Review Article

The Role of Infectious Mediators and Gut Microbiome in the Pathogenesis of Celiac Disease

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Abstract

Celiac disease (CD) is an immune disorder that is associated with gluten sensitivity in people who are genetically predisposed. In celiac disease, food containing gluten mounts inflammatory response that results in villous atrophy in small bowel and increased permeability. This disorder is not only related to complications in the small bowel, but also has association with manifestations outside the GI tract. Small bowel mucosal immunity, exposed to infectious agents, is affected by CD; therefore, it is likely that patients with untreated celiac disease are more susceptible to infectious diseases. It is possible that sensitivity to gluten increases in patients infected with infectious diseases, and consequently infection may trigger CD in susceptible individuals. It is likely that, due to reduced immunity following the loss of intestinal villi, viral, bacterial, and parasitic infections develop faster in celiac disease patients and systemic complication occur more frequently. In addition, increased permeability, changing the microbiota following the chronic inflammation of the small intestine and abnormal immunological reactions are associated with celiac disease. PubMed, Medline, Google scholar, SID, and Magiran were searched for full text articles published between 1999 and 2014 in Persian and English. The associated keywords were used, and papers, which described particularly the impact of infectious agents on celiac disease, were selected. In this review, we have focused on the role of infectious agents and gut microbiota in the pathogenesis of celiac disease.

Keywords: Celiac disease, infectious agents, microbiota, pathogenesis

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Introduction

Celiac disease (CD) is an autoimmune disorder which is triggered by an exogenous antigen called gluten. It occurs in patients with specific genetic susceptibility (HLA DQ2/DQ8 and non-HLA genes).[1] Upon exposure to gluten, the enzyme tissue transglutaminase modifies the gluten, and the immune system cross-reacts with the small bowel tissue, causing an inflammatory reaction leading to malabsorption syndrome. The only effective treatment of CD is a lifelong gluten-free diet.[2]

Celiac is associated with other disorders and the questions around these associations seems to be one of the most debated topics. Obvious reasons for this widespread interest in this multisystem immunologic disorder is probably due to its multi-factorial etiology with a wide range of manifestations and complications inside and outside the small bowel.[3,4] Environmental factors associated with complex genetic susceptibility potentially lead to destructions of the small intestinal villi resulting in malabsorption syndrome.[3,4]

The associations between celiac disease and different infectious agents have been previously studied and several intestinal and extra intestinal simultaneous disorders with CD have been reported.[5] The simultaneous presentation of infectious agents has been implicated in the pathogenesis of many autoimmune disorders such as celiac disease and the studies suggested their roles in two ways: the association between specific microorganisms and CD; and the possible relationship between severe gastroenteritis and CD.[4] Even now, the association between CD predisposition and specific infectious agents e.g., *enterovirus,* hepatitis C and *rotavirus* has been suggested but remains unconfirmed.

On the other hand, among more than 50 bacterial phyla, only four including *Firmicutes*, *Bacteroidetes*, *Actinobacteria,* and *Proteobacteria* are predominant human gut-associated microbiotas.[6] Depending on the physiological environment in unity with their hosts, microbiotas will develop as the human body grows. Therefore, normal intestinal microflora may contribute to the development of celiac disease in susceptible individuals.[7]

The results of previous studies have shown that the main microbiota populations are established during the first decade of life. The small intestine microbiota contains the majority of immune cells and is involved in functions correlated to carbohydrate absorption, metabolism, and immune system.[8] Accordingly, the small intestinal microbiota could play a role in advancement and preservation of mucosal and systemic homeostasis. For this reason, searches were performed in PubMed, Medline, and Google scholar for articles published in English, as well as in SID and Magiran for Persian-language journals from 1999 to November 2014; the following keywords were used alone or in combination: "celiac disease," "pathogenesis," "infectious agent," "infection," "microbiome," "microbiota," "anti-endomysial," and "anti-tTG." However, according to our explorer, no Persian-language papers were found.

The aim of this review was to present the causal relationship and/or coincidence of some infectious agents and microbiota in the pathogenesis of celiac disease.

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Correlation between infections and celiac disease

Besides the commensal microbiome, a number of other factors including childhood infections notably *rotavirus*, mode of delivery, gluten introduction to infants, and breastfeeding have been studied in celiac disease. Intolerance in celiac disease patients is most likely due to genetic factors (e.g., types of genes on chromosomes 5, 6, and 19).[9] The environmental factors beside gluten intake are viral, bacterial, or parasitic infections and these infections agents play an important role in triggering the disease (Table 1). Most probably, mucosal infection may contribute to lowering the tolerance to gluten, leading to intestinal inflammation and tissue damage in CD patients.[9]

Review of published medical studies indicated that infectious agents may contribute to the development of CD in susceptible individuals. The finding of a seasonal pattern of higher rates of summer births in children with celiac disease also suggests a role of infectious agents.[10] In a study by Ivarsson *et al.*, 2,151 children below 15 years of age with CD were studied and the relative risk for CD were estimated by season of birth. The result of this study showed that an increased risk of CD in children born in summer compared with winter and this finding reflects causal environmental exposure(s) such as infectious agents with a seasonal pattern.[10]

Immunological cross-reactivity between antigenic elements shared by viruses and α-gliadin might be implicated.[11] There is no convincing evidence that patients with *enterovirus* are at increased risk of developing CD.[12,13] In a study by Carlsson *et al*., although 4% of the mothers whose children developed celiac disease had positive anti-endomysial antibodies (EMA), no significant differences between cases and controls were reported in antibody titers during pregnancy for *enterovirus*.[13] The relationship between CD and infections caused by *adenovirus*, hepatitis C and *rotavirus* has been reported.[9–14] The result of a study by Ruggeri *et al.* (2008) showed that EMA were found in 5/244 (2%) of HCV-patients compared to 2/1,230 (0.16%) of healthy blood donors, with a significant difference between cases and controls.[9] In another study, the prevalence of *rotavirus* infection was not statistically significantly different between adults who were tTG antibody positive and those who were tTG antibody negative.[14] Stene *et al*. concluded in their study that *rotavirus* infections may increase the risk of celiac disease autoimmunity in childhood.[15]

Some studies suggest that the majority of children and adults with CD have low rates of responding to standard vaccination regimens for hepatitis B virus due to the genetic background of celiac patients, which seems to be linked to human leukocyte antigen (HLA) DQ2.[16–18] Also the level of anti-HBs antibody is reported to be lower in untreated celiac patients compared with healthy controls.[17]

In agreement with previous findings, untreated CD may be one of the immune diseases associated with a high rate of non-response to HBV vaccination but it might not be permanent and early diagnosis and treatment of celiac patients will increase the rate of response in treated and HBV vaccinated cases.[19] Recently, it has been hypothesized that hepatitis A virus (HAV) may trigger immunologic reaction related to gluten intolerance in susceptible patients.[20] In a study by Sari *et al*., 33 CD patients and 62 healthy controls were evaluated by inactivated HAV vaccine.[21] They concluded that there was no association between HLA alleles and antibody titers of hepatitis A. It seems that children with CD had a maximum immune response to hepatitis A immunization similar to healthy controls.

In several studies, the relationship between the presence of *H. pylori* and CD among patients undergoing endoscopy for a variety of symptoms has been reported. The result of these studies presented the dissimilar relationship between *H. pylori* and CD. Various studies have reported lower or higher prevalence of *H. pylori* among CD patients compared with controls.[22–28] In a study by Konturek *et al.*, a slightly increased prevalence of *H. pylori* was shown in CD patients.[29] Association of CD with other infectious agents, such as *Campylobacter jejuni* and *Giardia lamblia*, has been mainly described as case reports.[30,31]

In a study by Plot *et al.* the sera of 297 healthy subjects and 90 patients with celiac disease were analyzed for the presence of *Toxoplasma gondii*, *rubella virus*, *Treponema pallidum*, *cytomegalovirus* (CMV) and *Epstein-Barr virus* (EBV).[5] The results showed higher prevalence of positive serology in the control group than in the CD group for *T. gondii* (25.9% vs. 23.3%), *rubella virus* (94.9% vs. 87.8%), and CMV (67.7% vs. 54.4%). On the other hand, a higher prevalence of antibodies against *T. pallidum* antigens and IgM antibodies against EBV was observed in the CD patients compared to the control group.

In one of our studies in 2011 on 827 pregnant women, both CD and IgG, IgM antibodies levels against *Toxoplasma* infection were studied.[32] Anti- tTGA was positive for celiac disease in 27 (2.3%) out of the 827 pregnant women. *Toxoplasma gondii* IgG was

Table 1. Correlation between celiac disease and infectious agents; result of different studies.

Authors	Patients	Results (%)	Ref.
Ruggeri *et al.*	244 HCV-patients, 121 non-HCV-patients, 1,230 blood donors	5/244 (2%) HCV, 1/121 (0.8%) non-HCV, 2/1,230 (0.16%)	9
Rostami Nejad *et al.*	827 pregnant women	1/27 (0.11%) of celiac patients was positive for HCV	12
Carlsson *et al.*	76 mothers whose children developed CD & 327 mothers with children without CD	no significant differences were found	13
Rostami Nejad *et al.*	670 Gastrointestinal symptoms	150 infected with rotavirus and 8 of them had CD	14
Stene *et al.*	1,931 children	27 cases positive CD and 1.9% infected by rotavirus	15
Leonardi & La Rosa	60 HBV	Non were positive for CD	35
Sari *et al.*	33 CD and 62 healthy controls	Children with CD have a good immune response to hepatitis A vaccination	21
Ciacci *et al.*	690 CD patients	*H. pylori* infection was significantly lower in untreated celiac	24
Aydogdu *et al.*	96 children with CD	21.8% were infected with *H. pylori*	26
Rostami Nejad *et al.*	827 pregnant women	16 of 27 CD patients were positive for *T. gondii*	32

positive in 154 (18.6%) patients out of 827 pregnant women and 58 (37.6%) patients were positive for IgM. It was observed that 16 out of 27 (59%) tTGA positive patients were seropositive for *Toxoplasma gondii*. This indicated 3.71-fold risk for T*oxoplasma gonadii* in patients positive for celiac antibodies. According to the findings obtained from this study, the authors suggested that celiac disease may perhaps lead to faster development of *Toxoplasma gondii* oocysts in the gut.

Infiltration of *Toxoplasma*-infected cells through the small intestine may increase the production of pro-inflammatory cytokines, such as TNF-α, IL-1α, IL-8, and IFN-γ, and this could be involved in the development of mucosal damages.[33] In the same study, also the level of IL-8 was higher in celiac patients infected with *Toxoplasma gondii,* especially in those who were positive for IgM, compared to the rest of the study population.[32] A possible mechanism behind the role of infection in triggering CD has been illustrated in Figure 1.

Severance and colleagues studied the immune response against *T. gondii* infection in mice following gluten ingestion.[34] Significant increases in levels of *T. gondii* IgG were recorded in all 24 mice and their children with chronic infection exposed to gluten compared to the control group. In this study, the level of *T. gondii* IgG against gluten in infected female mice was higher than males, suggesting that the gastrointestinal parasitic infection leads to the production of anti-gluten response in a sex-related manner.

In his review article, Prandota suggested that a chronic latent infection with parasites can increase the risk of developing celiac disease in susceptible individuals.[33] Our recent study provided further evidence for this hypothesis and showed that celiac disease increases the risk of *T. gondii* infection in a large cohort of Iranian pregnant women.[32]

The role of microbiome

A microbiota is the ecological community of commensal, synergetic and pathogenic bacteria that live in all body spaces. Intestinal microbiome is the community of live microorganisms residing in the digestive tract and is necessary for accurate body growth, the immunity expansion, and diet.[36] Despite technological advances in studying the human intestinal microbiome, many questions remain to be answered about the role of commensal bacteria in immune-mediated gastrointestinal diseases such as celiac disease or inflammatory bowel diseases. The first and perhaps the most important question is whether the intestinal microbiota is a cause or a consequence of intestinal inflammation. There is evidence to support either side.

Several intestinal viral triggers, bacterial and parasitic infections capable of initiating or expanding gut mucosal responses to gluten were suggested to play a role in the pathogenic mechanism of celiac disease.[5] Changes in the fecal and duodenal microbiota structure of celiac patients on a gluten-free diet have shown that some commensal bacteria, such as *E. coli* and *Bifidobacteria* stimulated the initiation of innate immune cells by gliadin and have inhibitory effects, respectively.[37,38] The diverse studies indicated the differences in the intestinal microbiota between children and adults with celiac disease.

In one study, duodenal bacteria populations in 15 adults and 13 children with/without celiac disease were investigated by 16S rRNA gene sequencing.[39] The authors reported that 3 phyla including *Firmicutes*, *Proteobacteria*, and *Bacteroidetes* were detected in both groups while upper small intestine bacterial abundance was significantly lower in the untreated children CD pa-

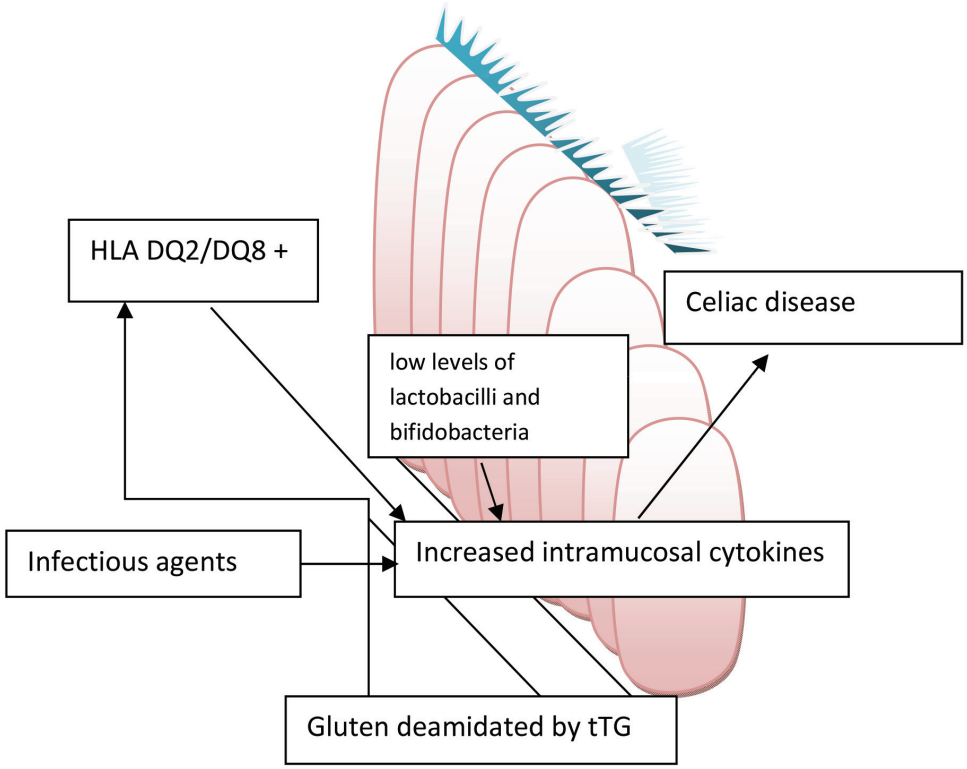

Figure 1. Untreated celiac patient's small bowels usually have increased intra-mucosal cytokines and a different microbiome. Cytokines will increase further in infected patients susceptible for CD, triggering the disease phenotype.

Table 2. More prevalent gut microbiotas in CD patients; result of different studies.

Authors	Date of publication	Population	Type of sample	Method of detection	Microbiota phylum/class	Ref.
Nadal *et al.*	2007	Children	Intestine biopsy	FISH, Flow Cytometry	*Bacteroidetes E.coli*	43
Sanz *et al.*	2007	Children	Stool samples	PCR-DGGE	*Actinobacteria Firmicutes*	44
Medina *et al.*	2008	Children	Stool sample	PBMC, flow Cytometry	*Actinobacteria*	45
Kaufman & Rousseeuw	2009	Children	Intestine biopsies	PCR	*Proteobacteria*	46
Sánchez *et al.*	2010	Children	Intestine biopsy	PCR-DGGE	*Bacteroidetes*	47
di Cagno *et al.*	2011	Children	Stool sample, Intestine biopsy	RAPD-PCR	*Eubacteria*	48
Sánchez *et al.*	2011	Infants	Stool samples	PCR-DGGE	*Bacteroidetes*	49
Nistal *et al.*	2012	Adults & children	Intestine biopsy	PCR	*Firmicutes Proteobacteria Bacteroidetes Actinobacteria Fusobacteria*	39
Sellitto *et al.*	2012	Infants	Stool samples	qPCR	*Bacteroidetes Firmicutes*	50
Cheng *et al*.	2013	Children	Intestine biopsy	qRT-PCR	*Bacilli Bacteroides Clostridium Proteobacteria*	51
Wacklin *et al*.	2013	Adult	Intestine biopsy	PCR-DGGE	*Firmicutes Bacteroides Proteobacteria Actinobacteria*	52

tients compared to untreated CD adults due to age.[39] The result of another study on pediatric patients with active celiac disease indicated that high microbiota variety was found in these patients compared with treated CD patients as well as controls.[40] Sanchenz *et al*. reported that members of the families *Proteobacteria, Enterobacteriaceae* and *Staphylococcaceae* were the most common and, in contrast, the phyla *Firmicutes* and *Streptococcaceae* were the least common bacteria in pediatric patients with active celiac disease compared to non-active celiac disease and controls, respectively.[40] But in a study by de Meij *et al.*, microbiome profiles were analyzed in small bowel biopsies of 21 children with untreated CD and 21 controls and the results showed no difference in intestinal microbiome pattern and diversity, with high abounds of the *Streptococcus*, *Lactobacillus*, and *Clostridium.*[41]

On the other hand, in a recent study by Nistal *et al*. in Spain, stool samples were collected from 10 untreated CD patients, 11 treated CD patients and 11 healthy adults and evaluated by PCR denaturing gradient gel electrophoresis (DGGE) and gas liquid chromatography of short chain fatty acids (SCFAs).[42] The result of this study showed a decrease in the diversity of *Lactobacillus* and *Bifidobacterium* species in the treated CD patients, but *Bifidobacterium bifidum* was significantly higher in untreated CD patients than healthy adults.

Various studies show that the intestinal microbiota of CD patients presents variations in the diversity and abundance of different cultivable bacterial species, which could be a result of CD pathogenesis.

Conclusion

Celiac disease results from the interplay of environmental (e.g., gluten intake, infectious agents, and intestinal microbiota) and immunologic factors in genetically susceptible individuals. Among environmental factors, infectious agents and intestinal microbiota have been implicated; however, the principal mechanism underlying this association is not well understood. The following reasons may be an explanation for possible mechanisms: 1) Intraepithelial migration of infectious agents are associated with their motility and virulence, 2) adhesion interaction between human intercellular adhesion molecule 1 (ICAM-1) and the parasite MIC2 and therefore immune precipitation could be accrued, 3) pathogenic microbiota may attack the intestinal epithelial cells and affect epithelial binding proteins (tight-junctions), as a result of which the permeability of the intestinal wall of the host will be increased. Understanding the correlation between infectious agents and autoimmune disorders may provide insight into the disease mechanism. In addition, it may enable the development of potential therapeutic targets to combat this common genetic disorder.

Differences in the bacterial communities in children and adults with celiac patients have been reported in some studies (Table 2).[43–52] Also, the population of bacteria in treated and untreated CD patients is different according to the diagnosis in adults. Some studies suggest a similarity between the microbial communities of treated celiac patients with the known microbial communities of healthy adults.

According to these studies, more investigations are required to assess the importance of some of these bacteria for CD patients, such as the unknown bacterium not detected in treated and untreated CD patients, and the role of the microbiota in healthy individuals. Also, infectious mediators may stimulate an immune reaction and act as a trigger factor for CD in susceptible individuals.

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