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Letter: low population mortality from COVID-19 in countries south of latitude 35° North supports vitamin D as a factor determining severity. Authors' reply

EDITORS,

We thank Dr Mansur for his interest in our editorial in which we highlighted the association between northern latitude and increased COVID-19 mortality[1] and for his helpful comments about the potential importance of vitamin D effects on cathelicidin and on the renin-angiotensin system, which could be important in protecting against severe COVID-19.[2] Vitamin D is a secosteroid hormone, derived like cortisol and sex hormones from cholesterol, so not surprisingly it has a broad range of actions reflecting the several hundred or more genes that are vitamin D responsive.[3,4]

Thrombosis is another aspect of severe COVID-19 illness where vitamin D may be very important, as previously highlighted by Tian and Rong.[5] The lupus anti-coagulant abnormality, characterised by prolonged activated partial thromboplastin time, has recently been reported in COVID-19.[6] This is the coagulopathy associated with anti-phospholipid syndrome in which there is evidence of seasonality[7] and a strong association with vitamin D deficiency.[8] Kawasaki syndrome, currently being reported with increasing incidence while countries are in 'lockdown', also has a winter predominance and here too a causative role for vitamin D deficiency has been suggested.[9]

All the associations between vitamin D deficiency and COVID-19 severity are circumstantial but they are stacking up and obtaining more direct evidence will not be easy. If low serum vitamin D levels are found in patients with severe COVID-19 these could reasonably be attributed to the well-recognised negative acute phase reactant response of vitamin D to illness.[10] A controlled trial of vitamin D supplementation would be intellectually neatest but this too will be difficult. Giving vitamin D to patients who are already ill may be too late. A placebo-controlled trial of prophylactic vitamin D in the community might be best but it could be very hard to find people willing to take the chance of being randomised to placebo rather than to a vitamin that is known to be essential—the clue is in the name!

If the vitamin D hypothesis is correct, then we would hope to see some reduction of COVID-19 severity in the Northern Hemisphere as we move into summer—provided that people who are not taking supplements get sufficient sunlight. Meanwhile people in the Southern Hemisphere might be well advised to take vitamin D supplements as they move into winter.

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LINKED CONTENT

This article is linked to Rhodes et al and Mansur papers. To view these articles, visit https://doi.org/10.1111/apt.15777 and https://doi.org/10.1111/apt.15820.

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Letter: assessing iron deficiency in patients with IBD—a step in the right direction, but uncertainty remains

We commend Daude et al for attempting to address the clinical conundrum of assessing iron deficiency in patients with inflammatory bowel disease (IBD), but, without assessing bone marrow stores or response to supplementation, their data only partially addresses the circular argument regarding accuracy of blood-based biomarkers.[1]

Iron deficiency affects 50%-90% of patients,[2] and is associated with reduced quality of life.[3,4] Monitoring of iron stores, and replacement when deficient, is recommended in patients with IBD.[3] Inappropriate supplementation of iron without absolute or functional iron deficiency may risk gastrointestinal adverse events with oral dosing, or infusion-related reactions and hypophosphatemia with intravenous iron.[5,6] Hence, the need for an accurate, sensitive marker to complement clinical acumen is paramount.

Central to the problem is that ferritin, the most sensitive marker of iron deficiency in patients without inflammation, is an acute phase reactant. The precise threshold of ferritin that retains sensitivity and specificity for indicating iron deficiency in IBD is a moving target, dependent on degree of inflammation, for which markers such as C-reactive protein (CRP) and faecal calprotectin themselves have suboptimal accuracy. When serum ferritin exceeds 100 ng/mL, transferrin saturation <20% has been used as a threshold for iron replacement in pivotal trials, but with little evidence base, no formal evaluation in patients with IBD, or consensus across medical specialties.[3,7,8]

We have analysed 1603 iron studies of 459 patients (mean age 45.5 [range 16.5-88.2] years; 307 Crohn's disease, 139 with ulcerative colitis [UC], and 13 IBD unclassified, Table S1) over 6 years. Transferrin saturation inversely correlated with markers of systemic inflammation (Figure 1). The correlation coefficient of transferrin saturation with CRP (Spearman $r = -0.440$, $P < 0.0001$) was stronger than that for ferritin and CRP ($r = 0.124$, $P < 0.001$). Whether this represents hepcidin-mediated reduced intestinal iron absorption, or displacement of iron from transferrin, and how this change affects specificity of transferrin saturation as a marker of iron deficiency in inflammation, requires further study.

Soluble transferrin receptor (sTFR), used by Daude et al as the reference marker, is unaffected by inflammation, and therefore more useful in differentiating iron deficiency from anaemia of chronic disease, but limited by availability.[9] The positive predictive value of sTFR >2.8 mg/L for iron deficiency in anaemic patients having a bone marrow aspirate or documented response to iron therapy was only 44%.[9] Hence, without assessing bone marrow iron stores or response to replacement, the figures by Daude et al regarding sensitivity and specificity of ferritin and transferrin saturation, especially in a population where only 16% had anaemia, must be regarded