

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 62755

Title: Hypophosphatemia after high-dose intravenous iron treatment in patients with inflammatory bowel disease: Mechanisms and possible clinical impact

Reviewer's code: 01434943

Position: Editorial Board

Academic degree: PhD, BSc, RCPA

Professional title: Professor

Reviewer's Country/Territory: Australia

Author's Country/Territory: Norway

Manuscript submission date: 2021-01-28

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-01-29 01:46

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Review time: 1 Hour

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|---------------------------------|---|
| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion | <input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection |
| Re-review | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| Peer-reviewer statements | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |



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SPECIFIC COMMENTS TO AUTHORS

This is a useful study of iron-based compounds in the context of IBD treatment. The numbers of data points (eg subjects) for the various analyses is difficult to determine in many cases. This needs to be made more explicit. As an example, the number of subjects is not even mentioned in the methods. Similarly, the massive SD's with some of the analyses would suggest either under-powering or technical problems. Figure 2 is a good example. Numbers/group should be stated in the figure legends. Otherwise the work is explained well. Some attention to grammar is required. For example, the abstract could be made more concise...eg 'has shown to be associated'; could just be 'has been associated'. For some reason a dot-point style has been used for the aims. It should either be 'A total of 106 patients was available' or either '106 patients were available'; the word 'total' is not plural.

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Name of journal: World Journal of Gastroenterology

Manuscript NO: 62755

Title: Hypophosphatemia after high-dose intravenous iron treatment in patients with inflammatory bowel disease: Mechanisms and possible clinical impact

Reviewer's code: 05401003

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Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: United States

Author's Country/Territory: Norway

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|---------------------------------|---|
| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion | <input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection |
| Re-review | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| Peer-reviewer statements | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

The manuscript by Detlie et al attempts to explain the mechanism of FCM-induced hypophosphatemia previously described in their prior manuscript in APT 2019 and to assess whether this biochemical change is associated with any clinically relevant sequelae. The analyzed baseline and longitudinal laboratory changes as well as physiological factors over a 6 week uncontrolled observational period. The authors noted a significant decrease in serum phosphorus correlating with increased FGF23 (intact) among those treated with FCM but not FDI. However, the changes were transient and began to normalize within the 6 week mark and were not associated with changes in pulmonary function, SF-36, or a visual analog scale (VAS) of clinical symptoms pertaining to hypophosphatemia. Overall, the authors do thoroughly assess factors which might help to explain the mechanism of hypophosphatemia following FCM, so the overall aims are accomplished.

1 Title. Does the title reflect the main subject/hypothesis of the manuscript? Yes

2 Abstract. Does the abstract summarize and reflect the work described in the manuscript? Yes

3 Key words. Do the key words reflect the focus of the manuscript? Yes

4 Background. Does the manuscript adequately describe the background, present status and significance of the study? Yes

5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? Yes

6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? The objectives are met adequately. The authors have previously reported the clinical data demonstrating hypophosphatemia and iron indices in their previous manuscript and in this manuscript are trying to mechanistically explain the findings. While they do successfully achieve this, the overall significance of the biochemical changes on clinical outcomes are

questionable given the lack of pulmonary, SF-36, or VAS differences despite the changes in the lab parameters. 7 Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? Adequate discussion, might address a few minor points as below. 8 Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends? Adequate 9 Biostatistics. Does the manuscript meet the requirements of biostatistics? Adequate 10 Units. Does the manuscript meet the requirements of use of SI units? Yes. I would include the normal values in Tables 1 and 2 for reference. 11 References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? Yes 12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? Yes 13 Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting? All adequate 14 Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s)

must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics? Documents adequate. Further Critique: 1. The data presented in Detlie et al APT 2019 show that FCM resulted in a more sustained improvement in serum iron and related indices. The findings of low phosphorus and other indices described in the current manuscript are of questionable significance but the more effective iron repletion may actually be the more important clinical outcome here. 2. The overall mean vitamin D levels at baseline, while reported as deficient in 36% of patients at baseline, are actually substantially higher than most IBD cohorts. In my hospital, vitamin D >30 is listed as sufficient and most IBD patients, especially in the Winter, have vitamin D levels in the 10's and 20's. It is possible that if this population had lower baseline values, the effect of phosphorus depletion might actually correlate with clinically meaningful changes in vitamin D and PTH metabolism. The findings in this manuscript mostly highlight the difference in 1,25 Vitamin D and there was no major impact on 25-OH-vitamin D. 3. Please reference the normal ranges for serum phosphorus and other lab values in the tables. The units of mmol/L are different than the values commonly used in US clinical practice and should be placed in context. 4. The impact of hypophosphatemia on serum ionized calcium, respiratory function tests, SF-36, and VAS was minimal between groups suggesting that the differences, although statistically significance, may have limited clinical relevance or only theoretical clinical impact. 5. It is hypothesized that FCM may have a direct impact on FGF23 cleavage. Is data presented to justify this conclusion? If purely speculative, this should be clarified in the discussion (Page 14, first paragraph)

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Title: Hypophosphatemia after high-dose intravenous iron treatment in patients with inflammatory bowel disease: Mechanisms and possible clinical impact

Reviewer's code: 00049433

Position: Editorial Board

Academic degree: BM BCh, PhD

Professional title: Doctor, Senior Lecturer

Reviewer's Country/Territory: United Kingdom

Author's Country/Territory: Norway

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|---------------------------------|---|
| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
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| Re-review | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| Peer-reviewer statements | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

Generally well written and presented paper looking at the well-recognised side-effect of hypophosphataemia following IV iron. I have some comments with regard to the explanation of the methodology and the statistical analysis – a formal statistical review would be of benefit. Introduction: this is too long; much of the text (esp. the 3rd paragraph, beginning “Many organ systems...”) is more of discussion than introduction – this should be addressed. Methods: 1. Although the authors have previously published the methodology in a previous manuscript, this paper should still be able to be read independently. Readers should not have to read 2 papers in order to understand the methods and outcomes. Although a brief outline is fine, the authors still need to clearly provide inclusion and exclusion criteria, definitions of iron-deficiency and iron deficiency anaemia, whether patients were recruited randomly or consecutively and if patients were treated per protocol or by physician choice. Additionally there is no mention of the study visit times points. I would suggest that possibly a flow diagram of the study recruitment may address many of these issues without needing a significant amount of text. 2. Does using the FEPO4 formula negate the fact that two different assays were used? I don’t think it does. The formula is merely a function of the inputs (which vary by assay) – would a brief analysis of variance of the formulas address this better? 3. Why was hypophosphataemia defined as <0.8 ? This seems quite high (i.e. is 0.79 clinical relevant)? 4. Although the authors have provided a biostatistical letter of approval I am not sure that in this scenario if a pair t-test is appropriate. Would a two-way ANOVA not be the test of choice? Results: 1. In the phosphate results section it is important to know/understand if the 21.6% group is a subset of the 72.5% group; i.e. looking at these groups separately as a whole is not useful – each patient’s phosphate level (and change over time) is the important factor. So for both the FCM and FDI groups



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did 11 of the 37 (FCM) and 2 of the 6 (FDI) groups have low phosphate levels at both time points? This is a vital distinction to make. 2. Although the distribution of Vit D deficiency was the same in both groups, were those with low Vit D have lower phosphate levels (i.e. was there any correlation?) Discussion: this is also very low and could do with being more succinct/focussed