Reviewer's report

Title: Celiac disease: A comprehensive current review

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Reviewer: Concepción Nuñez

Reviewer's report:

The authors review the current knowledge about celiac disease, covering important aspects related to the disease and trying to include some novel discoveries, some of them from their own group.

It is a quite complete and well-written review. There are only some minor points that I consider that must be clarified or included.

1. At the end of the abstract, the authors conclude that the future challenge is related to the identification of new treatments. Even though it is an important point, many efforts should be also focused on diagnosis. Seronegative cases and those with mild histological lesions constitute an important challenge nowadays. Despite the great advances in pathophysiology and diagnosis, at present celiac disease is still a clearly underdiagnosed condition.

2. In the part related to Genetics the authors mention the roles of HLA class II genes, saying: "Also common to other autoimmune diseases is the relevant role of human leukocyte antigen (HLA) class II genes, specifically DQ2 and DQ8" (page 6 line 34). Although DQ2 and DQ8 are the main predisposing factors, they are not genes. HLA-DQA1 and HLA-DQB1 are the main genes involved in celiac disease. Depending on the alleles present in both genes the DQ8 haplotype or DQ2 haplotype or genotype can be present, leading to the DQ8 and DQ2 heterodimers, respectively, that are involved in CD pathogenesis.

3. The sentence "The erroneous adaptive immune response consequence of a highly specific interplay between selected gluten peptides and MHC class II HLA-DQ2/8-restricted T-cell antigens plays a paramount role in CD pathogenesis" (page 8, lines 56-60) needs to be rewritten. The interplay is between selected gluten peptides (which are indeed the HLA-DQ2/8 restricted antigens) and MHC class II HLA-DQ2/8 heterodimers. The authors probably meant: "...MHC class II HLA-DQ2/8-antigen restricted T-cells".
4. I find very interesting the inclusion of two terms absent in the Oslo definitions: seronegative CD and GFD non-responsive CD. However, regarding the definition of seronegative CD, it is noteworthy that lesions milder than Marsh 3a are more frequent in subjects with low titer or negative antibodies. Thus, I think seronegative CD should include the presence of milder lesions than atrophy (Marsh 1 and Marsh 2), although in those cases the differential diagnosis is more complicated due to the increased number of potential causes of milder enteropathy.

Related to this point, the authors consider CD only in presence of atrophy, including milder enteropathy with positive antibodies as potential CD. According to the ESPGHAN (J Pediatr Gastroenterol Nutr. 2012 Jan;54(1):136-60): "According to the Marsh classification, lesions include infiltrative, hyperplastic, and atrophic patterns... IELs in numbers>25/100 epithelial cells suggest an infiltrative lesion". Although it is also said "only 10% of subjects presenting infiltrative changes have CD", the possibility exists and if the authors prefer to exclude those cases, at least they should include a comment about it. In this context, consider to reference the paper "Intestinal intraepithelial lymphocyte cytometric pattern is more accurate than subepithelial deposits of anti-tissue transglutaminase IgA for the diagnosis of celiac disease in lymphocytic enteritis". F Fernández-Bañares et al. PLoS One. 2014; 9(7): e101249.

Following the same topic, in page 15 line 26, the authors used villous atrophy as one of the five criteria needed for CD diagnosis according to the rule "four out that five". I consider that Marsh 1 and Marsh 2 should be included, as in the original article: celiac enteropathy at the small bowel biopsy (Including Marsh-Oberhuber 3 lesions, Marsh-Oberhuber 1-2 lesions associated with positive celiac antibodies at low/high titers).

5. Include references about the test for monitoring the GFD (page 20 line 53).

6. Table 3. It is confusing why anti-DGP antibodies are named DGP-AGA, being AGA the term usually used for anti-gliadin peptides, please correct. Also in table 3, which papers have been used to obtain the diagnostic accuracy of the presented serological tests? To see better values for specificity and PPV for anti-DGP than for anti-tTG seems surprising. Please revise.

7. Table 5 should include Marsh 3a and 3b under grade B1.
8. Figure 1 needs better resolution.

9. Is Figure 2 referred to adult patients? Please, specify.

10. Figure 3. Please, delete "(continuous gluten exposure, slow response to gluten-free diet and refractory celiac disease)" of the legend, it can be seen in the Figure.

11. Legend of Figure 4 is misleading. The diagnosis is based on serological screening, but it is not a serological diagnosis since it uses biopsy for final decision. Please, modify.

12. Reference 66 does not deal with potential CD (page 18 line 41).

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