Name of journal: *World Journal of Gastrointestinal Pathophysiology*

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Title: Zinc and gastrointestinal disease

Replies to Reviewers

Reviewer 1

1. A table is now included summarizing various gastrointestinal morbidities associated with zinc deficiency, and whether Zn supplementation relieves the morbidity.
2. In the section discussing zinc and tight junctions, the following justification statement is now added: "In most of the GI morbidities discussed in this review, the role of transepithelial barrier leak specifically at the site of the epithelial tight junction, is very prominent. The recently documented ability of zinc to reduce TJ leak is very likely involved in zinc supplementation's ability to alleviate these morbidities, and the exacerbation of the morbidities in periods of zinc deficiency. For this reason, we present an expanded description of zinc action on the tight junctional complex."
3. We have attempted to add very recent references on zinc and GI disease where found to be appropriate (Zou et al., 2014; Dickinson and Surawicz, 2014; Kwon et al., 2014; Liu et al., 2014; Lamberti et al., 2013; El-Tawil, 2012; Christudoss et al., 2013; Maret, 2013).

Reviewer 2

1. The reviewer makes an excellent point. The *mode* in which zinc is taken is extremely important. Not all zinc salts have the same permeability and thus the same bioavailability. Moreover, the form in which zinc is taken orally (e.g. capsule vs lozenge) can have dramatic impact on adequate zinc delivery to the desired target tissue. This is best exemplified in zinc delivery to the esophagus. If topical delivery is desired/required then oral intake of zinc in capsule form is entirely inadequate and lozenge form (slow melt in the oral cavity) is much preferable (Valenzano et al., 2014). It is not really feasible in a review to discuss the mode of zinc administration in every citation (our review is already lengthy). The reader has to check on this by going directly to the cited material. These points however are very important and we now raise them, in addition to the zinc dosage/concentration, in the very beginning of the review article.
2. The reviewer is correct to ask us to introduce references concerning zinc induction of apoptosis, and we add those two references in the revision (Weissgarten et al., 2002; Chang et al., 2006). However we also point out that zinc, in other cell types, can induce proliferation or

differentiation. The exact effect that zinc exerts is likely dependent upon cell type and other external effectors. We mention this action by zinc (apoptosis) in our section on apoptosis. It is very important to cite here because one might assume that zinc induction of apoptosis (or cell division) would compromise epithelial barrier function. However this is not the case as shown in the work of Peralta Soler et al. (1996), who demonstrated that an otherwise healthy epithelium reacts to the presence of apoptotic cells by simply phagocytizing them, a process that transpires with only very limited effects on overall barrier function.

3. As the reviewer points out, this review should be restricted to gastrointestinal disease, based upon the review's title. We accordingly have removed the subsection on Alzheimer's Disease. However, the sections on alcohol toxicity, hyperthermia, chemotherapy, malnutrition and Chronic Fatigue Syndrome are retained, because even though they at first seem unrelated to the GI tract, we cite information that shows a potential link to gastrointestinal permeability.
4. The section on cadmium toxicity is expanded to include iron and copper toxicities, using the references suggested by the reviewer.
5. Corrections regarding subscript and superscript have been made. Thank you.

New References Added to the Revised Manuscript

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8: Maret W. Zinc and human disease. Met Ions Life Sci. 2013;13:389-414. doi: 10.1007/978-94-007-7500-8_12. Review. PubMed PMID: 24470098.
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11: Lamberti LM, Walker CL, Chan KY, Jian WY, Black RE. Oral zinc supplementation for the treatment of acute diarrhea in children: a systematic review and meta-analysis. Nutrients. 2013 Nov 21;5(11):4715-40. doi: 10.3390/nu5 114715. Review. PubMed PMID: 24284615; PubMed Central PMCID: PMC3847757.

12: Liu P, Pieper R, Rieger J, Vahjen W, Davin R, Plendl J, Meyer W, Zentek J. Effect of dietary zinc oxide on morphological characteristics, mucin composition and gene expression in the colon of weaned piglets. PLoS One. 2014 Mar 7;9(3):e91091. doi: 10.1371/journal.pone.0091091. eCollection 2014. PubMed PMID: 24609095; PubMed Central PMCID: PMC3946750.

13: Kwon CH, Lee CY, Han SJ, Kim SJ, Park BC, Jang I, Han JH. Effects of dietary supplementation of lipid-encapsulated zinc oxide on colibacillosis, growth and intestinal morphology in weaned piglets challenged with enterotoxigenic Escherichia coli. Anim Sci J. 2014 May 5. doi: 10.1111/asj.12215. [Epub ahead of print] PubMed PMID: 24799095.

14: Dickinson B, Surawicz CM. Infectious diarrhea: an overview. Curr Gastroenterol Rep. 2014 Aug;16(8):399. doi: 10.1007/s11894-014-0399-8. PubMed PMID: 25064318.

15: Zou TT, Mou J, Zhan X. Zinc Supplementation in Acute Diarrhea. Indian J Pediatr. 2014 Jun 24. [Epub ahead of print] PubMed PMID: 24954892.