Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Role of vitamin D supplementation in aging patients with COVID-19

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Good nutrition and a healthy lifestyle strengthen the immune system. Currently, the world is facing the COVID-19 pandemic and this has once again highlighted the importance of nutrition, particularly vitamin D. Vitamin D is a unique micronutrient which plays a critical role in a host of physiologies, including proper functioning of the immune system and modulation of inflammatory responses. Evidence has shown that low vitamin D levels have associations with increased risk of COVID-19 infection; in fact, individuals deficient in vitamin D are reported to have a 54 % greater SARS-CoV-2 positivity rate [1]. It is well established that SARS-CoV-2 is more lethal in aged individuals [2,3] than in those with additional comorbidities and frailty [4,5]. Older adults in residential care have represented a disproportionately large proportion of infections and COVID-19 fatalities, for a number of reasons, including infectious outbreaks in facilities, significant comorbidity and poor health status. Additionally, vitamin D deficiency is very common among aged individuals. This is likely due to less sunlight exposure, decreased appetite and reduced vitamin D absorption in the gut. It is hypothesized that vitamin D supplementation may have a protective role in the prevention or treatment of COVID-19 infection in aging individuals.

1. Why does COVID-19 affect the aging population more severely?

The severity of COVID-19 is significantly greater in older adults (≥65 years), with this age group representing 80 % of hospitalizations and having a 23 times greater risk of death compared with younger individuals [6]. The control of viral load through effective immune response is a key indicator of COVID-19 symptom severity. The suppression and elimination of any virus, including SARS-CoV-2, requires key immune processes; however, in older people, many of these mechanisms are dysfunctional and increasingly heterogeneous, limiting immune efficacy in the face of infection [7,8]. However, it is still unclear exactly which specific aging mechanisms are principally associated with the progression of COVID-19. The immune system undergoes a range of changes with aging, including 'immunosenescence', that is, the decline of immunity [9], and 'inflammaging', a gradual elevation in systemic inflammation. However, in addition to the decline in immune function, vitamin D deficiency is also very common in the older population. Surveys in Europe on nutrition in older adults reported that 37 % of men and 45% of women had serum vitamin D concentrations < 30 nmol/L [10–12].

2. Role of vitamin D supplementation in aging individuals

According to the European Calcified Tissue Society Working Group, vitamin D deficiency is classified as 25(OH)D serum levels lower than 30 nmol/L. To achieve adequate serum vitamin D levels, higher doses of vitamin D supplements, such as 11,000 IU/day, can be taken for four weeks, while lower doses, typically 4,000 IU/day, require 12 weeks to achieve the same levels. On the other hand, others caution against doses of vitamin D greater than 4,000 IU/day and particularly very high doses of 10,000 IU/day, due to the potential for toxicity [13]. Generally, older adults are advised to have a balanced diet and healthy lifestyle with regular sun exposure alongside a supplement of 400–1000 IU/day in order to avoid deficiency [13,14]. Maintaining an optimal serum level of vitamin D is vital for adequate immune response, particularly in high-risk aging populations.

People with a low level of vitamin D have been shown to be 4.6 times more likely to be affected by COVID-19 than those with normal levels [15]. A study of 105 COVID-19 patients aged ≥65 years showed that older adults with vitamin D deficiency had a greater incidence of non-invasive ventilation support and were more likely to be admitted to a high-dependency unit; however, there was no change in mortality [16]. A study of 9,940 participants aged 50–75 found that vitamin D insufficiency or deficiency was statistically responsible for 41 % of all cases of respiratory disease mortality. The authors proposed that vitamin D3 supplementation could attenuate the burden of the COVID-19 pandemic [17]. Vitamin D supplementation boosts immunity and reduces the risk of COVID-19 infection, its severity and mortality [18,19].

In a quasi-experimental study, 77 older participants with COVID-19 were recruited and divided into three groups. Group 1 were those who

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received oral bolus doses of vitamin D3 (50,000 IU/month, or 80–100,000 every 2–3 months) prior to COVID-19 infection; Group 2 received 80,000 IU vitamin D3 immediately on COVID-19 diagnosis but had not received treatment previously; Group 3 were untreated controls. Group 1 reported a higher clinical response, with 93.1 % 14-day survival, compared with 81.2 % and 68.7 % in Group 2 and Group 3, respectively. This suggests that adequate vitamin D at the time of infection is associated with improved outcomes; however, immediate supplementation also decreased mortality [20]. Similarly, in a study of 66 participants aged 63–103 years, in a residential care facility, who received an 80,000 IU bolus of vitamin D3 on suspicion or diagnosis of COVID-19 or during the month prior, it was noted that vitamin D3 supplementation had an inverse relationship with the clinical improvement score in COVID-19 patients, and improved survival rates compared with those who did not receive supplements [21]. In a cohort study, 43 COVID-19 patients aged ≥50 were provided with dietary supplements consisting of 1000 IU vitamin D3, 150 mg magnesium and 500 μg vitamin B_{12}, which reduced the need for oxygen and intensive care support [22,23].

In order to reduce the spread of secondary infections, it is important to reduce the transfer of the virus among close household contacts. A pragmatic cluster-randomized trial evaluated the use of 3200 IU vitamin D3 daily in 1500 newly diagnosed COVID-19 patients. The vitamin D intervention decreased the rates of hospitalization and mortality while also proving to be beneficial in preventing infection among close household contacts [24].

While others have proposed that very large bolus doses of 300,000 IU of vitamin D could be beneficial in the prevention and treatment of COVID-19, there is no convincing evidence from randomized control trials to support this – particularly in light of increased risk of falls and toxicity with excessive doses [25]. While there remains much to be revealed regarding the impact of vitamin D in COVID-19, a number of ongoing clinical trials are exploring its use in managing and preventing SARS-CoV-2 infection (Table 1).

3. Recommendation

It is vital to maintain optimal vitamin D status, particularly in older adults, as it has beneficial effects across various body systems. Therefore, the following guidelines have been developed to protect musculoskeletal health, provide a proper immune response and minimize the risk of vitamin D deficiency. General recommendations for the aging population from the European Food Safety Agency are 800 IU/day vitamin D supplementation, while the UK Scientific Advisory Committee on Nutrition (SACN), US Institute of Medicine (IOM), and European Food Safety Agency recommend limiting intake to 4000 IU/day for adults. In addition to supplementation, exposure to sunlight for at least 13−15 min three times per week at noon is advised, to avoid deficiency. In the face of its well demonstrated beneficial effects outside COVID-19, and possible protective impacts in SARS-CoV-2 infection, vitamin D supplementation is likely a safe, cost-effective intervention that could decrease morbidity and mortality. Although evidence related to the effective dosage of vitamin D in COVID-19 is scarce, the recommended 800 IU/day is very likely to be safe and may be effective. Further randomized control trials are required in this area to validate the effectiveness of vitamin D supplementation in COVID-19 patients and establish a dose response. Nevertheless, preventative interventions to ensure adequate vitamin D status, particularly in vulnerable populations, is likely to improve COVID-19 outcomes.

Contributors

Hira Shakoor contributed to drafting of the editorial and to review and editing of the draft.

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Conflict of interest

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Table 1
Registered clinical trials of vitamin D in aging patients with COVID-19.

Trial Number	Study design	Intervention	Condition or Disease	Age	Phase	Country	Primary outcomes Measure
NCT04351490 [26]	Randomized, Parallel Assignment, Open Label	2000 IU of 25-OH cholecalciferol and 30 mg Zinc gluconate for 2 months	SARS-CoV-2	≥ 60 Years (Older Adults)	Not Applicable	France	The survival rate in asymptomatic subjects
NCT04344041 [27]	Randomized, Parallel Assignment, Open Label	200,000 IU and 200,000 IU of cholecalciferol	SARS-CoV-2	≥ 65 Years (Older Adults)	Phase 3	France	Number of deaths during the 14 days
NCT04507867 [28]	Randomized, Sequential Assignment, Single (Investigator)	2000 IU of cholecalciferol and other nutritional support	SARS-CoV-2, Diabetes Mellitus, Hypertension, Obesity	30−75 Years (Adults, Older Adults)	Not Applicable	Mexico	Supportive care
NCT04751669 [29]	Double-blind, placebo-Controlled, Randomized Clinical Trial	10 μg of Cholecalciferol and various other nutrient supplements	SARS-CoV-2	18−80 Years (Adults, Older Adults)	Not Applicable	Spain	Need for hospital admission
NCT03188796 [30]	Randomized, Parallel Assignment	540,000 IU of vitamin D3 followed by 10 drops daily (4000 IU) for 90 days	SARS-CoV-2, Critical Illness, Vitamin D deficiency	18−100 Years (Adults, Older Adults)	Phase 3	Austria, Belgium	28-day mortality, length of stay at hospital
NCT04636086 [31]	Randomized, Parallel Assignment	25,000 IU/mL of cholecalciferol enterally	SARS-CoV-2	≥ 18 Years (Adults, Older Adults)	Phase 4	Belgium	Clinical improvement, length of stay at the hospital
NCT04386850 [32]	Multicenter Randomized, Double-Blinded, Placebo-Controlled Clinical Trial	25 μg of 25(OH)D3 for 2 months	SARS-CoV-2	18−75 years (Adults, Older Adults)	Phase 2 Phase 3	Iran	Disease severity, length of stay at the hospital

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