

### PERSPECTIVES IN NUTRITIONAL SCIENCE

## COVID-19: the older adult and the importance of vitamin D sufficiency

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(Received 17 August 2020 – Accepted 18 August 2020)

*Journal of Nutritional Science* (2020), vol. 9, e40, page 1 of 5

doi:10.1017/jns.2020.36

#### Abstract

In December 2019, in Wuhan, China, the novel coronavirus 'severe acute respiratory syndrome 2' (SARS-CoV-2) was discovered as the cause of a pneumonia-like illness and subsequently named coronavirus disease 2019 (COVID-19). COVID-19 spread and is now a global pandemic. With few exceptions, countries in the Northern hemisphere have higher mortality rates from COVID-19. This may be due to an increased prevalence of older people in Northern Europe at higher risk of having cardio-pulmonary and metabolic comorbidities as well as hypovitaminosis D. With increasing age, immunosenescence and 'inflammaging' lead to impaired and maladaptive immune responses to SARS-CoV-2 infections, contributing to the enhanced prevalence of severe COVID-19 in older patients. The association of ageing with increased vitamin D deficiency, which is associated with cardiovascular risk factors and disease and worse prognosis in COVID-19 infection, is discussed. Considerable experimental evidence demonstrates the immuno-modulatory properties of vitamin D, in particular, its role in regulating and suppressing the inflammatory cytokine response to viral respiratory infections links the importance of vitamin D sufficiency as a potential protective factor in COVID-19. There is an urgent need for prospective randomised studies to examine whether hypovitaminosis D correlates with severity of COVID-19 disease and the actual benefit of repletion. Moreover, given what has been described as a 'pandemic of vitamin D deficiency', especially in Europe, and in the context of the SARS-CoV-2 contagion, the authors support the call for public health doctors and physicians, with support from Governments, to prioritise and strengthen recommendations on vitamin D intake and supplementation.

**Key words:** COVID-19: Vitamin D sufficiency: Vitamin D deficiency: Older adult

In December 2019, in Wuhan, China, the novel coronavirus 'severe acute respiratory syndrome 2' (SARS-CoV-2) was discovered as the cause of a pneumonia-like illness<sup>(1)</sup> and subsequently named coronavirus disease 2019 (COVID-19)<sup>(2)</sup>. COVID-19 spread and is now a worldwide pandemic<sup>(3)</sup>. Globally, SARS-CoV-2 has infected 20,439,814 people and resulted in 744,385 deaths (13 August 2020)<sup>(4)</sup>. In a retrospective Chinese multicentre cohort study, multivariable regression analysis determined that older age was associated with an increased odds of in-hospital death (OR 1.10; 95% CI: 1.03, 1.17, per year increase;  $p=0.0043$ )<sup>(5)</sup>. While older people do not appear to be at an increased risk of contracting

COVID-19, they are more vulnerable to developing serious complications and have the highest mortality rate<sup>(5–7)</sup>. Many older people have comorbidities such as cardiovascular disease, diabetes and frailty that deplete their reserves and weaken their immune response<sup>(8)</sup>. Moreover, hospitalised patients with concomitant cardiac disease and COVID-19 have an extremely poor prognosis compared to those without a history of cardiac disease<sup>(9)</sup>.

However, increases in these comorbidities alone do not fully explain the preponderance of particularly severe COVID-19 infections in older people. Through the process known as immunosenescence, the immune system, including its ability

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to recognise, activate the system, obliterate and remove a virus such as SARS-CoV-2, is impaired in an extremely unpredictable fashion with increasing age<sup>(10,11)</sup>. There is an ongoing debate over which of these tasks is most important to the progression of COVID-19 in a given older individual<sup>(12)</sup>. Both innate (reduced pathogen recognition and recruitment of macrophages) and adaptive (atrophy of the thymus with dysfunctional memory lymphocytes) immunity become defective in older age. Moreover, a chronic increase in systemic inflammation, known as 'inflammaging', thought to arise from an overactive but less effective immune alerting system is more prominent with increasing age<sup>(13)</sup>. There is impressive evidence that 'inflammaging' in association with sedentary lifestyle habits, obesity and nutritionally unbalanced diets is a major driver of cytokine storm which is associated with up to half of the fatalities in COVID-19 infections<sup>(14,15)</sup>.

The main physiological causes of vitamin D insufficiency are lack of exposure to sunlight (UVB radiation at 290–315 nm), the concentration of melanin in the skin, and as we age, the decreased capacity of human skin to synthesise vitamin D<sup>(16,17)</sup>. Vitamin D deficiency is associated with incident cardiovascular disease<sup>(18)</sup>, increased risk of ischemic heart disease and early death<sup>(19)</sup>, although supplementation has not been shown to reduce the risk of invasive cancer or cardiac events<sup>(20)</sup>. The VITAL authors conclude that although their study did not show a benefit of supplementation it remains plausible that a study exploring the effects of supplementation in those with extremely low 25(OH)D (<50 nmol/l) could illustrate a benefit; however, maintaining blinded groups 25 (OH)D (<50 nmol/l) for a long period would not be ethical so this research question will remain difficult to answer<sup>(20)</sup>.

Ecological studies have attributed the reported higher rates of coronary heart disease and hypertension to the higher prevalence of vitamin D deficiency in regions at increasing distance from the equator<sup>(18)</sup>. Striking differences in mortality rates from COVID-19 have been reported between countries at different latitudes worldwide, with those in the Northern hemisphere having higher mortality rates<sup>(21)</sup>. On 3 April 2020, the death rate per million of the population in the United Kingdom was reported as sixty-eight compared to two in Australia reported one week later<sup>(22)</sup>. The higher mortality rates observed in countries that lie above 35° North may be due to an increased prevalence of older people in Northern Europe, who have higher risk of having cardio-pulmonary and metabolic comorbidities<sup>(21)</sup> as well as those with vitamin D deficiency, especially during the winter months when 25 (OH)D levels are lowest<sup>(17,23,24)</sup>. Exceptions include countries like Brazil and Mexico, which serves to emphasise the multifactorial nature of control of COVID-19 related morbidity and spread. In particular, these outliers highlight the vital importance of excellent public health measures including hand hygiene, respiratory etiquette, ability to test and trace, social isolation, as well as availability and correct use of personal protection equipment<sup>(25)</sup>.

Evolution of SARS-CoV-2 to infect humans is thought to have resulted from mutations in its spike glycoprotein, the mechanism through which it enters cells, and in the nucleocapsid N protein which regulates viral replication and

transcription<sup>(26)</sup>. Vitamin D can potentially reduce the risk of infections by inducing antimicrobial and host defence peptides (cathelicidins and defensins) that can lower viral replication rates. Reduced concentration of pro-inflammatory cytokines occurs which produce inflammation injurious to the lining of the lungs resulting in pneumonia, and Vitamin D also increases the concentration of anti-inflammatory cytokines<sup>(27)</sup>. While the virulence mechanism of SARS-CoV-2 has yet to be fully elucidated, it has recently been demonstrated that human dipeptidyl peptidase-4 receptor (DPP-4/CD26) binding interacts with the S1 domain of the SARS-CoV-2 spike glycoprotein, suggesting that it may be an important virulence factor in SARS-CoV-2 infection<sup>(28)</sup>. Importantly, correction of vitamin D deficiency has been shown to significantly reduce the *in vivo* expression of the DPP-4/CD26 receptor<sup>(29)</sup>. Vitamin D also reduces the production of IL-6, a pro-inflammatory cytokine, in monocytes<sup>(30)</sup> which is implicated in the development of the aforementioned cytokine storm, more common in older people and the major contributor to severe COVID-19 infection in many cases<sup>(31)</sup>. A recent meta-analysis which included results from 25 randomised controlled trials (*n* 11 321), determined that regular daily vitamin D2/D3 supplementation of up to 2000 IU reduced the risk of acute respiratory tract infection among all participants (adjusted odds ratio (AOR) 0.88; 95% CI: 0.81, 0.96; *p* < 0.001) and was safe<sup>(32)</sup>.

The protective effects of supplementation with vitamin D were stronger in those with baseline 25(OH)D levels <25 nmol/l (AOR 0.30; 95% CI: 0.17, 0.53; *p* < 0.001) when compared to those with a baseline 25(OH)D levels ≥ 25 nmol/l (AOR 0.75; 95% CI: 0.60, 0.95; *p* = 0.006)<sup>(32)</sup>. However, considerable heterogeneity in the trial results observed most likely due to the differences in study settings, vitamin D supplemental dose, definitions of acute respiratory tract infection and inclusion of populations with pre-existing respiratory disease, may limit the generalisability of these findings<sup>(33)</sup>.

Autier *et al.* systematically reviewed meta-analyses of vitamin D supplementation and non-skeletal disorders published between 1 January 2013 and 31 May 2017 that included study participants of all ages, including pregnant women. They indicated that vitamin D supplementation may help to prevent common upper respiratory tract infections and asthma exacerbations<sup>(34)</sup>. Rejmanek *et al.* systematically reviewed the characteristics of 30 randomized clinical trials included in seven meta-analyses on non-skeletal effects of vitamin D supplementation<sup>(35)</sup>. In four of the seven meta-analyses evaluated benefit was not observed, while in three, the authors found that the risk of respiratory tract infection was likely to be attenuated by vitamin D supplementation; in particular, for those with a low baseline serum 25(OH)D concentration. It should be appreciated that for individuals with minimal or no exposure to sunlight, the Scientific Advisory Committee on Nutrition (SACN) in the United Kingdom (UK) recommends vitamin D supplementation of 10 µg (400 IU) daily to maintain 25OHD concentrations above 25 nmol/l (the level required to protect musculoskeletal health in the majority of the population) over an entire year<sup>(36)</sup>.

Vitamin D supplementation has been shown to increase T helper (CD4<sup>+</sup>) cells that play a key role in the adaptive immune



system in HIV infection<sup>(37)</sup>. Venous thromboembolism is common in those with severe COVID-19 infection<sup>(38,39)</sup> and hypovitaminosis D has been reported to correlate with increased thrombosis, which may reflect a direct aetiological effect of vitamin D deficiency or be a surrogate marker of relative immobility for those at most risk<sup>(40,41)</sup>. Furthermore, protracted activation of the renin–angiotensin–aldosterone system may contribute to chronic cardiorespiratory disease with decreased lung function in patients with hypovitaminosis D<sup>(42)</sup>.

Older adults are at increased risk of vitamin D deficiency and they produce 75% less cutaneous vitamin D<sub>3</sub> than young adults, even with regular sun exposure<sup>(43)</sup>. Intestinal resistance to 1,25(OH)<sub>2</sub>D develops with increasing age, leading to impaired intestinal absorption of calcium associated with reduced numbers of vitamin D receptors. The age-related reduction in renal function impairs vitamin D activation<sup>(44)</sup>. Other risk factors for vitamin D deficiency include reduced oral intake, nutritionally deficient diets, limited sun exposure, hepatic and renal impairment, together with some antiepileptic medications, all of which occur more frequently in older people, with residents of care institutions at particular risk<sup>(45)</sup>.

Vitamin D deficiency is a major global health problem<sup>(46,47)</sup>, worse in Northern latitudes<sup>(21,48)</sup> without good programmes for supplementation of vitamin D or fortification of food-stuffs, as occurs in some Nordic countries with reduced mortality from COVID-19<sup>(49)</sup>. Ireland is no exception, with new research from the Irish Longitudinal Study on Ageing (TILDA) reporting similar high rates of vitamin D deficiency (25(OH)D: <30 nmol/l) in both men and women during the winter: 21.3 % (*n* 244, 209) in those aged over 55 years, 29.6 % (*n* 23, 987) for those between 80 and 84 years and 46.6 % (*n* 31,480) in those aged >85 years<sup>(49)</sup>. Deficiency was particularly severe in the West of Ireland with a rate of 59.5 % (*n* 8,738) in those >85 years. The latter finding of low vitamin D status amongst older adults is corroborated by our group<sup>(17,50–52)</sup>. Moreover, high prevalence rates of vitamin D deficiency were more common in nursing homes (NH) residents (50.5 %, *n* 138) and inpatients (45.1 %, *n* 1,055) compared to patients in the community (20.3 %, *n* 3,101) or outpatients (24.5 %, *n* 1,585)<sup>(24)</sup>. Interestingly, almost 50% of all deaths due to COVID-19 in Ireland involve residents of NHs<sup>(53)</sup>. It is also worth highlighting that the ‘cocooning’ strategy advocated by the Irish government serves to further reduce access to sunlight (UVB) for those most at risk with potential exacerbation of vitamin D deficiency. Recent meta-analyses of randomised controlled trials concluded that the use of vitamin D supplements was associated with lower total mortality in elderly, predominantly vitamin D deficient participants<sup>(54,55)</sup>. Together, this evidence provides a rationale for vitamin D supplementation in those with vitamin D deficiency or at risk of vitamin D deficiency with a view to ameliorating the severity, complications and poor outcomes for those with COVID-19 disease<sup>(48,56)</sup>.

While it is important to supplement with vitamin D during times of self-isolation with minimal exposure to sunlight, the public need to be counselled against the use of high doses of vitamin D which may be harmful and where there is no evidence of benefit. Prescribing high dose vitamin D is the

domain of clinical practice<sup>(56)</sup>. Critically, advice given to the public should be evidenced-based, accurate, clear, accessible, timely and aligned to government recommendations. There is a variance in country-specific recommendations, UK: 400 IU/d<sup>(36)</sup>, United States of America (USA)<sup>(57)</sup> and European Union (EU)<sup>(58)</sup>: 600 IU/d (800 IU/d >70 years)<sup>(59)</sup>. In June, Public Health England (PHE) issued an advisory statement informing of the absence of evidence to support taking vitamin D supplements to specifically prevent or treat COVID-19<sup>(60)</sup>. This advice re-enforced the position statements from the SACN report published in 2016<sup>(36)</sup> and recommended that all people should continue to follow UK Government advice on daily vitamin D supplementation to maintain bone and muscle health during the COVID-19 pandemic.

As considerable experimental evidence demonstrates the immuno-modulatory properties of vitamin D and in particular, its role in regulating and suppressing the inflammatory cytokine response to viral respiratory infections<sup>(61–64)</sup>, there is an urgent need for future prospective studies to examine whether hypovitaminosis D correlates with severity of COVID-19 disease<sup>(22)</sup>. Randomised controlled trials evaluating the impact of vitamin D therapy on the course of COVID-19 and the potential of optimisation of vitamin D status to benefit patient outcomes are warranted. Furthermore, given what has been described as a ‘pandemic of vitamin D deficiency’, especially in Europe<sup>(65)</sup> and in the context of the SARS-CoV-2, the authors support the call for public health doctors and physicians, with support from Governments, to prioritise and strengthen recommendations on vitamin D intake and supplementation<sup>(22,49,56)</sup>.

### Acknowledgements

The author(s) declared no potential conflict of interest that could be perceived as prejudicing the impartiality of the research, authorship, and/or publication of this article.

The authors received no financial support for this commentary.

P.M.O.S. researched the literature and wrote the first draft of the manuscript. T.P.G., M.B. and E.C.M. critically revised and approved the final version of the manuscript.

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