Author's response to reviews

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

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Author's response to reviews: see over
Re: MS: 6526838417103976

September 11, 2015

Research article

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

Dear Associate Editor:

Thank you for your thoughtful comments regarding our manuscript. Below please find our point-by-point responses to these comments. We hope that you find the revised manuscript suitable for publication in BMC Nutrition.

Sincerely,

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Reviewer 3

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.

Comment:
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.

Response:

Thank you for your thoughtful comments about the limited nature of studies that have investigated the association of vitamin D supplementation with nonskeletal outcomes. We had 254 participants with PTH measures. The Aloia et al study that you highlight in your comments had only 235 Black postmenopausal women. We acknowledge that the present data is inconclusive. Ongoing trials such as the NIH-funded VIITamin D and OmegA-3 Trial (VITAL) (1 U01 CA138962), a large-scale, randomized, primary prevention trial testing 2000 IU/d vitamin D₃ (cholecalciferol) and 1 g/day omega-3 (ω-3) fatty acids (840 mg EPA+DHA in 1.3:1 ratio) will provide detailed investigation of the association of vitamin D supplementation with nonskeletal outcomes. Added the following lines to the introduction to highlight the limitations of current reported results “For extra skeletal outcomes, including cancer, cardiovascular disease (CVD), diabetes mellitus (DM) and autoimmune disorders, the evidence was inconsistent, inconclusive as to causality and insufficient to inform nutritional requirements.” “The U.S. Preventive Services Task Force (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.” “Therefore, more data are needed to assess the need for vitamin D supplementation for non-skeletal outcomes and to identify potential threshold effects for non-skeletal outcomes.” Future studies will investigate outcome measures. The goal
of this study was just to evaluate the role of vitamin D supplementation on PTH homeostasis.

Whether common laboratory reference ranges are appropriate for all ethnic groups is unclear.

The USPTF did conclude that the harms of screening for and treating vitamin D deficiency are likely “small to none”, but it still is not possible to determine whether the benefits outweigh even the small amount of harm. The Institute of Medicine has no formal guidelines for vitamin D screening. Currently, no national primary care professional organization advises screening of the general adult population for vitamin D deficiency. The American Academy of Family Physicians, the Endocrine Society, the American College of Obstetricians and Gynecologists, the American Geriatrics Society, and the National Osteoporosis Foundation all recommend screening for patients at risk for fractures or falls only.

Furthermore the IOM and the USPTF are focused on providing a firm evidential base for disease prevention. But clinicians may need to consider a different focus- full nutrient repletion to optimize their patients’ health (e.g. reduction in mortality). A strict disease-avoidance strategy is too simplistic with regard to micronutrients, because they may not directly cause the effects often attributed to them. Alternatively, when supplies of micronutrients are inadequate, cellular responses may be blunted. This is dysfuction, but not clinically manifest disease. Such dysfunction may lead ultimately to various diseases, but disease prevention is a dull tool for discerning the defect. A disease-prevention paradigm doesn’t clearly show whether there is enough of the nutrient present to enable appropriate physiological responses.

Please see line 91-101

Also added a statement to the conclusion highlight your statement that we have proven that vitamin D supplementation raises vitamin D levels and lowers PTH in Blacks but whether it should be done and whether it is safe remains unproven.

“In conclusion, this study highlights a dose-dependent decrease in PTH in Blacks with vitamin D supplementation confirming correction of vitamin D deficiency, but whether reduction of PTH it is safe to do is unproven.” Please see line 361-363

Also added a reference to the systematic review of vitamin D and Parathyroid hormone clinical trials that showed similar findings to ours that vitamin D supplementation reduces PTH.
“In agreement with our findings, a systematic review of clinical trials on the response of parathyroid hormone to vitamin D supplementation shows that PTH decreases linearly during vitamin D supplementation for any given 25OHD level. Furthermore, the review suggests that longitudinal vitamin D supplementation studies on populations with wide range of mobility and age are needed to further elucidate their confounding effects and the inter-individual variation in responses of PTH to vitamin D supplementation.(1)”

Please see line 292-298

Comment:
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.

Response:
Thank you for highlighting that we do not have an outcome measure. We have added a statement to the discussion in the limitations paragraph “Lastly, this study shows that vitamin D supplementation changes vitamin D and PTH levels, but it has 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. However, our previous work showed that vitamin D supplementation in this cohort reduced blood pressure (Forman et al, 2013) without causing severe hypercalcemia (Chandler et al 2014).” Please see line 356-360

Added stronger language and cited the USPSTP statement as stated above.

Comment:
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)

Response:
Thanks for suggesting the inclusion of the Aloia studies. We have added these studies to the discussion. The Aloia study only includes Black women and White women( number of Black women n=235). Our study includes Black women and Black men. The Aloia study only study one measurement of 25(OH)D. Our study examines the effect of vitamin D supplementation. Vitamin D supplementation is the active introduction of vitamin D into the circulation. Vitamin D supplementation must be considered a form of hormone replacement therapy.
Therefore it raises all the questions about efficacy, dose, and side effects. Multilevel feedback and the kinetics of hormone action/reaction within the bone-kidney parathyroid loop system can complicate the investigation of a hormone of interest. Aloia’s population was younger mean age=43.7 years compared to our mean age of 52.

The normal level of PTH has not been defined in Blacks in a randomized control setting with low calcium supplementation. Aloia et al gave vitamin D 800 iu/day versus placebo and supplemented with calcium to insure a calcium intake of 1200-1500 mg/day. It is known that Blacks handle calcium differently than whites with lower calcium renal excretion in blacks compared to whites. Thus, calcium requirements may differ between Whites and Blacks.

Comment

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.

Response

Thank you for your comment. We have included the Women’s Health Initiative study in our discussion section. “The Women’s Health Initiative (WHI) nested case-control study suggested that 25(OH)D greater than 20 ng/mL is associated with increased fractures in Blacks,(2) but the cases had about 50% more treated diabetes than the controls (11% versus 16%, difference between groups p=0.05) and diagnosed diabetes is associated with greater risk of fractures in Blacks than Whites.(3) Furthermore, they could not test whether the association between low 25(OH)D levels and fracture was independent of BMD because only three WHI clinics measured BMD.(2) Interestingly, this WHI study found no association between PTH and fracture risk in any ethnic group.(2) “ Please see line 328 - 336

Comment

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.

Response

Thanks for your comment regarding the inclusion of the HCTZ users. Since our previous study documented that HCTZ users did not develop significant
hypercalcemia with vitamin D supplementation,(4) we included them in the analysis. HCTZ is a commonly prescribed anti-hypertensive medication and adds to the generalizability of our findings in Blacks who commonly have hypertension and are prescribed HCTZ. PTH response to vitamin D supplementation was measured in 254 and our findings agree with previously reported and recently reported findings of the effect of vitamin D supplementation on PTH in Blacks. A recent study in children also shows that vitamin D supplementation decreases PTH in Blacks.(5)

Comment

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 Reviewer 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.

Response

Thanks for your comments about potential limitations of measuring PTH in only 254 individuals. We have added a statement to address this potential limitation (lines 162-165). “In this ancillary analysis, PTH was measured only in 254 participants because of lack of stored blood samples for the others. Although the lower number reduces our power and statistical precision, the unavailability of sample is unlikely to cause a bias. “

Heartland Assay has declared that their range for normal PTH is 13-54 pg/mL. Of note, the normal range of PTH reported in laboratory manuals is 10-65 pg/mL.(6, 7)

The surgical literature supports the lower limit of around 12 for normal PTH. Individuals with PTH less than 12 pg/mL were much more likely to develop severe hypocalcemia. A single one hour post-thyroidectomy parathyroid hormone (1 hr
PTH) level could accurately stratify patients into high and low risk groups for the development of hypocalcemia. (8)

Efforts to reach agreement on how vitamin D deficiency is defined are complicated by the issue that the cutoff points used in reports from clinical laboratories vary.

Comment
Therefore they need to provide references to justify this lower threshold of 54 pg/mL.

Response
Heartland Assay has declared that their range for normal PTH is 13-54 pg/mL.

Comment
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.

Response
The lower threshold of 54 is defined by Heartland Assay. We decided on a threshold of 60 to be a value in between laboratory manual upper limit and the Heartland Assay upper limit.

The upper limit for PTH has been defined by Heartland Assays and lab manuals based on 1000s of individuals.

Secondary hyperparathyroidism is most frequently associated with vitamin D deficiency, very low calcium intake, impaired renal function, malabsorption, drugs interfering with calcium/bone metabolism, such as lithium salts and antiresorptive osteoporosis therapies, hypercalciuria due to a renal calcium leak. The mean PTH in our group is normal even though our participants have low calcium intake and vitamin D deficiency.

Comment
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
Response

An additional column with ranges was added to Table 1 which provides the characteristics of the overall populations with ranges specifically for calcium, vitamin D and PTH.

Reviewer 2

Reviewer’s report: This is a well-written manuscript of a recently conducted trial investigating the effect of varying doses of vitamin D3 supplementation (from 1000 up to 4000 IU per day) on plasma parathyroid hormone (PTH) levels in US blacks. The main finding is that PTH levels decrease in a dose-dependent manner with increasing daily doses of vitamin D. The study fills an important gap in the literature given the limited publications on this topic for African-Americans. A major strength of the study is its very high compliance (nearly 97%).

Major compulsory revisions

1. The manuscript is missing a CONSORT flow diagram. Nearly 80 participants from baseline Table 1 are missing from follow-up. Table 2. More detail needs to be provided about the reasons for their exclusion in the second table. If these have been reported in a previous publication, this should be described in the text and referenced so that readers don’t have to go hunting for this information.

Thanks for this suggestion. A consort diagram has now been added. PTH was measured in only 254 participants because of lack of blood for the others. Thus, Table 2 only shows the baseline and change in PTH for the 254 participants. Please see figure 1.

Minor essential revisions

1. Lines 97-98: the text in this sentence should be changed, or its references, as neither reference 13 nor 14 is an RCT of vitamin D supplementation, as implied by the text.

The references have been changed.

2. Lines 239-243: it would help readers if the p-values for the comparisons in this sentence (presumably >0.05) are added to the text so that they can be certain about this.
3. Line 278: presumably this should be ‘PTH’ which is suppressed, not ‘25(OH)D’.

Thanks for pointing out this mistake. We have made the correction. Please see line 102-103

4. Reference 21: missing volume and page numbers.

The missing volume and page numbers have been included. Please see reference

5. Table 1: abbreviations (BMI, PTH, 25(OH)D, HCTZ) should be footnoted so that readers don’t have to go searching through the text to find their full spelling.

The abbreviations have been added as part of footnote. Please see table 1

6. Table 2: footnote abbreviations (as above).

The abbreviations have been added as part of footnote. Please see table 2

Discretionary revisions 1. The authors may like to consider adding the following publication, which is the largest ever study on the association between blood concentrations of 25OHD and PTH (Valcour A, et al. , Effects of age and serum 25-OH-vitamin D on serum parathyroid hormone levels. J Clin Endocrinol Metab. 2012;97:3989-3995). This manuscript reported data from >300,000 patients in the US, and found no threshold in the association, between 25OHD and PTH, which supports the findings in the current manuscript.

Thanks for this suggestion. We have included this new reference in our discussion section. Line 279-282

Level of interest:An article of outstanding merit and interest in its field 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 that I have no competing interests.

Reviewer 1.

Reviewer:Justin Silver Reviewer’s report: This is an extension of their study on vitamin D supplementation given to Black people in the USA. The serum samples have now been measured for PTH which is now reported. It would have been useful to have these same results included in the original paper. However, the results are of interest and the response of serum PTH is a surrogate for vitamin D insufficiency so the results are of interest. Level of interest:An article whose findings are important to those with closely related research interests Quality of written English:Acceptable Statistical review:Yes, but I do not feel adequately qualified to assess the statistics.
References


