Comparison of vitamin D2 and vitamin D3 supplementation in increasing serum 25-hydroxyvitamin D status: a systematic review and meta-analysis

Dear Sir:

We thank Tripkovic et al (1) for their recent comprehensive review, which will be of particular interest to those involved in recommending vitamin D supplementation. The authors reviewed and updated the evidence with regard to the effectiveness of vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) in increasing serum 25-hydroxyvitamin D [25(OH)D]. However, it appears that the conclusion paragraph in the Abstract is based on bolus administration only as there was no difference between vitamin D2 and vitamin D3 at increasing serum 25(OH)D concentration from daily supplementation. Whereas the conclusion is valid when considering treatment options where a loading dose may be required before prescribing a maintenance dose in the longer term, it may not be applicable where recommendations are based on daily intakes. We believe that in the interest of public health, the message should be that there is an option for those who for religious reasons and strong vegan principles may prefer to take vitamin D2. Also, although unlikely to be a major problem, at least in the short term when considering vitamin D sources, there could be issues around sustainability in the future. Ultraviolet irradiation of plant-based foods to produce ergocalciferol would be an alternative option that might need to be considered when deciding on large-scale fortification (2).

The issue of the different metabolic fates of vitamin D2 and vitamin D3 is an interesting one. Vitamin D2 appears to be metabolized more rapidly (3), which may underlie the rationale that vitamin D2 is less effective in increasing serum 25(OH)D concentration. It has been inferred that vitamin D2 may be less toxic than vitamin D3 when given in large amounts (3).

Our data from the VICtORy (Vitamin D and CardiOvascular Risk) study (4) during which participants [healthy postmenopausal women; mean (±SD) age: 64 ± 2 y] were supplemented for 1 y with vitamin D3 (400 or 1000 IU) or placebo daily in a parallel-group, double-blind randomized controlled trial of cardiovascular disease risk outcomes shows that increases in mean serum 25(OH)D3 concentration resulted in concomitant decreases in mean serum 25(OH)D2 concentration (Figure 1). An important feature of

FIGURE 1. Mean (±SEM) serum 25(OH)D2 and 25(OH)D3 responses to daily supplementation with vitamin D3 [400 IU (n = 83) or 1000 IU (n = 87)] or placebo (n = 87) for 1 y. 25(OH)D2, 25-hydroxyvitamin D2; 25(OH)D3, 25-hydroxyvitamin D3.

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this study is that all participants were randomized simultaneously between January to March in the same year. These data suggest there may be interaction between the 2 forms of vitamin D, with a dose-dependent response. This is not caused by assay interference because the addition of increasing concentrations of 25(OH)D3 into samples containing varying concentrations of 25(OH)D2 does not result in a decrease in the measured 25(OH)D2 concentration. These effects, although small, may have implications in the assessment of the benefit-risk ratio of different vitamin D treatment regimens and in furthering our understanding of vitamin D metabolism.

We agree with the authors that further research is required to examine other metabolites of vitamin D. Developments in tandem mass spectrometry may allow for their more accurate and precise measurement, which could be particularly important after administration of high doses of vitamin D either orally or intramuscularly.

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Reply to HM Macdonald et al

Dear Sir:

We appreciate the comments made by Macdonald et al regarding our article, which is the first-ever systematic review and meta-analysis of the current evidence available comparing the relative efficacy of vitamin D2 and vitamin D3 in increasing serum 25-hydroxyvitamin D [25(OH)D] concentrations.

Because this particular area of the vitamin D field is controversial due to the conflicting opinions on the likelihood of equipotency between vitamins D2 and D3, the purpose of this meta-analysis was to highlight that, at the moment, the research is not consistent in either study design or outcome and is also underpowered. Therefore, the article was written to describe and explain what data are currently available, stimulate discussion within the field, and show the urgent need for a cohesive approach to investigating the comparative effects of vitamins D2 and D3. It was initially hoped that the meta-analysis would unequivocally determine whether vitamin D2 or vitamin D3 was more efficacious; however, it rapidly became apparent that the field is far too underdeveloped at the moment to be able to achieve that aim.

Overall, when all available studies were included and a random-effects model was used to account for heterogeneity, it was found that vitamin D3 appeared to be more effective at increasing serum 25(OH)D concentrations than vitamin D2. The conclusion that vitamin D3 appears to be more efficacious than vitamin D2 was clearly drawn from this main analysis of the data, which included all studies that were available at the time that directly compared vitamins D2 and D3.

The data within the meta-analysis to which Macdonald et al are referring is the latter subanalysis, which was executed to explore the data available and to see whether further insight was possible when the frequency of dosage administration was considered. It is at this point that there appears to be some discrepancy between the properties of vitamins D2 and D3—there was no significant difference between the 2 vitamers when they were taken in a daily dosage. However, there still appeared to be a nonsignificant trend ($P = 0.10$) toward vitamin D3 retaining preference in increasing 25(OH)D concentrations (1). Vitamin D3 was significantly more efficacious than vitamin D2 ($P = 0.0002$) when given as a bolus dose (1).

This result was intriguing, yet there is still little evidence available within the included studies or beyond to explain the mechanism behind how and why the body appears to differentiate between vitamins D2 and D3. This brings us back again to the call for further studies that are specifically designed to determine the mechanism between vitamin D2 and D3 metabolism and that are highly powered to help prevent uncertainty in the outcome.

Macdonald et al make a valid point that vitamin D2 is a valuable source to those individuals unable to consume vitamin D3 sourced from animals, because of various cultural, religious, and ethical reasons. This is not disputed in our article; vitamin D2 is clearly effective in increasing serum 25(OH)D concentrations, as shown by the data collated in the meta-analysis. Indeed, we state that it should always remain an option when seeking to improve vitamin D intake from dietary sources for those who require it. However, it is also important to note that there are now nonanimal vitamin D3 supplement sources available on the market (Vitatrine; ESB Developments Ltd).

The data presented by Macdonald et al from the VICTORY study provide interesting, yet when compared with other studies, generally contradictory data in terms of the metabolic fates of vitamins D2 and D3 and how they affect 25(OH)D metabolites. From the data, it appears that the vitamin D3 supplementation initiated an increase in 25(OH)D3, yet a decrease in 25(OH)D2; however, contradictions to this result are present within the literature. The study by Glendenning et al (2) was the only study involved in the meta-analysis that published complete 25(OH)D metabolite data. It was found that after vitamin D3 supplementation of 1000 IU/d for 3 mo,