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Role of Chronic Viral Hepatitis B and C as Risk Factors for Celiac Disease

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MSM and HASI designed the study and wrote the protocol, Author MSM managed the literature research, performed the statistical analysis and wrote the first draft of the manuscript. Authors MSM, HASI and KMH managed the analyses of the study, and revised the final manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Celiac disease (CD) is an autoimmune disease and hepatitis B virus (HBV) is suspected to trigger immunologic gluten intolerance in susceptible individuals. The aim of this study is to assess the role of chronic HBV and HCV infection in adult patients as risk factors of celiac disease.
Study Design: Case-control study.
Place and Duration of Study: Department of Medical Microbiology and Immunology and Department of Clinical Pathology, College of Medicine, Qassim University, between September 2012 and November 2014.
Methodology: This study included 30 chronic HBV patients and 30 chronic HCV patients, thirty normal individuals were included as controls. Anti-tissue transglutaminase (Anti-tTG) IgA was assessed in the three groups, non-organ specific autoantibodies (NOSA) including

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antimitochondrial (AMA), antinuclear (ANA) and anti-smooth muscle (ASMA) antibodies were also assessed.
Results: Anti-tTG IgA revealed significantly higher levels in both HBV (mean = 41.72, SE = 1.70) and HCV (mean = 46.93, SE = 5.46) groups compared to the controls (mean = 29.60, SE = 1.27), (*P* = .01, < .001 respectively). The positivity of ASMA was significantly higher in HBV patients than in the controls (46.7%, 16.7%, *P* = .01). ANA and AMA showed insignificant difference between the three groups.
Conclusion: The higher levels of anti-tTG autoantibodies in adult patients with chronic HBV and HCV infections reflect higher incidence to develop CD than normal population. Screening for CD in such patients is recommended.

Keywords: Celiac disease; hepatitis B virus; hepatitis C virus; Anti-tissue transglutaminase antibodies; non organ specific autoantibodies.

1. INTRODUCTION

Celiac disease (CD), a common disease which appears to be a widespread public health problem, is an autoimmune enteropathy characterized by malabsorption resulting from inflammatory injury to the mucosa of the small intestine which is triggered by the ingestion of gluten-containing cereals in genetically predisposed individuals. The gliadin fraction of wheat gluten and similar alcohol-soluble proteins in other grains are the environmental factors responsible for the development of the intestinal damage. Tissue damage seen in CD results from inappropriate T cell-mediated response against ingested gluten [1]. Both serological screening in the general population and serological testing among at-risk groups are also necessary for an early identification of CD cases [2]. The European Society for Pediatric Gastroenterology, Hepatology and Nutrition proposed that CD be defined as an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and characterized by a variable combination of gluten-dependent manifestations, CD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy [3].

The first metabolomics investigation, i.e. analysis of the complete metabolites profile, of CD revealed a characteristic metabolic fingerprint for CD, which accounts for three different but complementary components: malabsorption, energy metabolism, and alterations in gut microflora and/or intestinal permeability. Decreased blood pyruvate and lactate and increased glucose in celiac patients were observed, probably as a consequence of impaired glycolysis. In CD patients on a gluten-free diet, some of the metabolites that form the metabolomic signature of this autoimmune disease, such as glucose and 3-hydroxy-butyric acids, revert to normal [4,5].

It has been hypothesized that hepatitis B virus (HBV) and hepatitis C virus (HCV) may trigger immunologic gluten intolerance in susceptible people [6]. The liver damage in chronic viral hepatitis is mainly induced by T helper-1 (TH-1) cells and/or cytotoxic T lymphocytes related responses [7], this immunopathological pathway could be one plausible explanation of the higher prevalence of celiac disease observed in patients with chronic HCV infection as compared to HCV-negative ones [6]. Moreover, administration of interferon-α (IFN-α) alone or in combination with ribavirin as a treatment of chronic viral hepatitis may enhance immunologic TH-1 cells and cytotoxic T lymphocytes responses that could favour the immune-mediated damage of the gut mucosa [8].

No single test has been universally accepted as the standard for diagnosing celiac disease. However, serological testing as well as small bowel biopsy are highly sensitive and specific in making the diagnosis, particularly in patients with symptoms suggestive of CD and in those at increased risk**.** Diagnostic testing must be performed while the patient is on a diet that includes gluten-containing food. Testing for gliadin antibodies is no longer recommended because of the low sensitivity and specificity for CD [9]. Anti-tissue transglutaminase IgA (Anti-tTG IgA) and anti-endomysial IgA (AEMA IgA) have proven to be the current most sensitive and specific markers for the diagnosis and follow-up of patients on gluten-free diet, at the exception of IgA-deficient patients [10]. AEMA assay is based on immunofluorescence [11], whereas Anti-tTG IgA antibody is measured by an ELISA-based test that avoided the difficulties inherent in immunofluorescence and with higher sensitivity

and similar specificity compared to AEMA [9]. Tissue transglutaminase (tTG) is a calcium dependent ubiquitous enzyme which is believed to be a key step in the pathogenesis of celiac disease. It is suggested that it exerts two crucial roles; (1) as a target autoantigen in the immune response [12,13], (2) and as a deamidating enzyme that acts on glutamine-rich gliadin peptides producing deamidated negatively charged peptides which have much higher affinity for the HLA-DQ2 and HLA-DQ8 molecules which have strong association with CD [13].

A study reported that CD was confirmed in all patients with positive anti-tTG IgA antibodies, those patients had a duodenal histological picture compatible with CD [6]. Better standardization of serological testing may enable them to replace in the near future histological confirmation brought by small bowel biopsies which remains the gold standard test to diagnose CD. Indeed, serological testing represents an attractive alternative as it is less invasive and more objective in interpretation [10]. Furthermore, a study concluded that small intestinal biopsy may not be needed to confirm CD in paediatric patients with high anti-tTG level in whom symptoms improve upon consuming gluten free diet [14]. Hence testing of anti-tTG antibody is the recommended single serologic test for CD screening in the primary care setting [9].

Non organ specific autoantibodies (NOSA) are considered as an indirect marker of autoimmune disorders. A study reported that NOSA were detected in HCV patients, it also reported that 20% of HCV patients treated with IFN-α developed NOSA under therapy [15].

The aim of this study is to assess the role of chronic HBV and HCV infection in adult patients as risk factors of celiac disease. Anti-tTG IgA and NOSA autoantibodies were assessed and compared in the HBV, HCV and the control groups.

2. MATERIALS AND METHODS

This study included 30 patients with chronic HBV infection (HBV group); diagnosed by hepatitis B serological markers and molecular detection of viral DNA (age: 35.87±15.8, 18 males and 12 females), we also included 30 patients with chronic HCV infection (HCV group); diagnosed by serological detection of HCV antibody and molecular detection of viral RNA (age: 37.57±16.158, 17 males and 13 females). In addition 30 normal individuals were included as healthy control population (control group); (age: 43.2±11.981, 21 males and nine females). The three groups were matched for age and gender (Table 1). Receiving anti-viral therapy by patients was recorded. Written informed consent was obtained from each participant. This study was approved by the local ethical committee.

Fasting blood samples were collected from all HBV and HCV patients as well as the controls. All samples were collected in pyrogen-free tubes under aseptic conditions and centrifuged. Sera were stored frozen at -70°C in duplicates until used for analysis. All sera were qualitatively and quantitatively analysed for Anti-tTG IgA by an ELISA-based technique using recombinant human tissue transglutaminase antigen (Immulisa Coeliac tTG IgA, IMMCO Diagnostics, New York, USA). Antinuclear antibody (ANA) and anti-mitochondrial antibody (AMA) were qualitatively assessed by using Immulisa Antinuclear Antibody and Immulisa Mitochondrial (M2) Antibody tests respectively (IMMCO Diagnostics, New York, USA). Anti-smooth muscle antibody (ASMA) was assessed by an indirect immunofluorescence test (ImmuGlo, IMMCO Diagnostics, New York, USA). Patients having negative anti-tTG IgA were tested for total serum IgA to rule out IgA deficiency. Total serum IgA antibodies were quantitatively measured by Immunoglobulin A Turbidimetry test (Spinreact, Santa Coloma, Spain). The cut-off values of ELISA assays for anti tTG, ANA and AMA are 25 EU/mL (ELISA units/mL). The ASMA positivity was determined by the detection of fibrillar network of fluorescence staining throughout the cytoplasm of Hep-2 cells. All tests were performed according to the manufacturer's instructions.

2.1 Statistical Analysis

Data were analyzed using SPSS version 16. Values were expressed as mean ± SE. Differences between each parameter in the control and patients groups were assessed by Chi square independence test. One Way ANOVA test was performed to compare the levels of anti-tTG antibodies between the three groups. Results were considered statistically significant at P value ≤ .05.

Table 1. Demographic and laboratory data of the three study groups

Parameter	HBV patients (n=30)	HCV patients (n=30)	Controls (n=30)
Age	35.87±15.8	37.57±16.158	43.2 ±11.981
Male gender	18(60%)	17(56.7%)	21(70%)
Antinuclear	16.7%	20%	6.7%
Anti-mitochondrial	0	0	0
Anti-smooth muscle	46.7%	63.3%	16.7%
Anti tTG	13.3%	33.3%	3.3%
Anti tTG level	41.72 ± 1.70	46.93 ± 5.46	29.60 ± 1.27

3. RESULTS

3.1 Comparing the HBV and the Control Groups

The positivity of ASMA antibodies was significantly higher in HBV group than in the controls (46.7%, 16.7%, *P* = .01). The positivity of ANA, anti-tTG IgA antibodies was higher in HBV patients than in the controls but with non-significant difference (16.7%, 13.3% in HBV group, and 6.7%, 3.3% in the controls, respectively), *P* values were .23 and .16 respectively.

3.2 Comparing the HBV and the HCV Groups

There was no significant difference of ANA, ASMA and anti-tTG IgA antibodies between the two groups (20%, 63.3%, 33.3% in HCV group, and 16.7%, 46.7%, 13.3% in the HBV group, respectively), *P* values were .74, .19 and .07 respectively. Interestingly, it was observed that four out of nine HCV-infected patients receiving interferon-α and/or ribavirin as antiviral treatment were positive for anti-tTG IgA.

3.3 Comparing the HCV and the Control Groups

The positivity of ASMA and anti-tTG IgA was significantly higher in HCV group (63.3% and 33.3% respectively) than in the control group (16.7% and 3.3% respectively), *P* values were < .001 for ASMA and .003 for anti tTG IgA. The positivity of ANA antibodies was higher in the HCV than in the control group but without significant difference (20% in HCV group and 6.7% in the control group; *P* = .13) (Table 2). AMA antibodies were negative in all individuals of the three groups.

One-way ANOVA test was conducted to compare the levels of anti-tTG IgA in the three groups. The results revealed a statistically significant difference among the three groups (F = 6.904, *P* = .002). Post-hoc Games-Howell tests revealed statistically significant higher level of anti-tTG IgA in the HBV group compared to controls (*P* = .01). It also revealed a statistically significant higher level of anti-tTG IgA in the HCV group compared to controls (*P* < .001). There was no statistically significant difference between the HBV and the HCV groups (*P* = .28) (Table 3).

4. DISCUSSION

In the present study we reported an insignificant difference in the positivity rate of anti-tTG antibodies between the HCV and the HBV groups (*P* = .07). We also reported a significantly higher positivity of anti-tTG antibodies in the HCV group than in the controls (*P* = .003). However, there was a higher but insignificant difference in HBV group than in the controls (*P* = .16).

Quantitative assessment of anti-tTG antibodies revealed a statistically significant higher levels in the HBV and the HCV groups compared to the controls (*P* = .01, < .001 respectively). There was no statistically significant difference between the HBV and the HCV groups (*P* = .28). These results support the association between chronic viral hepatitis and celiac disease.

In concordance to the present study, Sima and colleagues (2010) reported a relatively higher prevalence of celiac autoantibodies in chronic HBV patients compared with the normal population, they reported positive anti-tTG in 8/88 (9.1%) of chronic HBV patients [16]. On the other hand, Leonardi and Rosa found that none of the HBV recovered persons or HBV carriers had AEMA IgA or Anti-tTG IgA [17] which can be explained by the absence of immunopathological effects of HBV in resolved HBV infection or HBV carriers. These findings strengthen the evidence that the increased risk of CD in chronic HBV infection is a result of the immunopathological mechanisms against HBV.

Table 2. Results of NOSA and celiac disease associated antibodies in the three groups

	HBV (n=30)	HCV (n=30)	Control (n=30)
ANA, n (%)	5(16.7%) P = .23, P* = .74	6 (20%) P** = .13	2 (6.7%)
ASMA, n (%)	14 (46.7%) P = .01, P* = .19	19 (63.3%) P** < .001,	5 (16.7%)
Anti tTG IgA, n (%)	4 (13.3%) P = .16, P* = .07	10 (33.3%) P** = .003	1 (3.3%)

HBV; Hepatitis B virus, HCV; Hepatitis C virus, ANA; Antinuclear antibody, ASMA; anti smooth muscle antibody, Anti tTG IgA; Anti tissue transglutaminase immunoglobulin A
P; vs. control, P; vs. HCV, P**; vs. control*

Table 3. Mean and standard error of anti tTG IgA in the three groups

	Group	Mean ± SE (EU/mL)	P value
Anti tTG IgA	HBV	41.72±1.70	.01
	HCV	46.93±5.46	<.001
	Control	29.60±1.27	

Anti tTG IgA; anti tissue transglutaminase immunoglobulin A, SE; standard error

In this study, a significantly higher positivity of ASMA was reported in both HBV and HCV groups compared to the controls (*P* = .01, < 0.001 respectively). The positivity of ANA was higher in the HBV and the HCV groups compared to controls but with insignificant difference (*P* = .13 and .23 respectively). There was insignificant difference between HCV and HBV groups for both ASMA and ANA.

A study found positive NOSA antibodies in 34% among chronically infected HCV children and in 12% among HBV-positive children compared to none of healthy children [18]. Other studies revealed that 19-30% of HCV patients developed NOSA under IFN-α therapy [15,18]. Activation of silent CD during antiviral treatment for HCV with IFN–α and ribavirin either alone or in combination was also reported [6,19,20]. Activation of CD in predisposed individuals might be caused by the impairment of TH1/TH2 balance exerted by IFN and ribavirin [19]. Consequently, routine serological screening for CD has been proposed in HCV patients before starting antiviral therapy and the achievement of the histological normalization of the intestinal mucosa after gluten-free diet has been advised before starting the therapy [6].

The serological tests for the diagnosis of CD are more accurate than most other antibody-based tests currently used for inflammatory or autoimmune disorders. Their sensitivity and specificity in detecting untreated CD are close to or above 95%, putting them among the top few serological tests for autoimmune and inflammatory disorders [21]. Furthermore, a study by Bertini et al. (2010) revealed that potential CD patients who have CD-specific antibodies but no evidence of intestinal damage, showed metabolic patterns similar to overt CD patients, almost all patients with positive antibody test are predicted as overt CD. Interestingly, 12 out of 13 subjects revert to a normal metabolomics signature after a gluten-free diet. Therefore, although free from intestinal injury, placing potential CD subjects on a gluten-free diet is recommended as they are experiencing most of the pathological alterations in CD [5,22]. Obviously, a study with systematic gastroscopy and duodenal biopsy in asymptomatic patients was both ethically and pragmatically impossible [6]. Therefore, jejunal biopsy was impractical to be conducted in our group of patients who appear at risk but with no clinical symptoms. Moreover, anti-tTG antibodies were shown to be highly sensitive and specific serological marker for CD [9,10,21].

This study showed a significantly higher level of anti-tTG in the HBV and HCV patients compared to the control group, it also showed an insignificant difference of this CD-related antibody when compared between both HBV and HCV patients. These results, together with the significant higher positivity rate of ASMA in HBV and HCV patients compared to the controls and its insignificant difference between both groups of chronic viral hepatitis, support the association between chronic viral hepatitis and CD. HBV and HCV are non-cytopathic viruses. Viral clearance by the host immune response is associated with

concomitant inflammatory liver cell injury. In addition, HBV and HCV infections provoke various immunopathological manifestations. Evidence of altered immune system homeostasis in HCV patients is further indicated by the high prevalence of NOSA [23]. A frequently offered explanation is that the release of intracellular antigens at the time of hepatocellular injury triggers immune responses in the form of autoantibody production. This would explain why different viruses are able to induce similar autoantibody patterns and why the same virus is associated with antibodies reacting with a variety of cellular components [24]. Three nuclear antigens and three smooth muscle antigens that have a high degree of amino acid homology with HCV polyproteins were identified, serving as targets of cross reactive immune responses [25]. Another mechanism by which HCV can induce autoimmunity was proposed by Toubi et al. (2006) who reported elevated serum B-lymphocyte activating factor (BAFF) in patients with chronic HCV infection. This elevation was associated with clinical and laboratory features of autoimmunity, suggesting that BAFF may play a role in HCV-related autoimmune diseases [26].

5. CONCLUSION

Adult patients with chronic viral hepatitis; chronic HBV and HCV, have higher levels of CD-related autoantibodies (anti tTG) which might reflect the higher incidence to develop CD than normal population. Screening for CD in such patients is recommended, particularly before antiviral treatment, alternatively, antiviral treatment should be given on gluten free diet. Further studies are required to investigate large series of HBV patients of different age groups for NOSA and CD autoantibodies in order to assess the incidence of CD in such patients.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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