Reviewer’s report

Title: Mechanistic Study of the Cause of Decreased Blood 1,25-Dihydroxyvitamin D in Sepsis

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Reviewer: Zuleyha Karaca

Reviewer's report:

In this paper, the authors investigated possible mechanisms of renal active vitamin D formation such as parathyroid hormone (PTH), insulin-like growth factor 1 (IGF-1), fibroblast-growth factor 23 (FGF-23), and kidney function in patients with severe sepsis. They demonstrated in both human subjects and mice that sepsis was associated with 1,25(OH)2D deficiency. Although PTH was found to be increased in the patients, active vitamin D deficiency could not be overcome. This effect was attributed to decreased serum levels of IGF1, increased serum levels of FGF-23, and kidney failure.

The authors proposed a model for the mechanisms underlying sepsis-induced 1,25(OH)2D deficiency. In the model, an infection leads to activation of immune cells followed by secretion of pro-inflammatory cytokines, IL-6, IL-1β, IL-1α and TNF-α. These cytokines and liver failure cause inhibition of the expression and signaling of growth hormone receptor in liver, which leads to reduced production of IGF-1 in liver and decreased IGF-1 levels in blood. Additionally, kidney failure increases FGF-23 levels in blood. Consequently, the decreased serum levels of IGF-1, increased FGF-23, and kidney failure cause suppressed activity of kidney to reduced production of 1,25(OH)2D in kidney and decreased 1,25(OH)2D levels in blood. Collectively, the increased FGF-23 levels, decreased IGF-1 levels, and decreased 1,25(OH)2D levels in blood worsen systemic inflammation and multi-organ failures in sepsis patients. The study is interesting but I have some concerns:

1. In the results section: the authors start to discuss their results. These discussion parts should be taken into discussion or some to introduction part.

2. Do the authors have the data regarding survi of sepsis patients? If yes, was there a difference between survivors and non-survivors?

3. When was the serum sample was taken form sepsis patients? How long after the diagnosis of sepsis? And how did it affect the the results?

4. Are there any other possible mechanisms that have been shown to be associated with low vitamin D levels? This issue may be discussed by the authors.

5. A correlation analysis can be made between 1,25 OH D2 levels, FGF23, IGF-1 and Cr to support their hypothesis.
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.

I recommend additional statistical review

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

Needs some language corrections before being published

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