Annals of Medical Research
DOI: 10.5455/annalsmedres.2019.05.296 2019;26(8):1478-83

Original Article

Factors affecting hepatitis B immunization in celiac disease

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Abstract

Aim: While 90-95% of the adult population responds to hepatitis-B vaccination, it is known that, this rate is lower in patients with CD. In our study, determination of response rates of vaccinated celiac patients, and the affecting factors associated with vaccine responses were the aims of our investigation.

Material and Methods: The study included 280 celiac patients who applied to the polyclinic between 2015-2019 years. Demographic, anthropometric characteristics (age, gender, onset age, disease duration, smoking, body mass index(BMI), waist-hip ratios) and symptoms in patients were documented. Hepatitis B, C, delta serology were examined. The prevalence of chronic hepatitis and associated risk factors were evaluated. Hepatitis-B vaccination rates and vaccine responses were determined. The risk factors associated with the immune response were reviewed.

Results: 212 (75.7%) of the patients were female, the mean-age of the patients was 33.4±10.8 and the disease duration was 4.9±3.7 years. In 14 (5%) of the patients there were chronic viral infections, 18 (6.4%) had natural immunity, 92 (32.9%) were immunized, 58 (56.4%) were not encountered with viral infection. No significant correlation was found between the presence of chronic viral hepatitis and risk factors. 28 (30.4%) patients who had not vaccine response. It was observed that; the dietary incompatibility and absence of immunological remission were significantly higher, the BMI and the waist size were significantly lower in non-response group (P<0.05).

Conclusions: Considering the mild-high prevalence of chronic viral infection in celiac patients, it is important to vaccinate these patients against infections. It is of great importance to implement re-vaccination protocol in the patients without vaccine response.

Keywords: Celiac disease; hepatitis B; vaccination.

INTRODUCTION

Celiac disease (CD) is an autoimmune enteropathy due to gluten intake, a protein present in wheat, rye and barley (1). The correlation between celiac disease and non-gluten-related environmental factors is not fully understood. Breastfeeding, smoking and viral infections can contribute to the onset of the disease (2). Many studies have shown that, there is a correlation between adenovirus, rotavirus, enterovirus and hepatotropic virus infections and the development of celiac disease (3,4). Hepatotrophic viruses are associated with pathophysiological processes leading to mucosal inflammation along with gluten and may trigger autoimmune events during the course of the disease (4).

Hepatitis B virus (HBV) infection is a major public health problem worldwide. One third of the world's population is infected with HBV, which causes acute and chronic liver disease, cirrhosis and hepatocellular carcinoma (5,6). In a systematic review of studies conducted between 1999 and 2009 in Turkey, HBsAg positivity was 2-4% and approximately 3.3 million people were infected with chronic HBV and anti HCV positivity was reported to be approximately 0.5% (7,8).

Many studies have reported that, chronic viral hepatitis prevalence in celiac patients is higher than the normal population (9,10). It had been hypothesized that chronic HBV could trigger immunological gluten intolerance in susceptible individuals (11). Also some studies have shown that an increased prevalence of celiac disease was observed among hepatitis B patients (12). In addition, vaccination is an effective and reliable protection tool

Received: 28.05.2019 **Accepted:** 18.06.2019 **Available online:** 23.07.2019
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against widespread HBV infections, but is reported to be less effective in celiac patients (5,13). The immune response rate for HBV vaccination in the adult population is around 90%. The effectiveness of HBV vaccines in celiac patients has been reported to be 4% to 10% lower than the healthy population (14-18). The ability to respond to recombinant HBV vaccines is considered to be associated with the immunogenic status due to multiple candidate genes, and in this context some specific HLA haplotypes are the most important genetic markers (19). It has been emphasized that high chronic hepatitis prevalence and high unresponsiveness in celiac patients may be associated with immune system ineffectiveness (19). The aim of our study is firstly, to determine the prevalence of chronic viral hepatitis in celiac patients and response rates of vaccinated celiac patients, and secondly to determine the risk factors associated with vaccine responses.

MATERIAL and METHODS

Study design

The patients who were diagnosed and followed-up in the clinics of Gastroenterology were included in the present study. The celiac patients whose records were included in the hospital database between 2015 and 2019, together with newly diagnosed celiac patients in our outpatient clinics were included in the study. For all patients who were diagnosed with CD, the inclusion criteria for the study was having positive results of the antibody level test (anti-Endomysium and Tissue Transglutaminase antibody (anti-TTG)), which is carried out due to clinical and laboratory suspicion, and having consistent results of the tissue samples taken in endoscopy in histopathological examination according to the Marsh classification (20). The patients who did not continue their follow-up in our clinic, whose data could not be obtained, data lost and pregnant were not included in the study. A total of 280 patients with CD, whose ages varied between 18 and 65 years, whose data was complete, and who continued their follow-ups regularly, were included in the study. Written informed consent forms were received from all participants.

Evaluation of demographic and clinic features

The demographic and anthropometric characteristics (age, gender, onset of disease, duration of disease, smoking use, Body Mass Index (BMI)) of the patients who were included in the study were documented. Height (meter) and weight (kg) measurements were made to calculate the BMI of the patients. The BMI was calculated with the following formula: Weight/Height x Height. The waist circumference, hip circumference, waist/hip rates were also documented. In men waist/hip ratio of 0.9 and 0.85 in women, was considered to be a risk factor for abdominal obesity and chronic diseases (21). The symptoms of the participants at admission were documented. Diarrhea, constipation, reflux, bloating, abdominal pain, nausea and vomiting were evaluated as gastrointestinal (GIS) symptoms.

Dietary compliance and immunological evaluation

In patients who had CD, gluten-free diet compliance was retrospectively by the responsible physician and dietician from patient records of patient visits. In addition, compliance with gluten-free nutrition was evaluated by analyzing the questionnaire that was given to patients. The diet was classified into two categories; strict diet (complete dietary compliance) and normal gluten-containing diet. For the purpose of evaluating the immunological remission at the last visit of the patients, the antibody levels were evaluated again. The patients who had negative antibody levels were accepted to be in immunological remission.

Viral hepatitis serology

HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc IgG, antibody against hepatitis delta virus (anti-HDV), HBV-DNA (Amplicor HBV MonitorTM test, Roche Diagnostic Systems, Inc., Branchburg, NJ), antibody against hepatitis C virus (anti-HCV), HCV-RNA (Amplicor HCV MonitorTM test, Roche Diagnostic Systems, Inc, Branchburg, NJ), were studied. HBsAg, HBeAg, anti-HBe, anti-HDV, anti-HCV and anti-HIV tests were used in the evaluation of enzyme linked immunosorbent assay (ELISA) method; HBV-DNA and HCV-RNA were tested using quantitative PCR. A seroconversion rate was defined by anti-HBs titers >10 IU/L. Patients with an anti-HBs titer < 10 IU/L were regarded as unresponsive, and >10 IU/L as responsive. Patients with HBsAg positive, anti-HBs negative, HBeAg negative, anti-HBe positive, HBV DNA <2000 IU/ml and normal levels of transaminases were regarded inactive carriers of hepatitis B. Patients with HBsAg positive, anti-HBs negative, HBV DNA >2000 IU/ml, high levels of transaminases and patients diagnosed with chronic inflammation in liver biopsy were regarded chronic active hepatitis. Patients with HBsAg negative, HBeAg negative, anti-HBs positive, anti-HBe positive, anti-HBc IgG positive patients were regarded naturally immune. Patients with isolated anti-HBc IgG positive and HBV DNA > 000 IU/ml were regarded occult hepatitis B infection, Anti-HCV and HCV RNA positivity were regarded chronic HCV infection, and all serology negative were regarded never encountered with viral infection.

Ethical approval

To conduct this study, ethical approval was obtained from the Ethics Committee of our hospital. All the applicable procedures of the ethical standards of the human testing committee of our institution and the Helsinki Declaration were complied with.

Data analysis

The results of our study were analyzed with "the Statistical Package for Social Sciences 19.0 (SPSS Armonk, NY: IBM Corp.)" program. The data that had continuous values were given as (mean ± standard deviation), and the categorical data were given as frequency and percentage (n, %). The data was tested for compliance to normal distribution with the Kolmogorov-Smirnov Test, Histogram and ± SD. The nonparametric data of the groups were compared by using the Mann Whitney U-test, and the parametric data

were compared with the Parametric T-test. The Chi-square Test was employed to test the categorical data. A P value <0.05 was considered to be statistically significant.

RESULTS

The study included 280 patients who were followed-up for CD. Two hundred and twelve of the patients (75.7%) were female and the mean age of all patients was 33.4±10.8 years (in the range of 18-65 years). The onset age range of the disease was 5-60 years and the mean age was 28.3±11.1 years. The duration of the disease was in the range of 0-17 years and the mean was 4.9±3.7 years. The mean BMI level of the patients was 22.5±4.2, and the waist-hip ratio was 0.82±0.07 (0.63-0.98 range). The waist-hip ratio was 0.86±0.06 in men and 0.8 ± 0.07 in women. In 200 (71.4%) of the patients the waist-hip ratio was below normal. Histopathologic findings of the patients (stage 2 and 3a were mild, and stage 3b, 3c and stage 4 were advanced disease) are examined; 115 (41.1%) of the patients were mild and 165 (58.9%) patients were seen at a severe stage. 2 (0.7%) patients had inactivated hepatitis B, 2 (0.7%) had occult hepatitis B infection, 2 (0.7%) had chronic hepatitis C infection and 8 (2.9%) had chronic hepatitis B infection. Eighteen (6.4%) of the patients were naturally immune, 92 (% 32.9) were immunized with vaccination and 58 (% 56.4) had not encountered hepatitis B or hepatitis C (Table 1).

In the analyzing the risk factors associated with presence chronic hepatitis in celiac patients; there are no significant correlation between age, age of disease onset, duration of disease, BMI, waist circumference, celiac disease stage, dietary compliance, immunologic remission, initial admission symptoms and presence chronic hepatitis (p>0.05). However, there is a significant relationship with smoking and presence chronic hepatitis (P<0.05) (Table 2).

When the vaccination status is evaluated in celiac patients, 92 (32.8%) patients had hepatitis B vaccine, with three doses. In vaccinated patients, 64 (69.6%) patients were with responsive (anti-HBs > 10 I/U), while 28 (30.4%) patients were with unresponsive (anti-HBs < 10 I/U). Risk factors associated with vaccination response were evaluated. It was observed that; the dietary incompatibility and absence of immunological remission were significantly higher, the BMI and the waist size were significantly lower in the non-response group (P<0.05). However, there were no significant correlation between vaccine response and smoking, it was seen that non-response group had more smoking. There was no significant correlation between vaccine response and age, disease onset age, gender, disease duration, celiac disease stage, initial admission symptoms, smoking (p>0.05) (Table 3).

Table 1. The incidence of chronic viral hepatitis in celiac patients

	N - (%)		N - (%)
Inactivated Hepatitis B Carrier	2 (0.7%)	With Vaccination	92 (32.9%)
Chronic Hepatitis B Infection	8 (2.9%)	Occult Hepatitis B Infection	2 (0.7%)
Chronic Hepatitis C Infection	2 (0.7%)	Natural Immunity	18 (6.4%)
Never Encountered with Infection	158 (56.4%)	Total Patient Count	280 (100%)

N: Number of patients

Table 2. Risk factors associated with chronic viral hepatitis in celiac patients

Variables	Celiac disease without chronic hepatitis (N=268)	Celiac disease with chronic hepatitis (N=14)	Total (N=280)	P value
Age (year)	33.6±11.1	34.1±10.1	33.4±10.8	0.870
Age at disease onset (year)	28.5±11.4	29.1±11.3	28.3±11.1	0.874
Duration of illness (years)	4.9±3.7	5.0±2.4	4.9±3.7	0.959
BMI (kg/m^2)	22.6±4.2	21.7±4.1	22.2±4.2	0.392
Waist/hip ratio				
Below limit	190 (71.4%)	9 (66.7%)	199 (71.1%)	0.566
Above limit	76 (28.6%)	5 (33.3%)	81 (28.9%)	
Stage of celiac disease				
Mild (Stage 2-3a)	108 (40.6%)	7 (50%)	115 (41.1%)	0.486
Severe (Stage 3b,3c,4)	158 (59.4%)	7 (50%)	165 (58.9%)	
Dietary compliance				
Strict	96 (36.1%)	3 (21.4%)	99 (35.4%)	0.263
No Compliance	170 (63.9%)	11 (78.6%)	181(64.6%)	
Gender				
Female	204 (76.1)	8 (66.7%)	212 (75.7%)	0.455
Male	64 (23.9)	4 (33.7%)	68 (24.3%)	
Immunologic remission				
Yes	112 (42.1%)	112 (42.1%)	115 (41.1%)	0.125
No	154 (57.9%)	154 (57.9%)	165 (58.9%)	
Cigarette usage				
Smoking	47 (17.7%)	6 (42.9%)	53 (18.9%)	0.03*
Does not smoke	198 (74.4%)	6 (42.9%)	204 (72.9%)	
Quit smoking	21 (7.9%)	2 (14.3%)	23 (8.2%)	
Initial admission complaints				
GIS symptoms	216 (81.2%)	12 (85.7%)	228 (81.4%)	0.672
Non-GIS symptoms	50 (18.8%)	2 (14.3%)	52 (18.6%)	

BMI: Body Mass Index, SD: Standard deviation, GIS: Gastrointestinal system*: Statistically significant (p<0.05)

Table 3. Risk factors associated with response after vaccination in celiac patients

Variables	Response N=64 (%69.6)	Non-response N=28 (%30.4)	Total N=92 (%10	P value
Age (year)	31.1±11.1	28,64±11.3	29.8±11.2	0.324
Age at disease onset (year)	25.8±11.1	24.1±11.4	24.9±11.2	0.509
Duration of illness (years)	5.4±4.2	4.6±2.8	5.1±3.8	0.342
BMI (kg/m2)	22.6±3.3	19.8±2.7	21.7±3.4	<0.001**
Waist/hip ratio				
Below limit	44 (68.8%)	26 (92.9%)	70 (76.1%)	0.013*
Above limit	20 (31.3%)	2 (7.1%)	22 (23.9%)	
Stage of celiac disease				
Mild (Stage 2-3a)	22 (34.4%)	14 (50%)	36 (39.1%)	0.158
Severe (Stage 3b,3c,4)	42 (65.6%)	14 (50%)	56 (60.9%)	
Dietary compliance				
Strict	29 (45.3%)	6 (21.4%)	35 (38%)	0.030*
No Compliance	35 (54.7%)	22 (78.6%)	57 (62%)	
Gender				
Female	44 (68.8%)	44 (68.8%)	62 (67.4%)	0.674
Male	20 (31.3%)	20 (31.3%)	30 (32.6%)	
Immunologic remission				
Yes	31(48.4%)	7 (25%)	38 (41.3%)	0.036*
No	33 (51.4%)	21 (75%)	54 (58.7%)	
Cigarette usage				
Smoking	16 (25%)	4 (14.3%)	20 (21.7%)	0.459
Does not smoke	42 (65.6%)	20 (71.4%)	62 (67.4%)	
Quit smoking	6 (9.4%)	4 (14.3%)	10 (10.9%)	
Initial admission complaints				
GIS symptoms	48 (75%)	24 (85.7%)	72 (78.3%)	0.252
Non-GIS symptoms	16 (25%)	4 (14.3%)	20 (21.7%)	

BMI: Body Mass Index, SD: Standard deviation, GIS: Gastrointestinal system* : Statistically significant (p<0.05),** (p<0.001

DISCUSSION

Chronic viral hepatitis can trigger immunologic gluten intolerance in genetically sensitive individuals and that, chronic hepatitis are seen at a higher rate in celiac patients were reported (3,4). Bardella et al. in their study reported that, the prevalence of HBsAg in celiac patients was 2.5% and that there was a connection between celiac disease and HBV infection (22). Gamal et al. found the prevalence of HBsAg in 9.9% in celiac patients, and indicated that it was significantly higher than chronic hepatitis B prevalence in the country (9). Various possible mechanisms have been proposed in the role of HBV infection in the development of autoimmune diseases. Molecular imitation, based on the amino acid similarities that the virus and the host share, is stated to be an important pathogenic mechanism. They also suggested that the immune response developed in HBV triggered intestinal tissue damage (23). In the study of 280 celiac patients, we determined that, chronic hepatitis B prevalence was 4.3% and chronic hepatitis C prevalence was 0.7%. When the prevalence of chronic HBV in Turkey is 2-4% and the prevalence of chronic HCV is around 0.5%, there is a moderate increase in the prevalence of chronic hepatitis in celiac patients (8). However, in the analysis between the presence of chronic viral hepatitis and risk factors in celiac patients, we did not establish a significant relationship with the exception of smoking.

It is well known that, the HBV vaccine is a highly effective and a safe protection tool against HBV infections. Studies have reported that, the effectiveness of HBV vaccinations in celiac patients is low (15,16). Although celiac disease is not considered an immunosuppressive condition, the low efficacy of the vaccine is thought to reflect a specific immunodeficiency in the development of anti-HBs antibodies (24). It has been claimed that the formation of B cells required for induction and immunization of type 2 helper cell response required for B cells differentiation may be insufficient (24). Both HBsAg protein fragments and gliadin peptides are linked to HLA-DQ2 molecules, suggesting that their competitiveness could result in a faulty antibody response against HBV vaccines in celiac patients. Although there are studies stating that there is no significant difference in the vaccine response in terms of celiac and the normal population (10,25), in the study conducted by Ahishali et al, the vaccine response in the healthy control group after vaccination was 100% while in celiac patients it was 68% (5). Similar to Filippelli et al, they identified the vaccine response as 69.4% in celiac patients (26). Ertem et al. reported the comparing healthy control group and celiac patients, post-vaccination response rates were 85.2% versus 67.5% (15). In our study, we determined the proportion of patients who responded to the vaccine in celiac disease as 69.6%. Similarly, we found in our study that the rate of naturally immune people was 6.4%, and that the rate of those who had never encountered the virus was 57.1%.

The results are contradictory in studies evaluating the risk factors associated with the vaccination response. In the study of Jouneghani et al, showed that the vaccine

response was significantly lower in the elderly and with BMI <20 (27). The meta-analysis of the compilation of 37 studies and included 21.053 patients was reported the vaccine response significantly decreased in the age ≥40, male, BMI> 25, smokers and with additional comorbid illness (28). However, Merki et al. did not find any significant relationship between the risk factors and the vaccine response (29). Ertekin et al. also found that the vaccine response was significantly lower in celiac patients with HBV vaccine who were not compatible with the gluten-free diet (16). We also found that in our study, the vaccine response was significantly lower in those who were not compatible with the gluten-free diet, non-immune remission, low BMI and low waist-hip ratios. Although there is a higher rate of unresponsiveness in elderly patients due to decreased seroprotective antibody levels after vaccination in time, it was found that, age was not a predictive factor in studies in which patients under 40 years of age were taken (30). It is also reported that the immune response to the HBV vaccine is less due to diet mismatch. In overweight people, it is indicated that the vaccine is distributed in the adipose tissue and consequently the absorption is inhibited and the response of the vaccine antigen with the enzymatic action of the vaccine is low (28). However, in our study, it was found that the vaccine response was low as a result of attenuation due to diet incompatibility. We think that diet adaptation plays a more effective role in the vaccine response.

CONCLUSION

In conclusion chronic viral hepatitis prevalence was seen to be more in celiac patients. It is also observed that the majority of patients are not vaccinated and one in three vaccinated patients do not have a vaccine response. The patients are vulnerable to HBV infection that may cause chronic liver disease and hepatocellular carcinoma due to absence of an immune response. In addition, considering that liver damage could occur due to celiac disease, the importance of immunization against HBV infection increases. For this reason, it is of great importance to vaccinate all celiac patients under a state policy, to follow the immune response after vaccination and to implement a re-vaccination protocol in the case of no vaccine response.

Competing interests: The authors declare that they have no competing interest.
Financial Disclosure: There are no financial supports
Ethical approval: Ethical approval was obtained from the Ethics Committee of our Van Education and Research Hospital (Decision number: 2019/10. Date: 16.05.2019).

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