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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 59758

Title: Colonic vitamin D receptor expression is inversely associated with disease activity and Jumonji domain-containing 3 in active ulcerative colitis

Reviewer's code: 00487119
Position: Peer Reviewer
Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: Australia

Author's Country/Territory: Christmas Island

Manuscript submission date: 2020-09-27

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-09-28 23:23

Reviewer performed review: 2020-10-12 04:38

Review time: 13 Days and 5 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Vitamin D alleviates the disease activity of human ulcerative colitis via Jmjd3-H3K27 me3 signaling Most major single point How can the authors say this? "This knowledge unveiled a novel mechanism by which vitamin D involves in the alleviation of UC pathology via anti-inflammation." Where are the inflammatory measurements? Where are the silencing/over-expression expts of said mechanisms in cell systems to back up these claims.Unless such expts exist these claims can NOT be made and we are simply looking at a series of physiological correlations. Please change this language to reflect your data. This is all simply correlation? Major points 1 The VDR correlation with Mayo score is frankly startling?? Fig 5B?? and definitely the most provocative bit of data presented. It would have been nice to see some quatitative measure used, i.e western blot or Elisa but I understand these were sampled during endoscopy and there would be limited tissue available. 2 Statements such as "VDR may down-regulate the expression of Jmjd3," really need to at least have some in silico support. i.e. are there VDRes in promoters of any of the genes correlated? 3 As expected patients were taking anti-inflammatory or steroid agents. This would have a long term effect on inflammatory outcomes of course but how can the authors rule out effects on the measures taken here? 25OHD status appears unaffected by steroids? Fig 2C but what about the other anti-inflammatory treatments. 4 Healthy levels of 25OHD are in dispute and many American studies would say levels below 20ng/ml (i.e. the mean of both groups) would be vitamin D deficient? So all patients were deficient. On ta related point what does a 2.5ng/ml i.e 6.25nM decrease in 25OHD really mean? Minor points Typos I can't give page position because it was NOT included. There are numerous small mistakes that need fixing. shown to be inversely {associated} with disease activity[8-10]. Loss of VDR in intestinal were measured in the all UC patients ?? In UC patients of smokers not presented a significantly low vitamin

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D level?

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Reviewer's code: 03258954
Position: Editorial Board
Academic degree: MBBS

Professional title: Assistant Professor

Reviewer's Country/Territory: United States

Author's Country/Territory: Christmas Island

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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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Comments Comment 1 TITLE Vitamin D alleviates the disease activity of human ulcerative colitis via Jmjd3-H3K27 me3 signaling This is an observational study showing that VDR/Serum vitamin D had an inverse correlation with disease activity in UC patients and tissue JMJD3 levels. The study is not designed to establish firmly that vitamin D alleviates the disease activity of human ulcerative colitis via jmjd3-H3K27. Hence the title is misleading. A more suitable topic would clearly state the firm results of the study without speculation. Comment 2 Background Authors state: the potential role of vitamin D receptor (VDR) on Jmjd3 activation remains unknown. The activation of NF-κB as an early and central event in inflammation (Pasparakis 2009). Molecular studies have revealed the reason why JMJD3 transcription could be rapidly induced by NF-κB. It is because that the promoter sequences from the first coding exon of JMJD3 contain two conserved κB sites (de Santa et al. 2007). VDR is known to downregulate NF-κB signaling and ameliorate intestinal inflammation through its interaction with NF-κB and its inhibitor inhibitory kappa B kinase beta (IKKβ). Thereby downregulating jmjd3. Comment 3 Aim To explore the impact of vitamin D on disease activity and its related mechanism. The aim of the study needs to be more specific. Vitamin D is ubiquitous and has a spectrum of effects on a variety of tissues. As mentioned by the authors in the manuscript, "The purpose of this study is to study the relationship between VDR, Jmjd3 and H3K27me3." … A more descriptive aim would be to "Study the relationship between VDR, jmjd3 and H3K27me3 in patients with ulcerative colitis" Comment 4 Conclusions Immunohistochemistry staining of Jmjd3 and H3K27me3 in colonic mucosa are helpful for the diagnosis of ulcerative colitis. This statement needs to be deleted or changed. This study was able to show increased levels of jmjd3 levels in colonic biopsies of UC patients in comparison to healthy controls. The study does not compare these

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biopsies to other inflammatory conditions of the colon. Jmjd3 is increased in a variety of tissues in a variety of conditions and is merely a marker of inflammation based on the data presented. There is no data presented here that argues in favor of jmjd3 being a specific marker for Ulcerative Colitis. Comment 5 Core Tip This knowledge unveiled a novel mechanism by which vitamin D involves in the alleviation of UC pathology via anti-inflammation. Additionally, detection of signaling molecules of Jmjd3 and H3K27me3 in colonic mucosa may help for development of the diagnostic markers of UC. Please correct this statement. Surely VDR has been shown to downregulate NFKB and mitigate the downstream inflammation. Additionally NFKB manifests its inflammatory effects by recruitment of jmjd3 in some tissues. However jmjd3 is known to have both pro and anti inflammatory effects depending on the type of cells being studied. Similarly end results of VDR upregulation vary widely. For instance, Fabio Periera et al have shown through their work that 1,25(OH)(2)D(3) activates the JMJD3 gene promoter and increases the level of JMJD3 RNA in human cancer cells. JMJD3 upregulation was strictly dependent on vitamin D receptor (VDR) expression and was abolished by cycloheximide. in colon cancer cells, VDR promotes the transcription of jmjd3 RNA Therefore, It would be more accurate to say that our findings show that VDR expression is inversely related to jmjd3 expression and disease activity in colonic mucosa of patients with UC. Further studies are warranted investigate this relationship. Comment 6 Discussion Second paragraph A multiyear cohort study showed that low serum vitamin D level increased the frequence Change to “frequency” Comment 7 Vitamin D level and VDR expression decreased and were inversely correlated with the disease activity, and simultaneously, increased Jmjd3 and decreased H3K27me3 expression was noted in active UC patients, suggesting that the alleviated affect of Vitamin D and VDR on the disease activity of human ulcerative colitis is associated with activation of Jmjd3 and inhibition of H3K27me3 presumedly via NF-κB and STAT 1/STAT 3 signaling. Change to “effect”