

March 7, 2017

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 32815-REVISED Anania et al.doc).

**Title:** Immune response to vaccines in children with celiac disease

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**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 32815

The manuscript has been revised according to the suggestions of the reviewers.

Reviewer #3025970

The reviewer suggests to discuss the role of the GFD on immune response in children with celiac disease. He also asks if there are studies that evaluated the antibody response in the same patients before and after GFD. Although there are no studies reporting antibody response before and after GFD in the same patients, some authors have evaluated the response to vaccination in untreated and treated groups of CD patients, as well as according to GFD compliance.

“Nemes et al. evaluated HBV vaccine response in CD children in relation to disease activity, assessed by measuring serum antibody concentrations to transglutaminase, and dietary gluten in the failure to reach protective antibody titers. The authors studied 128 biopsy-proven CD children and adolescents and 113 age-matched controls: 22 patients with CD on GFD were prospectively given a recombinant HBV vaccine, while the remaining 106 CD patients received a recombinant HBV vaccine which was not related to the diagnosis of CD or compliance to GFD. They found that the rate of seroconversion for anti-HBs was 95.5% (95% CI: 78.25-99.2%) in the patients prospectively immunized. However, for the other patients the response rate was 50.9% and was related to gluten consumption (youths on gluten-containing diet, 25.9%; patients non-compliant to GFD, 44.4%; patients on strict GFD, 61.4%)” (page 6, lines 19-29 of revised manuscript).

“Urgancy and Kalyoncu determined the response rate to hepatitis A (HAV) and HBV vaccination, persistence of protection against HAV and HBV, and the occurrence of acute HAV or HBV infections during a period of follow-up in 30 children affected by CD in comparison with 50 healthy controls matched for age, sex, and body mass index. .... Of

note, there was a difference in GFD compliance between responders and nonresponders, though it was not statistically significant.” (page 8, lines 7-20 of revised manuscript)

Reviewer #3476360

According to this reviewer suggestions we have:

- modify the sentence at line 7 page 3 to read “HLA-DQ2 is present in 90% to 95% of celiac patients, HLA-DQ8 haplotype in 5%, and at least one of the two DQ2 alleles in 5% of them”;
- rephrased the introduction paragraph “The available literature indicates that the immunological response to vaccines in children with CD is generally similar to that of general population and antibodies titres are sufficiently high to give lasting protection. However, among CD patients a lower response to the hepatitis B virus (HBV) vaccine was demonstrated several years ago” to read “The available literature indicates that the immunological response to vaccines in children with CD does not differ markedly from that of general population and antibodies titres are enough high to provide long-term protection, except for hepatitis B virus (HBV)”;
- deleted the sentence “found in 90-95% of celiac patients”;
- appended references to sentences in the last paragraph of the Introduction;
- reported the results of the two papers by Zingone et al. (new references # 22, 23 ) “Zingone et al. evaluated the response to HBV vaccine in relation to gluten consumption in three groups of patients with CD and in a control group: group A, adolescents on gluten-containing diet vaccinated at age 12 years in whom CD was diagnosed after vaccination; group B, adolescents vaccinated when 12-years old who were on GFD at the time of vaccination; and group C, patients who received HBV vaccine at birth; and group D, healthy subjects. An insufficient response to HBV immunization was observed in 43.9%, 34.8%, and 58.3% of CD patients in group A, B, and C, respectively, versus 8.3% of subjects in group D. Thus, the authors suggested that the immune response to HBV vaccine is independent of gluten exposure and that the human leukocyte antigen possibly act as the principal immunological determinant of poor responses to HBV vaccine in CD patients. Zingone et al. also investigated the duration of anti-HBs 11 years following primary vaccination and immune memory to HBV in adult individuals with CD who had been vaccinated when adolescents. They showed that the proportion of vaccinated persons with antibody titres  $\geq 10\text{mIU/mL}$  was less among CD patients than among controls.”(beginning on page 8, line 21 and ending on page 9, line 3 of revised manuscript);
- included two, more recent, references (new references # 29, 30) regarding the pneumococcal infection;
- added in table 1 the recent paper of Filippelli et al.;

- changed reference #23 of previous manuscript;
- written “authors” throughout the manuscript instead of “Authors”; and
- reported the meaning of GFD the first time we used it.

Reviewer #3700166

- As suggested by the reviewer, we have appended references to sentences in the last paragraph of the Introduction.

Reviewer # 3646970

As suggested by the reviewer, we have:

- modify the words “were positive for ” to read “responded to” (page 5);
- included into the revised manuscript “...disease activity, assessed by measuring serum antibody concentrations to transglutaminase...”. We have also included this possible additional pathogenetic mechanism of nonresponse to vaccines in the Introduction section;
- modify the words “CELIAC CHILDREN” to read “CHILDREN WITH CELIAC DISEASE”

Reviewer # 35743

We thank the reviewer for the positive comments on our manuscript.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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