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: 0 Date: 12 Oct 2016

Reviewer: Terry Aspray

Reviewer's report:

Abstract:

The abstract is confusing with a scattering of jargon terms and a lack of clarity.

Specific comments:

1. Background

"D deficiency" is not an acceptable term. Here (and throughout) "vitamin D deficiency" should be used.

2. The abbreviations D2 and D3 need to be defined

3. English is poor here: suggest, for example, "the relative potency of vitamin D2 and vitamin D3 and the appropriate dosing schedule for supplementation to improve serum 25—hydroxyl vitamin D…"

Methods:

4. It is convention to use the passive voice rather than "We randomized…"

5. D2 and D3 levels were not determined!

6. Primary endpoint was the AUC of what?

7. Adjusted for sex, BMI and baseline level of what?

8. How was 25(OH)D measured?
Results:

9. When referring to baseline 25(OH)D is this the total serum 25(OH)D, comprising serum 25(OH)D2 and serum 25(OH)D3?

10. Some definition of terms "AUC140", "AUC7" etc. arr required as they appear to be typos!

P4L7 I do not think that "D" is an appropriate abbreviation for "vitamin D". Here (and throughout) the term "vitamin D" should be used.

P4L11 "D-type" is an ugly term! Moreover, there is no suggestion that vitamin D2 is preferable. The question is about bio-equivalence!

P4L17 "Current unitage… " should read "The same units are used for both vitamin D2 and D3, suggesting biological equivalence"

P4L32 For "may follow a quadratic or exponential rather than linear function" I suggest "may be non-linear"

P4L35 D2 and D3 should read "Vitamin D2 and vitamin D3"

P4L39 A number of contentious assertions are made here e.g. differences in plasma (or serum) half-life, for which there is scant evidence.

P4L40 "1,25(OH2)D2" should be "1,25(OH)2D2" and "1,25(OH2)D3" should be "1,25(OH)2D3"

P4L49 instead of "increases" I suggest "increments"

P4L53 The suggestion that circulating colecalciferol or circulating ergocalciferol (which is how I read this sentence) having an important physiological role in many tissues is extremely contentious and, I believe, beyond the scope of this study!

P5L6 for "25(OH)D levels" I wonder whether the term "Total 25(OH)D levels" would be preferred, reflecting the sum of 25(OH)D2 levels and 25(OH)D3 levels?

P5L10 "The primary aim of this study was to systematically evaluate the relative efficacy of various dosing strategies of D2 and D3 oral supplements in raising 25(OH)D levels." This is not a primary objective. We need a simple null hypothesis. "The primary aim of this study was to evaluate the dose response of total 25(OH)D levels to D2 and D3 oral supplements.

P6L9 The term "partially blinded" is used here. What does it mean?

P6 There does not appear to have been an attempt at a power calculation or an estimation of what represents a clinically or statistically significant difference.
P6L46 strange to define D2 and D3 at this stage!

P7L10 "Daily doses (D2 2000 IU, D3 2000 IU, combined D2 1000 IU and D3 1000 IU, or placebo) on days 0, 1, 2, 3, 4, 7, and 14 and 2-weekly thereafter and all of the 2-weekly (D2 25,000 IU or D3 25,000 IU) and 4-weekly (D2 50,000 IU or D3 50,000 IU) doses": This is the 1st time when the intervention is clarified.

P7L15 I do not understand why "blood samples were obtained and a standardized meal was given."

P7L26 "out-of-the-ordinary sun exposure" is not well defined!

P7L34 HPLC is no longer an appropriate way to measure or discern between vitamin 25(OH)D2 and 25(OH)D3, never mind measurement of serum vitamin D2 or serum vitamin D3. This approach needs validation and more QC data!

P8L12 term "AUC140" is defined for the first time, I believe (although it has already been used!)

P8L14 I think the term is "hypercalcurea."

P8L15 "AUC from day 0 to 7, day 0 to 14 and day 0 to 28 (AUC7, AUC14, and AUC28) were also calculated. AUCs were analyzed using analysis of covariance" does not define the term(s) for which AUC is estimated!

P9L7 "Two hundred seventy nine participants were randomized to 8 groups" is not justified in terms of the ability to detect a difference between SO MANY groups!

Results section rambles on without a clear message, which is not surprising, since there is not a clear hypothesis!

P16L7 What does "partially-blinded" mean?

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

No

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.

No
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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I recommend additional statistical review

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