Endocrine
https://doi.org/10.1007/s12020-020-02407-0

VIEWPOINT

The D-side of COVID-19: musculoskeletal benefits of vitamin D and beyond

Flavia Tramontana[1] · Nicola Napoli[1,2] · Ghada El-Hajj Fuleihan[3,4] · Rocky Strollo[1]

Received: 7 June 2020 / Accepted: 26 June 2020

Abstract

Coronavirus 2019 disease (COVID-19) mostly adversely affects the elderly, a population at higher risk for low serum 25-hydroxyvitamin D (25(OH)D) levels. In this viewpoint, we highlight the well-known musculoskeletal properties of vitamin D, which are particularly relevant in the context of COVID-19, suggesting further potential benefits through extra-skeletal effects. Maintaining optimal 25(OH)D is crucial to prevent falls, frailty and fractures in elderly patients, with low activity levels due to lockdown, or who are relatively immobilized during hospitalization and after discharge for prolonged periods of time. Hypovitaminosis D is also associated with susceptibility to respiratory infections, admissions to the intensive care unit, and mortality. We underscore the importance of achieving desirable serum 25(OH)D in COVID-19 elderly patients, to ensure beneficial musculoskeletal effects and possibly respiratory effects of vitamin D, in the context of COVID-19.

Keywords COVID-19 · Vitamin D · Elderly · Frailty · ARDS · Fractures

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic has repositioned healthcare front and center and rendered prevention and treatment strategies a foremost global priority. COVID-19-associated mortality and morbidity increase with age (https://www.cdc.gov/coronavirus/2019-nCoV/index.html). Overall, 45% of hospitalizations, 53% of intensive care unit (ICU) admissions, and 80% of deaths associated with COVID-19 were among the elderly (https://www.cdc.gov/coronavirus/2019-nCoV/index.html). Serum 25(OH)D level is the best index of vitamin D nutritional status [1]. Hypovitaminosis D is highly prevalent in the elderly because of the impaired ability to synthetized vitamin D by the skin, limited sun exposure and malabsorption [2, 3].

The putative beneficial effect for vitamin D in COVID-19 patients is based on in vitro and in vivo evidence regarding its role as musculoskeletal and immune modulator, and its efficacy in co-morbidities these patients commonly suffer from, notoriously pulmonary complications. Patients affected with COVID-19 undergo prolonged hospitalization, are more likely to require ICU admission, and relative or complete immobilization. Full recovery and resumption in activities of daily living may take weeks following discharge. The elderly normally experiences a progressive age-related decline in muscle function. Immobilization exacerbates this process through a fast reduction in protein synthesis by 30%, lower extremity lean mass by 6.3% and muscle strength by 15.6% [4]. The end result of muscle loss is an impairment in daily living activities after discharge and a potentially increasing risk of falls, fractures and death [4]. Acute and chronic immobilization also promotes bone resorption [5] and it is likely that elderly, the large proportion of COVID-19 patients, will experience even more severe bone loss due to hypersecretion of inflammatory cytokines [6] and treatment with high doses

Supplementary Information The online version of this article (https://doi.org/10.1007/s12020-020-02407-0) contains supplementary material, which is available to authorised users.

✉ Nicola Napoli
n.napoli@unicampus.it

✉ Ghada El-Hajj Fuleihan
gf01@aub.edu.lb

[1] Unit of Endocrinology and Diabetes, Department of Medicine, Campus Bio-Medico University of Rome, Via Alvaro di Portillo 21, 00128 Rome, Italy

[2] Division of Bone and Mineral Diseases, Washington University in St Louis, St Louis, MO, USA

[3] Calcium Metabolism and Osteoporosis Program, American University of Beirut, Beirut, Lebanon

[4] Scholars in HeAlth Research Program (SHARP), American University of Beirut Medical Center, Beirut, Lebanon

Published online: 06 July 2020

of glucocorticoids. The detrimental effect on bone mass that ensues may result in bone loss, frailty and a higher risk of fractures [7]. Vitamin D replacement, combined with calcium, has been shown to be effective in reducing fracture risk. The most consistent protective effect is in reducing the risk of hip fracture by 16–33%, and of any fracture by 5–19%, compared to placebo or control [8]. This effect is demonstrated when combining trials in community-dwelling and institutionalized individuals but it is likely driven by data from institutionalized individuals, as consistently shown in three meta-analyses [8]. Importantly, hip fractures incur mortality rates as high as 15–30% within 1–3 years, and half of subjects lose functional independence [9]. Vitamin D also has a direct effect on muscle health by improving muscle strength and function [10, 11]. These muscular benefits of vitamin D should be also translated into a reduction of risk of falls. Although results from meta-analyses on the effect of vitamin D on falls are variable, they are explained by differences in interventions, populations of interest and trial duration. Importantly, the 2018 Cochrane meta-analysis on interventions for fall prevention demonstrated a 28% risk reduction in the rate of falls with vitamin D supplementation in patients in care facilities [12]. The projected beneficial effects of vitamin D on muscle and bone in COVID-19 patients would ultimately translate into a reduction of risk of falls and fractures, throughout hospitalization and rehabilitation.

Specific extra-skeletal properties of vitamin D cannot be ignored [13]. COVID-19 infection is characterized by an increase in pro-inflammatory cytokines, that in severe cases triggers the dreaded "cytokines storm" leading to lung as well as systemic inflammation. Elevated serum levels of interleukin-6 and other pro-inflammatory cytokines are hallmarks of systemic inflammation of COVID-19, which is associated with disease severity and adverse clinical outcomes [14]. Therefore, modulation of inflammatory response has been suggested as a potential therapeutic strategy [15]. Vitamin D may modulate inflammatory response through its effects on innate and adaptive immunity [16]. Calcitriol, the active vitamin D metabolite, targets macrophages, activated B and T cells, through vitamin D receptors, and induces immunoglobulin and cytokine production [16, 17]. It is also involved in the toll-like receptor (TLR) 2/1 pathway [16]. Although the pathophysiology of the virulence of Coronaviruses is unfolding, TLR2 is known to recognize also viral proteins, and therefore may be potentially involved in the cellular pathway leading to COVID-19 pulmonary complications.

Low serum concentration of 25(OH)D is associated with impaired respiratory health and increased susceptibility to acute respiratory infections [18]. Sixty-seven to 85% percent of patients with COVID-19 experience acute respiratory distress syndrome (ARDS) which represents one of the leading causes of mortality (https://www.cdc.gov/coronavirus/2019-nCoV/index.html). Previous studies have found that vitamin D deficiency was ubiquitous in patients with ARDS while serum $1,25(OH)_2D$ was higher in those who survived compared to non-survivors [19]. A meta-analysis of 25 randomized controlled clinical trials showed that vitamin D supplementation prevents acute respiratory infections by 12% (adjusted OR:0.88, 95% CI 0.81–0.96), mostly in those with low 25(OH)D levels at baseline (adjusted OR:0.58, 95% CI −0.40 to 0.82) [18]. In chronic obstructive pulmonary disease, a risk factor for COVID-19 complications, muscle weakness is associated with poor prognosis independently of lung function [20], and could improve with vitamin D. Vitamin D deficiency is common in critically ill patients and associated with disease severity, higher mortality and reduced survival time in ICU [21]. Likewise, in patients with pneumonia vitamin D deficiency resulted in a higher risk to ICU admission and mortality [22]. In a retrospective observational study on 655 ICU patients, an increased chance of survival was reported in those with 25(OH)D > 20 ng/mL compared to those with vitamin D deficiency [23]. In a randomized double-blind, placebo-controlled trial in critically ill patients with vitamin D deficiency, high-dose vitamin D did not reduce hospital length of stay, hospital mortality, or 6-month mortality. However, investigators observed a lower hospital mortality in the severe vitamin D deficiency subgroup (25(OH)D ≤ 12 ng/mL) [24].

Taken together all these data may suggest a broader potential of vitamin D [25]; while effects on muscle-skeletal outcomes have been largely proved, potential benefits on the immune system require more evidence.

In conclusion, reaching an optimal vitamin D status will be beneficial for COVID-19 patients in order to prevent falls, frailty, and fractures either during and after hospitalization. Preventive measures should include also supervised physical activity, adequate intake of calcium, and other micronutrients, which are known to improve bone mass and sarcopenia also in the elderly and frail subjects [26–29].

We recommend daily or weekly regimens with 800 IU/day of cholecalciferol (or equivalents) [30, 31]; higher doses, if needed (for e.g. if vitamin D deficiency), should be given according to the local guidelines, and provided they do not exceed the upper tolerable level of 4000 IU/day [32]. Lessons learned from large trials teach us that more is not better, and that bolus doses can be harmful, increasing bone resorption and fall risk [33]. On-going vitamin D trials will inform best practices on optimal dosing for patients with COVID-19 and will provide the needed evidence for proving its putative beneficial effect on immune-modulation and respiratory function.

Facing the COVID-19 pandemic, many clinical services including osteoporosis outpatient clinics, rehabilitation facilities have been closed. It is crucial to intensify efforts to improve the current management of muscle and bone health in COVID-19 patients, and strive to restore functional ability and quality of life [34].

Acknowledgements The authors thank Drs Aya Bassatne, Maya Basbous, Ola El-Zein, and Mrs Maya Rahme for their contributions to the literature search and screening of relevant papers retrieved.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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