Reviewer’s report

Title: Vitamin D deficiency among patients with pulmonary hypertension

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Reviewer: Tomas Pulido

Reviewer's report:

Thank you to the editors for allowing me to review this interesting paper from Atamañuk and coworkers about the relationship between Vitamin D levels and pulmonary hypertension.

As pulmonary hypertension, specially groups 1 (pulmonary arterial hypertension or PAH) and group 4 (chronic thromboembolic pulmonary hypertension or CTEPH), are getting more interest due to novel therapeutic options, it has become imperative to find new prognostic variables that can predict outcome. I commend the authors for this paper, especially for the number of patients included. Atamañuk and coworkers seek to correlate vitamin D levels with well-established prognostic factors in pulmonary hypertension (PH) such as 6-minute walk distance and functional class among others. Vitamin D levels and its metabolism has been described as a prognostic biomarker in cardiovascular disease but it’s role in pulmonary hypertension it's not clear. In this paper, authors found abnormal lower levels of vitamin D as compared with subjects with left ventricular failure (LVF) and healthy controls. In PH patients these levels significantly correlated with 6-minute walk distance.

General comments:

Vitamin D metabolism is rather complex, and its levels depend upon several factors as magnesium levels, calcium absorption, parathyroid hormone axis integrity, etc. Although real deficiency is defined as a level < 20 ng/ml, normal levels are defined as > 30 ng/ml (the range between 21 and 29 ng/ml is considered as relative insufficiency); all these patients have levels (mean +/- SD) less than 30 ng/ml, even healthy subjects, probably attributed to a Latin American cohort? It has been showed that in underserved countries vit. D levels are lower than in those developed countries probably to malnutrition. I think the authors should clarify this or at least make a comment about it.
Is it possible to have serum calcium, phosphorus and magnesium levels to table one? Or at least calcium? As the authors pointed out, it is not easy to find if lower vit. D levels are a cause or a consequence, but I could assume that if there is an association in these levels and hypocalcemia, for example, there could be a problem with calcium absorption (perhaps due to right heart failure and/or intestinal congestion).

Vitamin D metabolism and levels correlate with age, it is clear that the authors excluded patients that were receiving vit. D and calcium supplements, do they also excluded patients that were receiving specific osteoporosis treatment? This could affect also the results and should be specified as an exclusion criteria. Keeping-up with this line of thought, is it possible to increase the number and paired healthy subjects by age and sex? This could strengthen the results adjust for some age-related bias.

Although the authors comment on the issues that bias the differences in vit. D levels among the different groups, they should specify the limitations in a separate section of the text (before conclusions) these limitations include: different time-frame in the hemodynamics and the blood samples (commented on the text), but also, they should address a probable treatment effect. That is, did the authors correlate the different PAH treatment with vit. D levels? Was there any difference?

They should also address the mean time form diagnosis (which I assume is the date the right heart cath was made) to inclusion in this study and the mean time the patient was treated with specific drugs before the vit. D levels were measured.

I recommend the discussion to be more thorough, what do the authors think about vit. D levels in the different PH groups? Levels are higher in congenital heart disease? Does this mean that RV function is better? I know is hard to imply this from the results, but at least a theory and a future study could be proposed.

Specific comments:

Homologate among all the text "vit. D levels" not values.

Also homologate PVR either as WU or Dynes (I suggest Wood Units, WU, not UW,). in the text PVR is expressed as PVR but in table 1, the unites are dynes.

Page 3, line 32: Results: change to "Mean vit. D levels were lower in…"

Page 3, line 34: Change to "Vit. D deficiency prevalence was higher in PH as compared to the other groups…"
Conclusions. Change to "Vit. D levels were lower in patients with PH as compared to patients with LVF and HS and correlated directly with six-minute walk distance." (There was no correlation with prognostic parameters except 6MWD)

Page 6, line 4. Modified to: "…"Vit D, calcium supplements or receiving treatment for osteoporosis, …"

Page 7, line 18, change to "WU" not UW

Page 7, line 117. Change to "…patients with right ventricular dysfunction…” Please, defined the criteria used for right ventricular dysfunction.

Page 7, line 57. Change to: "A significant correlation (p=0.01)…” Please Add the "r" value for the correlation.

Page 9, line 4. Change to "No correlation…"

Page 9, line 12. Change to "Significant correlation between exercise capacity measured with the 6 minute walk distance test and vit D levels was observed…”

Page 9, line 43. Change to "With some exceptions, the characteristics of the PH patient cohort were similar to those found in international registries [23]. They differed in age and FC at the time of the diagnosis…”

Table 1. I suggest to add in table one. Time from diagnosis to Vit. D level measurement.

TABLE 1, LINE 22. Add in the variables (n=X, +/- SD). In the p value column specify that comparison is between which variables (PH vs LVF, etc.)

Figure 1. Add standard deviation to the vit. D levels in number and in the graphs. Add an Asterix (*) in the columns with a significant p value

Figure 2. Add an Asterix (+) for the columns with significant p value

Figure 3. Add the identity line for the correlation and add both the "r" and the "p" value in the graph.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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