Reviewer’s report

Title: Reduction of Parathyroid Hormone with Vitamin D Supplementation in Blacks: A Randomized Controlled Trial

Version: 2

Date: 27 July 2015

Reviewer: Anne Sumner

Reviewer’s report:

1) The manuscript by Chandler et al. evaluates the effect of placebo and 3 different doses of vitamin D on PTH levels in 328 blacks in a randomized double-blind trial conducted over 3 years in the autumn months to avoid the effect of sunlight on vitamin D. Even though PTH was in the normal range for 214 of the 254 participants who had PTH levels, the goal was to lower PTH with vitamin D supplementation. The two big challenges with this manuscript have to do:

a) Lack of outcome measures.

b) PTH response to vitamin D supplementation when only 254 of 328 had baseline PTH levels.

c) High number of persons with missing PTH levels.

Compulsory Revisions:

2) In regard for the justification of performing the study:

The IOM, Endocrine Society and United States Preventive Task Force do not support providing vitamin D supplementation for reasons other than bone health (The references are ref 10 from the manuscript, Holick JCEM 2011; 96:1911-1030 and Ann Intern Med 2015:162:133-140).

a) The statement from the IOM is: For extra skeletal outcomes, including cancer, CVD, DM and autoimmune disorders, the evidence was inconsistent, inconclusive as to causality and insufficient to inform nutritional requirements.

b) The USPTF statement is: The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of screening for vitamin D deficiency in asymptomatic adults (and therefore by extension the need for supplementation).

d) The part in parentheses in the sentence above was added by the reviewer. Chandler et al. have proven they can raise vitamin D levels and lower PTH in blacks but whether they should and whether it is safe to do is unproven. Especially when PTH levels for the most part were normal. If 40 persons had secondary hyperparathyroidism then PTH was normal in 214 of 254 participants. References beyond 6 and 7 should be provided.

In short the authors need to revise the manuscript both introduction and discussion to provide a fairer view about how deep the controversy is. They cite a
few articles to support their review but the IOM (ref 11) cites hundreds of reference which have led them to conclude that the data is inclusive.

In addition, they should discuss in the study they are conducting that they are only proving they can change vitamin D and PTH levels, but they have no outcome measure as to long term effect on health of changing either vitamin D or PTH levels and this is a major limitation of the study design.

So the authors must cite the USPSTP statement and they need to provide stronger language about the inherent controversy regarding the study. In addition, they must cite more recent publications about the PTH-Vitamin D axis by Aloia. Reference by Aloia be added including ones from AJCN 2006 and JCEM 2010)

3) Furthermore the authors need to provide more discussion on whether it is safe or appropriate to raise vitamin D levels in blacks when PTH is not elevated. In fact, raising vitamin D levels in blacks could actually have an adverse on bone health in blacks. The authors are referred to the Women’s Health Initiative (JBMR 2011;26:2378-23880) and they must cite this reference.

4) The wisdom of providing vitamin D supplementation to the 83 people on HCTZ is unclear. HCTZ raises calcium levels and thereby influence the calcium, vitamin D, PTH axis. These people should be excluded and the analyses performed again. They made many adjustments for these people, but they should be excluded.

5) The authors must clear up some key issues on PTH.

a) First, they state in Table 1 footnote that baseline PTH levels were available only in 254 of 328. If baseline PTH levels are missing in 74 persons (23% of the total) how can PTH response to vitamin D supplementation be measured. This needs to be addressed.

b) The normal range for PTH is controversial. When the Reveiwer reviewed the literature on this topic in the past, the most common upper threshold for PTH was 65 pg/mL. However, the authors state without any references on ln 163 that normal PTH levels are 13-54 pg/mL. Therefore they need to provide references to justify this lower threshold of 54 pg/mL. In addition, they have to correct some internal inconsistencies. On ln 207 they say that 40 persons had secondary hyperparathyroidism with PTH>60 pg/mL. The authors need to be consistent. Is their upper threshold for PTH>55, >60 or >65 and provide references for their choice. And then they need to define secondary hyperparathyroidism according to the definition they provide for the upper limit of PTH.

Minor essential revisions:

1) An additional column with ranges should be added to Table 1 which provide the characteristics of the overall population with ranges specifically for calcium, vitamin D and PTH.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare I have no competing interests.