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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 34938

Title: Non-Celiac Gluten Sensitivity: All Wheat Attack is Not Celiac

Reviewer's code: 00050853

Reviewer's country: Lebanon

Science editor: Ya-Juan Ma

Date sent for review: 2017-06-07

Date reviewed: 2017-06-20

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

The authors have written a very good review on NCGS. It is up to date, and overall well written. I suggest the following revisions/modifications: 1-It is well established that GFD is associated with better outcome in celiac disease, including lower mortality, better bone health, and reduced risk of cancer. Whether this is the case in NCGS is not known. Some recent data suggest increased cardiac mortality in patients who take GFD and who don't have celiac disease. The authors need to address that. 2-The conclusion is too long. It should be reduced into a succinct summary. 3-The English of the text needs some polishing as there are some misprints/mistakes.



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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 34938

Title: Non-Celiac Gluten Sensitivity: All Wheat Attack is Not Celiac

Reviewer's code: 00001787

Reviewer's country: Italy

Science editor: Ya-Juan Ma

Date sent for review: 2017-07-05

Date reviewed: 2017-07-10

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

I read with interest the review MS "Non-Celiac Gluten Sensitivity: All Wheat Attack is Not Celiac" by J. Steven Alexander and coworkers. It deals with an emerging, intriguing issue, thou often poorly addressed. The Authors should be commended for providing such a well organized and structured review. No additional points on this side.



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 34938
Title: Non-Celiac Gluten Sensitivity: All Wheat Attack is Not Celiac
Reviewer’s code: 00159281
Reviewer’s country: United Kingdom
Science editor: Ya-Juan Ma
Date sent for review: 2017-07-05
Date reviewed: 2017-07-11

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

This is an interesting review by Igbinedion et al on NCGS, I have few comments Introduction It mentioned that NCGS present with relatively non-specific set of symptoms which affects diverse organ systems(7). Symptoms of NCGS are often so vague and non-specific presenting as gastrointestinal and/or extra-intestinal symptoms I disagree with this statement, as NCG could be very disabling Non-coeliac gluten sensitivity. BMJ 2012;345:e7982 Epidemiology Causal links between IBS and NCGS have been frequently suggested since most of the gastrointestinal symptoms in NCGS resemble IBS (similar Rome III criteria), including abdominal pain/discomfort, bloating, diarrhea and constipation(14). There is also a debate as to whether a GFD can help symptom resolution in IBS after excluding CD as clinical trials have shown that GFD can reduce symptoms in patients with diarrhea-predominant IBS (IBS-D)(16). Based on multiple RCT could say with confidence that there is no causal links in my opinion, it is simply mislabelling NCGS with IBS. This should be discussed here Diagnosis The



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proposed diagnostic work-up includes 3 vital steps: Why the authors do not simply recommend Salerno expert criteria Ref 34? The authors suggest performing wheat specific IgE and skin prick test, and CD; IgA-tTG, IgG-DGP and IgA-EMA. What is the evidence behind doing all these tests? Should the tests not be advised according to presenting symptoms in each individual?



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 34938

Title: Non-Celiac Gluten Sensitivity: All Wheat Attack is Not Celiac

Reviewer's code: 00034179

Reviewer's country: Italy

Science editor: Ya-Juan Ma

Date sent for review: 2017-07-05

Date reviewed: 2017-07-17

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
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		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

This paper is a review of the current knowledge of NCGS, highlighting the remaining challenges and questions which may improve its diagnosis and treatment. The data are presented in a thorough and balanced manner, however there are corrections and issues that should be dealt with that are: - Sapone et al. (20) observed in NCGS expression of TLR2, and to a lesser extent TLR1 but not TLR4, as was erroneously reported in the manuscript (Pathogenesis) - Table 1 Comparison of Gluten Sensitivity Disorders, is confusing: remove IBS for their unclear relation to gluten ingestion, as authors themselves reported in the table; in NCGS we don't have diagnostic biomarkers, it was shown a positivity for AGA in approximately 50% of cases but low specificity and we can talk about mechanism potentially involved (innate immunity); with regard to diagnosis it must be reported for NCGS: Double-blind, placebo-controlled, cross-over trial, as the authors themselves reported in figure 2; As Management of NCGS patients, a gluten-free regimen should be considered; Please change: Colonic and



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extra-manifestations with intestinal and extra intestinal manifestation; Cytomorphology with duodenal histology; Immunophenotype with HLA Haplotypes (DQ2 and DQ8) - With regard to the management of NCGS it is important to include the potential use of ancient wheat variants (diploid wheat species) as new dietary opportunities for NCGS patients both for their marked reduction of toxicity demonstrated in in vitro cellular assays (Gianfrani C et al. Immunogenicity of Monococcum wheat in Celiac Patients Am J Clin Nutr 2012;96:1338-44; Mazzarella G et al. Extensive in vitro gastrointestinal digestion markedly reduces the immune-toxicity of gliadin from ancient Triticum monococcum wheat: implication for celiac disease prevention. Mol Nutr Food Res. 2015 Sep;59(9):1844-54) as well as for their lower concentration of ATIs respect modern wheat (Zevallos VF et al. Nutritional Wheat Amylase-Trypsin Inhibitors Promote Intestinal Inflammation via Activation of Myeloid Cells.Gastroenterology. 2017 Apr;152(5):1100-1113. - The discussion must be reviewed and reduced; some information may be reported in the respective paragraphs for example the information about the biomarkers as CD14 and LBP must be reported in Pathogenesis; the ex-vivo gluten challenge as a method for diagnosis must be removed because to date, there are no validated mucosal biomarkers that can differentiate CD from NCGS. Moreover, such technology requires a well-equipped laboratory therefore it is not at all a simplified diagnostic strategy for the clinician. Finally, endoscopy for duodenal biopsies howsoever is invasive subjecting the patient to stress. - ATIs engage TLR4 and not TRL2 as erroneously reported by the authors - I suggest to assemble epidemiology and clinical presentation in a single paragraph;