

## Peer Review File

Article information: <https://dx.doi.org/10.21037/jlpm-23-63>

### Reviewer Comments

**Comment 1:** The authors of this review article summarized the current knowledge on alkaline phosphatase from the laboratory medicine viewpoint. The review contains a large amount of material that is important for clinicians and laboratory medicine physicians alike. I believe that the review markedly facilitates the interpretation of the ALP test in clinical practice. I have no major comments related to the review. In particular, the abstract should be restructured to be more representative of the material contained in the review. Hof notes, in the opinion of this reviewer, that the structure of many sentences throughout the material should be improved. Below are some examples that I suggest the authors have to take action.

**Reply 1:** Thank you, your thoughts are much appreciated.

**Comment 2:** Abstract, lines 27-30, the background should be re-structured to represent the true background for the review and not to guide the reader through the material. In addition, I propose changing “reader” to “physician”.

-lines 25-28,

**Reply 2:** Thank you changes made.

**Comment 3:** Line 36, there is no following schema, at least not in the abstract.

-Line 34, Does this refer to the algorithms in the paper,

**Reply 3:** That is correct, the wording has been changed to also accommodate the recommendations of point 3.

**Comment 4:** If possible, the abstract section may be expanded to offer a summary of the review. The search methodology may be presented later.

**Reply 4:** Agreed, very sensible suggestion, some of the most salient recommendations now added to the abstract

**Comment 5:** Line 69, Alkaline Phosphatase Metabolism may be substituted with “Metabolic role of alkaline phosphatase”.

**Reply 5:** changed as recommended, thank you.

**Comment 6:** Line 96, “ALP in the liver is synthesized in many tissues...” may be restructured.

**Reply 6:** changed to “Liver-based ALP is synthesized” Thank you

**Comment 7:** The plasma half-life of ALP should be reported.

**Reply 7:** Good though, added on, stated as 7 days.

**Comment 8:** Reference range for ALP may be provided (according to the IFCC method).

**Reply 8:** Thank you, added as IFCC states = Adults: 45 - 135 U/L

**Comment 9:** Line 174, what does “Pseudo” mean?

**Reply 9:** Changed to “Pseudo Hypophosphatasia”, Thank you.

**Comment 10:** Line 183, what does “Primary” mean? Please expand these subheadings.

**Reply 10:** Good spot, thank you. changed to “Primary Hypophosphatasia”

**Comment 11:** Line 192, what does “in some” mean? Please complete the sentence.

**Reply 11:** Additional context added about the seizures and link to ALP, thank you.

“ALP deactivates active B6, PLP, to form pyridoxal, and the accumulation of pyridoxal may account for the seizures seen in some babies with hypophosphatasia, occurring a few days after birth. Though not demonstrated in humans, restoring ALP levels in deficient mice has ended those seizures”

**Comment 12:** Lines 216-217, please complete the sentence. “ALP activity” should be instead of “activity”.

**Reply 12:** Changed as suggested, thank you.

**Comment 13:** Line 214, subheading should be expanded.

**Reply 13:** “Endocrine and Metabolic links to ALP” added thank you.

**Comment 14:** Line 237, “inpatients” does it mean “in hospitalized patients”?

**Reply 14:** Great point, yes it does, changed to “In hospitalized patients”

**Comment 15:** Line 239, please substitute “benign disease”.

**Reply 15:** Changed to “underlying conditions”, Thank you.

**Comment 16:** Please re-structure the sentence in lines 240-242.

**Reply 16:** Agreed, altered, thank you.

**Comment 17:** Line 250, please expand the subheading.

**Reply 17:** Changed to “ALP and its association with the Liver and Biliary Tract”

**Comment 18:** Line 255 “is primarily liver in origin” is awkward.

**Reply 18:** Thank you changed

**Comment 19:** Line 311, rickets is more than impaired mineralization... Please improve the structure of the sentence.

**Reply 19:** Thank you, has been changed to “Rickets, a rare condition in the UK, is the clinical consequence of impaired mineralization...”

**Comment 20:** Line 347, please explain “Regan isoform”.

**Reply 20:** Thank you for adding context that Regan isoform is a rare variant of placental alkaline phosphatase.

**Comment 21:** Line 350, please add isoform between Regan and include.

**Reply 21:** Thank you, changed as recommended

**Comment 22:** Lines 352, please complete the “Kahasara” and “Nagao” variants of ALP.

**Reply 22:** Thank you, updated as “Other examples include Kasahara a foetal intestinal ALP isoform (Moss 1988) e.g., in renal cell carcinoma (133), and Nagao a placental-like ALP isoform (Moss 1988) (134).”

**Comment 23:** The authors may add information on the impact of physical exercise, alcohol, smoking, coronary artery bypass surgery, and radiotherapy on circulating levels of ALP. This may be of interest from the laboratory medicine aspect.

**Reply 23:** Thank you, mentioned