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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

early evaluation with transthoracic echocardiography (TTE) in patients with ischaemic stroke.

In relation to the first point, CPF is a very infrequent cause of stroke. Due to this rarity, (also considering CPF as the cause of 1% of all cardioembolic infarctions, cardioembolic strokes as 30% of all ischemic strokes and eligibility for alteplase of about 8%), the probability for a stroke physician to treat with thrombolysis a patient with stroke due to an unknown CPF would be less than one patient in every 4,000.[2,3] Furthermore, in the cases described in literature, outcome was generally good, without significant increase of intracerebral hemorrhage; unlike myxoma, CPF usually do not cause invasive destruction of the cerebral vasculature, so reducing hemorrhagic risk.[3] Hence, neurologists should not fear a CPF as the underlying cause of stroke in the setting of thrombolysis.

As to the importance of early completion of cardiac investigations after ischaemic stroke, current evidence on cost-effectiveness seems insufficient to justify routine use of TTE in all stroke patients.[4,5] The reported yield of TTE ranges from 1.3% to 48.0% with differences mainly due to the used definition of 'yield' (any echo abnormality, any potential cardiac source of embolism and major risk sources only).[6,7] In a recent series considering more relevant clinical criteria, TTE might lead to a change in clinical management in ~1/10 patients, but changed acute treatment decisions in <1% of patients.[8] The importance of an early TTE investigation is probably not generalisable and dependent on age and vascular risk burden of the patient and on the type of the stroke. Stroke due to CPF are generally embolic stroke of undetermined source in patients under 60 years and often without major vascular risk factors, a subgroup with clear indication to TTE as first-line investigation. ■

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