Reviewer’s report

**Title:** Vitamin D in children with growth hormone deficiency due to pituitary stalk interruption syndrome

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**Reviewer:** Gianpaolo De Filippo

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The paper of Cécile Delecroix et al. deals with the possible relationship between vitamin D status and GH/IGF-1 axis. The first objective is to evaluate the vitamin D status (i.e. 25OHD and 1,25(OH)2 D circulating levels) in a group of patients with GH deficiency (GHD) belonging to a pituitary stalk interruption syndrome. The secondary one is to investigate the relationship between Vitamin D status and patients characteristics, specially, GH peak after pharmacological stimulation test.

The idea is of interest and strength of the is study the studied population, with a homogeneous diagnosis (stalk interruption syndrome), permitting to avoid considerable selection biases affecting several studies on GH deficiency. However, some concerns need to be clarified.

1. Vitamin D status has been shown to be potentially able to increase IGF-1 circulating levels and a regulatory role of 1,25(OH)D3 was shown in GH/IFG1 axis gene expression in human epiphyseal chondrocytes; at the state, no evidence of a feedback vitamin D/IGF1 or vitamin D/GH has been proven. In other words, if it is possible that low levels of vitamin D could affect GH secretion and/or IGF-1 levels, no clear evidence exists that in turn IGF-1 levels could affect vitamin D status. The cited studies of Wei and Saggese (references 19 an 20) show an influence of GH therapy (inhibition of 24 hydroxylase?) at pharmacological doses. Thus, the finding that these patients have normal vitamin D status is probably independent from their GHD. The present observation has the value to assess it, but this result should be more discussed and detailed.

2. More interestingly, a relationship is observed between vitamin D status and GH peak. This result is on my opinion the real strength of the study, leading to several considerations for the evaluation of GH status in clinical practice, for example, to assess vitamin D status and if a deficiency exists, to correct it before testing. To do that, more details should be done on GH stimulation tests. First, the relationship should be evaluated only on mUI/L values and not ng/mL: in effect, the standardisation process varied on the time. The entire study group originating from a total of 86 patients has been formed over
long time (1982-2016) and the GH standard was not the same. The recombinant DNA derived standard (IS 98/574) replaced the pituitary derived standard IS 80/505 in this period and the correspondence 20 U/l = 6.7 ng/mL reported in the text corresponds to the former. This item should be discussed in the methods section. Second, the type of stimulation test should be specified, pointing out the differences in responses (i.e. simple versus coupled pharmacological test), if any.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

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.

Yes

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

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable
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