PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Vitamin D Status and TB Treatment Outcomes in Adult Tanzanian Patients
AUTHORS	Mehta, Saurabh; Mugusi, Ferdinand; Bosch, Ronald; Aboud, Said; Urassa, Willy; Villamor, Eduardo; Fawzi, Wafaie

VERSION 1 - REVIEW

REVIEWER	Dr. Michael Holick Professor Boston University Medical Center USA
REVIEW RETURNED	16-Aug-2013

GENERAL COMMENTS	The authors have nicely documented vitamin D status and outcome measures in TB patients 1. This manuscript would be greatly strengthened if they had used similar terminology for vitamin D status as used by the endocrine Society i.e. vitamin D deficiency <50 nmol/l and vitamin D insufficiency as 51-74 nmol/l. Low vitamin D levels is not very meaningful. It would be of interest since the results suggest that there is an inverse relationship with the outcome measures and serum 25-hydroxyvitamin D levels to see what the effect was for those who had 25-hydroxyvitamin D level less than 50 nmol/l versus 51-74 nmol/l versus >74 nmol/l. This would strengthen the argument that blood levels should be above 74 nmol/l for maximum benefit. 2. The authors sometime used the term Vitamin D concentrations when they mean 25-hydroxyvitamin D concentrations or vitamin D status. This should be corrected throughout the manuscript. 3. AIDS and TB medications can influence vitamin D status by altering the metabolism of 25-hydroxyvitamin D. Was there any association with medications and blood levels of 25-hydroxyvitamin D independent of season?

REVIEWER	Professor Paul Kelly Barts & The London Queen Mary, University of London No conflict of interest
REVIEW RETURNED	22-Sep-2013

THE STUDY	The Methods do not make clear whether the measurements were made and blood drawn before initiation of the micronutrient supplements which are the focus of the original trial. This is important, as if the samples were drawn after the randomisation was done, we need to be informed about any possible interaction with the treatment allocation.
RESULTS & CONCLUSIONS	My main difficulty with this paper is the construction of Tables 2, 3 and 4. They are not easy to comprehend. Having ploughed through them, I am confused why mortality data are available only on 344 patients. I cannot find an explanation, and this leads me to conclude that there is a lack of clarity in the denominators. I do not doubt the validity of the conclusions drawn, but it is always preferable to show the raw data before going on to more advanced analysis, so as to enable the reader to see what is going on. This aspect of this paper needs improvement.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Dr. Michael Holick
Professor
Boston University Medical Center
USA

The authors have nicely documented vitamin D status and outcome measures in TB patients

1. This manuscript would be greatly strengthened if they had used similar terminology for vitamin D status as used by the endocrine Society i.e. vitamin D deficiency <50 nmol/l and vitamin D insufficiency as 51-74 nmol/l. Low vitamin D levels is not very meaningful. It would be of interest since the results suggest that there is an inverse relationship with the outcome measures and serum 25-hydroxyvitamin D levels to see what the effect was for those who had 25-hydroxyvitamin D level less than 50 nmol/l versus 51-74 nmol/l versus >74 nmol/l. This would strengthen the argument that blood levels should be above 74 nmol/l for maximum benefit.

Dear Dr. Holick,

Thank you for reviewing this manuscript and for your valuable feedback. We have changed the terminology throughout the manuscript per your suggestion.

2. The authors sometime used the term Vitamin D concentrations when they mean 25-hydroxyvitamin D concentrations or vitamin D status. This should be corrected throughout the manuscript.

We have also corrected this in the revised paper.

3. AIDS and TB medications can influence vitamin D status by altering the metabolism of 25-hydroxyvitamin D. Was there any association with medications and blood levels of 25-hydroxyvitamin D independent of season?

We agree that both antiretroviral and antitubercular drugs may affect the metabolism and concentrations of 25-hydroxyvitamin D. However, this trial was conducted before antiretroviral treatment (ART) was widely available in Tanzania and none of the HIV-infected participants were receiving ART. All participants were receiving antituberculosis medications, and we did not measure blood medication levels, thus limiting our ability to evaluate any association with 25-hydroxyvitamin D. Additionally, HIV infection itself may alter 25-hydroxyvitamin D metabolism; therefore, we chose to

present results for HIV-infected and HIV-uninfected participants separately in the manuscript.

Reviewer: Professor Paul Kelly
Barts & The London
Queen Mary, University of London

No conflict of interest

The Methods do not make clear whether the measurements were made and blood drawn before initiation of the micronutrient supplements which are the focus of the original trial. This is important, as if the samples were drawn after the randomisation was done, we need to be informed about any possible interaction with the treatment allocation.

Dear Dr. Kelly,

We appreciate your review of the manuscript and your comments. The baseline measurements and blood draw occurred before the initiation of micronutrient supplements; we have now clarified this in the methods section. Further, our analyses have adjusted for treatment allocation.

My main difficulty with this paper is the construction of Tables 2, 3 and 4. They are not easy to comprehend. Having ploughed through them, I am confused why mortality data are available only on 344 patients. I cannot find an explanation, and this leads me to conclude that there is a lack of clarity in the denominators. I do not doubt the validity of the conclusions drawn, but it is always preferable to show the raw data before going on to more advanced analysis, so as to enable the reader to see what is going on. This aspect of this paper needs improvement.

We apologize for the confusion. Table 2, which presents the mortality data, has information for only the HIV-infected patients. All HIV-infected patients (n=344) are included in this table. There were very few deaths in the HIV-uninfected participants (13/333); therefore we chose to only present the results for the HIV-infected subset. We have now added text in the results section to mention the number of deaths in both the HIV-infected and HIV-uninfected subsets to increase the clarity. The denominators in the other tables reflect the number of participants that we had information on for the specified outcomes.

Bibliography

1. Villamor E, Mugusi F, Urassa W, et al. A Trial of the Effect of Micronutrient Supplementation on Treatment Outcome, T Cell Counts, Morbidity, and Mortality in Adults with Pulmonary Tuberculosis. J Infect Dis 2008; 197:1499-505.

VERSION 2 – REVIEW

REVIEWER	Dr. Michael Holick Boston University Medical Center USA
REVIEW RETURNED	11-Oct-2013

GENERAL COMMENTS	The authors have responded well to my recommendations. They forgot to correct vitamin D levels in the abstract which I pointed out to them. I find the manuscript to be acceptable once they make this minor revision.