

Prospective Study

## Immune response to hepatitis B virus vaccine in celiac subjects at diagnosis

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**Author contributions:** Filippelli M, Garozzo MT and Leonardi S revised the manuscript for final submission; Filippelli M, Capizzi A, Manti S, Tardino L and Salpietro C contributed to writing of the article; Garozzo MT analyzed the data; Spina M performed the research; Leonardi S designed the study; all authors read and approved the final manuscript.

**Institutional review board statement:** The study was reviewed and approved by the Institutional Review Board of the University Hospital "Policlinico Vittorio Emanuele".

**Informed consent statement:** All study participants, or their legal guardians, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** The authors have no conflicts of interest related to the manuscript.

**Data sharing statement:** No additional data are available.

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**Manuscript source:** Invited manuscript

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Received: May 20, 2016

Peer-review started: May 20, 2016

First decision: July 4, 2016

Revised: July 14, 2016

Accepted: July 29, 2016

Article in press: August 1, 2016

Published online: September 18, 2016

### Abstract

#### AIM

To evaluate hepatitis B virus (HBV) vaccine response and correlation with human leukocyte antigens (HLA) and/or gluten intake in celiac patients at diagnosis.

#### METHODS

Fifty-one patients affected by celiac disease, diagnosed at the Department of Pediatrics of the University of Catania (Italy), were recruited. All patients were tested at admission for immunization against HBV, according to findings from analysis of quantitative HBV surface antibody (anti-HBs). The anti-HBs titer was measured by enzyme-linked immunosorbent assay. Following the international standards, subjects with antibody titer < 10 IU/L were defined as non-responders. The prevalence of responders and non-responders among celiac subjects and the distribution of immunization for age were examined. In addition, the prevalence of responders and non-responders was assessed for correlation to HLA and clinical features at diagnosis of celiac disease.

#### RESULTS

The entire study population was divided into three groups according to age: 24 patients aged between 0

to 5.5 years (48.9%, group A); 16 aged between 5.5 and 9.5 years (30.61%, group B); 9 aged between 9.5 and 17 years (18.75%, group C). Comparison of the percentage of responders and non-responders between the youngest and the oldest age group showed no significant difference between the two groups ( $P > 0.05$ ). With regard to the HLA haplotype, comparison of the distribution of vaccination response showed no statistically significant difference between the different genotypes (homozygosity for the HLADQ2 haplotype compared with HLADQ2/DQ8 heterozygosity or other haplotypes;  $P > 0.05$ ). Moreover, distribution of the responders according to clinical features of celiac disease showed no statistically significant differences ( $P > 0.05$ ).

## CONCLUSION

This prospective study confirmed the lower percentage of response to HBV vaccine in celiac subjects. However, the underlying mechanism remains unclear and further studies are needed.

**Key words:** Celiac disease; Hepatitis B virus vaccination; Human leukocyte antigens; Gluten; Poor response

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**Core tip:** Correlation between celiac disease and lower response to hepatitis B virus (HBV) vaccine has been demonstrated, but the causes remain unclear. The lack of prospective data represents an extensive gap between the time of vaccination and development of the immune response, contributing to select “false non-responders” (*i.e.*, those who are destined to lose the antibody titer over time). The originality of our prospective study is that of analyzing the response to HBV vaccine in a group of celiac patients at the time of diagnosis in an attempt to nullify the percentage of error related to confounding factors.

Filippelli M, Garozzo MT, Capizzi A, Spina M, Manti S, Tardino L, Salpietro C, Leonardi S. Immune response to hepatitis B virus vaccine in celiac subjects at diagnosis. *World J Hepatol* 2016; 8(26): 1105-1109 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v8/i26/1105.htm> DOI: <http://dx.doi.org/10.4254/wjh.v8.i26.1105>

## INTRODUCTION

Celiac disease (CD) is a permanent immune-mediated enteropathy, triggered by gluten in genetically predisposed individuals. The genetic predisposition consists of the presence of alleles encoding for the molecules DQ2 or DQ8 of the human leukocyte antigen (HLA)<sup>[1]</sup>. A significant correlation between CD and a lower response to the hepatitis B virus (HBV) vaccine was demonstrated several years ago, but the causes of this phenomenon remain unclear. Many authors have postulated the role of

HLA molecules (DQ2 and DQ8) in affecting an impaired immune response to HBV vaccine in CD<sup>[2]</sup>. On the other hand, it has been theorized that gluten intake could represent the main factor involved, because according to some studies the percentage of responders among celiac patients who are compliant with a gluten-free diet (GFD) is similar to that among healthy subjects<sup>[3,4]</sup>.

Despite the many hypotheses, the debate on poor response to hepatitis B vaccination in CD remains largely open. It could be hypothesized that many confounding factors in some of the previous studies have contributed to maintaining this uncertainty. First of all, the lack of prospective data determines a more extensive gap between time of vaccination and development of the immune response, contributing to select “false non-responders” (*i.e.*, those who are destined to lose the antibody titer over time)<sup>[5]</sup>. Moreover, it could be easier to evaluate the effective role of HLA in influencing HBV vaccine response when CD has just been diagnosed and no other factors have yet intervened.

For all these reasons, the aim of our prospective study was to eliminate or reduce such confounding factors and to evaluate hepatitis B vaccination response in celiac patients at diagnosis of the disease and its possible correlation with HLA and/or gluten intake.

## MATERIALS AND METHODS

In this prospective study we recruited 51 patients affected by CD, diagnosed at the Department of Pediatrics of the University of Catania (Italy). The diagnosis of CD was made according to the European Society for Paediatric Gastroenterology, Hepatology and Nutrition criteria updated in 2012<sup>[6]</sup>. The total serum IgA levels were measured in all patients in order to exclude the presence of a selective deficit of IgA. Inclusion criteria required that subjects must have completed obligatory vaccinations, including the HBV vaccine. All patients were tested at admission for immunization against HBV, according to finding from quantitative analysis of the HBV surface antibody (anti-HBs). The anti-HBs titer was measured by enzyme-linked immunosorbent assay. Following the international standards, subjects with antibody titer < 10 IU/L were defined as non-responders<sup>[7]</sup>.

Two of the 51 celiac patients were excluded because of insufficiency of their serum samples for analysis of the anti-HBs titer.

We examined the prevalence of responders and non-responders among celiac subjects and the distribution of immunization for age. For this, all patients were divided into three groups on the basis of their age at diagnosis: Group A children were aged between 1.5 and 5.5 years; group B children were aged between 5.5 and 9.5 years; group C children were aged between 9.5 and 17 years.

Moreover, we divided all 49 patients on the basis of clinical features at diagnosis of CD and distinguished them in the following three groups: Group 1 patients had typical form (onset with diarrhea, abdominal pain, cramping or distension, dyspepsia, vomiting or failure to

**Table 1** Serologic and histologic findings of the duodenal biopsies for celiac disease diagnosis

	TTG IgA ( $\mu$ A/mL)			Marsh score	
	70-200	201-300	> 300	3C-B2	3B-B1
Patients, <i>n</i>	20	10	19	26	23

thrive); group 2 patients had atypical form (onset with other symptoms such as deficiency iron-anemia, chronic fatigue, behavior change, dermatitis and joint pain); group 3 patients had silent form (asymptomatic onset). The prevalence of responders and non-responders was assessed for correlation to HLA and the clinical features at diagnosis of CD (typical or atypical onset).

At the end, we compared the results obtained by the present observational study with the results of a retrospective study previously conducted in our Department of Pediatrics.

### Statistical analysis

The statistical analysis of data was performed with the use of SPSS version 21.0 software (SPSS Inc. Chicago, IL, United States). The results for quantitative variables were expressed as mean  $\pm$  SD, and those of qualitative variables were expressed as frequencies and percentages. Differences between groups were compared using the Mann-Whitney *U* test for two independent samples. The Fisher's exact test was used to compare frequencies. For all analyses, statistical significance was defined as  $P < 0.05$ .

## RESULTS

Data for the serologic and histologic findings of duodenal biopsies (according to Marsh classification) used for the diagnosis of CD are summarized in Table 1, while characteristics of the 49 patients included in the study (sex, age, percentage of responders, HLA haplotype) are summarized in Table 2.

When we divided the entire study population into the three age groups, we found 24 patients were aged between 0 to 5.5 years (48.9%, group A), 16 were aged between 5.5 and 9.5 years (30.61%, group B) and 9 were aged between 9.5 and 17 years (18.75%, group C). The responders were distributed into the three age groups as follows: 19 (38.77%) in group A; 11 (22.44%) in group B; 4 (8.16%) in group C. Comparing the percentage of responders and non-responders between the youngest and the oldest group, no significant difference was found ( $P > 0.05$ ).

With regard to the HLA haplotype, comparison of the distribution of vaccination response showed no statistically significant difference between the different genotypes (Table 2). Moreover, the distribution of responders according to clinical features of CD was as follows: 20 out of 26 patients in group 1; 11 out of 17 in group 2; 3 out of 6 in group 3. The typical form showed significant association with the presence of

**Table 2** Patient characteristics and distribution of human leukocyte antigens and clinical features

	Responders	Non-responders	<i>P</i> value
HBV vaccination	34 (69.4%)	15 (30.6%)	
Female sex	22 (66.7%)	11 (33.3%)	
Male sex	12 (75%)	4 (25%)	
Median age	5.55 ( $\pm$ 3.25 SDS)	8.04 ( $\pm$ 4.3 SDS)	> 0.05
HLA			
DQ2/DQ2	8	4	
DQ2/DQ8	6	1	
Other HLA <sup>1</sup>	19	10	
Distribution according			> 0.05
HLA			
Clinical form of CD			
Typical form	20	6	
Atypical form	11	6	
Silent form	3	3	
Distribution according			> 0.05
clinical form			

<sup>1</sup>Includes heterozygosis for HLA DQ2, heterozygosis for HLA DQ8 and homozygosis for HLA DQ8 patients. HBV: Hepatitis B virus; CD: Celiac disease; SDS: Standard deviation score; HLA: Human leukocyte antigens.

HLADQ2 ( $P < 0.05$ ). Comparison of the immunological vaccine response between the three groups showed no statistically significant differences related to the clinical features (Table 2).

Finally, we found a statistically significant difference in the vaccination response for patients in the present observational study as compared to patients analyzed in the previous retrospective study. In the present study, 34 out of 49 patients were responders compared to 30 out of 60 patients in the retrospective study ( $P < 0.01$ ).

## DISCUSSION

CD is defined as an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically-susceptible individuals and is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, HLADQ2 or DQ8 haplotypes and enteropathy<sup>[6]</sup>.

The reasons why CD could be related to an inadequate response to hepatitis B vaccination have long been discussed. Some previous studies have suggested a genetically-related failure of response, attributed to particular HLA antigens, mainly the DQ2 haplotype, which is also involved in autoimmunity<sup>[8,9]</sup>. In fact, while DQ2 is present in only approximately 40% of the general population, it is expressed in up to 81% of CD patients. The HLADQ2 status would induce an inadequate Th2 response, leading to inefficient B cell differentiation and formation of memory T cells<sup>[8,10,11]</sup>. In 2007, a study by Park *et al.*<sup>[2]</sup> demonstrated that more than 50% of the enrolled children with CD did not show a response to standard vaccination regimens for HBV, in contrast to a physiological response that was observed with other vaccinations (tetanus, rubella, and *Haemophilus influenzae* type b). This finding supported the hypothesis that HLA haplotype played a specific role in response

to HBV vaccine. One year later, a subsequent study conducted by Ahishali *et al.*<sup>[12]</sup> confirmed this theory by finding responsiveness to hepatitis B vaccination in 68% of celiac patients, in contrast to the 100% response observed for the controls, emphasizing the genotypic coincidence.

In 2009, Leonardi *et al.*<sup>[13]</sup> published a case control retrospective study about the prevalence of HBV vaccine non-responders among celiac and healthy subjects. The anti-HBs titer was measured after a successful period of time on a GFD, as demonstrated by the normalization of serum markers of CD. The study confirmed that celiac patients have a lower percentage of response to hepatitis B vaccination than healthy controls. However, the authors also found a significantly higher number of responders among the celiac patients that were younger than 18-month-old at diagnosis and a significantly lower number of responders in adolescent patients older than 14-year-old at diagnosis. The drawback of the study was that the HLA typing was performed in few patients, so that the study could not demonstrate the correlation of the phenomenon observed with HLA-DQ2 or HLA-DQ8, and that there was a long interval between the time of hepatitis B vaccination and the time of collecting samples for analysis of the anti-HBs titer. In this regard, a recent case control retrospective study by Zanoni *et al.*<sup>[11]</sup> investigated the serological response to HBV and measles-containing vaccines in three groups of individuals: Diabetes mellitus type 1 (T1DM) patients, celiac patients and controls. No significant differences were found in the percentage of responders to HBV and measles vaccines among the T1DM and CD patients and the control group, and there was also a lack of correlation between HBV vaccine response and DQ2. According to the authors, these conflicting results between their findings and the data reported in the literature may be due to differences in ages of the examined subjects at time of vaccination and in time intervals between vaccination and blood sample collection for testing. They concluded that prospective studies of pathological and healthy groups, with same age at hepatitis B vaccination and same time interval for blood sample collection to determine antibody levels, are necessary to provide more conclusive data.

For these reasons, the originality of our prospective study is that of analyzing the response to hepatitis B vaccination in a group of 49 celiac patients at the time of diagnosis, helping us to nullify the percentage of error related to a long interval from time of hepatitis B vaccination to time of serum anti-HBs analysis. In fact, when we compared the results of our prospective study (based upon patients at time diagnosis of CD) with those retrospectively obtained by Leonardi *et al.*<sup>[13]</sup> in 2009 (based upon celiac patients on a GFD), we found a higher percentage of responders among the celiac subjects, probably due to our study design having eliminated more of the potential confounding factors related to loss of immunity over the time, which have been documented extensively in the literature<sup>[14-16]</sup>.

Meanwhile, we also observed that whereas more than half of our celiac population represented responders (69.39%), the percentage still remained lower than in the general population (90%), suggesting a role of genetic predisposition. However, comparison of the distribution of vaccination response showed no statistically significant difference between the different genotypes, providing an argument against the theory that homozygosity for the HLA-DQ2 haplotype could act in isolation to negatively influence the response to vaccination, in comparison with the HLA-DQ2/DQ8 heterozygosity or other haplotypes.

In this regard, several studies hypothesized that gluten intake at the time of vaccination could influence immune response, *via* competition of both gliadin peptides and hepatitis B surface antigen protein fragments for binding to HLA-DQ2 molecules, which could result in defective antibody production<sup>[3,17,18]</sup>. In support of this hypothesis, Nemes *et al.*<sup>[19]</sup> showed that seroconversion after hepatitis B vaccination was 95.5% in CD patients vaccinated during dietary treatment; in contrast, in a second group of CD patients that were either untreated or with a diet status ranging from strict to non-strict, the response was 50.9%. The HLA-DQ alleles did not seem to play a primary role because all of the patients carried the HLA-DQ2. In our study, patients were enrolled at diagnosis of CD, when their diet contained gluten; although, we do not know the exact period of exposure. It could be of interest to administer a booster dose of HBV vaccine in these subjects after a period of GFD and to subsequently evaluate the effects on the immune response. However, since our study did not reveal a significant correlation between HBV vaccine response and HLA alone, we now question whether it is possible that impaired immune response in CD is the result of a combination of several factors. Indeed, it could be possible that genetic predisposition, gluten intake and phenotype of the disease interact to influence a lower HBV vaccine response in CD.

In conclusion, our study is the first prospective study on HBV vaccine response in CD. The findings confirm the lower percentage of response to hepatitis B vaccination in the celiac population, as compared with healthy subjects. The mechanism that causes this phenomenon, however, remains unclear. According to our results, the mechanism does not appear to be related to HLA haplotype alone but could result from several variables working in combination. Further studies are needed to support this hypothesis and to establish the best surveillance program of response to HBV vaccine in CD.

## COMMENTS

### Background

The correlation between celiac disease and a lower response to the hepatitis B virus (HBV) vaccine has been demonstrated, but the causes remain unclear. Many confounding factors identified by previous studies have contributed to this uncertainty; moreover, the lack of prospective data represents a more extensive gap between the time of vaccination and the development of an immune response, contributing to select false non-responders (*i.e.*, those who are destined to lose the antibody titer over time). The originality of the authors' prospective



study lies in the authors' analysis of the response to hepatitis B vaccination in a group of celiac patients at the time of diagnosis, which allowed the authors' study to nullify the percentage of error related to these confounding factors.

### Research frontiers

In this study, there is suggestion that genetic predisposition, gluten intake and phenotype of celiac disease could work in conjunction to influence a lower HBV vaccine response.

### Innovations and breakthroughs

This study is the first prospective study in literature on the topic of lower HBV vaccine response in patients with celiac disease. This study confirms the lower percentage of response to hepatitis B vaccination in the celiac population, as compared with healthy subjects. According to the authors' results, the mechanism that causes this phenomenon is unlikely to be related to human leukocyte antigens haplotype alone but could be a result of several variables together.

### Applications

This study provides additional evidence that, along with the collective data in the literature, will help to establish an optimal surveillance program of response to HBV vaccine in celiac disease.

### Terminology

Non-responders are all subjects with a titer of hepatitis B surface antibody < 10 IU/mL after the primary vaccination cycle.

### Peer-review

The authors have studied antibody response to HBV vaccine in celiac patients. This is an interesting study, well designed and performed.

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**P-Reviewer:** Balaban YH, Saez LR, Sener AG  
**S-Editor:** Gong ZM **L-Editor:** A **E-Editor:** Li D





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