

Response to the reviewers:

Reviewer 00609371

- 1) We agree with the Reviewer that there are many factors that influence the intestinal  $\text{Ca}^{2+}$  absorption. GSH is in fact one of them. We have demonstrated that GSH is essential to have an optimal intestinal  $\text{Ca}^{2+}$  absorption (Tolosa de Talamoni et al., CBP 1996).
- 2) Calcitriol or  $1,25(\text{OH})_2\text{D}_3$  is the main hormone that regulates the intestinal  $\text{Ca}^{2+}$  absorption. Calcitriol is mainly produced in kidney and regulates this process after binding to its receptor named VDR. The importance of GSH resides in the intestinal epithelial cell. GSH is the main reductant molecule that maintains the thiol redox state in the cell and its depletion causes inhibition of the intestinal  $\text{Ca}^{2+}$  absorption. Both of them are important and are not comparable. The role of calcitriol is better if the intestinal cell maintains its GSH content at normal levels.
- 3) The review shows the new advances in this area of knowledge.
- 4) In patients with moderate ulcerative colitis, the use of N-acetyl-L-Cysteine, a precursor of GSH synthesis, caused clinical improvement without provoking side effects (Guijarro L. et al., World Journal of Gastroenterology, 2008). This drug is considered well-tolerated antidote for cysteine/GSH deficiency (atjuri K et al., Curr Opin Pharmacol., 2007). It has been used with positive results in IBD animal models and clinical trials, bronchitis, HIV/AIDS, COPD, diabetes, etc (Moura F et al., Redox Biology 2015).

Reviewer 00506564

- 1) Introduction was shortened, as suggested.
- 2) The first sentence of Introduction was changed, as suggested.
- 3) The sentence "A reduction in more than 70% in the active intestinal...." was eliminated in order to shorten the Introduction.
- 4) Tables were changed, as suggested.
- 5) The animal models were cleared in the Reversion/Prevention section.
- 6) A new paragraph was added with regard to the colitis and IBD, as suggested.

Reviewer 02629138

- 1) It has been postulated that certain intestinal diseases such as CD, ulcerative colitis and colon cancer are developed by environmental factors such as dietary components, smoking, enteric infections, lifestyle choices, changes in the intestinal microbiota, etc. Chemicals presented in the environment that derived from DDT or 1,2-dimethylhydrazine stimulate the oxidative stress through GSH depletion causing colon cancer. It is quite possible that the use of antioxidants that avoid GSH depletion or replenish the intracellular tripeptide could benefit the intestine attenuating the symptoms of those pathologies.

Response to the Editor

Since the Introduction was shortened and a new paragraph was included, there is a rearrangement of references and new references (88 to 93) were added.