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Vitamin D and COVID-19

This rapid review of the science of Vitamin D and COVID-19 from the Royal Society is provided to assist in the understanding of COVID-19.

This paper is a pre-print and has not been subject to formal peer-review.

Summary

Vitamin D deficiency is associated with an increased risk of both respiratory viral infections and inflammatory conditions. Vitamin D has an important regulatory role in the human immune system, so a deficiency of Vitamin D is likely to cause immune dysregulation, which may reduce the first line of our defence against COVID-19. It is therefore biologically plausible that Vitamin D deficiency may contribute to susceptibility to COVID-19 infection. However, there is no direct causal link yet between Vitamin D deficiency and increased susceptibility to COVID-19.

Deficiency in Vitamin D is more commonly found in older individuals, those of black or Asian ethnic origin, and people who are obese. These are also factors known to increase risk of more severe COVID-19. However, correlations are not the same as causality.

The UK has one of the highest levels of Vitamin D deficiency in Europe. There is a direct causal relationship between Vitamin D deficiency and bone, tooth and muscle health. Vitamin D also has an important regulatory role in the human immune system. It is clearly prudent to prevent Vitamin D deficiency as part of a healthy lifestyle strategy. NICE recommends that "all adults living in the UK should be advised to take a daily supplement containing 400 international units (10 micrograms) of Vitamin D throughout the year, including in the winter months." High doses of Vitamin D supplements are unnecessary in most individuals and very high doses can be toxic. We recommend that HMG provides a stronger public message about the importance of preventing Vitamin D deficiency.

More research is required to test the possibility that Vitamin D deficiency predisposes to COVID-19, particularly in those groups with a high risk of COVID-19 mortality, such as the institutionalised elderly and people with a black, Asian or minority ethnic (BAME) background. We also recommend that hospitals consider assaying serum Vitamin D levels in patients with SARS-CoV-2 infection.

Introduction

Vitamin D is essential for good health. Ninety percent of the Vitamin D in the human body is produced in the skin from exposure to the sun. Only about 10% comes from food. It is only relatively recently that humans have moved from a mainly outdoor lifestyle (farming, etc.) to one which is mainly indoors (office work, etc.). It is reasonable to suppose that a deficiency of Vitamin D in many humans is therefore a modern phenomenon, mainly due to a lack of sunlight.

The spectrum of visible light from the sun, from red to violet, has insufficient energy to generate Vitamin D in the skin. It is the higher energy ultra-violet (UV) light that is needed. The UVB part of the spectrum (290-315 nm) generates Vitamin D, as well as causing damage to the DNA in most vertebrate skin. UVB is almost 100% blocked by standard window glass, unlike visible light: direct exposure to sunlight is required.

1. Vitamin D deficiency

NICE estimates that about one-quarter of the UK population is deficient in Vitamin D, rising to about one-third in winter months, owing to reduced sun exposure[1]. Vitamin D status is reflected by the level of serum 25OHD. There is no consensus on a precise definition of Vitamin D deficiency, but the NICE guidelines are that serum 25OHD levels greater than 50 nmol/L are sufficient, and less than 30 nmol/L are deficient[1]. Vitamin D deficiency has been associated with a variety of health problems: weak immune system, rickets, fatigue, bone fractures, headaches and cancers, with varying degrees of evidence to support the claims. Vitamin D toxicity, from taking too high a dose of Vitamin D, is rare and associated with serum levels of at least 300 nmol/L, and usually above 600 nmol/L[2].

Low Vitamin D status is expected to be exacerbated in many people by staying indoors during lockdown. It is therefore important that individuals take outside activity where possible. NICE's recommended oral supplement is 10 micrograms/day[13], however, in the USA the recommendation is 15 micrograms/day for those under 70 years old, and 20 micrograms/day for the over 70s[4].

1.1 Vitamin D deficiency in Europe

The UK has one of the highest levels of Vitamin D deficiency in Europe. Serum 25OHD levels in adults in 17 different European countries show that only Finland and Norway are more deficient than the UK[5].

It is interesting to compare the prevalence of Vitamin D deficiency (serum 25OHD concentrations less than 30 nmol/L) in the UK, Germany and Ireland, countries of broadly similar latitudes. Averaged over a year, Germany has 13.8% deficient, Ireland has 12.4% and the UK has 22.1%. The UK population is 32% Vitamin D deficient in the winter and 15% deficient in summer[6]. Some northerly countries strongly fortify their food with Vitamin D to counter their lack of sunlight, for example, Canada, whose population is only 10% Vitamin D deficient following their Vitamin D food fortification.

2. Vitamin D and acute respiratory infections

Numerous laboratory studies report that Vitamin D metabolites support innate immune responses to respiratory viruses other than SARS-CoV-2[7, 8, 9, 10, 11, 12], the virus that causes COVID-19. Clinically, Vitamin D deficiency has been shown to associate independently with an increased risk of diverse acute respiratory infections (ARI)[13]. A 2017 meta-analysis of data from 11,321 participants in 25 randomised controlled trials (RCTs) of Vitamin D supplementation to prevent ARI revealed a modest protective effect of the intervention (OR 0.88, 95% CI 0.81 to 0.96) that was stronger in those with the lowest baseline Vitamin D status (OR 0.58, 95% CI 0.40 to 0.82)[14]. It is unknown whether Vitamin D deficiency also predisposes to SARS-CoV-2 infection. Importantly, Vitamin D also diminishes the production of inflammatory cytokines, which appear to play a central part in the pathogenesis of severe COVID-19[15].

2.1 Vitamin D and COVID-19

RCTs of Vitamin D supplementation for the prevention or attenuation of COVID-19 have yet to be published, but several lines of evidence suggest a possible role of Vitamin D deficiency in its pathogenesis. First, an epidemiological study[16] reported that severe outbreaks with high fatality rates have occurred exclusively above the +30°N latitude line, in the winter hemisphere, where deaths per million ranged from 3% to 37% with (mean = 11%) in latitudes between 30°N and 55°N. By contrast, outbreaks in the tropics and southern summer hemisphere were very mild with an average of 0.2% deaths per million. This pattern was not explained by the trajectory of spread of infection[17]. COVID-19 mortality has been concentrated in groups at increased risk of Vitamin D deficiency including people of black, Asian or minority ethnic (BAME) background; people with higher body mass index; and the institutionalised elderly. Where Vitamin D status has been measured, a lower 25OHD level was associated with higher mortality[18]. Third, adverse outcomes of COVID-19 are associated with virus-driven hyper-inflammation[19]: evidence from an RCT indicated that Vitamin D supplementation accelerates resolution of systemic inflammation in another pulmonary infection (tuberculosis)[20].

3. Next steps

3.1 Further research

More research is required to test the possibility that Vitamin D deficiency predisposes to COVID-19. We also recommend that hospitals consider assaying serum Vitamin D levels in patients with SARS-CoV-2 infection. It will be important to compare the 25OHD levels between those with asymptomatic or mild SARS-CoV-2 infection and those with COVID-19.

3.2 Vitamin D supplementation

In order to prevent Vitamin D deficiency, NICE proposes[21]:

- All adults living in the UK should be advised to take a daily supplement containing 400 international units (10 micrograms) of Vitamin D throughout the year, including in the winter months.
- Dietary and lifestyle advice should also be given.

We recommend that HMG provides a stronger approach to Vitamin D intake. The magnitude of the dose should be updated as more evidence becomes available. It is important to emphasise that higher doses of Vitamin D supplements are unnecessary in most individuals and very high doses can be toxic.

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DISCLAIMER

This paper has drawn on the most recent evidence up to 18 June 2020 and has not been subject to formal peer-review. Further evidence on this topic is constantly published and the Royal Society may return to this topic in the future. This independent overview of the science has been provided in good faith by subject experts and the Royal Society and paper authors accept no legal liability for decisions made based on this evidence.

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