Author's response to reviews

Title: Dose and Time Responses of Vitamin D Biomarkers to Monthly Vitamin D3 Supplementation in Overweight/Obese African Americans with Suboptimal Vitamin D Status: A Placebo Controlled Randomized Clinical Trial

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Author's response to reviews: see over
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**Editorial board**
BMC Obesity
BioMed Central
236 Gray’s Inn Road
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Dear BMC Obesity Editor,

Attached is a manuscript titled “Dose and Time Responses of Vitamin D Biomarkers to Monthly Vitamin D3 Supplementation in Overweight/Obese African Americans with Suboptimal Vitamin D Status: A Placebo Controlled Randomized Clinical Trial” that was originally submitted to one of your sister journals BMC Medicine. A critical need exists to understand the physiological sequel of vitamin D supplementation in obese individuals and African Americans, based on the most recent IOM Report. As such, for the first time, this study comprehensively evaluated dose- and time-responses of a panel of vitamin D biomarkers to vitamin D supplements in this population. Our data provide several novel findings, as reported in the manuscript.

Reviewers of BMC Medicine provided overall positive comments with minor concerns, as the BMC Medicine chief editor summarized “As you will see in the reviewers reports, the reviewers are generally happy with your study methodology, and have made some minor suggestions to improve the clarity of your work.” The BMC Medicine chief editor also recommended that the manuscript would be better suited to a specialist journal, and favored transferring this manuscript to BMC Obesity after the concerns are addressed. All the communications via email are included in the next section.

Encouraged, we have now addressed all the previous concerns and followed all the suggestions expressed by the BMC Medicine Editorial Board member, the two reviewers, and the BMC Medicine chief editor. We have provided point to point responses. We believe that our manuscript be appropriate for publication at your prestigious journal.

Sincerely,

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Response to reviewers

To the BMC Medicine Editorial Board member:
In addition to the reviewer’s reports, we also sought advice from an Editorial Board Member who gave us the following advice:

“This is an interesting study, but I’m struggling to see the novelty/major advance. Dose response and the timing needed is well known. This study, unsurprisingly, doesn't show any major difference in this population.”

Based on the concerns regarding novelty, we felt that your manuscript would be better suited in a specialist journal, as BMC Medicine only considers manuscripts of a significant clinical advance. As you will see in the reviewers reports, the reviewers are generally happy with your study methodology, and have made some minor suggestions to improve the clarity of your work. Regarding reviewer 2's comments on lack of functional measure - we suggest that you add this point to the limitation section of your work. If you are able to address these comments, I believe BMC Obesity would be appropriate for your research.

Response: Thank you very much for the positive editorial comments and constructive suggestion of transferring the manuscript to BMC Obesity. We have now addressed all the previous critiques and given point to point responses.

Novelty: A critical need exists to better understand the physiological sequel of vitamin D supplementation in obese individuals and African Americans. For the first time, we comprehensively evaluated dose- and time-responses of a panel of vitamin D biomarkers including 25(OH)D, 1,25(OH)2D, PTH, FGF-23, phosphorus, and urinary calcium to vitamin D supplementation in this population. One of our several novel findings is that although 4,000 IU/day do not seem to be superior to 2,000 IU/day in increasing 25(OH)D concentrations, 4,000 IU/day, but not 2,000 IU/day suppressed iPTH, which is clinically relevant.

Lack of functional outcome measures: The objective of the current study is to study a panel of circulating vitamin D biomarkers in response to vitamin D supplementation. Skeletal and extra-skeletal functional outcomes, that are not part of this study, would deserve investigations in the future, to help to select doses and time scheme. We have added this as a limitation of the study on line 23-25, page 13.

Reviewer 1:

This small RCT deals with bolus (monthly) dosing of vitamin D on both endocrine (PTH) and paracrine (FGF-23) pathways for vitamin D. This dosing schedule may well account for the lack of effect observed on FGF-23. This point should be thoroughly discussed in light of a recent publication by Hollis and Wagner 2013 JCEM 98 4619, which deals with this topic.

Response: Thank you for your suggestion. Indeed, the control of circulating concentrations of FGF-23 is a complex matter, and monthly versus dialing dosing may result in fluctuations in the concentrations of circulating FGF-23. (Reference #39). This has been discussed in line 6-8, page 13. Because of the compliance issue, changes of the vitamin D biomarkers including FGF-23 in response to monthly vitamin D dosing, which might help in the selection of monthly vitamin D doses and understanding the physiology of vitamin D, need to be disclosed. The results from this current study warrant further studies with monthly doing of vitamin D supplementation.

Reviewer 2:
This paper represents a well-designed trial to study the dose response effects on status and biochemistries of monthly supplementation of vitamin D in overweight African Americans. Vitamin D measures had adequate quality control. Addition of FGF-23 is a novel aspect of this study.

Response: Thank you for your positive comments.

Major:
1. The context of the paper overvalues vitamin D deficiency when no functional measures were made to evaluate adequacy. The introduction begins this overstatement because the authors use the IOM RDA as a cutoff for deficiency which is inappropriate as it includes a safety margin. If a cutoff value is to be used, it would be appropriate to use the EAR of 16 ng/mL. It is true that we have a scarcity of dose response data in blacks, but why assume they have the same criteria for deficiency/adequacy? After all, they have lower fracture risk with lower serum 25(OH)D levels and higher serum PTH on average yet lower fracture risk. The same argument applies for overweight/obese lower vitamin D status but lower risk of fracture.

Response: Thank you for your comments. The 2011 IOM Report on Dietary Reference Intakes states, “For vitamin D, the 2011 DRIs are based primarily on the integration of bone health outcomes with evidence concerning 25(OH)D levels, which suggest that levels of 16 ng/ml (40 nmol/liter) meet the needs of approximately half the population (median population requirement, or EAR), and levels of at least 20 ng/ml (50 nmol/liter) meet the needs of at least 97.5% of the population (akin to the RDA).” Given the lack of conclusive evidence, the IOM bases its Recommended Dietary Allowance (RDA) for vitamin D on bone health, which is 600-800 IU/day corresponding to a 25(OH)D serum level of ~20 ng/mL.(Reference #6) The target 25(OH)D level is ~30 ng/mL recommended by many other experts for large swaths of the population, although it is controversial.(Reference #7-10) This is has been clarified in the Introduction on line 7-9, page 3. But it is agreeable that there is no consensus for the definition of vitamin D deficiency in African Americans. Thus, we have deleted the jargon, vitamin D insufficiency or deficiency in the entire manuscript including the title.

2. It is disappointing that functional outcome measures were not included in the trial. In the Gallagher studies, functional outcome measures related to bone were not improved despite increased vitamin D status. In references 8 and 9, what was the BMI compared to this study? Was it a factor in response to vitamin D supplementation? The statement on p. 10 “Our results indicated that the current RDA may be inadequate for overweight/obese African Americans with vitamin D deficiency to optimize their vitamin D status” cannot be known without a functional status measure.

Response: Thank you for your comments. A critical need exists to understand the physiological sequel of vitamin D supplementation in African Americans and obese individuals. As such, the primary aim of our study was to comprehensively evaluate dose- and time- responses of circulating vitamin D bio-markers to monthly vitamin D supplementation in this population. Thus, functional outcome measures were not part of the study design, but will be explored in future analyses regarding skeletal and extra-skeletal outcomes. However, we have added lack of functional outcome measures as a limitation of this study on line 23-25, page 13.

As discussed above, we have deleted the jargon, vitamin D insufficiency/deficiency in the entire manuscript. We also agree that the statement previously on page 10, “Our results indicated that the current RDA may be inadequate for overweight/obese African Americans with vitamin D
deficiency to optimize their vitamin D status” cannot be known without a functional status measure. Thus, this statement has been deleted.

In addition, in references 11 and 12, mean BMIs in “Effects of vitamin D supplementation in older African American women” and “Vitamin D does not Increase Calcium Absorption in Young Women: A Randomized Clinical Trial” studies were 32.7±7.0 kg/m2 and 30±7 kg/m2 (for the African American subgroup, BMI was 32.0±7.0 kg/m2). In our study we did not observe any differences in the dose-responsiveness before and after adjusting for BMI, which was included in our statistical analyses.

Minor: Abstract-specify age range and both male and female.
Response: Thank you. Age range and male/female is now included in the abstract.