

# Prevalence and clinical features of celiac disease in patients with hepatitis B virus infection in Southern Brazil

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## ABSTRACT

**Introduction:** Celiac disease is an autoimmune disorder that involves gluten intolerance and can be triggered by environmental factors including hepatitis B virus (HBV) infection. This study aimed to describe the prevalence of celiac disease in individuals with HBV infection and to describe the clinical and laboratory characteristics of celiac disease associated with HBV. **Methods:** This cross-sectional study included 50 hepatitis B patients tested for IgA anti-endomysial antibodies (EMAs) and tissue anti-transglutaminase (TTG) between August 2011 and September 2012. **Results:** Fifty patients were included with a mean age of  $46.0 \pm 12.6$  (46.0) years; 46% were female and 13% were HBeAg+. Six patients had positive serology for celiac disease, four were EMA+, and five were TTG+. When individuals with positive serology for celiac disease were compared to those with negative serology, they demonstrated a higher prevalence of abdominal pain (100% vs. 33.3%,  $p = 0.008$ ), lower median creatinine (0.7mg/dL vs. 0.9mg/dL,  $p = 0.007$ ) and lower mean albumin ( $3.6 \pm 0.4$ g/L vs.  $3.9 \pm 0.3$ g/L,  $p = 0.022$ ). All individuals with positive serology for celiac disease underwent upper digestive endoscopy, and three of the patients exhibited a macroscopic pattern suggestive of celiac disease. Histologically, five patients demonstrated an intra-epithelial lymphocytic infiltrate level > 30%, and four patients showed villous atrophy associated with crypt hyperplasia on duodenal biopsy. **Conclusions:** An increased prevalence of celiac disease was observed among hepatitis B patients. These patients were symptomatic and had significant laboratory abnormalities. These results indicate that active screening for celiac disease among HBV-infected adults is warranted.

**Keywords:** Hepatitis B virus. Hepatitis B. Celiac disease.

## INTRODUCTION

Celiac disease (CD) is an intolerance to gluten, a protein found in wheat, rye and barley. It is recognized as a chronic autoimmune disorder that occurs in genetically predisposed individuals, both children and adults<sup>1-3</sup>, and it affects approximately 1% of the world population<sup>4</sup>.

Celiac disease involves chronic inflammation of the gut mucosa from an inappropriate T-cell-mediated response to gluten ingestion<sup>1</sup>. A possible pathogenic mechanism involves increased permeability of the intestinal epithelium to gliadin (the immunogenic component of gluten) caused by dysregulation of the innate and adaptive immune systems<sup>5</sup>. Intestinal cluster of differentiation antigen 4 (CD4) T cells interact with gliadin peptides presented by human leukocyte antigens (HLA)-DQ2

or DQ8 and produce interferon-gamma, which leads to mucosal inflammation and structural and functional damage<sup>1,3</sup>.

The correlation between celiac disease and environmental factors other than gluten is not completely understood. Breastfeeding, smoking and viral infections may contribute to the disease onset<sup>1</sup>. Cross-reactivity has been proposed as a source of autoimmunity<sup>6</sup>, and several studies have demonstrated a relationship between adenovirus, rotavirus, enterovirus and hepatitis C virus infection and the development of celiac disease<sup>2,6</sup>. Hepatitis B virus (HBV) infection leads to the activation of several immune system components that has been suggested to culminate in the production and release of interferon and interleukins that disrupt the intestinal mucosal barrier, allowing the penetration of immunogenic peptides and activation of CD4 T lymphocytes. There appears to be an increase in the production of HLA-DQ8, which links gluten peptide molecules and facilitates activation of other immune cells. It is suggested that HBV can trigger the pathophysiological processes that lead to mucosal inflammation induced by gluten<sup>6</sup>. However, concrete data regarding the association of celiac disease and HBV are not available, although two billion people in the world have been infected by this virus<sup>6,7</sup>. The highest prevalence rates are found in Eastern Europe and countries with European colonization<sup>8</sup>.

Because of the large number of European descendants in Santa Catarina, southern Brazil, a high prevalence of celiac

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disease is expected. Because the relationship between HBV and celiac disease has yet to be established, this study aimed to describe the prevalence of celiac disease in individuals with chronic HBV infection and to describe their clinical and laboratory characteristics.

## METHODS

This descriptive case series study included consecutive hepatitis B surface antigen (HBsAg)-positive adult patients who presented at the Gastroenterology and Hepatology Outpatient Clinic at our institution between August 2011 and September 2012 and underwent celiac disease screening for anti-endomysial (EMA) and anti-transglutaminase (TTG) antibodies. The study subjects gave written informed consent. Patients with incomplete clinical and laboratory data registration in their medical records were excluded from the study.

Clinical, laboratory and histological findings were collected from data contained in the medical records. The patients were analyzed according to the following clinical and demographic characteristics: sex, race, age, comorbidities (diabetes mellitus, dyslipidemia and hypertension) and the presence of diarrhea or abdominal pain. The laboratory variables analyzed were: hepatitis B e antigen (HBeAg), hepatitis B virus-deoxyribonucleic acid (HBV-DNA), creatinine, hemoglobin, platelets, ferritin, transferrin saturation, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), direct bilirubin, albumin and prothrombin activity. The biochemical tests were expressed as absolute values. The immunoglobulin A (IgA) TTG and IgA EMA serological tests were used for celiac disease screening<sup>1,3</sup>. EMA was detected by indirect immunofluorescence, and TTG was detected using a commercial enzyme linked immunosorbent assay (ELISA). Patients with either EMA- or TTG-reactive antibodies were considered to have positive serology for celiac disease. Total serum IgA was quantified in patients negative for both EMA and TTG to exclude the presence of a selective IgA deficiency.

Upper digestive endoscopy and duodenal biopsy were indicated for individuals with positive serology for celiac disease. Duodenal fragments were fixed in 10% formalin, processed with paraffin and stained with hematoxylin and eosin (HE). For diagnoses of celiac disease, the following histological variables were analyzed: lymphocytic infiltrate, villous atrophy and crypt hyperplasia.

The continuous variables were compared using Student's t test or the Mann-Whitney test when appropriate. The categorical variables were compared using the chi-square test or Fisher's exact test to identify characteristics associated with the positivity of celiac disease antibodies in individuals with hepatitis B. All of the tests were two-tailed and conducted using the statistical software *Statistical Package for the Social Sciences* (SPSS) version 17.0 (SPSS; Chicago; Illinois; USA).

### Ethical considerations

The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration and was approved by the review

board of the Universidade Federal de Santa Catarina as Study Number 131.513.

## RESULTS

### Patient characteristics

From August 2011 to September 2012, 112 HBV-infected patients were considered for study enrollment, and sixty-two individuals were excluded from the study because they were not tested for EMAs or TTG antibodies.

The characteristics of the 50 consecutive patients fulfilling the inclusion criteria are summarized in **Table 1**. The mean age was  $46.0 \pm 12.6$  years, 46% of the patients were female and 13% of the patients were HBeAg-positive. Regarding the laboratory characteristics, the mean  $\pm$  standard deviation (median) values for ALT, albumin, prothrombin activity and platelet count levels were, respectively,  $51.8 \pm 39.2$  (41.0)U/L,  $3.9 \pm 0.4$  (3.9)g/dL,  $81.9\% \pm 14.8\%$  (77.9%) and  $197,580.0 \pm 70,495.1$  (188,000.0)/mm<sup>3</sup>.

### Factors associated with positive serology for celiac disease

When compared to other patients, the patients with positive serology for celiac disease presented a higher prevalence of abdominal pain (100% vs. 33.3%,  $p = 0.008$ ), a lower median creatinine concentration (0.7mg/dL vs. 0.9mg/dL,  $p = 0.007$ ) and a lower mean albumin concentration ( $3.6 \pm 0.4$ g/dL vs.  $3.9 \pm 0.3$ g/dL,  $p = 0.022$ ). The median hemoglobin level tended to decrease (12.8g/dL vs. 14.7g/dL,  $p = 0.088$ ) and the proportion of patients reporting diarrhea tended to be higher (40% vs. 5.6%,  $p = 0.066$ ) among the celiac disease patients. No differences were observed regarding age; presence of diabetes mellitus, dyslipidemia or hypertension; platelet count; ferritin; transferrin saturation; prothrombin activity; or levels of ALT, AST, GGT, ALP, direct bilirubin or HBV-DNA.

### Characteristics of individuals with positive serology for celiac disease

Six (12%) of the 50 patients had positive serology for celiac disease; four (66.7%) of the six patients were EMA-positive, and five (83.3%) of the patients were TTG-positive. Three individuals were reactive for EMA and TTG antibodies, two were reactive for TTG, and one was reactive solely for EMA. All six individuals underwent upper digestive endoscopy, and three (50%) exhibited a macroscopic pattern suggestive of celiac disease. A duodenal histological evaluation demonstrated no significant alterations in one patient. Five (83.3%) subjects presented with intra-epithelial lymphocytic infiltration of at least 30%, and four (66.7%) patients exhibited villous atrophy and crypt hyperplasia (**Figure 1**).

The clinical, laboratory and histological characteristics of individuals with positive serology for celiac disease are described in **Table 2**. All six patients had abdominal pain, whereas diarrhea was reported in 40% of the cases, and no patients exhibited anemia. None of the patients were positive for HBeAg, but all presented HBV-DNA titers greater than or equal to 20,000IU/mL.

TABLE 1 - Clinical and laboratorial characteristics of 50 patients with hepatitis B infection according to the presence of celiac disease antibodies: anti-endomysial and anti-transglutaminase.

Characteristics	Total	CD (+) n = 6	CD (-) n = 44	p
Age (years)*	46.0 ± 12.6	44.3 ± 9.0	46.3 ± 13.1	0.728 <sup>t</sup>
Female sex (%)	46.0	83.3	40.9	0.082 <sup>f</sup>
HBeAg (%)†	13.0	0.0	14.6	1.000 <sup>f</sup>
HBV-DNA ≥20.000U/mL (%)‡	53.1	100.0	48.3	0.229 <sup>f</sup>
Diabetes mellitus (%)	10.0	0.0	11.4	1.000 <sup>f</sup>
Dyslipidemia (%)	5.0	0.0	5.7	1.000 <sup>f</sup>
Hypertension (%)	17.1	0.0	19.4	0.567 <sup>f</sup>
Diarrhea (%)	9.8	40.0	5.6	0.066 <sup>f</sup>
Abdominal pain (%)	41.5	100.0	33.3	0.008 <sup>f</sup>
Creatinine (mg/dL)§	0.9 ± 0.1	0.7 ± 0.1	0.9 ± 0.1	0.007 <sup>m</sup>
Hemoglobin (g/dL)§	14.5 ± 0.9	12.8 ± 0.3	14.7 ± 1.0	0.088 <sup>m</sup>
Platelets (mm <sup>3</sup> )§	188,000 ± 42,500	245,500 ± 94,500	188,000 ± 39,500	0.204 <sup>m</sup>
Ferritin (ng/mL)§	132.0 ± 112.0	65.7 ± 48.7	140.0 ± 113.1	0.457 <sup>m</sup>
Transferrin saturation (%)*	32.4 ± 14.7	27.3 ± 17.6	33.5 ± 14.1	0.352 <sup>t</sup>
AST (xULN)*	33.7 ± 19.7	55.8 ± 38.6	30.6 ± 13.9	0.165 <sup>t</sup>
ALT (xULN)§	41.0 ± 9.0	39.0 ± 11.5	41.0 ± 9.0	0.927 <sup>m</sup>
ALP (xULN)§	85.0 ± 15.0	87.0 ± 15.0	85.0 ± 17.5	0.988 <sup>m</sup>
GGT (xULN)§	28.0 ± 7.0	27.5 ± 6.5	28.0 ± 7.0	0.473 <sup>m</sup>
Direct bilirubin (mg/dL)§	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.378 <sup>m</sup>
Albumin (g/dL)*	3.9 ± 0.4	3.6 ± 0.4	3.9 ± 0.3	0.022 <sup>t</sup>
Prothrombin activity (%)*	81.9 ± 14.8	77.1 ± 14.9	82.6 ± 14.8	0.409 <sup>t</sup>

CD: celiac disease; HBeAg: hepatitis B *e* antigen; HBV-DNA: hepatitis B virus-deoxyribonucleic acid; xULN: times upper limit of normal; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyltransferase; \*mean ± standard deviation; †available in 46 patients; ‡available in 32 patients. §: median ± median absolute deviation; <sup>t</sup>Student's t-test; <sup>f</sup>Fisher's exact test; <sup>m</sup>Mann-Whitney test.

## DISCUSSION

In Brazil, 16,775 cases of hepatitis B were reported in the year 2011<sup>9</sup>, but the actual number of cases is not completely known; there have been few studies, and Brazil has a poor notification system and a large geographic area<sup>10</sup>. In the State of Santa Catarina, the described seroprevalence of HBsAg is 0.7% to 1.2% among blood donors in Florianopolis<sup>11-13</sup>. The prevalence of HBsAg-positive individuals in Western Santa Catarina is 1.63%, which is higher than that described in the northern and Southern regions of the state (1.12% and 0.91%, respectively)<sup>12</sup>.

The mean age of the HBV carriers varies between 38 and 52 years in the literature, which is similar to that described in this study<sup>14,15</sup>. Most affected individuals are male, with a prevalence of 52% to 61% in the United States<sup>16-18</sup>, 86.6% in China<sup>19</sup> and 41.8% to 76.1% in Brazil<sup>10,20,21</sup>, where males are 1.3 fold more

likely to be infected with HBV than females<sup>22</sup>. In this study, 54% of the HBV carriers were male, which is similar to the rate described in the literature.

The prevalence of markers of viral replication varies among different populations. Following an evaluation of serum HBV-DNA, the prevalence of undetectable levels of HBV-DNA (<20IU/mL) was 46.6% among immigrants in Italy<sup>23</sup>, 21.7% among pregnant women in Amazonas<sup>24</sup> and 32% in São Paulo<sup>25</sup>. In a study by Kiesslich et al.<sup>24</sup>, quantitative analysis of HBV-DNA showed that 73.9% of pregnant women had levels lower than 200IU/mL, 14.4% had levels between 200 and 20,000IU/mL and 8.7% had levels higher than 20,000IU/mL<sup>24</sup>. Palumbo et al.<sup>23</sup>, found that 53.4% of patients had HBV-DNA levels between 4,600 and 260,000IU/mL<sup>23</sup>. In São Paulo, 27% of patients had HBV-DNA levels higher than 2,000IU/mL, and 9% had HBV-DNA levels higher than 20,000IU/mL<sup>25</sup>. A study that included four of the five Brazilian regions (the South, Southeast, Midwest and Northeast) found undetectable HBV-DNA levels in 21.6% of patients,



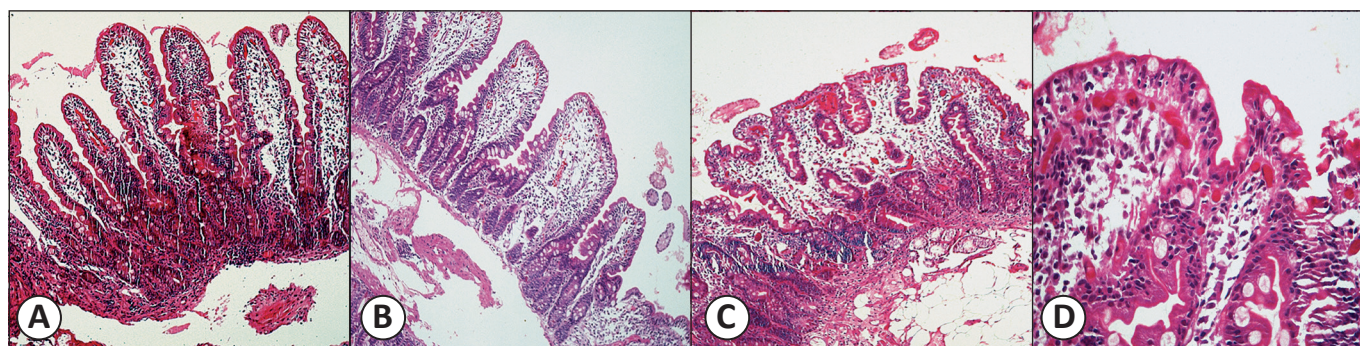


FIGURE 1 - A second duodenal portion biopsy showing mucosa with normal histological pattern (A) and biopsy showing the suggested histological changes of celiac disease (B, C, D). A: Duodenal mucosa showing conserved architecture with long parallel fingerlike villi (hematoxylin-eosin, HE; 100x); B: Duodenal mucosa showing slight villous shortening with crypt hyperplasia (HE 100x). C: Duodenal mucosa showing inflammatory changes and intense structural villous shortening (HE 100x); D: Details of the duodenal mucosa with many plasma cells and congestion in the lamina propria; intraepithelial lymphocytosis (HE 400x).

TABLE 2 - Clinical and laboratory characteristics of six individuals with hepatitis B infection and positive serology for celiac disease (n=6).

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)	55	32	42	37	47	53
Sex	F	F	M	F	F	F
Caucasian	Y	Y	Y	Y	Y	Y
Diarrhea	N	N	Y	N	*	Y
Abdominal pain	Y	Y	Y	Y	Y	Y
HBeAg	(-)	*	(-)	(-)	(-)	(-)
HBV-DNA $\geq 20.000$ UI/ml	*	*	Y	Y	*	Y
Hemoglobin (g/dL)	13.0	12.5	17.2	11.5	12.4	13.9
Albumin (g/dL)	3.5	3.87	3.8	3.0	3.3	3.9
Creatinine (mg/dL)	0.6	0.5	0.8	0.8	0.7	0.7
Antiendomysial	(+)	(-)	(-)	(+)	(+)	(+)
Antitransglutaminase	*	(+)	(+)	(+)	(+)	(+)
UDE with biopsy	Y	Y	Y	Y	Y	Y
villous atrophy	N	Y	Y	N	Y	Y
crypt hyperplasia	N	Y	Y	N	Y	Y
lymphocytic infiltration	Y	Y	Y	N	Y	Y

HBeAg: hepatitis B e antigen; HBV-DNA: hepatitis B virus-deoxyribonucleic acid; F: female; M: male; \*result not available; Y: yes; N: no; (+): positive; (-): negative; UDE: upper digestive endoscopy.

HBV-DNA levels lower than 2,000IU/mL in 45.9% of patients, HBV-DNA levels between 2,000 and 20,000IU/mL in 12.6% of patients and HBV-DNA levels higher than 20,000IU/mL in 19.8% of patients<sup>26</sup>. HBeAg was found in 14.3% of patients with chronic hepatitis B in Turquia<sup>27</sup>, 19.6% in China<sup>28</sup>, 30% in Campinas in southeastern Brazil<sup>29</sup> and 37.3% in Rio Grande do Sul in southern Brazil<sup>30</sup>. The prevalence of HBeAg-positive patients in this study was slightly lower than that found in the literature, but the prevalence of high levels of HBV-DNA was higher than that previously described. This inconsistency can be explained by the presence of HBV precore mutations, which

alter the expression of HBeAg, with viral replication in HBeAg-negative patients and/or HBeAg-positive patients. In the State of Santa Catarina, HBV genotype D is common. This genotype is also found in Europe, particularly in the Mediterranean region, and it has a high rate of precore mutations<sup>20,31</sup>. This finding could reflect the European immigration profile in southern Brazil<sup>32</sup>.

Celiac disease affects approximately 1% of most populations<sup>4</sup>, but in Sweden, it has been reported in 3% of children of approximately 12 years of age<sup>5</sup>. In the United States, celiac disease affects one in every 120-300 people<sup>8</sup>. There are few studies regarding the prevalence of celiac disease in the general

population of the Americas, and almost none of these studies have included intestinal biopsies to confirm the diagnosis<sup>33</sup>. Serological screening studies conducted in Brazil have shown a positivity rate of 0.15% to 1.7%<sup>34-36</sup>. In Curitiba, Paraná, the prevalence was one in 417 blood donors<sup>32</sup>. In Brasília, among 2,045 evaluated blood donors, 62 were positive for anti-gliadin (AGA) IgG and two were EMA-positive; only three individuals exhibited histological features of celiac disease<sup>33</sup>. A similar study conducted in São Paulo evaluated 4,000 serum samples from blood donors, and 24 showed positive serology: 11 were TTG- and EMA-positive, 10 were only TTG-positive and three were only EMA positive. Among the 21 patients who underwent duodenal biopsy, six (29%) patients had some histological abnormality<sup>37</sup>.

Celiac disease classically presents with diarrhea (37.2% to 91.3%), abdominal pain (71%) and anemia (3% to 50.3%)<sup>3,38</sup>. This study contained patients with clinical complaints, which is unusual for a seroprevalence study but has been described by other authors<sup>32,37</sup>. All patients reported abdominal pain (100%,  $p = 0.008$ ), whereas only 40% complained of diarrhea, which is the classic symptom of the disease<sup>1</sup>. Although anemia secondary to iron, vitamin B12 or folic acid deficiency<sup>8</sup> is a typical symptom of celiac disease, it was not identified in any patients. Hemoglobin levels tended to be lower among individuals with celiac disease, but no significant changes in iron stores were observed.

The albumin level was lower in patients with celiac disease, which may have been secondary to the malabsorption that occurs in the disease and can lead to malnutrition<sup>39</sup>. This study found lower values of creatinine in patients with celiac disease compared to the other patients. The few studies that have described the renal function of patients with celiac disease have shown impaired renal function in these patients<sup>40</sup>. Most patients with positive serology for celiac disease in this study were female, and it is already known that females have lower creatinine levels than males because of the characteristic body mass of each sex. Renal function in patients with HBV and celiac disease must be further investigated in subsequent studies with a larger number of patients.

The literature that addresses the relationship between celiac disease and hepatitis B is limited; only three studies are available in PubMed, and none are from Brazil. Sima et al.<sup>41</sup> performed serologic screening for celiac disease with EMA, TTG and AGA (IgA and IgG) in patients with chronic hepatitis B. The serologic screening was followed by duodenal biopsy in patients positive for EMA and/or TTG. The results demonstrated a prevalence of 10% for AGA IgA, 28% for AGA IgG, 3% for EMA and 9% for TTG<sup>41</sup>. Iglesias et al.<sup>6</sup> reported two patients who received the diagnosis of celiac disease following an acute hepatitis B infection<sup>7</sup>. Recently, Leonardi et al.<sup>7</sup> evaluated the prevalence of positive serology for celiac disease in 60 patients who had an HBV infection during childhood; none of the patients tested were positive for EMA or TTG, and seven patients were positive for AGA, despite having no symptoms of celiac disease. The authors considered the anti-gliadin antibodies to have a low sensitivity and specificity for the diagnosis of celiac disease, and duodenal

biopsy was not performed in any of the seven patients with positive serology<sup>7</sup>. Some studies have reported a lower efficacy of the vaccine against HBV in patients with celiac disease<sup>42-44</sup>. Although celiac disease is considered an autoimmune disorder and not an immunosuppressive condition, the lower efficacy of the vaccine may reflect a specific immunodeficiency in the development of anti-HBs antibodies and mechanisms of viral clearance. It is possible that individuals with celiac disease have a higher risk of chronic HBV infection compared to the general population. The association between celiac disease and hepatitis B, although not well understood, justifies further investigation.

Although there are no previous data concerning the prevalence of celiac disease in the State of Santa Catarina, Brazil, this study found a higher prevalence of celiac disease in patients with HBV when compared to other populations in our country and around the world. The prevalence of celiac disease confirmed by biopsy was high among the HBsAg-positive patients, and these individuals were symptomatic and had significant laboratory abnormalities. Subjects with chronic HBV infection should be screened for celiac disease, including screening for the EMA and TTG antibodies, because the early diagnosis and treatment of the disease may prevent systemic complications and mortality<sup>5,41,45</sup>.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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