BRITISH SOCIETY FOR ECOLOGICAL MEDICINE

20/11/2020

The Rt Hon Matt Hancock MP,
House of Commons
London
SW1A 0AA

Dear Mr Hancock,

OPEN LETTER CONCERNING VITAMIN D USAGE GUIDELINES

As longstanding advocates of vitamin D for COVID-19 prevention and treatment, we are delighted that you are proposing to provide free vitamin D to vulnerable and elderly individuals. We would also recommend providing it to members of the black, Asian and minority ethnic (BAME) community and all frontline healthcare workers, as well as a general recommendation for supplementation to the UK population.

We would like to help formulate the guidelines.

We have therefore put forward our proposals below, backed up by the necessary scientific references.

Blood vitamin D levels in the UK

The target level of blood vitamin D is currently 50 nmol/l; levels below 50 nmol/l are classed as 'insufficiency' or 'deficiency'. The level of 50 nmol/l was set some years ago for the prevention of rickets; it is not a level that has been set with any regard to optimum functioning of the immune system. All recommendations for supplementation since then have been based on achieving this level of 50 nmol/l to avoid rickets, not COVID-19. Indeed, NICE guidance to GPs on testing vitamin D is based purely on the patient presenting with bone or physical problems [1]. Nevertheless, a number of doctors and researchers have for some time been calling for this target level to be raised to at least 75 nmol/l, if not 100 nmol/l.

A 2019 study showed that UK serum levels average only 50 nmol/l [2]. However, since this is the average level, this means that approximately 50% of the population will be below 50 nmol/l. It is therefore hardly surprising that rickets has returned to the UK, a disease that should have been eradicated several centuries ago. Low vitamin D levels have been implicated in many chronic diseases, including obesity, type 2 diabetes and cardiovascular disease, all risk factors for severe COVID-19 [3]. The financial cost of the UK's vitamin D deficiency alone has been estimated at around £20 billion per annum, even prior to COVID-19.

Appropriate vitamin D dosage for COVID-19

When deciding on individual dosage it is preferable to be guided by the blood vitamin D level (serum 25(OH)D). A study of COVID-19 mortality found that it was not until blood levels of vitamin D reached 85 nmol/l that patients did not die from COVID-19.

Nevertheless, we recognise that testing everyone is impractical, so we recommend the following:

- For anyone without COVID-19 risk factors and who is not a member of the BAME community: 4,000 IU/day, with 10,000 IU/day for the first two weeks to bring blood levels up quickly.
- For anyone who is elderly, has COVID-19 risk factors or who is a member of the BAME community: 8,000 IU/day, with 15,000 IU/day for the first two weeks to bring blood levels up quickly.

Concerns about vitamin D toxicity

Daily doses of 10,000 IU and even 30,000 IU in the short term have been demonstrated to be perfectly safe by the European Food Safety Authority Panel [4]. Annex E covers concerns about potential vitamin D toxicity arising from the UK Scientific Advisory Committee on Nutrition (SACN) 2016 report [5].

When to start taking vitamin D

It is already mid-November, so it is imperative that vitamin D supplementation is begun immediately. In any case, there is little point in waiting until COVID-19 symptoms are experienced, since these normally develop around 10 days after infection; by this time, the virus has a strong foothold in the body.

Yours sincerely

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Annex A: Studies showing that vitamin D is essential for a healthy immune response and that low levels are associated with respiratory complaints, while supplementation is protective
Annex B: Studies showing vitamin D deficiency in severe COVID-19
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Annex A: Studies showing that vitamin D is essential for a healthy immune response and that low levels are associated with respiratory complaints, while supplementation is protective

Vitamin D can regulate both innate and adaptive immunity; the vitamin D receptor is expressed on both innate and adaptive immune cells. Furthermore, vitamin D can reduce infection risk by lowering viral replication rates through the induction of antimicrobial peptides. [6-13] Vitamin D is also a key modulator of the renin-angiotensin system and may counteract the alteration in angiotensin-converting enzyme 2 (ACE2) activity, seen when COVID-19 binds to ACE2 receptors; it is able to increase the activity of ACE2 protein levels and alleviate damage in acute lung injury [3,14-16]. Vitamin D can also suppress the excess inflammatory response (the 'cytokine storm', common to severe COVID-19), and has an anticoagulant effect (abnormal coagulation has been observed in COVID-19) [3,7,17-22].

Many studies have shown that Vitamin D deficiency not only impairs immune function but also promotes excessive inflammatory reactions; deficiency is most common in older adults, those with darker skins and those taking statins. A systematic review found that low vitamin D status was associated with increased risk of both upper and lower respiratory tract viral infections (COVID-19 can manifest as both), while a 2019 meta-analysis of observational studies involving 20,966 patients found that those with vitamin D levels <50 nmol/l experienced a significantly increased risk of pneumonia [23-25], often a development of COVID-19. A US study found that vitamin D concentrations of at least 95 nmol/l were associated with a significant two-fold reduction in the risk of developing acute respiratory tract infections and with a marked reduction in the percentages of days ill [26]. A UK study found that Vitamin D deficiency is common in people who develop acute respiratory distress syndrome (ARDS) and appears to contribute to ARDS development [27]; ARDS is frequently seen in severe COVID-19. Similarly, a large US study showed an inverse relationship between vitamin D status and the frequency of acute respiratory infection (ARI) up to 25(OH)D levels around 75nmol/L, with an almost linear association over the range of 25-75 nmol/L; in multivariate analysis, 25OHD levels <75nmol/L were associated with 58% higher odds of ARI [28]. Vitamin D deficiency was also associated with a 2.5-fold increase in respiratory disease mortality [29].

The UK National Diet and Nutrition Survey Rolling Programme recently reported that vitamin D intake from supplements, but not diet, was associated with reduced prevalence of respiratory complaints, while a Swedish study found that in patients with frequent respiratory tract infections, 4000 IU/day for a year significantly reduced infection incidence. Supplementation of 1,200 IU/day reduced the risk of influenza in Japanese schoolchildren, while children in Mongolia given only 300 IU/day had half the rate of acute respiratory infection. [30-33]

Two meta-analyses, the latest in 2017 comprising 25 trials and involving 11,321 subjects, found that vitamin D supplementation reduced the risk of acute respiratory tract infection. Patients not receiving bolus doses (but lower, more regular doses) and who had those with baseline 25(OH)D of <25 nmol/L experienced the greatest protective effect. A systematic review reported that observation studies showed statistically significant associations between low vitamin D status and increased risk of both upper and lower respiratory tract infections. Two literature reviews found that Vitamin D supplementation decreases the risk of acute respiratory distress syndrome (ARDS) and can reduce secretion and expression of pro-inflammatory cytokines. [34-38]

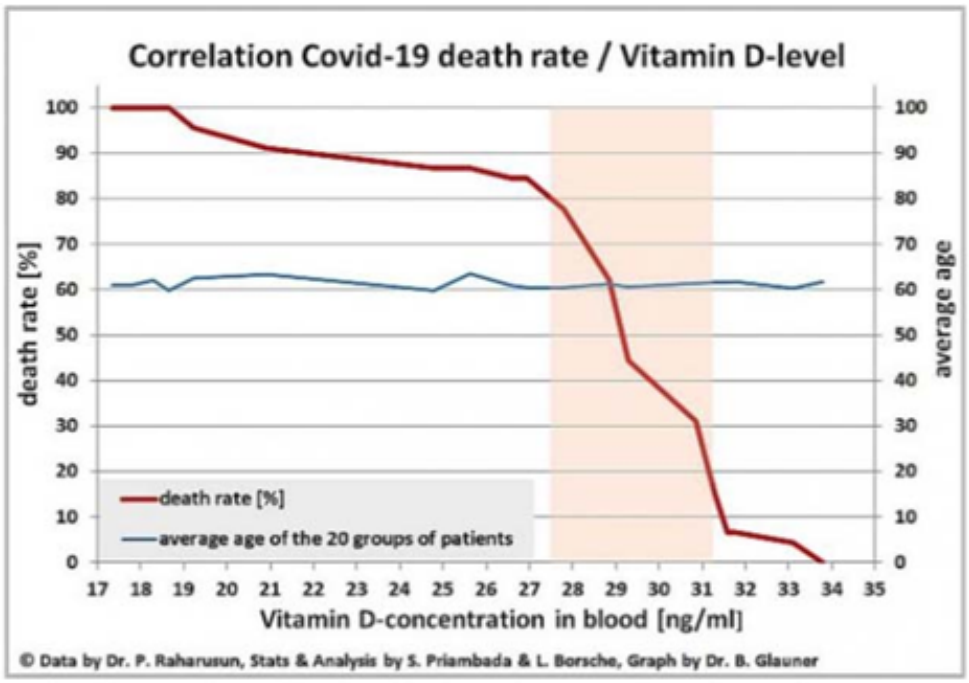
Annex B: Studies showing vitamin D deficiency in severe COVID-19

A UK study found that the majority of COVID−19 inpatients had vitamin D insufficiency (30-50 nmol/l), 37% were deficient (<30 nmol/l) and 22% had severe deficiency (≤15 nmol/L); only 19% of COVID-19 intensive care patients had vitamin D levels greater than 50 nmol/L, compared to >39% in ward patients. UK, US, Belgian, Irish and Italian studies all found that testing positive for COVID-19, or developing acute respiratory distress syndrome (ARDS), were independently associated with lower serum vitamin D levels. Patients who progressed to ARDS had a mean vitamin D level of 27 nmol/L, whereas those who did not progress to ARDS had a mean level of 41 nmol/L. A recent study of 20 European countries by Queen Elizabeth Hospital Foundation Trust found a correlation between level of vitamin D deficiency and COVID-19 related deaths and cases; the UK was among those countries with the greatest mean vitamin D deficiency in COVID-19 patients. [39-48]

Similarly, US and Israeli studies found that vitamin D status was strongly inversely associated with COVID-19 incidence, hospitalisation, transfer to intensive care and mortality and that testing positive for COVID-19 was inversely associated with vitamin D levels, irrespective of ethnicity, sex or age; vitamin D insufficiency (30-50 nmol/l) prevalence in intensive care patients was 84.6%, vs. 57.1% in ward patients. A joint US/Egyptian study found that mean serum vitamin D levels among COVID-19 patients was 22.9 nmol/L (i.e. deficiency), with lower levels correlating with a worse outcome. In a Spanish study, vitamin D deficiency was found in 82.2% of hospitalised COVID-19 patients. [24,49-56]

A study from the Philippines showed that for each standard deviation increase in serum vitamin D levels, the odds of experiencing only mild COVID-19 rather than severe illness was 7.94 times greater and the odds of having a mild clinical outcome rather than a critical outcome was as high as 19.61 times greater. Furthermore, a German study found that vitamin D levels <30 nmol/L was associated with a high risk of invasive mechanical ventilation (HR 6.12) and/or death (HR 14.73), while a Korean study also found that subjects with COVID-19 showed significantly lower vitamin D values than the healthy control group. Similarly, an Iranian study showed that COVID-19 patients with serum 25(OH)D of ≥75 nmol/L showed a marked reduction in clinical severity, inpatient mortality and inflammation; fewer than 10% of patients aged >40 with vitamin D levels ≥75 nmol/L died compared to 20% who had vitamin D levels <75nmol/L. [57-60].

As a guide to the level of vitamin D required to avoid death in COVID-19, one study showed that the majority of the COVID-19 cases with vitamin D levels <50nmol/l died; in multivariate analysis, vitamin D status was strongly associated with COVID-19 mortality. This is demonstrated admirably in this graph, where deaths start to reduce sharply at 27.5ng/ml (approx. 70nmol/L) but do not reach zero until around 35ng/ml (approx. 85nmol/L). [61]



Results of the age-adjusted clinical study by the working group of Dr. Prabowo Raharusun.

While these are cross-sectional studies, a prospective study of patients who had a vitamin D level measured in the year before COVID-19 testing, the relative risk of testing positive for COVID-19 was 1.77 times greater for patients with vitamin D deficiency compared with patients with vitamin D sufficiency. Among those who were tested up to 10 years previously, a significant association was also seen between low vitamin D levels and the risk of COVID-19 infection, with the highest risk observed for severe vitamin D deficiency. [62]

Annex C: Studies showing effectiveness of vitamin D for treatment of COVID-19

There are now numerous clinical trials of vitamin D administration for COVID-19 registered on various clinical trial websites; we do not yet have results for these. Nevertheless, among trials of protocols including vitamin D, a Singapore study gave 1000 IU/day oral vitamin D3, 150mg/day magnesium and 500μg/day vitamin B12 to COVID-19 patients aged ≥50 who did not require oxygen on admission; in multivariate analysis, supplementation was associated with a significant reduction in the proportion of patients with clinical deterioration requiring oxygen support and/or intensive care support (17.6% versus 61.5%). Similarly, US researchers have successfully used several micronutrients for treatment, including vitamins C and D, while the MATH+ protocol, used in several US hospitals, includes 4000 IU/day vitamin D for both prevention and treatment. [63-67]

Recently a Spanish study gave all COVID-19 patients normal standard care (azithromycin and hydroxychloroquine) and then patients were randomised to calcifediol (a vitamin D analogue) or placebo. Those receiving vitamin D were given a high dose on admission and then a lower dose twice over the first week and then weekly until discharge. Among the patients on placebo, 50% had to be transferred to intensive care versus 2% on vitamin D; among those on placebo, 8% died versus none on vitamin D. [68]

Annex D: Vitamin D and the Black, African and Minority Ethnic (BAME) community

The BAME community in the UK have much lower vitamin D levels, which is probably because the screening effect of melanin pigment in darker skin means far stronger sunlight is required to make vitamin D from sun exposure [69].

A study of UK NHS healthcare workers showed that those from a BAME ethnic group were significantly more likely to have vitamin D deficiency, particularly among males. Being a member of the BAME community was a significant independent predictor of vitamin D deficiency (OR 8·86; $p<0·001$), i.e. the BAME community were nearly nine times more likely to have vitamin D deficiency [70].

A survey of UK NHS staff mortality found a disproportionately high rate of BAME individuals. They reported that 21% of healthcare workers come from the BAME community but they accounted for 63% of deaths in total. The figures were much worse among medical staff (i.e. not nursing or support staff), where 44% were from the BAME community but 95% of COVID-19 medical staff mortalities were from the BAME community. [71]

Annex E: Potential vitamin D toxicity

A belief has arisen that intakes above 2,000 IU/day risk inducing vitamin D toxicity. This belief originated from the UK Scientific Advisory Committee on Nutrition (SACN) 2016 report [5], which set the upper limit at 2,000 IU/day. SACN cited a paper by Veith [72] showing toxic effects above this level. However, this paper actually states that toxicity may occur at 25(OH)D concentrations beyond 500 nmol/L, which could not be achieved unless an individual was taking extremely high doses for a prolonged period of time (30,000 IU/day for three months). This warning has been misunderstood and misquoted and has given rise to a lot of pointless restriction of vitamin D intake.

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