Author’s response to reviews

Title: Effects of vitamin D supplementation on liver fibro-genic factors in non-alcoholic fatty liver patients with steatohepatitis: study protocol for a randomized clinical trial

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Author’s response to reviews:

Dear Dr. Hiemstra,

Thank you very much for your letter informing us of your decision regarding the manuscript entitled “Effects of vitamin D supplementation on liver fibro-genic factors in non-alcoholic fatty liver patients with steatohepatitis: study protocol for a randomized clinical trial” (TRLS-D-18-00643R1). The manuscript has been revised according to the editor’s comments. Responses to the reviewer’s comments have been provided below. Revised texts have been provided in red font. Thank you so much in advance.

Yours Sincerely,

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Response to Reviewer 1 #

The revised version of the manuscript is an improvement. However, there are some unresolved issues without which I cannot recommend this paper for publication.

1) Sample size calculation.

The authors now state 'considering the serum laminin mean of 136.7 ng/ml (12), based on the suggested formula for parallel clinical trials, we reached a sample size of 18 patients in each group'. First, I can find no evidence of a mean of 136.7 ng/mL in the reference (12 - Santos et al 2005). Second, without providing the data distribution and the magnitude of the anticipated treatment effect, AND detail of the magnitude of the treatment effect for which the study is powered, it is impossible to replicate the sample size calculations. Unless this is provided explicitly, it is not possible to recommend this manuscript for publication.

Authors: Thanks for your attention. In the mentioned study, mean levels (±SEM) of serum laminin in patients without fibrosis (n=19) was 244.7±11.9 ng/ml and the corresponding value in patients with fibrosis (n=11) was 381.4±38.9 ng/ml. We converted the given SEMs to SDs considering the sample size in each group. Therefore, SDs of laminin in patients with and without fibrosis was 129.148 and 51.884. In addition to the use of SDs from this study, we considered the mean difference of the two groups in the formula: (381.4-244.7)=136.7.

Considering the type I error of 0.05 and the study power of 90% and given the SDs in each group and mean difference in the formula, we reached the sample size of 18 persons in each group.

\[ Z_{1-\alpha/2}=1.96 \]
\[ Z_{1-\beta}=1.28 \]
\[ S_1=129.148 \]
\[ S_2=51.884 \]
\[ \Delta=136.7 \]

We re-calculated this based on the mentioned study and reached the same sample size in each study group.

Therefore, the data distribution was considered based on SDs of the mentioned study (as given above) and the magnitude of the effect was considered to be a difference of 136.7ng/ml in serum laminin between the two groups.

2) Safety
The authors have not adequately addressed my point concerning the use of PTH to monitor safety. In reply the authors reference the use of PTH as a surrogate for hypovitaminosis D. While this is of course true, this is irrelevant in the context of this trial. The IMP is cholecalciferol, and measures of safety in the trial should assess the safety of the IMP. Here, HYPOvitaminosis D is not a concern, but vitamin D toxicity potentially is. The authors need to explain how the safety of the intervention will be assessed, and PTH will not achieve this. Without adequately addressing this point, the manuscript cannot be recommended for publication.

Authors: Thank you. In the revised version, we changed PTH to serum calcium concentrations.