Reviewer’s report

Title: The effects of single high-dose or daily low-dosage oral colecalciferol treatment on vitamin D levels and muscle strength in postmenopausal women

Version: 0 Date: 23 Feb 2018

Reviewer: Zaki Hassan-Smith

Reviewer’s report:

Apaydin and colleagues have made a potentially useful addition to the literature. There remains uncertainty as to the optimum dosing regimen for vitamin D deficiency. The study is logically designed with appropriate end points to answer its research question. As such it should be reported. Baseline demographics (table 1) are reassuring in view of the level of detail that has been collected on treatment groups i.e. sun exposure, physical activity, style of dress etc. Good that at baseline all participants had true vitamin D deficiency with serum 25-OHD <20ng/ml. I have some comments on the paper listed below that should represent minor amendments:

1. nmol/L and mmol/L may be helpful for wider audience when discussion 25-OHD and serum calcium concentrations.

2. What method of randomisation was used? Were clinicians/ study team blinded to this?

3. A comment on study limitations and effects of multiple comparisons is needed (particularly with regards the different groups and muscle function measures).

4. It appears that there is a trend to increased muscle strength across the different measures, but only 2 groups (daily dosage dominant, knee extension and daily dosage non-dominant, knee flexion) reached statistical significance - as the authors state, it may be that the study is underpowered. How were power calculations made? Alternatively, recent evidence has suggested that there are differential effects of different vitamin D metabolites on muscle (PLoS One. 2017 Feb 15; 12(2):e0170665). In particular 1,25OHD has direct effects on muscle mitochondrial function and gene expression (Endocrinology 2016 Jan; 157(1):98-111, J Biol Chem 2016 15;29(3):1514-28). This may explain some of the complexity in relationships observed in this study between post-treatment vitamin D status (serum 25OHD) and muscle function. Multi-metabolite analysis in a future study would be interesting.

5. There have been some concerns regarding the safety of single large doses of vitamin D supplementation with regards to falls risk - some acknowledgment of this would be useful.

6. Table 4 is confusing to look at in current format. May be better presented as a graph.

A couple of minor points on typos and grammar:
Colecalciferol preferred to cholecalciferol.

Unclear meaning of phrase: 'On the other hand, the form of vitamin D therapy, the dose and dosing interval, and route of administration is considered negligible because it does not deserve specific recommendations or guidelines'

Difficult to follow, would review language and consider fragmenting this sentence: 'In a systematic review of studies using large, single dose, oral vitamin D supplementation in adult populations, the authors mentioned that a single vitamin D3 dose of ≥100,000 IU provided a perdurable effective means of increasing short-term vitamin D concentrations to >20 ng/mL, although vitamin D3 doses of ≥300,000 IU were required to achieve 25(OH)D3 concentrations >30 ng/mL and decreased plasma PTH concentrations [20].'

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

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