Article published online: 2022-07-07

Original Article

# Anti-Hepatitis B Antibody Status in Children with Coeliac Disease

**Areej Abdussalam Hweta[1,2], Asma Ali Shagleb[1], Mohamed Omer Elgadi[1], Abulraouf Mohamed Zaghdani[1,2], Fauzi Abdalla Sagher[1,2]**

[1]Department of Paediatric Gastroenterology, Hepatology and Nutrition, Tripoli Medical Centre, [2]Department of Paediatric, Faculty of Medicine, University of Tripoli, Tripoli, Libya

## Abstract

**Objective:** This study aimed to compare the antibodies response to hepatitis B virus (HBV) vaccine between Libyan children with coeliac disease (CD) and healthy control. **Subjects and Methods:** A total of 66 children with CD on a gluten-free diet (GFD) and 31 randomly allocated healthy children who received HBV vaccination according to the standard immunization schedule were included. Hepatitis B virus surface antigen (HBsAg) and the production of specific anti-HBs antibodies were evaluated in all patients and control participants using standard techniques. Patients with <10 IU/L anti-HBs antibodies were considered nonresponses to the vaccination. **Results:** None of the participants were HBsAg reactive. Forty-one of the 66 patients (62%) were female, and 25 (37.8%) were male. The mean age of the CD patients was 8.2 years (range, 22 months-15 years). Anti-HBs titers were positive in 40 (60.6%) patients and negative in 26 (39.3%) patients, whereas they were positive in 19 (61.2%) of the children in the control group and negative in 12 (38.7%).There was no significant difference in response to vaccine between the two groups ($P = 0.83$), the study revealed a statistically significant relation between negative anti-HBs titers and duration from the last dose of HBV vaccine ($P = 0.004$). **Conclusion:** In the present study, the response rate in Libyan children with CD on GFD was not different from healthy control. However, not all children need booster dose; only nonresponders need an intradermal test-booster dose to reassess the state of their memory cell before considering revaccination.

**Keywords:** Anti-hepatitis B antibodies, children, coeliac, hepatitis BV vaccine

## Introduction

Coeliac disease (CD) is an immune-mediated disease, characterized by villous atrophy of the proximal small intestine and malabsorption.[1] Human leukocyte antigen (HLA) and nonHLA genes also play a role besides gluten and additional environmental factors in CD pathogenesis.[2]

Recently, it has been shown that more than half of the children with CD did not show a response to the standard hepatitis B virus (HBV) vaccination, and the rate of nonresponse to HBV vaccine has been reported to be even higher when the adult coeliac patients are concerned.[3-7] However, there are few studies addressed to the link between CD and HB vaccine nonresponse in coeliac children.[5]

HBV infection is an important global public health problem; one-third of the world's population has been infected with HBV, which has caused acute, chronic liver disease, cirrhosis, and hepatocellular carcinoma.[3-5,8,9] HB vaccines were introduced in the early 1980s.[10,11] The implementation of mass immunization program, which has been recommended by the World Health Organization (WHO) since 1991, has dramatically decreased the incidence of HBV infection among infants, children, and adolescents in many countries,[4] In Libya, a routine immunization program was initiated by the Ministry of Health in 1993.

Protective serum titers of anti-HBs (>10 IU/L) may develop in 95%–99% of healthy infants, children, and young adults who receive a series of three intramuscular doses.[10] In the healthy population, 4%–10% of vaccine recipients fail to produce protective levels of antibodies to the HBV after standard immunization depending on age and the presence of various

Access this article online

Quick Response Code:

Website: www.ijmbs.org

DOI: 10.4103/ijmbs.ijmbs_25_18

**Address for correspondence:** Prof. Fauzi Abdalla Sagher, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Tripoli Medical Centre, Tripoli, Libya.
E-mail: f_sagher@yahoo.com



**How to cite this article:** Hweta AA, Shagleb AA, Elgadi MO, Zaghdani AM, Sagher FA. Anti-Hepatitis B Antibody status in children with coeliac disease. Ibnosina J Med Biomed Sci 2018;10:83-7.

underlying diseases.[3,8,11] Many nongenetic factors including age, obesity, smoking, drug abuse, alcoholism, infections, immune suppression, and route of vaccination are known to be associated with variable responsiveness.[8,12]

## Subjects and Methods

The study is a cross-sectional study involved 66 children who previously diagnosed with CD based on serological markers and typical histopathological features of CD (i.e., villous atrophy with crypt hyperplasia and increased intraepithelial lymphocytes from small intestinal biopsies) and clinical response to gluten-free diet (GFD). Children with positive serologies, but normal or nonconclusive histopathology were excluded and randomly allocated 31 healthy children at different age groups who received HBV vaccination according to the standard immunization schedule which composed of three doses of HB vaccine, at 0, 1 month, and 6 months.

The production of specific anti-HBs antibodies was evaluated in all patients and control participants who were nonreactive to Hepatitis B virus surface antigen (HBsAg), the serum of children was tested for anti-HBs antibodies by enzyme-linked immunosorbent assay technique (Biocentia, Institute fur Medizinische Diagnostik, Germany). Patients with <10 IU/L anti-HBs titers were considered nonresponders to the vaccination, and titers higher than or equal to 10 IU/L was included in the anti-HBs positive group, and considered responders. Clinical data were collected through a questionnaire; these data included current age, gender, age at diagnosis of CD, family history, compliance to the GFD, medical history of any chronic illness, drug history, the age when HB vaccine was completed, and reactivity to HBsAg.

The extracted information was tabulated using Microsoft Excel spreadsheets and then submitted to meta-analytical evaluation SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.), The Mann–Whitney U-test used for statistical evaluation. The Pearson Chi-square test was used to compare the difference in response between patients and controls, and multiple logistic regression was used to detect the effect of variables on the response to HBV vaccine. $P < 0.05$ was considered as statistically significant.

## Results

### Demographic and clinical characteristics

Forty-one of the coeliac patients (62.1%) were female and 25 (37.9%) were male. The mean age of the CD patients at the time of the study was 8.2 years. Eleven of the CD patients (16.7%) had a family history of CD, and ten patients had some other comorbidities. The mean age of patients at the time of diagnosis was 4.6 years (6 months–13 year, 6 months). The mean duration of GFD was 2.4 years (2 weeks to 9 years). There were no significant differences between CD and control groups regarding gender, but CD group were significantly older than control ($P < 0.05$) [Table 1].

### Frequency of hepatitis B antibodies

A remarkable number of patients in the CD group respond to HB vaccine where the anti-HBs titers were positive (≥10 IU/L) in 60.6% and negative in 39.4% [Table 1]. They were positive in 61.3% in controls. There was no statistically significant difference in response to vaccine between CD and control groups. There was a positive family history of CD in 20% of those who respond to the vaccine, compared to 12% of those who tested negative for the HBsAb. Multiple logistic regression [Table 2] showed no significant difference in response to vaccine between male and female $P = 0.96$, (95% confidence interval (CI), 0.32–3.23) and age when vaccination was completed. $P = 0.132$, (95%; CI 0.93–1.71). However, it showed an inverse statistically significant relationship between the time gap from the last vaccine dose and titer of antibodies to HBV vaccine $P = 0.004$ (95% CI, 0.96–0.99) [Figure 1].

## Discussion

Whether patients with CD have nonprotective antibody responses to HBV vaccination more frequently than nonaffected subjects is debatable[13] the nonresponsiveness to HBV vaccine has also been reported in healthy people.[3,8,11] The results of the present study revealed that patients with CD on a GFD have statistically significant higher rates of protective antibody titer which is not different from the control group, despite their older age ($P < 0.05$). Consequently, a large number of the patients with CD on a GFD are considered as responders to HBV vaccination. This is at variance with the findings of Ertem *et al*.[11] Out of their fully vaccinated 40 coeliac patients, on a strict GFD, two-thirds were anti-HBs positive, and one-third were anti-HBs negative at enrolment into the study 54% and 85.2% of the healthy children were anti-HBs positive, and the difference between patients and controls was statistically significant.[11]

HB vaccination produced protective antibody in 95% of children and adolescents with CD who were on a GFD, compared to 51% of those who were not on a GFD.[8] Zingone

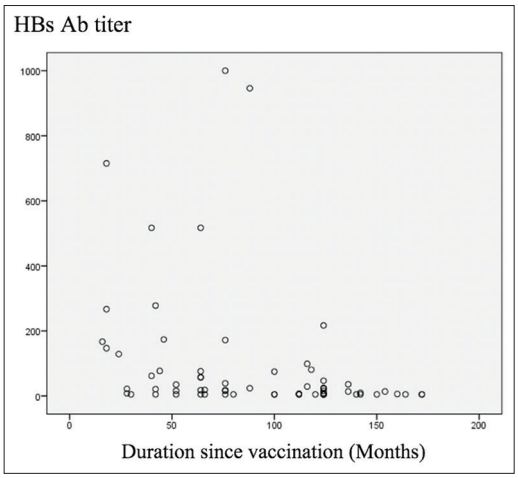


**Figure 1:** Levels of hepatitis B Ab titer in relationship to months since last vaccination. $P = 0.004$ (95% confidence interval, 0.96–0.99)

**Table 1: Patients' demographic, clinical characteristics and hepatitis B surface antibody status**

| Characteristics | Celiac disease | Controls | Statistics |
|---|---|---|---|
| *n* | 66 | 31 | |
| Age: Mean (range) | 8 year 3 months (22 months-15 years) | 5 years 11 months (1 year 6 months-14 years 5 months) | *P*<0.05* |
| Gender: Male/female | 25/41 | 11/20 | *P*=0.697* |
| Duration on gluten-free diet mean (range) | 2 years 5 months (2 Weeks-9 years) | - | NA |
| Mean age at diagnosis (range) | 4 years 7 months (6 months-13 years 6 months) | - | NA |
| Time from complete of vaccination to date of sampling mean (range) | 7 years 8 months (15 months-14 years 5 months) | 5 years 4 months (11 months 13 years 10 months) | *P*<0.05* |
| HBs anti-body titer | | | |
| HBs anti-body titer <10 | 26 | 12 | *P*=0.133* |
| HBs anti-body titer ≥10 | 40 | 19 | *P*=0.83* |

*Mann–Whitney U-test and Pearson $\chi^2$ test. HBs: Hepatitis B surface, NA: Not available

**Table 2: Result of multiple logistic regression to assess the effect of some factors on response to vaccination**

| | *B* | SE | Wald | Significant | Exp (B) | 95% CI. for EXP (B) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Step 1 | | | | | | | |
| Age | −0.17 | 0.007 | 6.836 | 0.009 | 0.983 | 0.970 | 966 |
| Months from last vaccination | −0.021 | 0.007 | 8.495 | 0.004 | 0.979 | 0.965 | 0.993 |
| Age when vaccination was completed | 0.233 | 0.155 | 2.274 | 0.132 | 1.263 | 0.932 | 1.710 |
| Gender | 0.023 | 0.587 | 0.002 | 0.969 | 1.023 | 0.324 | 3.232 |
| Constant | 0.599 | 1.255 | 0.228 | 0.633 | 1.821 | | |

SE: Standard error, CI: Confidence interval

*et al*. proposed that gluten intake at the time of vaccination could decrease the efficacy of the same vaccination.[13] Leonardi *et al*. confirmed that a complete cycle of reactivation during a well-controlled GFD might be more effective than the primary vaccination performed on a gluten-containing diet.[4]

To confirm the role of gluten in the unresponsiveness to HBV vaccine in coeliac patients, Ertekin *et al*. observed 52 children with CD and 20 age-matched healthy children who received HBV vaccination according to the standard immunization schedule. They found that anti-HBS positivity was significantly higher in the coeliac patient who was the complaint to GFD than in those who were noncompliant.[14] CD has associated with the extended major histocompatibility complex haplotypes, DQ2, DQ8, and B8, but most specifically with DQ2. In fact, HLA DQ2 is found in 90%–95% of coeliac patients and individuals lacking the DQ2 haplotype are positive for DQ8.[3-5] There was no relationship between HLA type and vaccine nonresponse in Ertem *et al*. study group.,[11] CD may be one of the immune diseases associated with a high rate of HBV vaccine nonresponse, but it might not be permanent, and treatment with GFD and compliance to the management improve the immune response to HBV vaccine in coeliac children, which is in agreement with our results.

Concerning 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. Moreover, the distribution of the responders according to clinical features of CD showed no statistically significant differences ($P > 0.05$).[15] Previous workers found no correlation between HBV vaccine response and DQ2.[16]

The response to HB vaccine was evaluated in 6–18-year-old students from a total of 644 students in Iran,[17] 61.5% of these had a titer <10 IU/L and 38.5% had a titer higher than 10 Iu/L. Therefore, the level of responding to the vaccine with 95% confidence was 38.5% (34.7%–42.4%). Levels of respond to the vaccine were related to age, body mass index (BMI), and educational level and were not associated with gender and habit of students. They detected a significant reverse relation between the response to vaccine and age and BMI in a way which the titers of antibody were lower in students with higher age and BMI.[18] In this study, the age and duration from last vaccination showed significant reverse relation to positive anti-HBs antibody titer. In a recent study by Filippelli *et al*.,[15] CD population was divided into three groups according to age between 0 and 5.5 years (48.9%), between 5.5 and 9.5 years (30.61%); and between 9.5 and 17 years (18.75%). They detected no significant difference between the percentage of responders and nonresponders to HB vaccination between the youngest and the oldest age subgroups. Furthermore, Zanoni *et al*.[16] investigated in a case–control retrospective study the serological responses to vaccines containing

HBV and measles in three groups of individuals. These included type 1 diabetes mellitus (T1DM) patients, CD, and healthy controls. There were no significant differences in the percentage of responders to HBV and measles vaccines among the T1DM and CD patients and the control group. The conflicting results between findings of different groups may be due to the differences in ages of the examined subjects at the time of vaccination and in time intervals between vaccination and blood sample collection for testing. Zanoni *et al*. proposed that to prospective studies should include patients and controls with same age at HB vaccination and same time interval for blood sample collection to determine antibody levels. On the other hand, some studies showed that serum antibodies level decreases with the time following vaccination.[19] Long-term studies of newborn vaccination showed that antibodies become negative in 15%–50% among the vaccine responders within 5–10 years.[20]

The HBV vaccination schedule in Libya follows international recommendations (1st dose at birth, 2nd after 1 month and 3rd after 6 months). Madour *et al*. evaluated the long-term protection of the HBV immunization program in Tripoli and determined the best age to administer booster doses.[20] Serum levels of HBs antibodies were measured in 277 randomly selected children aged 1–12 years. The response to HBV vaccine in 1–3-year-old was 93.2%. Failure rate to vaccination was 6.8% which is more than reported in Taiwan (3.3%), Turkey (2.3%), Gambia (5.1%), and Palestine (5.5%). Furthermore, the response declined with age and at 7–9 years after initial vaccination, 53.1% of the children had protective titers (≥10 IU/L).[21] This rate in this group was between that of Iranian study, 47.9% at the age of 10 years postvaccination.[22] Moreover, 67% in Huang *et al*. study.[20] The results of the present study are more compatible with the previous Libyan study.

The present study showed that time gap from last vaccine dose might be operative in lowering the antibodies response rate to the vaccine. We concur with the recommendation of continuing the HBV vaccination program and restricting a test-booster dose to nonresponsive coeliac children. The immunological memory for HBs Ag can outlast antibody detection, (in providing long-term protection against the disease and the development of carrier state), to test their memory cells and to ensure maximum protection during the period of school entry and beyond which is in agreement with the WHO recommendations and other workers.[20,23,24] We suggest the use of the intradermal route for a test-booster vaccine for three counts: the lower dose of the vaccine can be used for the test, the low cost incurred, and that cellular immune responsiveness to the test can be easily assessed by the development of a skin reaction at the injection site. There is no need to check the serum anti-HBs antibodies concentration after test-booster.[12,25,26]

It is obvious that untreated patients with CD, like other patients with chronic conditions, have an important humoral immune response to recombinant HBV vaccine. Immunized patients with CD on a strict GFD usually develop protective immunity with success rates similar to healthy people. In light of the above evidence, we agree with the notation that the response to HBV vaccination in patients with CD and/or test-booster may be used as a marker of good compliance with GFD.[27]

## Conclusion

In the present study, the response rate in Libyan children with CD on GFD was not different from healthy control. However, not all children need booster dose; only nonresponders need an intradermal test-booster dose to reassess the state of their memory cell before considering revaccination.

### Acknowledgment

The authors would like to express their gratitude to Dr. Abdussalam Hweta for his assistance with the statistical analysis, and to the National center of Medical and Pharmaceutical Research for their financial support.

### Authors' contribution

All authors contributed to the conception and conduct of the study, preparation, revision, and approval of the final version of the manuscript.

### Financial support and sponsorship

This study was supported by a grant to (AAS) from The National Centre of Medical and Pharmaceutical Research. Tripoli, Libya.

### Conflicts of interest

There are no conflicts of interest.

### Compliance with ethical principles

The study was approved by the Ethical Committee of The National Centre of Medical and Pharmaceutical Research. Tripoli, Libya. Parents of all children gave an informed verbal consent before participation.

## References

1. van Heel DA, West J. Recent advances in coeliac disease. Gut 2006;55:1037-46.
2. Plenge RM. Unlocking the pathogenesis of celiac disease. Nat Genet 2010;42:281-2.
3. Ahishali E, Boztas G, Akyuz F, Ibrisim D, Poturoglu S, Pinarbasi B, *et al.* Response to hepatitis B vaccination in patients with celiac disease. Dig Dis Sci 2008;53:2156-9.
4. Leonardi S, Spina M, Spicuzza L, Rotolo N, La Rosa M. Hepatitis B vaccination failure in celiac disease: Is there a need to reassess current immunization strategies? Vaccine 2009;27:6030-3.
5. Park SD, Markowitz J, Pettei M, Weinstein T, Sison CP, Swiss SR, *et al.* Failure to respond to hepatitis B vaccine in children with celiac disease. J Pediatr Gastroenterol Nutr 2007;44:431-5.
6. Vitaliti G, Praticò AD, Cimino C, Di Dio G, Lionetti E, La Rosa M, *et al.* Hepatitis B vaccine in celiac disease: Yesterday, today and tomorrow. World J Gastroenterol 2013;19:838-45.
7. Noh KW, Poland GA, Murray JA. Hepatitis B vaccine nonresponse and celiac disease. Am J Gastroenterol 2003;98:2289-92.
8. Nemes E, Lefler E, Szegedi L, Kapitány A, Kovács JB, Balogh M, *et al.* Gluten intake interferes with the humoral immune response

to recombinant hepatitis B vaccine in patients with celiac disease. Pediatrics 2008;121:e1570-6.
9. Ertekin V, Selimoğlu MA, Altinkaynak S. Sero-epidemiology of hepatitis B infection in an urban paediatric population in Turkey. Public Health 2003;117:49-53.
10. Lemon SM, Thomas DL. Vaccines to prevent viral hepatitis. N Engl J Med 1997;336:196-204.
11. Ertem D, Gonen I, Tanidir C, Ugras M, Yildiz A, Pehlivanoğlu E, *et al.* The response to hepatitis B vaccine: Does it differ in celiac disease? Eur J Gastroenterol Hepatol 2010;22:787-93.
12. Leonardi S, Praticò AD, Lionetti E, Spina M, Vitaliti G, La Rosa M, *et al.* Intramuscular vs. intradermal route for hepatitis B booster vaccine in celiac children. World J Gastroenterol 2012;18:5729-33.
13. Zingone F, Morisco F, Zanetti A, Romanò L, Portella G, Capone P, *et al.* Long-term antibody persistence and immune memory to hepatitis B virus in adult celiac patients vaccinated as adolescents. Vaccine 2011;29:1005-8.
14. Ertekin V, Tosun MS, Selimoglu MA. Is there need for a new hepatitıs B vaccine schedule for children with celiac disease? Hepat Mon 2011;11:634-7.
15. Filippelli M, Garozzo MT, Capizzi A, Spina M, Manti S, Tardino L, *et al.* Immune response to hepatitis B virus vaccine in celiac subjects at diagnosis. World J Hepatol 2016;8:1105-9.
16. Zanoni G, Contreas G, Valletta E, Gabrielli O, Mengoli C, Veneri D, *et al.* Normal or defective immune response to hepatitis B vaccine in patients with diabetes and celiac disease. Hum Vaccin Immunother 2015;11:58-62.
17. Jouneghani AS, Chaleshtori MH, Khoshdel A, Kheiri S, Farrokhi E, Khalafian P, *et al.* Evaluation of response to hepatitis B vaccine in Iranian 6-18-year-old students. J Res Med Sci 2017;22:116.
18. Opri R, Veneri D, Mengoli C, Zanoni G. Immune response to hepatitis B vaccine in patients with celiac disease: A systematic review and meta-analysis. Hum Vaccin Immunother 2015;11:2800-5.
19. Liu HB, Meng ZD, Ma JC, Han CQ, Zhang YL, Xing ZC, *et al.* A 12-year cohort study on the efficacy of plasma-derived hepatitis B vaccine in rural newborns. World J Gastroenterol 2000;6:381-3.
20. Huang LM, Chiang BL, Lee CY, Lee PI, Chi WK, Chang MH, *et al.* Long-term response to hepatitis B vaccination and response to booster in children born to mothers with hepatitis B e antigen. Hepatology 1999;29:954-9.
21. Madour A, Alkout A, Vanin S. First evaluation of the serum level of anti-hepatitis B surface antigen after vaccination in Libya. East Mediterr Health J 2013;19:990-4.
22. Jafarzadeh A, Montazerifar SJ. Persistence of anti-HBs antibody and immunological memory in children vaccinated with hepatitis B vaccine at birth. J Ayub Med Coll Abbottabad 2006;18:4-9.
23. WHO Publication. Hepatitis B vaccines: WHO position paper – Recommendations. Vaccine 2010;28:589-90.
24. Zanetti AR, Mariano A, Romanò L, D'Amelio R, Chironna M, Coppola RC, *et al.* Long-term immunogenicity of hepatitis B vaccination and policy for booster: An Italian multicentre study. Lancet 2005;366:1379-84.
25. Sangfelt P, Uhnoo I, Reichard O, Weiland O. A low-dose intradermal hepatitis B vaccine programme in health-care workers and students is highly effective and cost saving: A retrospective follow-up survey in the clinical setting. Scand J Gastroenterol 2008;43:465-72.
26. Walkiewicz-Jedrzejczak D, Egberg M, Nelson C, Eickoff J. Evaluation of the response to vaccination with hepatitis B vaccine in pediatric patients diagnosed with celiac disease. SAGE Open Med 2014;2:2050312114563346.
27. Rostami K, Rostami Nejad M. Vaccinations in celiac disease. J Pediatr Gastroenterol Nutr 2013;56:341-2.