JIM Letter to the Editor

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Authors reply: Low vitamin D is a marker for poor health and increased risk for disease – but causality is still unclear in most cases

Dear Editor,

I have read the letter by Dr Grant with great interest [1]. The question whether vitamin D can prevent common diseases, such as hypertension, diabetes and cardiovascular diseases is often debated. The field is somewhat polarised between hard-line sceptics and more positive "believers". Both teams use a long line of evidence to support their respective views. In my editorial, I tried to shed light on some of the different views in the field and pointed out that there is still a lack of solid results from large, randomised and placebo-controlled clinical trials (RCTs) for most indications. One exception could be the effects on respiratory tract infections, where two large meta-analyses on RCTs have shown a small but statistically significant effects of about 8%–10% [2, 3]. However, two recent RCTs on vitamin D supplementation against COVID-19 failed to show any beneficial effect [4, 5]. These are just a few examples, but it is clear that we lack evidence from *bona fide* RCTs on the beneficial effects of vitamin D supplementation for most indications.

However, I do agree with Dr Grant that there are many other pieces of evidence that point in favour of vitamin D for many human diseases. For example, there is mechanistic evidence that vitamin D can modulate inflammation in T-cells from patients infected with SARS CoV-2 [6], vitamin D can directly induce antimicrobial peptides in human macrophages and fight tuberculosis [7] and – as an example, the vitamin D receptor is expressed in beta cells in the pancreas [8]. On top of these mechanistic leads, there are many observational studies that show that low vitamin D levels are associated with an increased risk for disease. And, more recently, several studies based on Mendelian randomisation analysis suggest that vitamin D levels can be linked to human disease. Up to this point, I agree with Dr Grant.

Nevertheless, the bar for certainty is higher than a plausible mechanism, observational evidence and Mendelian randomisation analyses and needs to be based on solid RCTs. It is always possible to find problems with available RCTs in the field and claim that they were not performed in the correct way. However, to be able to change paradigms and guidelines, we need solid evidence from RCTs and that is currently lacking for most indications, as I pointed out in my editorial. For medical doctors, including myself, it is important to follow guidelines and regulations. Thus, any clinical decision to start vitamin D supplementation has to be based on solid evidence. Dr Grant has a slightly different platform in this discussion, because he represents a company that produce and sell vitamin D supplements to the public. This difference might not be decisive for his standpoints but is nevertheless important to keep in mind as there could be a conflict of interest here.

To end in a more positive note, there is still a lot to discover in the field of vitamin D and the optimal RCT, which consider all possible confounders, has not yet been performed. Thus, there is more to learn and perhaps we will reach a more solid evidence base in this field in the future. Until then, I recommend a pragmatic approach where vitamin D supplementation should be directed towards risk-groups for vitamin D deficiency, such as the obese, pregnant women, and those with darker skin. A cut-off level of 50 nmol/L will work for most individuals and supplementation with 1000–2000 IU/day will support the bone, improve immunity, and potentially also reduce the risk for respiratory tract infections.

Conflict of interest

No conflict of interest to report.

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