

September 25, 2015

Response to Reviewer Comments

Protective links between vitamin D, inflammatory bowel disease
and colon cancer
ESPS Manuscript ID 19107

We thank the Senior Editor and the Reviewers for their thoughtful and insightful comments. We have modified our manuscript to address their concerns as below.

Reviewer 1:

"In the review an interesting overview about vitamin D and its putative role in IBD and colorectal carcinogenesis is given. Comments 1. Vitamin D metabolism should be illustrated with a scheme. 2. Primary sclerosing cholangitis is found in some patients suffering from ulcerative colitis. Is there any evidence that vitamin D could be involved in the genesis of UC-related PSC? Is there any data indicating that the risk for cancer in low level vitamin D UC-related PSC is increased?"

We have added a schematic illustrating the vitamin D metabolism pathway, Figure 1.

This reviewer raises an interesting question regarding how vitamin D deficiency could potentially be involved in Primary Sclerosing Cholangitis (PSC), a liver disorder that occurs in a subset of patients with IBD. This appears to be a field that is open for further study. There is some epidemiologic evidence suggesting that patients with PSC are at an increased risk of vitamin D deficiency^[1], however, it is difficult to determine if the vitamin D deficiency is a cause of or sequella of the liver disease. In addition, IBD patients with PSC have been found to be at an increased risk for developing colon cancer^[2]. Together this suggests that vitamin D deficiency could be affecting cancer formation in this population, however, at this time, there are not sufficient studies directly addressing the potential of vitamin D deficiency as a risk factor for cancer in the subset of UC patients with PSC to draw any conclusions. Limited work in mouse models of PSC suggests that vitamin D deficiency is associated with increased expression of profibrotic genes and more advanced liver fibrosis^[3], suggesting that vitamin D deficiency may play a role in exacerbating disease. While this is an interesting question, we are not able include any specific information in our review regarding this subset of patients due to insufficient data.

Reviewer 2:

"Dear Editor, Authors Thank you for sending the paper "Protective Links between Vitamin D, IBD, and Colon Cancer" for revision." - There is growing evidence of vitamin D role in many clinical conditions, IBD and cancer colon are significant examples . - Inspite search is still growing in this field but we are in need to such review to outline progress. The paper is well written and we can consider it as outline as mechanism of how vit D affect such diseases need to be more clarified. - So, if recent detailed search can be added to this point it will improve

understanding of such mechanism. - Few grammatical mistakes present within the context. Thanks”

We appreciate the reviewer’s kind remarks regarding our manuscript. We agree that despite a rapidly expanding pool of literature relating to vitamin D, inflammatory bowel disease and colon cancer, further work needs to be done to better understand the mechanisms through which vitamin D is able to elicit protective effects. Based on the reviewer’s suggestions, we have completed an updated literature search and added several new articles that were published following our initial submission.

1. Fialho A, Fialho A, Kochhar G, Shen B: **The presence of primary sclerosing cholangitis in patients with ileal pouch anal- anastomosis is associated with an additional risk for vitamin D deficiency.** *Gastroenterology report* 2015.
2. Torres J, Pineton de Chambrun G, Itzkowitz S, Sachar DB, Colombel JF: **Review article: colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease.** *Aliment Pharmacol Ther* 2011, **34**(5):497-508.
3. Hochrath K, Stokes CS, Geisel J, Pollheimer MJ, Fickert P, Dooley S, Lammert F: **Vitamin D modulates biliary fibrosis in ABCB4-deficient mice.** *Hepatology international* 2014, **8**(3):443-452.