean Countries such as Italy and Spain have been rapidly involved in the pandemic and are currently paying the highest death toll to COVID-19 infection in the whole world. Specifically, in Italy deaths are reaching today the impressive number of 100.000, about 3% of the 3 millions of known affected citizens (covid19@-gimbe.org, March 2021). The most relevant extrapulmonary conditions which impact on the severity of the disease include mainly thrombotic complications leading to myocardial infarction and dysfunction with arrhythmias, but also renal, gastrointestinal, liver, central nervous system, eye, and skin complications have been well described so far [1]. Pathophysiological basis for these pleiotropic manifestations of COVID-19 is the expression of angiotensin-converting enzyme 2 (ACE2), the receptor responsible for the cellular entry of SARS-CoV-2, at the level of many tissues besides the lung mediating the multiple damages caused by this viral infection [2]. Additionally, endothelial damages at endothelial and vascular levels as well as deranged immune response are also key in determining the multifacet manifestations of COVID-19 [3].

In this complex and evolving scenario a major role for endocrine diseases has progressively emerged. In fact, with accumulating experience on the clinical presentation of the disease it shaped up what we can call an "endocrine phenotype" of COVID-19 with many endocrine organs, tissues, and molecules being at risk of direct or indirect alterations and, in turn, negatively impacting COVID-19 [4, 5].

Aim of this article will be to shortly review the major endocrine comorbidities as well as some other related factors associated with COVID-19 with an emphasis on hypovitaminosis D [6] also in the light of the latter being the possible link between all of them and therefore representing *phil rouge* of the endocrine phenotype of COVID-19.

Methods

For this narrative review and critical analysis of available evidence, literature searches were performed by author to identify new data in English language papers published

✉ Andrea Giustina
  giustina.andrea@hsr.it

[1] Institute of Endocrine and Metabolic Sciences, San Raffaele, Vita-Salute University and IRCCS Hospital, Milan, Italy

between January and December 2020, and indexed in PubMed. Search terms included "COVID-19" and terms associated with each topic, including "endocrine glands", "gender", "age", "diabetes", "obesity", "body composition", "vitamin D", "hypocalcemia", "vertebral fractures", "hypovitaminosis D".

Review of the evidences

Endocrine comorbidities and other conditions associated with COVID-19 severity

Aging and sex

Aging Besides sex, age appeared to be a key factor in viral lethality. In fact, mortality data from Italy clearly indicated that most deaths occurred after the age of 70 years old, with about half of them occurring in the age decade from 80 to 89 years [7]. In fact, it was initially supposed that the high lethality of COVID-19 in Italy could have been linked to the high number of elderly people leading to the unlikely assumption that Italians were dying with COVID-19 rather than for COVID-19 [8].

Sex From the beginning of the COVID-19 pandemic it appeared clear how the outcome of the disease was largely sex dependent. In fact, men and women appeared to be equally affected, but men were at higher risk of a more severe disease as compared to women with a similar pattern in different countries. In a highly impacted country such as Italy male sex was associated with a more aggressive disease and increased mortality risk [7].

Diabetes mellitus and diabetic retinopathy

Diabetes mellitus From the first days of the COVID outbreak it was clear that one of the most frequent comorbidities of hospitalized patients was diabetes mellitus. However, progressively, it became apparent that between diabetes and COVID-19 there could be a bidirectional relationship [9].

According to different case series diabetes is seen in patients with COVID-19 with a prevalence ranging from 7 to 30%. In term of outcomes, persons with diabetes with SARS-CoV-2 infection are at higher risk of hospitalization, severe pulmonary involvement, and mortality with respect to nondiabetic subjects [10]. Interestingly, in a retrospective, nationwide analysis of registries of 157,291 patients with adult community acquired pneumonia in Portugal, from 2009 to 2012, 23.7 to 28.1% presented diabetes as a comorbidity, but hospital mortality was only slightly higher in diabetic (15.2%) vs nondiabetic (13.5%) patients [11].

Poor glyco-metabolic control at admission and during hospitalization has negative impact on outcomes and levels of disease activity markers as interleukin (IL)-6 and D-dimer are higher in hyperglycemic vs euglycemic patients [12]. Pathophysiologically, chronically elevated blood glucose may negatively impact both humoral and innate immunity as well as associate with low-grade inflammation, which, in turn, may predispose to an excessive inflammatory reaction leading to acute respiratory distress syndrome. Hyperglycemia may also negatively impact on the lung inducing several structural alterations leading to increased alveolo-capillary permeability and collapse of alveolar epithelium; consequently, diabetes may worsen respiratory damages caused by COVID-19 [5].

Interestingly, recent evidence suggested that pancreatic β-cells, which express the ACE2 receptor, may be directly affected by SARS-CoV-2 causing a more severe hyperglycemia with frequent episodes of ketoacidosis and hyperosmolarity in need of high-dose insulin treatment. Moreover, newly onset diabetes in previously euglycemic subjects was consistently reported in patients with COVID-19 [9] pointing toward a potential diabetogenic effect of SARS-CoV-2 [12]. The transitory or permanent nature of hyperglycemia in COVID-19 as well as the real incidence and type of this newly onset diabetes are all currently matters of investigation and a global registry is collecting those cases worldwide in the frame of an international collaborative project called CoviDIAB [9].

Diabetic retinopathy Recently, the CORONADO study demonstrated that a composite microvascular diabetic damage index, which included severe retinopathy and/or diabetic food and/or nephropathy predicted early mortality in COVID-19 patients [13].

Interestingly, a recent monocentric cross-sectional study on 187 hospitalized patients with poorly controlled diabetes and COVID-19 found that retinopathy, as well as obesity, was positively associated with intubation. Moreover, at multivariate analysis retinopathy was independently associated with an increased risk for intubation with a statistically significant odd ratio slightly lower than 6. Due to the nature of the study, causal link or underlying mechanism of the association was not established. However, authors speculated that diabetic microangiopathy could have been a surrogate marker of a preexisting endothelial dysfunction/damage which may represent a risk factor for an increased severity of respiratory dysfunction in COVID-19 [14].

Obesity and body composition

Obesity increases risk for hospitalization, ICU admission, mechanical ventilation, and mortality in COVID-19 patients.

Moreover, excess in visceral adipose tissue may be a negative prognostic factor in people with COVID-19 [5]. Interestingly, acute sarcopenia [15] appears to often characterize survivors of COVID-19 [16].

In fact, particularly severe obesity was consistently reported as one of the major predictors of the need of hospitalization in COVID-19 due to the severity of pneumonia. Severe obesity was also associated with requirement of invasive ventilation and death in ICU [5, 17].

A recent meta-analysis, which included more than 45,000 patients [18], showed both at univariate and multivariate analyses that obesity was related to a significantly increased (approximately doubled) risk of severe COVID-19, with similar impact on all evaluated clinical outcomes (hospitalization, admission in ICU, need for mechanical ventilation, and death). Highest obesity-related risk at multivariate analysis was found for mechanical ventilation (odd ratio 2.63). Interestingly, visceral adiposity was found to be increased in severe vs non-severe COVID-19 patients and significantly associated with all evaluated clinical outcomes (need for hospitalization, mechanical ventilation, and ICU admission).

Pathophysiologically, the high impact of obesity on prognosis in COVID-19 patients is likely related to the deleterious effects of obesity on pulmonary function. In fact, obesity can negatively impact on several parameters of lung function such as expiratory reserve volume, functional capacity, and pulmonary compliance. Severe obesity is also associated with sleep apnea syndrome, which, in turn, is associated with increased cardiovascular risk [19]. Moreover, increased abdominal fat may impair diaphragmatic and respiratory function [20]. Obesity per se may also increase the risk of comorbidities already known to contribute to COVID-19 severity such as diabetes mellitus and atherothrombosis [21].

Interestingly, obesity is also known to be a state of low-grade inflammation linked to adipocyte hypoxia and impaired function and self-maintaining due to a recruitment of immune cells and macrophages related to baseline excessive secretion of pro-inflammatory cytokines such as tumor necrosis factor α, IL-1β, and IL-6 [22], which are, in turn, involved in the cytokine storm typical of COVID-19 and likely overproduced in obese vs lean subjects [5, 23].

Vertebral fractures (VFs)

Recently, we performed a study in order to assess presence and clinical impact of VFs on lateral chest X-rays in 114 COVID-19 patients. Interestingly, we found that VFs were highly prevalent and one of the most frequent comorbidities in our study population, as up to 35% of patients presented VF with previous diagnosis of osteoporosis in very few of them [24]. In particular, VFs demonstrated to be a strongly impacting prognostic element since overall mortality rate was found to be doubled in patients with vs without VFs and significantly higher in patients with severe VFs as compared to those with mild and moderate VFs.

Briefly, thoracic VFs [25] at hospital admission were detected in 41 of 114 patients (36%) and were prevalently mild but in 41% of the cases moderate or severe [26]. Age was significantly associated with VFs in multivariate analysis. Patients with VFs required more frequently hospitalization and noninvasive mechanical ventilation vs patients without VFs. Mortality was doubled in the VFs+ vs VFs− group (22 vs 10%) and statistically higher in patients with severe VFs compared to those with moderate and mild VFs [24]. No sex differences in the VF group were observed.

Pathophysiologically, we hypothesized that the high prevalence of VFs in COVID-19 could have been due to negative VFs impact on respiratory function since prevalent VFs were previously associated with impaired pulmonary (restrictive) function and increased risk of pneumonia in patients without previous lung diseases. It can be thought that VFs and their severity could be an objective clinical marker of frailty and worse outcome in COVID-19 [24].

Hypocalcemia

Currently, hypocalcemia has emerged as one major biochemical finding in COVID-19. However, all initiated with the report of a single patient with COVID-19 presenting with severe hypocalcemia with possible latent hypoparathyroidism due to previous total thyroidectomy [27]. Subsequently, in a large monocentric study on more than 500 patients with COVID-19 hypocalcemia was reported in three quarters of them [28]. In the same series, hypocalcemia also demonstrated a relevant clinical impact since calcium levels at initial evaluation were lower in finally hospitalized vs nonhospitalized patients, and hypocalcemia was found to be an independent risk factor for hospitalization [28]. Moreover, it is interesting to note the strong association between high LDH and PCR levels with low calcium levels [28]. A subsequent study reported double rate of hypocalcemia with lower calcium levels in clinically matched 20 hospitalized patients for COVID-19 vs 20 non-COVID-19 patients with acute respiratory diseases suggesting that hypocalcemia may be a distinctive feature of COVID-19 [29].

These findings were substantially confirmed in many following studies which demonstrated: (a) lower calcium levels in patients tested positive to SARS-CoV-2 RT-qPCR with respect to negative patients; (b) negative association between inflammatory parameters, as CRP and LDH levels, with calcium levels; (c) hypocalcemia as an independent risk factor for worse clinical outcome, including not only hospitalization as shown in our cohort but also ICU admission and mortality [30–32].

Pathophysiologically, calcium was already well known to play a crucial role in the mechanism of action of enveloped viruses such as SARS-CoV, MERS-CoV, and Ebolavirus, directly interacting with their fusion peptides and favoring their replication [33–35]. Moreover, hypocalcemia was frequently reported in hospitalized SARS-CoV and Ebolavirus patients [36, 37].

Hypovitaminosis D and COVID-19

Vitamin D (VD) is a steroid hormone produced by the skin when exposed to sunlight as cholecalciferol while nutritional intake does not contribute more than 20% of daily VD requirement if food is not fortified with VD [6]. Hepatic and kidney hydroxylation in positions 25 and 1, respectively, are necessary to produce active VD. Kidney 1 alpha hydroxylase is under control of endogenous PTH [38]. VD is crucial for the calcium and skeletal homeostasis in physiological and disease states [39]. It also has many systemic functions which are also known as extra-skeletal effects [39], including immunomodulation, most of which are based on solid experimental evidences and positive observational studies. Assessment of total 25OH VD is widely accepted as a marker of the VD status, with 25OH VD levels below 12 ng/mL representing deficiency and levels above 30 ng/mL sufficiency [40].

Since our letter of March 2020 in which we hypothesized that widespread hypovitaminosis D could have been responsible for the huge lethality of COVID-19 in Italy [8], several reports corroborated our assumption. In fact, patients with hypovitaminosis D at time of evaluation were shown to be at increased risk of testing positive for COVID-19 vs patients with sufficient status [41, 42]. Moreover, low 25OHVD levels on hospital admission have been shown also to be associated with COVID-19 disease stage and mortality [43, 44].

Vitamin D and SARS-CoV-2 positivity and COVID-19 severity

In a recent study from Armenia, slightly less than half of the hospitalized COVID-19 patients showed 25OH VD < 12 ng/ml, while average levels of VD were lower than those recorded in general population [45]. This correlation was reported to remain strong even after adjusting for potential confounding factors (age, gender, latitude, or ethnicity) [46]. Other studies confirmed lower levels of 25OHVD among COVID-19 patients [47]. Negative relationship between VD status and hospitalization risk, disease severity and biochemical activity as well as a double mortality risk were reported [48]. Interestingly, also in the few studies not confirming the relationship between VD status and SARS-CoV-2 positivity or COVID severity such as those based on UK Biobank ethnicity did show a significant impact at least in univariate analysis [49].

Of note, in another very recent study male patients with COVID-19 showed progressively lower 25OHVD and prevalence of hypovitaminosis D with advancing stage of the disease based on chest CT. Hypovitaminosis D was also significantly associated with mortality (with an odds ratio slightly < 4) independently of other demographical and clinical variables [50].

Vitamin D intervention in COVID-19

Very few data from controlled studies on role of VD supplementation in prevention and treatment of COVID-19 are available at present despite the relatively strong associative data mentioned above. In a Spanish pilot clinical trial, 76 consecutive patients hospitalized with COVID-19 and pneumonia were randomized to receiving the center-specific standard of care alone or combined with calcifediol. Interestingly, the need of ICU admission was much lower in the VD-treated group (2%) vs standard treatment (50%). In this latter group, two patients died vs none in the VD-treated group [51]. Unfortunately, blood 25OHVD values at baseline or during treatment were not available [51]. However, authors did point out that adults living in their specific area of Spain and season of the year are on average VD deficient [51]. Importantly, calcifediol is known to be able to quickly elevate blood 25OHVD levels [52].

Epidemiological evidence linking hypovitaminosis D and COVID-19

Interestingly, according to epidemiological evidence in Italy, as in other Mediterranean Countries, the prevalence of hypovitaminosis D is one of the highest in Europe. In fact, in elderly Italian women prevalence of VD deficiency was found in about 75% of them [53].

Change to an indoor lifestyle and lack of food fortification with VD is likely the main reason accounting for the higher prevalence of low circulating VD levels in Italy and in other Mediterranean Countries vs many other central and North European Countries in which this is systemically the rule from several decades due to the low sun exposure leading to what is defined Scandinavian paradox [54, 55]. In fact, a geographical overlap between high prevalence of hypovitaminosis D and elevated number and severity of COVID-19 cases has been observed [43]. A few other studies reported an association between COVID-19 prevalence and related mortality with latitude and consequent sunlight availability [56]. Importantly, home confinement is the most used measure in order to prevent the spreading of SARS-CoV-2 infection but the drawback of this extremization of the above mentioned progressive changes in

lifestyle may be the worsening in the VD status in already at huge risk patients particularly in heavily VD-deficient countries [54].

Pathophysiological evidence linking hypovitaminosis D and COVID-19

Hypovitaminosis D was suggested to be linked to systemic infections and impaired immune response or even autoimmune diseases [39]. Moreover, a recent meta-analysis reported that VD supplementation can prevent respiratory infections [57].

VD is a negative modulator of renin–angiotensin–aldosterone system and through ACE2 downregulation may mitigate clinical manifestations of COVID-19 [58]. Moreover, since vitamin D-binding protein (VDBP) [59] may be involved in ARDS [60] through association with actin, CD44, and annexin A2 [61, 62] in the presence of low VD levels in the blood an increased availability of VDBP for complement and neutrophil activation may be observed [63, 64].

VD has also been hypothesized to be key in counteracting the cytokine storm characteristic of severe COVID-19 [6]. Mechanistically, VD may modulate production of pro-inflammatory cytokines [65, 66]. Moreover, active VD regulates T-cell differentiation vs Th2 phenotype [67] with anti-inflammatory effect in the cytokine storm of COVID-19 [68].

Finally, in severely compromised patients independently from their ICU admission, very low levels of 25OHVD were reported [69] and it was hypothesized that since poor VD status may negatively impact the outcome of ICU patients supplementation with high doses of VD could reduce their morbidity and mortality [70].

Hypovitaminosis D in endocrine comorbidities and conditions associated with COVID-19 severity

In this section, we will review the evidence that allow to hypothesize that low VD could be the link between age, sex, endocrine comorbidities, and increased susceptibility to severe COVID-19.

Aging and sex

Aging Advancing age impairs skin ability to synthesize cholecalciferol [71]. Moreover, emphasis on avoiding sun irradiation in order to prevent skin cancer progressively increased [72]. Combination of these factors may cause poorer VD status in older vs younger subjects [73]. In fact, some, but not all, studies showed lower 25OHVD levels with aging [74]. In this regard, a meta-analysis on 33,000 individuals reported that those aged > 75 years to had lower 25OHVD vs those aged 65–75 years [75]. However, despite many national surveys did not find huge age-dependent differences in 25OHVD

or in prevalence of VD deficiency [76], institutionalized older adults were reported to be at greater risk for VD deficiency [77]. Consequently, the Institute of Medicine, as well as the International Osteoporosis Foundation, recommended higher dietary intake of VD (800–1000 IU/day) for people older than 70 years of age vs that recommended for younger subjects (600 IU/day) [78, 79].

Sex Interestingly, VD is still mainly used in patients with osteoporosis, the vast majority of whom are post-menopausal women. In fact, in a recent study on patients with COVID-19, of the 59% VD-deficient subjects on admission the majority were males (67%) [50].

Therefore, it can be hypothesized that greater prevalence of hypovitaminosis D can be a predisposing factor to major vulnerability to COVID-19 in older men vs older postmenopausal women [80]. Our preliminary data suggested that women older than 50 years under pharmacologic treatment for osteoporosis were not at increased risk of either symptomatic or severe COVID-19 [81]. Interestingly, most of the patients were on VD in combination with bone protective agents [82–84]. Therefore, it was hypothesized that female patients with osteoporosis could have been somewhat protected from COVID by VD as part of the pharmacologic bone sparing treatments.

Diabetes mellitus and diabetic retinopathy

Diabetes It was widely reported that patients with type 2 diabetes had low 25OHVD levels [85]. Interestingly, in an observational Italian study postmenopausal diabetic women showed significantly greater prevalence of severe VD deficiency vs control subjects (39% vs 25%, respectively) [86]. In fact, reduced 25OHVD levels were hypothesized to be involved in the pathophysiology of diabetes-related skeletal fragility [87]. Recently, low circulating VD was reported to be associated with poor glycemic control in diabetic patients [88]. Moreover, large prospective studies suggested that low VD may predispose to a higher risk of developing impaired fasting glucose and diabetes [89, 90].

Recent studies and a meta-analysis of randomized trials showed that VD supplementation in diabetes can improve HbA1c, insulin resistance, and insulin secretion [91, 92] as well as fasting glucose particularly when glyco-metabolic control is poor [93].

Some studies also suggest that VD treatment may slow the progression to diabetes in either patients at high risk of diabetes or with prediabetes, specifically in those with low baseline 25OH VD [94]. Very recently, it was also reported that black people with diabetes and COVID-19 are more likely to be hospitalized and die than white ones [95].

Although convincing data on VD levels in the diabetic subgroup of COVID-19 patients in particular are not yet

available [96], it can be hypothesized that lack of VD may be detrimental or even causal in the bidirectional relationship between diabetes and COVID-19 increasing synergistically the vulnerability of diabetic patients to the infection as well as facilitating the diabetogenic action of COVID-19.

Diabetic retinopathy (DR) An inverse relationship between presence and severity of DR, and VD concentration is well established with lowest levels in proliferative DR and highest in diabetic patients without DR [97]. In cross-sectional studies, confirmed by meta-analyses from available observational studies, prevalence of DR was reported to be double in VD-deficient vs VD sufficient patients and DR was associated with VD deficiency. As well, higher prevalence of severe and mild DR in poorly controlled diabetic subjects with low vs normal VD and association between VD deficiency and DR severity (OR: 2.22; 95% CI: 1.36, 3.65) was found [98–101]. Interestingly, sub-analysis of the Field and Rotterdam prospective studies showed that subjects with hypovitaminosis D had a higher cumulative incidence of microvascular events and were at increased risk for DR, respectively [102, 103].

Pathophysiologically, an association between VD and vascular function has been described in patients with diabetes [104]; moreover, a report described improved vascular function parameters in patients with diabetes, after VD oral supplementation [105]. Furthermore, patients with diabetes and VD deficiency had reduced endothelium-dependent microvascular function [106]. It is noteworthy that VDR is expressed in endothelial cells (EC), pericytes, and vascular smooth muscle cells and suppression of VDR in EC alters vascular homeostasis [107].

Therefore, it can be hypothesized that low VD, which characterizes diabetic patients with retinopathy, can be a common denominator of the microvascular damage in COVID-19 of which, in turn, diabetic retinopathy may be an epiphenomenon.

Obesity and body composition

Low levels of 25OH VD were very frequently found in obese nondiabetic particularly elderly subjects being inversely related to BMI and adiposity [73, 108], with negative effects on bone and muscle health. Interestingly, VD deficiency was also reported to be associated with decreased muscle mass and function thereby predisposing to an obese osteosarcopenic phenotype which is also observed in patients with prostate or breast cancer under medical treatment [109, 110].

Therefore, VD may be considered key for maintaining of an healthy body composition protecting from obesity and sarcopenia. However, only a few and generally not adequately powered randomized trials tested efficacy of VD

supplementation on weight loss in obese subjects [111]. A recent meta-analysis which included more than 17,000 persons showed that circulating VD was inversely associated with body fat mass [112]. Interestingly, resistance to VD in overweight and obesity was recently reported in hypoparathyroid patients [113].

Pathophysiologically, despite the above reported epidemiological evidence the mechanisms underlying association between VD and obesity are still debated. Interestingly, it has been suggested that VD may exert a protective effect in obese individuals, by reducing systemic inflammation [114]. Adipose tissue is a direct target of VD, as confirmed by the presence of VDR in both subcutaneous and visceral adipocytes. In fact, VD has been suggested to play a role in modulating fat distribution and activity [115].

A direct relationship between VD status, body fat, age, and SARS-CoV-2 infection and COVID-19 outcomes has been suggested. In fact, fat accumulates with aging, and sequestrating active VD decreases its bioavailability and action [116]. Therefore, very low VD levels in obese subjects may be associated with more severe COVID-19 and eventually worsen the prognosis in those subjects admitted to ICU due to enhanced baseline inflammatory state. Low VD levels may also play an important role in the preservation of body composition also in the recovery phase post COVID-19.

Vertebral fractures

Low VD has been traditionally linked with low bone mass and increased risk of fractures. The VD-related increase in BMD of the hip was observed to be larger in young vs older adults [117]. Two recent randomized trials confirmed a positive effect of VD supplementation on BMD in subjects with low baseline VD [118, 119]. Several long-term studies also found an association between poor VD status and fractures in elderly people [120]. Also, a few trials reported that VD either alone or more effectively when combined with calcium determined a significant decrease of fracture incidence [121–124].

Overall, the available meta-analyses showed that the bone protective effects of VD were greater in institutionalized VD-deficient older subjects at sufficiently large dose (at least 800 IU/day) [125]. The Cochrane systematic review and meta-analysis showed that combined VD and calcium supplementation may obtain a decrease in hip fracture and non-VF risk around 15% [126]. In a Chinese study, women with morphometric VFs and hypovitaminosis D had higher PTH levels and more frequently secondary hyperparathyroidism as compared to fracture-free controls [127]. No trial/meta-analysis is available on VD and VFs but it can well be hypothesized that those COVID-19 patients by us observed bearing VFs at hospital admission could have been predisposed to these skeletal events by low levels of VD.

Hypocalcemia

Active VD acts on the small bowel to increase intestinal calcium absorption. VD deficiency leads to a compensatory increase in PTH to maintain calcium levels with the clinically relevant exception of patients with hypoparathyroidism [128–130]. Severe forms of VD deficiency can cause hypocalcemia and rickets/osteomalacia. Milder forms of VD insufficiency also can negatively affect bone via secondary hyperparathyroidism [39].

Interestingly, several studies showed that not only in patients with postsurgical hypoparathyroidism [26] but also in cases of blunted PTH secretion or impaired compensatory feedback mechanism low levels of VD may be associated with hypocalcemia. In fact, in prospective studies on patients undergoing thyroid surgery, positive correlation between preoperative VD deficiency and postoperative hypocalcemia is not necessarily linked to low PTH [131].

In fact, since intestinal calcium absorption is impaired in VD-deficient subjects, maintenance of eucalcemia depends mainly on the compensatory increase in PTH level, which mediates bone and renal calcium reabsorption. In the case typically observed in the post-thyroidectomy period of blunted PTH compensatory response even mildly vitamin D deficient patients can present severe hypocalcemia. Recently, no differences in PTH levels between VD-deficient and sufficient COVID-19 patients were observed [132] pointing toward an hypothesis of possibly impaired PTH compensatory response in such patients which, in turn, might result in hypocalcemia in pre-COVID-19 VD-deficient subjects

It has also been previously reported that particularly in COVID-19 elevated levels of pro-inflammatory unbound and unsaturated fatty acids (UFA) may cause hypocalcemia binding calcium [133].

Pathophysiologically, it is unlikely that one single mechanism could be able to explain a widespread finding such as hypocalcemia in a quite heterogeneous COVID-19 population with different degrees of severity and clinical manifestations [5]. In fact, we can hypothesize that low VD may act in synergism with factors directly predisposing to hypocalcemia such as calcium dependent viral mechanisms of action, enhanced cellular permeability to calcium ions and the increase in UFA as well with other still unexplored indirect mechanisms leading to a possibly blunted PTH response to hypocalcemia [134].

Conclusions

Hypovitaminosis D is a dangerous widespread condition particularly in the time of COVID-19 pandemic. In fact, it could be directly linked to an increased predisposition to SARS-CoV-2 infection as well as to an increased severity of COVID-19. This negative effect may be exerted directly through the lack of immunomodulating and vasoprotective actions of VD. Importantly, we have shown in this piece that most of the known conditions and endocrine comorbidities which associate with severe outcomes of COVID-19 are characterized or caused by low VD levels. Although data clearly relating low VD levels to the negative impact of these comorbidities are largely lacking, it seems reasonable to grant through appropriate supplementation an adequate level of VD to all patients bearing these comorbidities in a clinically sound, and largely safe, attempt to improve the endocrine phenotype of COVID-19.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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