Reviewer’s report

Title: Differential effects of vitamin D2 and D3 supplements on 25-hydroxyvitamin D level are dose, sex, and time dependent: a randomized controlled trial

Version: 1 Date: 15 Dec 2016

Reviewer: Malachi McKenna

Reviewer's report:

General comment:

This study compares the vitamin D dose response in terms of 25OHD concentrations to both vitamin D2 and vitamin D3 giving daily, 2-weekly, or 4-weekly. The study design, performance, and analysis are conducted to the highest standard as is the discussion and review of the relevant literature.

The issue of generalizability (Lines 607-609) needs to be expanded. A major limitation of the work that needs to be understood first and then expressed in the manuscript is the generalizability of their findings in the context of vitamin D intake requirements as recently deliberated in North America for the USA and Canada by the Institute of Medicine (IOM) in the 2011 report on "Dietary Reference Intakes for Calcium and Vitamin D" and in the UK by the Scientific Advisory Committee on Nutrition (SACN) in 2016 report "Vitamin D and Health" (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/537616/SACN_Vitamin_D_and_Health_report.pdf). The estimated average requirement (EAR) according to the IOM is 10 µg/day (400 IU/day) and the reference nutrient intake (RNI) according to SACN is also 10 µg/day (400 IU/day). Furthermore, according to IOM the EAR specification is for those with minimal sunlight exposure (such as housebound individuals), and the specification refers to total oral vitamin D intake not just supplemental intake. SACN makes a similar statement about the uncertain effect of sunlight exposure on determining the oral intake requirement. The supplemental dose in this study is 4.5-fold higher than the EAR and the RNI. Secondly, vitamin D status in the study population with average 25OHD at about 40 nmol/L already has an estimated total vitamin D intake (from oral and sunlight sources) equivalent to the EAR, because the IOM indicated that the corresponding 25OHD for EAR is 40 nmol/L (1-3). Thus, the findings of this study are not generalizable to populations at risk of vitamin D deficiency for whom public health measures regarding fortification and supplementation are needed to address the problem. The IOM specifications have been consistently misrepresented in the medical literature (4).
Another limitation is the difference in adherence between the 3 groups. Given that the findings of the study are counterintuitive in that the daily dosing is less potent than both the 2-weekly and sometimes the 4-weekly, suggests problems with adherence. The 2-weekly and 4-weekly doses were administered under supervision, but the daily doses were self-administered with adherence being dependent on capsule counting. Although compliance was recorded as being high, there is uncertainty about reliability, which needs to be stated. Given that 2-weekly dose response was superior to 4-weekly dose response, this would support the frequent finding in the medical literature that higher doses at less frequent intervals have a lower dose response compared to equivalent but lower doses given at shorter intervals. If administration of daily doses were supervised, then the dose-response would be at least equal to if not superior to both 2-weekly and 4-weekly dosing.

Specific Comment

In lines 88-89 the authors quite correctly state that "the dose-response curve may follow a quadratic or exponential rather than linear function." Yet, in lines 422-431, the authors interpret the dose-response as a rate constant. While correct when making comparisons of dose-response between populations given similar doses and having identical 25OHD, it is a flawed approach. The IOM using a simulated model demonstrated that the dose-response was defined by a logarithmic function (1). The ViDOS study using different doses in an RCT showed that the dose-response was best defined by a quadratic function (5). Interpreting the dose-response as a linear function rather than as a curvilinear function leads to gross overestimates of intake requirements (6). In simple terms, the clinician needs to know the total intake dose (of either D2 or D3) that is required to achieve a certain 25OHD rather than endorsing a fixed linear dose-response; this is one of the paradigmatic shifts in understanding vitamin D intake requirements that arose from the IOM report. By contrast to this section, the authors in lines 491-506 address comprehensively the many factors that account for individual variability in the dose response.

Lines 88-89: It should be changed to "Further, the dose-response is curvilinear not linear (1, 5)."

References


Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:
1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal