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Can vitamin D positively impact one or more post-acute-COVID-19 syndrome musculoskeletal and cognitive complications?

Abstract

The coronavirus disease known as COVID-19 has persisted in various forms now for three years without any major reduction on its detrimental health outcomes. This mini review highlights some aspects of the condition now known as the post-acute or long COVID-19 syndrome that has recently been seen to emerge among a fair percentage of COVID-19 survivors. It asks whether efforts to ensure vitamin D intake or exposure levels can impact one or more manifestations of the post-acute COVID-19 syndrome in some way. Using the key words: Vitamin D, Long COVID or Post-acute COVID-19 the PUBMED, PubMed Central, and Google Scholar were explored for articles of relevance. Described in narrative form, these data reveal that while this topic has not yet been articulated to any degree in most management articles as of December 2022, the challenges to musculoskeletal health alone of post-acute COVID-19 appear to warrant its due consideration.

Keywords: coronavirus, long- COVID -19, post-acute COVID-19, vitamin D

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Ray Marks
Department of Health and Behavior Studies, Teachers College, Columbia University, USA

Correspondence: Ray Marks, Department of Health and Behavior Studies, Teachers College, Columbia University, USA, Tel 2126783445, Email Rm226@olumbia.edu

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Introduction

In December 2019, an unexpected and deadly corona type virus that was later termed COVID-19 was reported to have spread from its origins in Wuhan, China to become a global epidemic.[1] Now, almost three years later, the persistence of this virus remains evident, even though it is in a transmuted form. Indeed, despite hundreds of thousands of articles published since 2019 and efforts to understand its origins and prevention, and while somewhat attenuated, COVID-19 disease remains a serious global health issue throughout the world. At the same time, a subgroup of children and adults who have duly survived one or more acute bouts of COVID-19 disease have now been found to remain variably impaired physically and mentally by the prolonged impacts of the disease, now known as 'long or post-acute COVID-19' syndrome,[2–5] which can persist for up to one year, but possibly longer, as the condition and its outcomes manifest over time, and especially among cases in the higher age ranges who may already suffer multiple related symptoms.[6]

To date, while articles vary, among the multiple health complications that have been documented are persistent symptoms of: fatigue, shortness of breath, coughing, joint and chest pain, muscle aches, headaches, and a cognitive condition termed 'brain fog'.[1,3,6–8] At the same time, organ specific COVID-19 disease targets include those of the cardiovascular system, kidneys, lungs, neuromuscular system.[7] Unsurprisingly, there are long-term effects on physical and leisure time function as well as mood among a sizeable number of cases who are no longer deemed in acute danger, along with possible symptoms of depression, anxiety and concentration challenges.[8,9]

In particular, long COVID may occur in those cases who sustained an acute bout of COVID-19 for nutritional reasons, especially with regard to nutrients such as vitamin D. Indeed, due to its well established anti inflammatory and many life affirming biologically crucial mediating properties,[10,11] a role for the presence of adequate vitamin D serum levels appears quite strong, even though one report indicated that persistent fatigue and reduced exercise tolerance following COVID-19 are independent of vitamin D,[12] rather than being an antidote for fostering a more rapid and full or substantive return to the patient's pre COVID-19 health status or for ameliorating or preventing COVID-19 infections directly[13,14] in those cases with poor nutritional and sunlight access[15] who may be highly susceptible to the consequences of a vitamin D deficiency.[16] On the other hand, vitamin D, an immunomodulatory hormone with proven efficacy against various upper respiratory tract infections has been shown to inhibit hyperinflammatory reactions and accelerate healing, especially in lung tissue.[1]

It is also found to impact COVID-19 disease severity and mortality rates, with a high prevalence of a deficiency being observed in a fair number of patients suffering from acute with COVID-19 illness and respiratory failure.[17] As well, vitamin D sufficiency may promote muscle function and reduce pain, while enhancing sleep and cognition favorably, as well as being instrumental in mitigating COVID-19 infections, plus its long term disease burden.[18,19]

Using the PUBMED database and others, the present scoping review provides a snapshot of past work as well as current trends in this regard. The rationale for focusing on vitamin D is its known potential as far as both COVID-19 infection exposure, as well as the ability to attenuate various pre-existing clinical conditions goes[16] including obesity, depression, and anxiety, and a failure of medicine to currently prevent COVID-19 effectively.[20,21] On the other hand, since many youth as well as adults suffer from a vitamin D deficiency, supplementation of this vital nutrient or exposure to adequate sunlight or both, along with nutrients containing vitamin D may help to prevent or reduce complications associated with COVID-19 disease, including its severity.[22]

Clearly, if found beneficial in any way, vitamin D applications could have far-reaching positive effects in the realm of the emergent long COVID complications that have been unanticipated, and in the current state of a failure of public health efforts to mitigate its spread,[23,24] even if negated by some.[12]

Methods

To obtain the data for this review, the electronic data sources PUBMED, PubMed Central, and Google Scholar were carefully

searched using the key words, COVID -19 [syndrome, symptoms, review], long COVID and its management, vitamin D, coronavirus, older adults, and post-acute COVID-19 syndrome. All forms of study or analysis were deemed acceptable. However, no in depth or consistent analyses concerning long term COVID disease and a role for vitamin D supplementation could be readily identified. As a result, a narrative summary of key data published between 2020 and 2022 including case studies, and uncontrolled observations was implemented. Selected material had to focus on long COVID issues and/or vitamin D related facts relevant to COVID infection risk and recovery. Excluded were articles that did not focus specifically on this set of issues and non English based articles. Preprints were used to highlight the possible scope and updated findings concerning this present topic, rather than for prescribing clinical guidelines.

Results

General findings

Of the more than 316,175 PUBMED listed publications on COVID -19, published as of December 13, 2022. Of these, 21, 788 were located when using the term Long COVID-19, 20, 5303 when using the terms long COVID syndrome, and 7,480 referred to long COVID-19 symptoms, with 78 that appeared linked to vitamin D. Very few additional articles were found on the additional web sites and a sizeable number were review rather than clinical trial studies. Excluded were articles discussing review protocols of vitamin D usage in the context of COVID-19.

Key findings

Multiple articles report that a high rate of vitamin D deficits exists among various cases deemed COVID-19 positive. In addition, many report a probable vitamin D deficit that raises the risk of more severe infection responses than not,[25,26] although this is not an accepted fact to any degree. However, other data are supportive of this aforementioned view because they show that there does appear to be a high rate of deficient vitamin D levels in the acute or post-COVID-19 studied groups although this is not well correlated or consistent.[27–32] Carpagnano et al.,[33] found 81% of their COVID-19 cases to be vitamin D deficient, and patients with a severe vitamin D deficiency reportedly had a 50% chance of dying, while those with adequate vitamin D levels, had lower death rates at 10 days.

What is less well studied is any link between symptoms of persistent fatigue and/or the cognitive impairments of a debilitating nature found in Long COVID-19 cases.[34–37] As in the case of acute COVID-19, long COVID-19 can also involve multiple organs and affect many body systems including, but not limited to the respiratory, cardiovascular, neurological, gastrointestinal, and musculoskeletal systems that require vitamin D for biological purposes. Although Huang et al.,[38] found that at six months after an acute infection, COVID-19 survivors examined appeared to be most troubled by feelings of fatigue or muscle weakness, sleep difficulties, and anxiety or depression, no link to vitamin D was forthcoming. Patients who were more severely ill during their COVID-19 hospital stay and found to have more severely impaired pulmonary diffusion capacities and abnormal chest imaging manifestations could have been at risk for or suffering from inadequate vitamin D levels. It has also been shown that COVID-19 survivors can experience significant residual clinical and biochemical alterations that necessitate comprehensive medical care and close follow-up for longer periods than was anticipated at the outset of the pandemic, including deficits in vitamin D levels, and this may help to foster musculoskeletal as well as neurocognitive health attributes[39] as indicated by Fillipo et al.[40] who noted a vitamin D deficiency along with an impaired parathyroid hormone response, and a high prevalence of skeletal complications, such as vertebral fractures in their COVID-19 sample. Low possible vitamin D exposure has also been linked to higher COVID-19 mortality rates.[41]

Ohaegbulam et al.,[10] report that the activation of the vitamin D receptor expressed on immune cells has been shown to directly reduce the secretion of inflammatory cytokine mediators, such as interleukin-6, and to indirectly affect C-reactive protein. However, patients that received a high dose of vitamin D supplementation readily achieved normalization of their vitamin D levels and showed an improved clinical recovery as evidenced by their shorter lengths of stay, lower oxygen requirements, and a reduction in inflammatory marker status. Merzon et al.,[42] who evaluated the degree of association between plasma vitamin D levels and the presence of COVID-19 disease and hospitalizations among 14,000 members of a Health Services unit found 10.1% to be COVID-19-positive, and that among this group the mean plasma vitamin D level was significantly lower than that of the negative COVID-19 group, even though this may not account for long COVID-19 fatigue and mobility dysfunction emergent post COVID-19 signs of impairment.[12] On the other hand, Smaha et al.,[43] show available data from epidemiological studies do suggest that low serum vitamin D levels are associated with an increased susceptibility to the new coronavirus infection, as well as with a more severe course of the disease.

Kerget et al.,[44] concluded that due to the COVID-19 pandemic associated, long-running quarantine approaches that prevailed, sizeable numbers of individuals may have acquired a vitamin D deficiency due to insufficient sunlight exposure. This is in contrast to observations that vitamin D supplementation does appear to reduce the risk of an acute respiratory tract infection, especially in cases deemed vitamin D deficient[45] and implies the possible emergence of a low-magnitude vitamin D causal effect of associated with the acute responses to COVID-19 infections cannot be ruled out, even if disputed.[46] Ali et al.,[24] further propose that since vitamin D is known to mitigate the scope of acquired immunity and to help regenerate endothelial lining damage, its thoughtful usage may be especially beneficial in minimizing the tissue damage observed to accompany COVID-19 disease flares. Furthermore, there is a possible 70% chance of an effective protective outcome when a vitamin D deficiency is corrected by supplementation.

Discussion

As noted above, the reports documented in this review, which are largely current, do imply that vitamin D supplementation may be able to reduce the risk of influenza, even if this is not a consistent finding,[47] and must thus be of sufficient current import to examine further.[48] As well, even though support for this idea may not be universal, a role for vitamin D in the realm of long COVID-19 cannot be ruled out, and is being proposed as a salient topic for further study as outlined in several PUBMED citations.

On the other hand, as proposed by Caccialanza et al.,[49] efforts towards ensuring safe efficacious vitamin D serum levels and methods of delivery that ensure optimal vitamin D serum levels[50] and that are forthcoming among vulnerable groups and individuals, may yet have a favorable impact on reducing COVID-19 risk as well the predisposition of many youth and adults with chronic health challenges acquiring severe forms of COVID-19, with its possible highly disabling long term musculoskeletal, neurological and neuropsychiatric complications. Vitamin D may also serve as

anti-inflammatory or immune-system modulating role that may well attenuate the harmful consequences of COVID-19,[51] which are emerging, even if deemed possibly non significant by some,[50] but not all. For example, findings by D'Avolio et al.,[52] obtained from a cohort of patients in Switzerland did tend to suggest vitamin D may be one potentially important adjunct to consider in the realm of efforts to mitigate the onset and severity of COVID-19 infections and its variants. Alternately, the presence of a sustained vvitamin D deficit may predispose vulnerable as well as healthy individuals to lung infections[26] and higher mortality rates than those deemed vitamin D sufficient,[53] plus a generally worse COVID-19 infection outcome even if this is only associated with obesity, ethnicity, and social deprivation explanatory factors.[50] Many reasons for being vitamin D deficient exist including low physical activity levels,[54] hence along with other vitamins, Catalano et al.[55] propose vitamins D as a possible alternative preventive and therapeutic means of support for fostering the health of COVID-19 disease outcomes in both adults as well as children, as well as for averting a COVID-19 infection and its possible severe outcomes in the event they acquire the disease.[56]

As such, and although further well designed studies are warranted, available evidence suggests that efforts to maintain an optimal serum vitamin D status in the case of the COVID-19 patient may significantly reduce the risk of acute respiratory distress syndrome as well as its severity, with possible beneficial effects on the need for mechanical ventilation and/or intensive care unit admission.[57]

As concluded by Thacher,[58] vitamin D may prove especially beneficial in those cases found to have mild or asymptomatic COVID-19. Because those at greatest risk of COVID-19 are also at greatest risk of vitamin D deficiency, Pal et al.,[59] recommend that consideration be given to the administration of vitamin D supplements among the general population during the ongoing COVID-19 pandemic, and especially those who live in areas with high air pollution or where outdoor activity or sun exposure is limited.[60]

Concluding remarks

Although modern medicine has not been quite successful in managing or arresting the reported rates of COVID-19 and its emergent variants, it is possible that some of its impact can be averted quite readily. This includes recovery from acute COVID-19 disease that is often attenuated and associated with multiple symptoms of ill health that may preside for up to one year after the initial infection but where evidence based intervention or prevention remains elusive at best.

However, it is possible some degree of amelioration against long COVID-19 symptoms and health complications may be possible as shown in some recent subgroup analyses where vitamin D supplementation was associated with improved clinical outcomes only in those COVID-19 patients who received this vitamin supplement. This may reflect the biological effects of vitamin D on diverse symptoms of multiple body systems implicated in long COVID-19 cases, including those of fatigue, muscle weakness, and diverse features of psychological distress61 that may or may not be associated with factors such as age and prior vitamin D deficiencies.[62] In this regard, vitamin D may have a strong bearing on post COVID symptoms of distress, in particular, and in the face of very few current guidelines for mitigating these complications and significant disability and negative daily life impact of any lingering COVID-19 manifestations,[63] it appears plausible to make a case for its possible application among high risk individuals who are shown to be vitamin D deficient.

Moreover, airway infections, as well as immune processes believed to be implicated in long COVID63 may be enhanced as well as muscle strength, pain alleviation, 'brain fog', sleep hygiene, and fatigue.[64] Indeed, although not discussed at any length currently, and several proposed clinical trial protocols that appear promising have not been implemented or completed to date, it appears that sufficient evidence shows those who are obese, those who are deemed 'food insecure', live in air-polluted neighborhoods, and those persons of Black or Asian origin may be markedly helped in this regard,[24] especially among those who reside in the most commonly affected countries.[65]

This is due in part to data showing vitamin D has the potential to modulate innate and adaptive immunity processes,[66] and the finding that less severe COVID-19 disease may emerge in the presence of adequate serum vitamin D.[67] In addition, even if children or adults are not vitamin D deficient when admitted to hospital, they may acquire a vitamin D deficit if hospitalization is prolonged, and their sunlight and healthy food exposure is reduced and their inflammatory condition persists.[63-76] Even those returning home with no long COVID symptoms may become re infected if their vitamin D levels remain deficient.[71,73]

Although still quite widely disputed, based on recent in depth analyses,[71,73,77,78] it appears the presence of a low vitamin D serum concentration level may adversely impact innate and adaptive immunity that can lead to COVID-19 infections, as well as mediating its inflammatory severity,[65] and the need for hospitalization.[71] It can be further anticipated that its presence in influencing musculoskeletal physiology and biology, as well as mood and chronic pain can be influential both in mitigating severe long term COVID-19 impacts that have not been well studied and should be studied further. Alternately, as per Tsourdi et al.,[68] even if vitamin D has some beneficial impact, but this remains unproven in the course of exploring efforts to speed up or counter long COVID symptoms, it appears attempts to employ vitamin D supplements as indicated will prove challenging at best, along with a poorer than desired COVID-19 prognosis.[67–75]

In the interim, this brief scoping review has shown

i. COVID-19 infections clearly remain immensely problematic to control and treat and do not afford future immunity or obviate persistent disabilities.

ii. Vitamin D deficiency aggravates COVID-19 disease.

iii. Optimal vvitamin D exposure may help diminish multiple disabling post-COVID-19 syndrome manifestations, as well as the risk of severe COVID-19 disease.

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Conflicts of interest

Author declares there are no conflicts of interest towards this manuscript.

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