Original Article

Insight into the Infectious Diseases Associated with Celiac Disease: A Guild to Novel Approaches for Diagnosis and Treatment

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ABSTRACT

Background:
Celiac disease (CD) is one of the most common and chronic immune-mediated disorders of the gastrointestinal tract that affects the small intestine. Genetic factors, including human leukocyte antigen (HLA), and non-HLA genes are major risk factors in CD pathology. Moreover, environmental factors such as infections may affect CD incidence.

Materials and Methods:
The goal of the present study is to investigate the association between CD and viral, bacterial, fungal, and parasitic infections. Databases including Scopus, PubMed, Google Scholar, and Web of Science were searched for relevant literature until 2022.

Results:
Several infections have been reported to be associated with CD including reovirus, rotavirus, hepatitis B virus, influenza virus, *helicobacter pylori*, *campylobacter jejuni*, *giardia lamblia*, *toxoplasma gondii*, *candida albicans*, etc.

Conclusion:
Moreover, antibiotic administration might be a risk factor for further CD development. On the other hand, there are reports regarding the susceptibility of patients with CD to some infections, as well as protective infections against CD. Consequently, more studies are required to explain the two-sided relations between CD and infectious diseases.

Keywords: Celiac, Infection, Risk factor, Immune-mediated disease, Antibiotics

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INTRODUCTION

Celiac disease (CD) is one of the most common and chronic immune-mediated gastrointestinal tract disorders that affects the small intestine. In such patients, intestine inflammation is triggered by exposure to gluten (cereal grain protein). CD is believed to be a genetic disorder that can be seen at any age or sex, and it is commonly considered a familial disorder. One of the most important genetic risk factors for CD is class 2 human leukocyte antigen (HLA) genes, including DQ2 and DQ8. Moreover, some investigations revealed that the non-HLA genes are of greater importance than the HLA genes (1). In addition, some common single nucleotide polymorphisms (SNPs) in non-HLA loci, associated with other autoimmune diseases (e.g., type 1 diabetes), have been found as genetic risk factors for CD (2).

Over the last two decades, it has been supposed that non-genetic factors, such as infections, may contribute to a considerable increase in the prevalence and incidence of CD (3).Recently, it has been shown that CD is more common in adulthood than in childhood, and risk factors associated with CD might be age-related (4).

At the molecular level, cooperation between genetic and non-genetic factors leads to celiac manifestations. Gluten-derived peptides, presented by HLA-DQ2 or HLA-DQ8, can activate T helper cells that express high levels of interleukin 21 (IL-21) and interferon γ (IFNγ), affecting epithelial cells as well as intraepithelial lymphocytes. Consequently, the epithelial cells are mal-affected, and eventually, villous atrophy would occur (2,5-6).

Clinical presentations of CD are highly variable. Some patients are asymptomatic, while others are symptomatic (4). Symptomatic patients can be classified as having classical CD with significant malabsorption and non-classical CD without malabsorption. In addition, the clinical presentations of CD are different in children and adults (7).

Common complications of CD include osteoporosis, impaired growth, iron deficiency anemia, micronutrient deficiencies, celiac hepatitis, and recurrent miscarriages (7,8). Various clinical presentations of CD are summarized in Figure 1. Laurikka and colleagues classified the complications of CD according to their response to the early initiated gluten-free diet (GFD) and the typical age of disease development (8).

MATERIALS AND METHODS

Databases including Scopus, PubMed, Google Scholar, and Web of Science were searched for relevant literature. The search was done using the keywords: "*Celiac disease*",

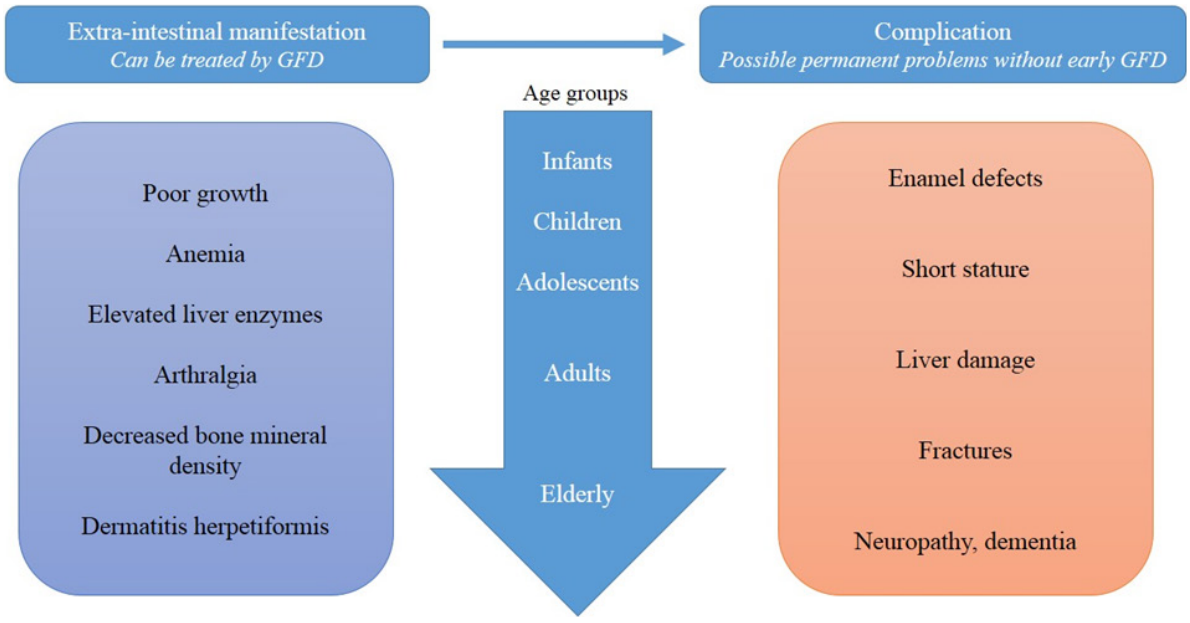

Figure 1. Different clinical presentations and complications of celiac disease (8)

"Infection", and *"Antibiotics"*. The most relevant studies published until Sep. 2022, regarding the association between CD and infections, as well as studies investigating the effect of antibiotic therapy on CD were selected.

RESULTS

The relations between CD and various infections are considered to be two-sided. CD triggers inflammation in the gut mucosa, which can sensitize the patient to the development of infections. In addition, infections caused by pathogenic agents may lead to the development of celiac manifestations (9). A recent study on American and European infants confirmed the effect of gastrointestinal infections on the incidence of CD (10).

Despite the "hygiene hypothesis," which conceives that decreased exposure to foreign antigens (including bacterial and non-bacterial pathogens) may trigger autoimmunity, some studies confirmed that infections could be considered risk factors for CD emergence (11-13). Although there is no strict fact regarding the relationship between infections and CD development; it is entirely case-specific based on the type of infection and the target population genotype.

Viral infections

Experimental studies showed that viral infections that can infect the intestine and stimulate immunity through Th1 responses in Peyer's patches (PP), such as the Reoviridae family, could induce oral intolerance to gluten. It is reported that pathogens stimulate immunity through Th1 and can promote transglutaminase 2 (TG2) activation, auto-antibodies production, and CD development (14).

Among other viral infections, the role of rotavirus (RV) infection may be more significant. A recently discovered mechanism of RV infection is triggering autoimmune responses. This relationship was confirmed through various studies. It was suggested that the similarity between capsid protein VP7 of RV and the human-tissue transglutaminase was the molecular basis for CD development after RV infection; however, enough evidence does not support this hypothesis (15, 16). It has been reported that oral rotavirus vaccination in children could not amend the risk of CD during the first 10 years after vaccination (17). On the other hand, another study suggests that thanks to efficient rotavirus vaccination coverage in Finland and the United States, vaccinated children show a reduced risk of CD in the cases of gluten introduction before the age of 6 months. Rotavirus vaccination had also accompanied by a lower incidence of gastrointestinal infections (10).

Some reports explain the development of CD after acute hepatitis B virus infection (18-21). Similarly, the association between CD and hepatitis C virus (HCV) infection has also been reported in some studies. However, there are controversial reports in this regard, and there is no clear evidence to support this relationship. It has been reported in some studies that the prevalence of CD in patients with chronic HCV is higher than the global prevalence (22,23). Furthermore, the development of CD is reported in HCV-infected patients with chronic hepatitis during treatment with interferon-alpha (24-26). While another study in the French population suggested that the prevalence of CD in HCV-positive patients was 0% (95% confidence interval: 0–0.59%), the low prevalence of CD in the whole French population should be considered (26). Some viral infections, especially those less common and less known, have been reported in patients with CD. For instance, a new astrovirus named VA1 was reported in a child with CD (27).

Moreover, susceptibility to herpes infection in CD might be due to the delayed maturation of the gastrointestinal immune system and mucosal overexpression of the epidermal growth factor receptor, and IL-33 results from the DQA1*0501/DQB1*0201 haplotype associated with CD (28).

Results of the study in Norwegians suggest a significantly increased hazard ratio for CD after seasonal and pandemic influenza even after one year. On the other hand, the hazard ratio for influenza after CD diagnosis was not significant, although hospital admission due to influenza increased in this population (29).

It should be mentioned that not all viral infections could increase the risk of CD development. A study on pregnant women suggested that developing enterovirus infection during pregnancy did not significantly increase the risk of CD development in the fetus (30).

Regarding the recent pandemic of COVID-19, there are a number of reports regarding CD as one of the post-

COVID gastrointestinal complications (31,32). Another study on 455 patients with CD suggests that the prevalence of COVID-19 among patients with CD was 2.4%. Results of this study suggest that although most of the patients were women (72.7%), CD could not be considered a risk factor for the mortality and severity of COVID-19 (33).

Effect of antivirals on CD

There are several reports about CD induction after antiviral therapy for hepatitis C, especially in those treated with interferon or ribavirin. Interferon may activate CD both by direct effects on tissues or indirectly by dysregulating the lymphocyte differentiation and cytokine production, leading to improvement of T-cell and natural killer cell cytotoxicity. In the case of interferon-induced CD, the symptoms resolve after drug discontinuation. On the other hand, ribavirin alters immune responses from Th2 in favor of Th1. In conclusion, antiviral agents that cause Th1/Th2 imbalance might activate CD (34-36).

Bacterial infections

Various studies reported the association between bacterial infection and CD in children. Patients with CD born during 'the Swedish CD epidemic' have mucosa-associated rod-shaped bacteria in their jejunum (including clostridiales, prevotella, and actinomyces) (37,38).

One study hypothesized the association between the infection with *Campylobacter jejuni* and CD development. This study suggests that the formation of anti-gangliosides antibodies in campylobacter infections could provoke autoimmune reactions against gangliosides in gastrointestinal mucosa cells (39). Also, there is a case report; of a young woman with no previous gastrointestinal complaints presented with irritable bowel syndrome (IBS) and positive CD serological tests after a confirmed case of *Campylobacter jejuni* enteritis (40).

In addition, it is believed that *Helicobacter pylori* (HP) infection may increase the risk of CD. Different studies showed that there is neither relation nor reverse relation between HP infection and CD prevalence (41,42). However, some studies did not confirm this hypothesis in pediatric patients with CD (43). Surprisingly, other studies showed that the prevalence of HP infection was considerably lower in untreated patients with CD compared with both treated patients and normal controls (44,45). Presumably, changes in the intestinal environment and immune responses following a gluten-free diet are responsible for increasing HP prevalence in treated patients with CD (44). Results of a meta-analysis of data from 141 355 participants suggest that patients with CD are 0.57 times more prone to HP than the control population (46).

Recently, some studies assessed the incidence of bacterial pneumonia and pneumococcal infection in children and young patients with CD. The results revealed an elevated risk of bacterial pneumonia in this population. Therefore, the authors suggested an anti-pneumococcal vaccination for young patients with CD (47,48). Another study found a positive relationship between CD in children hospitalized for the respiratory syncytial virus and invasive pneumococcal disease (49).

Controversially, a study on a group of Swedish infants with episodes of infectious disease in the first year of their life showed that the infections reported at the time of gluten introduction are not major risk factors for CD (50). On the other hand, it has been reported that the incidence of *Clostridium difficile* is nearly doubled in patients with CD compared with controls (51).

Effect of antibacterials on CD

It is presumed that the intestinal microbiome has a considerable effect on the risk of CD (52). Antibiotics may change the intestinal microbiome; therefore, several studies investigated the role of antibiotic administration as a risk factor for subsequent CD development. Marild and colleagues had several studies in this regard. They conducted a population-based case-control study and investigated the histopathology data of 2,933 Swedish individuals with CD. The results of this study confirmed a positive relationship between the antibiotic application and subsequent CD development (53). Another survey of 1836 fetuses exposed to antibiotic therapy during pregnancy revealed that only 0.7% of infants developed CD compared with 0.5% celiac incidence in unexposed ones. Therefore, no statistically significant association was seen between antibiotic exposure during pregnancy and CD occurrence in offspring (54).

A recent study on children in Denmark and Norway

showed that the administration of systemic antibiotics during the first year of life increased the rate of diagnosed CD. There was a positive dose-dependent relationship between the number of dispensed antibiotics and the risk of CD (55).

Results of a Meta-analysis regarding antibiotic exposure and CD risk suggest that antibiotic exposure was associated with a significantly increased risk of CD (OR, 1.15; 95% CI: 1.02–1.29; P=0.024; I 2=82.1%) in childhood. Analyses of antibiotic class revealed that penicillin V (OR, 1.16; 95% CI: 1.03–1.3; P=0.014; I 2=74.5%) was associated with CD; macrolide use was marginally associated with CD (OR, 1.17; 95% CI: 0.98–1.39; P=0.088; I 2=74.8%), while no such association was found for cephalosporins (OR, 1.3; 95% CI: 0.94–1.8; P=0.0115; I 2=87.8%) or antifungal drugs (OR, 1.55; 95% CI: 0.75–3.17; P=0.235; I 2=95%) (56).

Parasitic Infections

One of the oldest case reports regarding the relationship between CD and infection reported a child infected with *Giardia lamblia* who developed CD manifestations in 1939 (57). In a case-control study in 2013, the presence of toxoplasma-specific antibodies (IgG, IgM) in patients with CD was evaluated, and it was found that a history of infection with *Toxoplasma gondii* (*T. gondii*) could result in an increased risk of CD development (58). Another study showed a significant relationship between the severity of mucosal damage and anti- T. gondii IgG level (59). An approximately four-fold higher risk for *Toxoplasma gondii* is seen in individuals positive for CD autoantibodies (9).

Fungal infections

Candida albicans might induce CD through structural similarities of hyphal wall protein 1 and T-cell alpha-gliadin and gamma-gliadin epitopes. The hyphal wall protein 1 as transglutaminases substrate, mediate adherence of *Candida albicans* to enterocytes. After the attachment of tissue transglutaminase and endomysium to the yeast, the production of antibodies results in CD development (60).

On the other hand, there is a paralleled increase in IgG antibodies against recombinant hyphal wall protein 1 and IgA anti-gliadin antibodies in infection with *Candida albicans*. No statistical differences were observed in IgG antibody levels in patients with CD versus patients with Candida albicans infections. Hence, *Candida albicans* might trigger CD in genetically susceptible patients (61).

Infections with a positive effect on reducing CD

It is supposed that chronic helminthiasis, such as hookworm (*Necator americanus)* infection, might modulate the immune responses during autoimmune and pathogenic immune disorders in humans. Although chronic hookworm infection can be a well-controlled disease, studies showed that this chronic intestine infection could reduce the number of gluten peptide-specific T cells in the blood, suppress inflammatory reactions, and decrease histological damages following wheat challenge in patients with CD. This infection could also modulate the microbiome of the intestine toward maintaining gut homeostasis in the presence of an inflammatory insult (54, 62, 63).

DISCUSSION

Various environmental factors might trigger CD. Multiple infections, especially in the first year of life, may significantly elicit gluten intolerance or other serological manifestations of CD. There are still controversies

Table 1. Infections that might be associated with celiac disease

Viral infections	Bacterial infections	Parasitic Infections	Fungal infections
● Reovirus ● Rotavirus ● Hepatitis B virus ● Hepatitis C virus ● Astrovirus ● Herpes simplex virus ● Influenza virus	● Prevotella ● Actinomyces ● Clostridiales ● *Campylobacter jejuni* ● *Helicobacter pylori* ● *Clostridium difficile*	● *Giardia lamblia* ● *Toxoplasma gondii*	● *Candida albicans*

regarding the effect of infections on CD prevalence. Table 1 represents the infections that might be associated with CD. The similarity of antigenic structures between pathogens and natural human biomolecules is probably responsible (15,16). On the other hand, it is found that patients with CD are more susceptible to some types of infections, presumably because of the presence of pathologic inflammation or the mutations in genetic alleles underlying CD. In addition to the role of infections in the first year of life on CD initiation, several reports revealed the role of vaccination in preventing CD development (29). Therefore, vaccination of infants against pathogens seems to be a reasonable approach to reduce CD prevalence.

CONCLUSION

Several infections have been reported to be associated with CD including reovirus, rotavirus, hepatitis B virus, influenza virus, *Helicobacter pylori*, *Campylobacter jejuni*, *Giardia lamblia*, *Toxoplasma gondii*, *Candida albicans*, etc. Moreover, antibiotic administration might be a risk factor for further CD development. On the other hand, there are reports regarding the susceptibility of CD patients to some infections, as well as protective infections against CD. Consequently, more studies are required to explain the two-sided relations between CD and infectious disease.

CONFLICT OF INTERESTS

The authors declare no conflict of interest related to this work.

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