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Celiac Disease and HBV Vaccination

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Abstract

Celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamins in genetically susceptible individuals, characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, HLA-DQ2 and HLA-DQ8 haplotypes, and enteropathy. Hepatitis B virus (HBV) infection is an important global public health problem that can cause chronic liver disease, and it is associated to a high risk of death from cirrhosis and hepatocellular carcinoma. Since 1982, a safe and effective HBV vaccine has been available, and recommendation for HBV vaccination has been extended to all infants to achieve protection against HBV infection. HBV vaccination is highly effective in eliciting a sustained immune response in immune-competent individuals. However, research papers have suggested that celiac patients may have low rate of protective antibodies after HBV vaccination. The failure of CD subjects to respond to HBV vaccination has great importance for public health policies as the nonresponders could be regarded as a reservoir for HBV. The aim of our work is to revise and to discuss the scarce literature on this field in order to provide clinical practice guidelines to establish the best surveillance program of response to HBV vaccine in CD pediatric patient.

Keywords: celiac disease, children, hepatitis B vaccine, HLA, gluten-free diet

1. Introduction

Celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamins in genetically susceptible individuals, characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, HLA-DQ2 and HLA-DQ8 haplotypes, and enteropathy. Genetic, immunological, and environmental factors therefore appear to be responsible for the disease. HLA-DQ2 is present in 90%–95% of patients with CD, whereas 5% carry the HLA-DQ8 haplotype and the remaining 5% at least one of the two DQ2 alleles [1, 2]. The prevalence of CD is high in the European and

North American population (1%), reaching 10%–15% in patients who have first-degree relatives with this disease [1, 2].

HLA system has a fundamental role in identifying the antigens inoculated with the vaccines and in the production of specific antibodies [3, 4], and some HLA phenotypes seem to be predictive of a less effective immunological response [5].

In particular, the immunogenic peptides in the hepatitis B (HBV) vaccine determine the protective immune response to the virus through the HLA-DR and DQ molecules [6, 7], with the DR3-DQ2 and DR7-DQ2 haplotypes generally having a lower response rate [7–10].

HBV infection is one of the major causes of chronic liver disease, associated with a high risk of death from cirrhosis and hepatocellular carcinoma, and therefore represents an important global public health problem [11, 12]. To prevent it, since 1982, a safe and effective hepatitis B vaccine has been available. The one currently in use is a recombinant vaccine that contains HBV surface antigen (HBsAg) and causes the production of specific antibodies (anti-HBs) that protect against the infection [13]. Many epidemiologic studies have been conducted to determine the efficacy of the vaccine. A positive immune response to the vaccine is defined as the development of HBV anti-HBs at a titer of >10 mIU/mL, after a complete and appropriate immunization schedule, measured preferably 1–3 months after the last vaccine administration [14, 15]. The optimum response, conferring seroprotection against HBV infection, is defined as an anti-HBs titer ≥100 IU/l [14, 15]. Subjects that develop an anti-HBs titer between 10 and 100 IU/ml are referred to as "poor responders." Vaccinated subjects with an anti-HBs titer <10 mIU/ml after completion of primary vaccine series are called "nonresponders" [16]. HBV vaccination is very effective, showing a sustained immune response in immune-competent individuals: the antibody response has been found to occur in more than 90% of the healthy subjects vaccinated with the standard dose regimen of 20 µg HBV vaccine given at 0, 1, and 6 months of intervals [17, 18]. However, among healthy immunocompetent subjects, approximately 4–10% do not produce protective levels of anti-HBs after immunization [19] depending on age, male gender, obesity, inappropriate vaccine storage conditions, route of administration, smoking, drug abuse, state of immunosuppression, and presence of specific HLA haplotypes.

2. Responses to vaccinations in celiac children

Data concerning antibody response of patients with CD to vaccine are scanty. Most studies in this field are addressed to HBV vaccination response, while fewer works are available about the immunological response to other vaccinations.

Several research papers have suggested that celiac patients may have low rate of protective antibodies after vaccinations such as HBV. The failure of CD subjects to respond to HBV vaccination has great importance for public health policies as the nonresponders could be regarded as a reservoir for HBV [20]. The studies that have addressed the relation between CD and HBV vaccination in children are summarized in **Table 1** [21–29]. In the earliest report involving 26 celiac patients aged 9.2 ± 4.6 years and 18 age-matched controls, receiving the full complement of childhood vaccination (HBV, tetanus, rubella, *Haemophilus influenzae* type b), Park et al. [21] demonstrated that a significantly higher proportion of subjects in the CD group failed to

respond to HBV vaccine compared with controls (53.9% versus 11.1%; $p < 0.05$). However, all subjects in both groups tested positive for other vaccinations. These results led the authors to support the role of HLA haplotypes in response to HBV vaccine. Nemes et al. [22] evaluated HBV vaccine response in CD patients in relation to disease activity and examined the possible role of dietary gluten in the failure to achieve protective antibody titers. The authors studied 128 biopsy-proven CD children and adolescents and 113 age-matched control subjects; 22 patients with CD were prospectively vaccinated with a recombinant HBV vaccine after the diagnosis of CD during dietary treatment, while 106 CD patients received a recombinant HBV vaccine unrelated to CD diagnosis and dietary compliance. They found that a seroconversion rate for anti-HBs was 95.5% (95% CI: 78.25–99.2%) after vaccination in the patients prospectively immunized, while the response rate was 50.9% and correlates with gluten intake (untreated patients 25.9%, non-strict diet 44.4%, strict diet 61.4%) when HBV immunization was performed unrelated to diagnosis and diet status suggesting that disease activity may play a primary role in vaccination failure rather than specific HLA alleles [22]. Subsequently, Ertem et al., to assess the response to HBV vaccine prospectively in a group of CD children and to explore the potential link between CD and HBV vaccine nonresponse, evaluated serologically for anti-HBs status 63 previously biopsy-proven CD patients on a strict gluten-free diet (GFD) and 54 healthy children. CD children who were anti-HBs negative at baseline were fully vaccinated prospectively and reevaluated for the response to HBV vaccine. The authors found that the response rate to HBV vaccine in CD patients prospectively vaccinated was 96.9%, which was as high as the response rate obtained in healthy population, and they concluded that treatment with GFD and compliance to the treatment rather than the specific HLA alleles may improve the immune response to HBV vaccine in CD patients [23]. Balamtekin et al. conducted a study to compare the response rates to HBV vaccination in the first year of life, using two different immunization protocols. The total study group included 64 CD children (group 1 who received HBV vaccination at birth, 2 and 9–12 months of life, and group 2 at birth, 1 and 6 months of life) and 49 healthy controls. The authors found that the response rate to HBV vaccine and anti-HBs titers in CD patients who completed the HBV vaccination before 1 year of age were significantly lower compared to healthy controls, whereas no statistically significant difference was observed with the two different HBV vaccination schedules [24]. Ertekin et al. compared the response to HBV vaccine between children with CD and healthy children and investigated the relationship between the patients' responses to HBV vaccine, the clinical presentation of CD, and the dietary compliance in the patients. They evaluated the production of specific anti-HB surface antigen (HBsAg) in 52 CD patients and 20 age- and sex-matched healthy children who received HBV vaccination according to the standard immunization schedule. The authors found that anti-HBs titers of CD patients were positive in 32 (61%) and negative in 20 (38.5%) patients, while 18 (90%) of control subjects had positive anti-HBs titers. They found also statistically significant differences between negative anti-HBs titers, clinical presentation of CD, and dietary compliance in patients with CD ($P < 0.05$). Therefore, they concluded that, in children with CD, the immune response to HBV vaccination may be improved by compliance to the GFD [25]. Leonardi et al. [26] in a retrospective report confirmed that CD patients have a lower percentage of response to HBV vaccination than healthy subjects. In fact, they found that 30 (50%) of 60 CD patients were nonresponders to HBV vaccination, compared to 7 (11.6%) of 60 controls. The same authors also found that a significantly higher number of nonresponders in adolescent patients older than 14 years and concluded that a very early

diagnosis of CD seems to increase significantly the percentage of responders suggesting that a short time of gluten introduction seems to play a favorable effect on the antibody memory [26]. Leonardi et al. [27] in a subsequent retrospective study, including 66 CD patients and 50 healthy children, analyzed and compared the immunologic response against obligatory vaccination (HBV, diphtheria and tetanus component, and *Bordetella pertussis*) and against recommended vaccination (*Measles virus*, *Paramyxoviridae*, and *Rubella virus*) in the two groups. The authors found similar response to obligatory and recommended vaccines into the two groups, except for HBV vaccine. Moreover, they compared patients whose diagnosis was made before or after 18 months of age and found that an early or a delayed diagnosis does not significantly modify the immunological response, except for that one involved in the HBV vaccination. Thus, the immunologic response did not seem to be influenced by the natural history of CD [27]. Urganci and Kalyoncu determined the rate of response to hepatitis A (HBA) and HBV vaccine, the duration of protection against HAV and HBV, and the incidence of acute HAV or HBV infections during follow-up in 30 pediatric patients with CD and compared them with 50 healthy age-, sex-, and body mass index-matched controls [28]. They found that 14 (46%) of 30 CD patients and 15 (30%) of the controls had natural immunity for HAV, whereas all patients and controls did not show evidence of earlier exposure to HBV. Sixteen patients and 35 controls received HAV vaccine, and HBV vaccine was administered to all CD patients and controls; protective anti-HAV antibodies were developed in 12 (75%) of the patients and all the controls (75% versus 100%, respectively). Thirty patients and 50 controls received HBV vaccine, and 70% of the patients versus 90% of the controls achieved seroprotection. The authors concluded that the rate of seroconversion to the HBV and HAV vaccine is lower in CD patients than in healthy controls. Finally, in a very recent paper, Leonardi et al. comparing a group of patient affected by diabetes mellitus type 1 (DMT1) and CD and a group affected by DMT1 without CD (both groups had similar HLA haplotype) found a higher nonsignificant percentage of nonresponders in DMT1/CD group than in DMT1 (53.3% versus 38.2%); comparing the DMT1/CD group with CD group, the authors found a similar percentage (53.3% versus 50%) of nonresponders, and this result indirectly confirmed that gluten can favor a further decrease of efficacy to HBV vaccine, beyond the HLA system [29].

Author/ references	Year	Country	Study design	Patient population and sample size	Vaccine	(%) of nonresponders	HLA
Park et al. [21]	2007	Japan	Prospective	26 (mean age 9.2 ± 4.6 years) untreated CD vs 18 (mean age 10.4 ± 3.8) controls	HBV	53.9% vs 11.1%; P < 0.05	NA
Nemes et al. [22]	2008	Finland	Prospective	22 (mean age 8.8 years) treated CD prospectively immunized; 27 (mean age 16.7 years) untreated CD; 79 (mean age 16.7 years) treated CD vs 113 (mean age 16.1 years) controls	HBV	0.5% 74.0% 38.6% vs 24.8%; P < 0.001, P < 0.001, P = 0.102	Group 1 (22 treated CD): HLA DQ2 Group 2 (53/106 treated and untreated CD): 51: HLA DQ2 2: HLA DQ8

Author/ references	Year	Country	Study design	Patient population and sample size	Vaccine	(%) of nonresponders	HLA
Leonardi et al. [26]	2009	Italy	Retrospective	60 (mean age 9.32 years) treated CD vs 60 (mean age 10.1 years) controls	HBV	50% vs 11.6%; $P < 0.0001$	15/60: 13 HLA-DQ2 2 HLA-DQ8
Ertem et al. [23]	2010	Turkey	Retrospective Prospective	40 vaccinated (mean age 12.4 ± 5.4 years) treated CD vs 54 (mean age 9.8 ± 3.6 years) controls 28 prospectively vaccinated treated CD	HBV	32.5% vs 14.8%; $P < 0.05$ 3.6%	37.5% CD 23.8% controls: HLA DRB1*03 21% CD 2.4% controls: HLA DRB1*07 55% CD 14.6% controls: HLA DQB1*02 30% CD 47.6% controls: HLA DQB1*03
Ertekin et al. [25]	2011	Turkey	Retrospective	52 (mean age 10.7 ± 4 years) CD vs 20 (mean age 10.7 ± 4 years) controls	HBV	38.5% vs 10%; $P < 0.05$	NA
Balamtekin et al.[24]	2011	Turkey	Retrospective	64 (mean age 4.69 ± 2.31 years) treated and untreated CD vs 49 (mean age 5.45 ± 2.92 years) controls	HBV	21.9% vs 4.1%; $P = 0.001$	NA
Urganci and Kalyoncu [28]	2013	Turkey	Prospective	30 (mean age 6.15 ± 4.1 years) treated and untreated CD vs 50 (8.13 ± 1.7 years) controls	HBV	30% vs 10%; $P = 0.03$	NA
Leonardi et al. [27]	2011	Italy	Retrospective	66 (mean age 8.34 ± 3.47 years) CD vs 50 (mean age 7.58 ± 3.51 years) controls	HBV	53% vs 16%; $P < 0.0001$	NA
Leonardi et al. [29]	2015	Italy	Prospective	30 (mean age 6 years) CD/DMT1 vs 100 (mean age 13.6 years) DMT1 vs 60 (mean age 8.6 years) CD	HBV	53.3% vs 38.2% vs 50%; $P > 0.02$	NA

HBV hepatitis B virus; *CD* celiac disease; *HLA* human leukocyte antigen; *NA* nonavailable; *DMT1* diabetes mellitus type 1.

Table 1. Response to HBV vaccination in CD children and adolescents compared to healthy subjects.

3. Pathogenetic role of HLA system in vaccination unresponsiveness in celiac disease

The mechanism for hepatitis B vaccination failure in patients with CD is not clear. A few hypotheses have been proposed. Multiple candidate genes influence the ability to respond

to the recombinant HBV vaccine [9, 30–32]. HLA is believed to contribute significantly to the genetic susceptibility immune response variations to the vaccine [33]. Poor or nonresponsiveness to HBV vaccine has been associated with HLA-DQ2, DR3, and DR7 alleles, which are also associated with CD [9, 10, 34]. In particular, HLA genotype DQ2, found in 90–95% of celiac patients, may have a fundamental role in the predisposition to a weaker immunization to recombinant hepatitis B vaccine in these patients. The HLA is coded by the major histocompatibility complex (MHC) group of genes located on chromosome 6 in the human genome, and they are essential for determining the specificity of an individual's immune response [35]. There are three classes of HLA: HLA class I, HLA class II, and HLA class III. Among them, HLA class II molecules have the task of presenting antigens to the T lymphocytes from outside the cell. Antibody-producing B cells are then stimulated to produce specific antibodies by these antigens [36]. HLA-DQ2 haplotype would be responsible for the failure of induction of the Th2 response needed to promote the differentiation of B cells and the formation of memory B cells necessary for immunization.

Defective or insufficient HBsAg-specific T-helper cells, inadequate T-helper 1, and T-helper 2 cytokine production [37–39], or diminished expression of cell contact signal between activated T and B cells, like CD40L [40] may also be responsible for the lack of response to HBsAg [41, 42]. On this regard, interleukin genotypes (IL10, IL12, IL18) were associated with the anti-HBs antibody development in response to HBsAg in hemodialysis patients [43, 44]. Chen et al. in 2011 found that serum anti-HBsAg response to HBV vaccine in healthy population was closely related to four specific single-nucleotide polymorphism (SNPs) in the IL4, IL4RA, IL13, and Toll-like receptor (TLR2) genes and suggested that variation in these structures may influence the duration and intensity of HBV vaccine-induced immune response [45].

Other studies suggested that compliance with a GFD is responsible for the response to the hepatitis B vaccine in patients with CD. Several studies have hypothesized gluten intake as a cause of failed immunity upon vaccination. Gluten may be implicated because both HBsAg protein fragments and gliadin peptides bind to HLA-DQ2 molecules and induce proliferation of T lymphocytes. Defective antibody production may result from competition between the proteins [22, 23].

4. New approaches in hepatitis B vaccination in celiac children

Inadequate response to HBV immunization in CD patients represent a public health concern because the group of nonresponder patients could act as an HBV infection reservoir. For this reason, response to HBV vaccine should be investigated in children with CD. To protect this population and to achieve the goal of universal protection, new immunization strategies were proposed for CD: the first one is the use of booster and/or higher doses of HBV vaccine by intramuscular (IM) route, and the second one addresses on the use of intradermal route (ID). The studies that have addressed new immunization strategies in CD are summarized in **Table 2** [22, 23, 46, 47].

Author/references	Year	Country	Study design	Patient population and sample size	VAC Ag	Type of vaccine	Route	Number of booster doses	% Seroconversion
Nemes et al. [22]	2008	Finland	Prospective	37 (mean age 16.7 years) nonresponders CD on GFD	HBV	Recombinant	IM	1	97.3%
Ertem et al. [23]	2010	Turkey	Prospective	28 (12.4 ± 5.4 years) nonresponders CD	HBV	Recombinant	IM	Three doses of HBV vaccine	96.4%
Leonardi et al. [46]	2010	Italy	Prospective	20 nonresponders CD to IM vaccination	HBV	Recombinant	ID	4	90%
Leonardi et al. [47]	2012	Italy	Prospective Randomized	58 (mean age 9.8 ± 6.2 years) nonresponders CD	HBV	Recombinant	30 ID vs 28 IM	3	After first dose: ID:76.7% vs IM: 78.6% After third dose: ID: 90% vs IM: 96.4% High responders (anti-HBs >1000 IU/l): ID: 40% IM: 7%; $P < 0.01$

CD celiac disease; *IM* intramuscular; *ID* intradermal; *VAC* vaccine; *Ag* antigen; *GFD* gluten-free diet; *HBV* hepatitis B virus; *anti-HBs* anti-hepatitis B surface

Table 2. Seroconversion rate in CD children and adolescents after IM or ID HBV vaccination.

Nemes et al. administered intramuscularly to 37 nonresponder CD children on GFD, the booster dose of 20 μg of recombinant HBV vaccine, and found that 36 out 37 (97.3%) showed seroconversion 4 weeks after vaccination. However, success with the booster vaccination after controlled GFD suggests that disease activity may play a primary role in vaccination failure [22]. Few studies that exist about HBV vaccine administered by ID route in CD patients unresponsive to IM recombinant vaccine. Leonardi et al. revaccinated 20 CD children and adolescents with a 2 μg dose of recombinant intradermal HBV vaccine. After 4 weeks they found that 15 out 20 patients (75%) showed a protective titer of anti-HBs [22, 23].

Subsequently, Leonardi et al. conducted a prospective, randomized study on 58 CD patients, vaccinated in the first year of life, without protective HBV antibodies as demonstrated by blood analysis. They performed in all patients randomly an HBV vaccination booster dose by ID or IM route. In 30 CD children, a 2 μg dose of recombinant HBV vaccine was administered by the ID route, while 28 CD patients received by IM route 10 μg dose of the same vaccine. Four weeks after every booster dose, 90% of ID patients and 96.4% of IM subjects showed a protective anti-HBs titer after a third booster dose. The authors concluded that both routes are effective in revaccinating CD patients; however, the ID route seems to produce a significantly higher percentage of higher responders [47].

Data suggest that the ID route offers greater immunogenicity due to direct delivery of antigen to the skin immune system, using even lower doses of antigen than IM route [47]. Moreover, the presence of a skin reaction on the site of the intradermal injection could represent a less expensive strategy to test serum anti-HBs response after the booster dose [48]. Economic studies suggest that the substantial cost-saving benefits could be achieved using a fraction of the IM dose via an ID route [48, 49].

5. Conclusions

The available literature shows that HBV vaccine response is lower in celiac subjects compared with healthy ones. Some authors hypothesize that the failure to respond to HBV vaccination is related to specific HLA association, whereas others argue that exposure to gluten at the time of vaccination may play an important role in unresponsiveness to the HBV vaccine. Therefore, nonresponsiveness to the HBV vaccination in CD patients represents a serious public health problem because of the large diffusion of CD that affects about 1% of the European population. Consequently, new vaccination strategies have been proposed to achieve full protection in this context, including the administration of booster doses of HBV vaccine by the intramuscular or the intradermal route. An evaluation of the response to HBV vaccine should be considered as a routine assessment in children newly diagnosed with CD who were previously vaccinated for HBV. Whenever unresponsiveness occurs, certain measures must be taken into account, such as revaccination utilizing ID route, which offers a potentially greater immunogenicity than the IM one, even using lower doses, due to the direct delivery of antigen to the skin immune system. Moreover, the revaccination should be done after the decrease of specific antibodies, which usually occurs after about 1 year of GFD, seen as some studies support GFD

as crucial to vaccine responsiveness. More randomized controlled studies with a prospective design are needed for CD patients in order to clarify this topic.

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