

2 June 2024

Dear Editors,

Thank you for your interest in our editorial titled "Digesting gluten with oral endopeptidases to improve the management of celiac disease". We addressed the queries of reviewers in our resubmission, as detailed below. Thank you again for inviting us to write this editorial.

Yours sincerely,

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**Point by point response to reviewers' queries:**

**Quote 1:** In my opinion, the authors can improve their editorial by adding the critical role of markers allowing to explore the mucosal recovery, ideally, in a non-invasive way. When they stated that "One limitation of development of new therapeutics is lack of animal models that reflect various aspects of human disease. Another limitation is the lack of standardization of randomized controlled clinical trials..." they should recall previous studies trying to investigate the potential use [ ] in clinical practice of serological markers of mucosal damage and villous atrophy. In this regard, they should recall and underline that anti-tissue transglutaminase and anti-endomysial antibodies, unfortunately, do not correlate with severity of mucosal damage in adult celiac patients as previously demonstrated (World J Gastroenterol. Oct 14, 2009; 15(38): 4775-4780; doi: 10.3748/wjg.15.4775), while anti-actin IgA antibodies that are significantly correlated with villous atrophy, are not detectable in 100% of patients but only in nearly 50% of celiacs with severe villous atrophy. This support the urgent need of non invasive markers of mucosal damage to better follow celiac patients after gluten free diet initiation and

check potential exposure to gluten due to unintentionally ingest gluten from food contaminations.

**Response:** We thank the reviewer for this detailed critique. We addressed this concern in our response. This text reads as “Normalization of serology, however, ..” in the paragraph that starts with “Patients with celiac disease ...” (p.8). This entire part is highlighted.

**Quote 2:** A further clinically relevant point to recall is the current recommendation of the most recent international guidelines on the management of celiac disease. In fact, all guidelines (European Society Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 2020; European Society for the Study of Coeliac Disease (ECD) 2019; World Gastroenterology Organization (WGO) 2017; Central Research Institute of Gastroenterology, Russia, 2016; National Institute for Health and Care Excellence (NICE), 2015; British Society of Gastroenterology (BSG), 2014; and (7) American College of Gastroenterology (ACG), 2013), also provide information about the essential information that should be collected during follow-up evaluations to ascertain gluten-free diet response and accuracy.

**Response:** We addressed this by adding a reference (Reference #28) and the following sentence to the text that reads as “Guidelines from multiple societies .. (p.8)” in the paragraph that starts as “Patients with celiac disease..”. This text is highlighted.

**Quote 3:** "Key Words" does not meet the requirements.

**Response:** We added key words according to Journal’s guidelines and this is highlighted on the first page.