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Vitamin D

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Editor – In their recent article, Griffin *et al* suggest that all adults should receive 800–1,000 IU vitamin D daily supplementation, perhaps to reduce the impact of the COVID-19 pandemic.[1] They point to an observed association between low serum 25-hydroxyvitamin D (25(OH)D) concentration and COVID-19 seropositivity in a recent study involving two of the current article's authors.[2] In addition, they highlight a small, open label, pilot study from Spain (n=76), which suggested a lower rate of intensive care unit admission with vitamin D supplementation compared with placebo (baseline and on-treatment 25(OH)D concentrations not reported).[3]

There is a familiar tale of vitamin D that has been repeated over the last few decades. Observational studies associate low serum 25(OH)D with numerous adverse health outcomes.[4,5] Yet despite tens of thousands of people being randomised into studies, the evidence for any health benefit from vitamin D supplementation still evades us.[6–7] The reason for the association of low 25(OH)D and adverse outcomes is multifactorial; in part related to people with poorer health status getting less sunlight exposure and having reduced dietary intake; in part due to the negative acute phase response of serum 25(OH)D (ie it is lowered in times of bodily inflammation).[8]

Through the majority of their article, Griffin *et al* consider the serum concentration at which 25(OH)D would justify supplementation. The argument for a higher threshold (50 nmol/L) being mainly supported by the observation that elevating serum 25(OH)D concentration suppresses parathyroid hormone release. But does this lead to any tangible health benefits?

There is some evidence that only 25(OH)D concentrations of 10 nmol/L or below create significant biochemical disorders, such as hypocalcaemia.[9] Improved bone health has been examined as a potential major benefit of vitamin D supplementation. A study that randomised 2,578 people aged over 70 years (mean age 80) compared vitamin D supplementation with placebo over a median follow-up of 3.5 years.[10] Despite higher serum 25(OH)D concentrations achieved with supplementation (60 nmol/L vs 23 nmol/L), no reduction in fracture rate was detected. These data do not support accepting <50 nmol/L as the threshold for 25(OH)D deficiency.

In any case, Griffin *et al* are not advocating a treat-to-target approach, instead a blanket supplementation for all adults. Although the risk of harm may be small, adverse effects would include some gastrointestinal symptoms and occasional cases of hypercalcaemia.[7] Additional tablets would contribute to the growing burden of polypharmacy for many people. But perhaps most importantly, what would be the opportunity cost? Instead of using resources putting unwanted and unopened boxes of pills in every home in Britain and Ireland, we could be investing in shared decision-making processes to encourage health improvement for individuals under our care. Promoting non-pharmacological approaches, including smoking cessation and exercising outdoors, would have a far greater impact on our nations' well-being. ■

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Response

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We thank Dr Woodford for his interest in our article. In this we focus on the definition of vitamin D sufficiency as defined by serum 25(OH)D concentration and hence on the appropriate daily supplement to ensure this, particularly in countries such as the UK where the average serum 25(OH)D concentration falls by around 50% through winter.[1] He is sceptical about our support for 50 nmol/L as the appropriate target for sufficiency and cites as evidence for a much lower target level (10 nmol/L) a study that sought to define a 25(OH)D level below which the serum concentration of activated $1,25(OH)_2D$ can no longer be sustained.[2] Low levels of $1,25(OH)_2D$ are certainly a good predictor of mortality in patients with acute respiratory distress syndrome[3] but, as we reported, less extreme degrees of vitamin D deficiency are commonly found in rickets. Moreover, serum concentrations of $1,25(OH)_2D$ may not be so relevant to immune function because immune cells and many epithelial cells are able to synthesise $1,25(OH)_2D$ from 25(OH)D locally.[4] Unlike endocrine vitamin D metabolism by the kidneys, extra-renal production of $1,25(OH)_2D$ appears to be highly dependent on available 25(OH)D. The optimal level of 25(OH)D required for this process has yet to be determined but may be higher than the levels of 25(OH)D required to protect against rickets. In our article, we demonstrated the lack of evidence underlying the UK Scientific Advisory Committee on Nutrition (SACN) choice of 25 nmol/L as target for sufficiency and supported the 50 nmol/L target recommended by the European Food Safety Authority and the American Institute of Medicine (now National Academy of Medicine). Both these organisations have come to this conclusion by systematically reviewing a large body of evidence including musculoskeletal and adverse pregnancy-related health outcomes and they reference this extensively.[5,6]

We have subsequently reviewed the substantial evidence linking vitamin D deficiency with severity of COVID-19.[7] This includes seasonality-latitude-ultraviolet exposure; associations with obesity, ethnicity and living in institutions; and studies showing reduced severity with calcifediol (25(OH)D) treatment in hospital and vitamin D supplementation in the community. Previous studies with respiratory infections as the endpoint have also shown benefit from daily vitamin D supplementation.[8] A single 1,000 IU / 25 µg capsule or tablet per day will usually cost less than 10p and there should be no significant risk of side-effects. In the Cochrane review cited by Woodford, significant hypercalcaemia was not reported (risk ratio (RR) 1.57; 95% confidence interval (CI) 0.8–3.05) for vitamin D given as D2, D3 or 25(OH)D without calcium nor were gastrointestinal symptoms increased (RR 0.95; 95% CI 0.79–1.14).[9]

Attention should urgently be paid to avoidance of vitamin D deficiency during this pandemic. ■

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Cardiac investigations after ischaemic stroke

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Editor – I read with great interest the paper by Helliwell *et al*.[1] The authors describe the case of a patient with stroke due to cardiac papillary fibroelastoma (CPF) successfully treated with systemic thrombolysis. They discuss two main points: the safety of the reperfusion therapy in stroke due to CPF and the importance of