

November 5, 2013



Dear Lian-Sheng Ma,

Please find enclosed the edited manuscript in Word format (file name: 5850-review.doc).

Title: Vitamin D improves inflammatory bowel disease outcomes: basic science and clinical review

Author: Krista M. Reich, Richard N. Fedorak, Karen Madsen, Karen I. Kroeker

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5850

We wanted to thank the editors and the reviewers for their comments which have significantly improved the manuscript.

General Comments:

- 1 The format has been updated
- 2 The title has been changed to be more informative, specific and brief. It is now 12 words.
- 3 The core tip is now less than 100 words
- 4 Figure 1 was obtained from the New England Journal Of Medicine. We purchased a copyright license to reuse the image in this review paper. The image was sent in JPEG format; therefore, we are unable to coordinate the graphs to be decomposable.
- 5 The revisions have been made according to the suggestions of each individual reviewer and are listed below:

1) Reviewer No. 00004011

[It is a well written and documented review]

Thank you for your comments.

2) Reviewer No. 02446452

[This is a well structured, comprehensive review of the topic. There are some recent references which should be added to make your review as current as possible: 1) Melek J, Sakuraba A. 2013 Efficacy and Safety of Medical Therapy for Low Bone-Mineral Density in Patients with Inflammatory Bowel Disease: a Meta-Analysis and Systematic Review. 2) Miznerova E, et al The prevalence and risk factors for osteoporosis in patients with inflammatory bowel disease. 3) Ananthakrishnan AN.

Environmental risk factors for inflammatory bowel disease. 4) Boyd CA, Limdi JK. Vitamin D deficiency and disease outcomes in South Asian patients with IBD. 5) Blanck S, Aberra F. Vitamin d deficiency is associated with ulcerative colitis disease activity. and others from 2013 where appropriate.]

Thank you for your comments and for the suggestions on five recent publications. Below we have outlined how we have incorporated these 5 publications into our manuscript.

1. Paper 1 by Melek et al. 2013 *Clin Gastroenterol Hepatol*– This paper discusses two studies evaluating the management of low bone mineral density in IBD patients with vitamin D. They reported controversial results and therefore it is still unknown if vitamin D and calcium administration can reduce the risk of fractures. Since we only briefly discuss the use of vitamin D in IBD for improving bone health, we did not include this reference in our paper.
2. Paper 2 by Miznerova et al. 2013 *Bratisl Lek Listy*– We added this reference to page 4 lines 13-14
3. Paper 3 by Ananthakrishnan AN. 2013 *Gastroenterol Hepatol*– This paper reports very similar findings to our review article, and there is overlap in the papers we cite. We used 3 references from this review paper to add to our manuscript. See pg. 10 lines 12-13 where we added the paper by Zhu et al. (2005), demonstrating that vitamin D treatment down-regulates TNF-alpha-related genes in IL-10 KO mice. See pg. 15 lines 14-18, where we added the papers by Khalili et al. (2012) and Nerich et al. (2011) as these are two recently published articles on the association between sun exposure and the risk for IBD.
4. Paper 4 by Boyd et al. 2013 *Dig Dis Sci*– We added this reference to page 17 lines 23-27.
5. Paper 5 by Blanck et al. 2013 *Dig Dis Sci*- We added this reference to page 17 lines 18-23.
6. We also added the additional recent references to our review:
 - a. Guillot et al. 2013 *Handbook of vitamin D in human health*- page 5 lines 33-35 and page 6 lines 1-3
 - b. Palmer et al. 2013 *Inflamm Bowel Dis* – page 13 lines 1-4
 - c. Jorgensen et al. 2013 *J Crohns Colitis* – page 17 line 12
 - d. Hassan et al. 2013 *Med J Malaysia*– page 17 lines 29-30
 - e. Zator et al. 2013 *JPEN*- page 18 lines 33-35 and page 19 line 1
 - f. Yang et al. 2013 *Clin Transl Gastroenterol*– page 19 line 22-30 and page 23 in the table

3) Reviewer No. 02445239

[This is a nicely written review on a important condition IBD and role of vit D in its treatment covering up to date literature.]

Thank you for your comments.

4) Reviewer No. 02445834

[Dear Editor in chief I've read and reviewed the manuscript "The role of vitamin D in improving inflammatory bowel disease outcomes: a basic science and clinical review ". This topic is an

interesting topic in field of autoimmune diseases and its impact is obvious. I believe that it is written well and the harmonization of review is well organized. Considering scientific and linguistic points this article is acceptable and can be consider for publication.]

Thank you for your comments.

5) Reviewer No. 02445436

[Reich and colleagues present a nice review on the role of vitamin D in IBD. It is well written and well focused on the theme. My main criticism concerns the lack of any new vision on the role of vit.D in IBD. There is a substantial discrepancy between the in vitro data, that are exciting, and those of clinical trials that are poor. The conclusions of the manuscript add little or nothing if compared to older articles on the subject. Finally, Figure 1 is certainly one of the most explanatory figures regarding vitamin D metabolism. But it is dated and well known to all those who have studied, even marginally, vitamin D.]

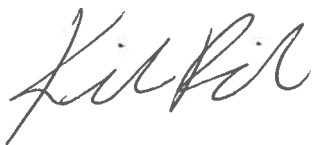
Thank you for your comments.

We have strengthened the conclusions to this review.

In regards to Figure 1, we recognize it demonstrates the basic pathways of vitamin D metabolism as well as the traditional actions of vitamin D. This summary figure is meant to appeal to the broad gastrointestinal health readership of the Journal, providing a quick and basic overview of its well-known actions. The review then follows on with the more detailed and complex mechanisms of action of vitamin D on specific epithelial and immune responses, first in murine models of IBD, and then in human IBD.

Thank you for considering our paper for publication in the *World Journal of Gastroenterology*.

Sincerely yours,



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