



Viral infections in celiac disease: what should be considered for better management

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Received: 26 November 2024 / Accepted: 20 December 2024
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Abstract

Following a gluten-free diet (GFD) is known as the main effective therapy available for celiac disease (CD) patients, which in some cases is not enough to heal all patients presentations completely. Accordingly, emerging researchers have focused on finding novel therapeutic/preventive strategies for this disorder. Moreover, previous studies have shown that celiac patients, especially untreated subjects, are at increased risk of developing viral and bacterial infections, which can become a challenge for the clinician. Viruses, such as *Rotavirus*, *Reovirus*, *Adenovirus*, *Enterovirus*, *Rhinovirus*, *Astrovirus*, *Hepatitis virus*, *COVID-19*, *Norovirus*, and *Herpesvirus*, have been related to CD pathogenesis. Therefore, clinicians need to pay more attention to evaluate CD patients' viral infection history (especially nonresponders to the GFD), to look for effective preventive strategies and educate patients about important risk factors. In addition, there are still viruses whose role in CD pathogenesis has not been fully studied. In this review, current information on the association between CD and various viral infections was gathered to improve knowledge in this subject area and draw researchers'/clinicians' attention to unstudied/less studied viruses in CD pathogenesis, which might guide future prevention approaches.

Keywords Autoimmune · Celiac disease · Gluten-free diet · Management · Viral infections

Introduction

Celiac disease (CD) is a hereditary autoimmune disorder of the small intestine triggered by gluten ingestion [1]. Gluten is a digestion-resistant glutamine and proline-rich protein found in wheat, rye, and barley that enters the intestinal lumen in a semi-digested form and causes further damage to the intestine [2]. The prevalence of CD is about 1% in the general population [3]. This disorder affects women more

than men and first-degree relatives of CD patients are at increased risk (4%–12%) for the disorder [3]. Celiac disease has a wide range of clinical manifestations including gastrointestinal symptoms (like diarrhea, bloating, weight loss, steatorrhea, etc.) and non-gastrointestinal symptoms (like fatigue, anemia, infertility, etc.) [4]. Human leukocyte antigen (HLA) DQ2 and DQ8 have a strong genetic association with CD; however, some other non-HLA genes also contribute to CD development [4]. Following the entry of semi-digested gluten peptides into the lamina propria of patients with CD, these peptides undergo deamidation by the enzyme tissue transglutaminase (tTG). This modified form of gluten is presented to antigen-presenting cells (APCs) expressing HLA-DQ2 or HLA-DQ8 on their surface. The interaction activates CD4+ T cells via the Th1 pathway, resulting in the production of pro-inflammatory cytokines. Additionally, CD8+ cytotoxic T cells are stimulated by interleukin-15 (IL-15), further contributing to the immune response. These pathological processes culminate in villous atrophy, crypt hyperplasia, and an increase in intraepithelial lymphocytes (IELs) [5–8].

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Type 1 diabetes, Down syndrome, Turner and Williams syndromes, immunoglobulin A deficiency, etc., are known as CD-associated disorders [9]. Environmental factors, such as viral or bacterial infections, changes in the intestinal microbiome, infant gluten consumption, and breastfeeding, are also known as predisposing factors for CD development [10, 11]. Previous studies have shown that celiac patients, especially untreated subjects, are at increased risk of developing viral and bacterial infections [12, 13]. Viruses, such as *Rotavirus*, *Reovirus*, *Adenovirus*, *Enterovirus*, *Rhinovirus*, *Astrovirus*, *Hepatitis virus*, *COVID-19*, and *Norovirus*, have been related to CD pathogenesis. Viral infections have the potential to disrupt immunological tolerance, influencing the expression of both pro-inflammatory and immunosuppressive factors, and may initiate pathogenic processes [14]. Additionally, these infections promote the production of type 1 interferon (IFN), subsequently activating Th1 immunity in response to gluten [15–17].

In this review article, we have tried to gather current information about viral infections in celiac diseases, which can help researchers and physicians come up with new ideas for novel diagnostics and therapeutic/preventive panels for CD.

Virus infection and oral tolerance breakdown

The ingestion of harmless antigens, such as dietary proteins, usually leads to a state of immune nonresponsiveness known as oral tolerance. This process is intricately linked to how the gastrointestinal tract manages a diverse community of beneficial microbes. Maintaining this balance requires complex interactions between nonimmune cells and the gut-associated lymphoid tissue (GALT). These interactions help control inflammation in response to resident bacteria and food proteins, preventing tissue damage while allowing the immune system to effectively respond to potential pathogens. An imbalance in these regulatory roles may result in a breakdown of tolerance, which can manifest as inflammatory conditions, or inappropriate immune responses to benign food antigens, as observed in disorders like celiac disease and IgE-mediated food allergies [18] (Fig. 1).

Viral infections can disrupt this delicate balance. When a virus invades, epithelial and innate immune cells recognize it through pattern recognition receptors. This triggers signaling pathways that produce inflammatory mediators such as type I and III interferons, along with cytokines like IL-6, IL-1 β , IL-18, and TNF- α . These mediators alert nearby cells to initiate antiviral defenses and recruit leukocytes to the site of infection [23]. Dendritic cells in the lamina propria capture viral particles and migrate to the mesenteric lymph nodes (MLN) to relay viral antigens to T cells. This

activation leads to the differentiation of virus-specific T cells into memory and effector cells, which then home back to the intestinal tissues. Here, they can eliminate infected cells via cytotoxic mechanisms. Meanwhile, B cells, activated in areas like Peyer's patches, produce virus-specific IgA antibodies, enhancing the immune response within the gut [24, 25] (Fig. 1). Importantly, the rapid immune response to viral infections can lead to an imbalance in the finely-tuned regulatory mechanisms of oral tolerance.

Virus infection and CD pathogenesis

As it was stated, oral tolerance to food antigens is primarily mediated by intestinal DCs that promote the activation of Treg responses. In individuals with CD, however, these DCs can instead initiate inflammatory responses characterized by CD4+ T cell activation against gluten. This alteration in DC function may be attributed to changes in the intestinal microenvironment, particularly the elevation of inflammatory cytokines such as type 1 interferons (IFNs). These findings suggest that viral infections within the intestinal tract may modulate immune responses to oral antigens, such as gluten, potentially exacerbating the development of CD [26, 27] (Fig. 2). For instance, reovirus is known to induce the production of type 1 IFNs [28]. Experimental studies in murine models demonstrate that administration of ovalbumin (OVA), as a model antigen, induces systemic tolerance characterized by the promotion of Tregs and a lack of OVA-specific Th1 cell responses [29, 30]. However, the oral inoculation of mice with reovirus strain T1L disrupts this oral tolerance, as evidenced by a reduction in Treg populations alongside an increase in OVA-specific Th1 cell responses. Furthermore, HLA-DQ8-transgenic mice inoculated with T1L and subsequently exposed to gliadin, a proteolytic fragment of gluten, develop antibodies specific to gluten and exhibit a delayed-type hypersensitivity (DTH) response, highlighting a failure to establish tolerance to gluten. Additionally, infection with T1L activates TG2, an enzyme that contributes to the immunopathogenesis of celiac disease [30]. Thus, viruses can elicit an inflammatory response to dietary gluten in celiac disease.

Rotavirus and celiac disease

Rotavirus is a double-stranded RNA virus in the Reoviridae family, which is known to be a major cause of diarrheal diseases in children [31]. Currently, there are nine species of *Rotavirus*, referred to as *Rotavirus* group A to I [32]. *Rotavirus* has fecal–oral transmission pathways and *Rotavirus* A is known as the major cause of human infections [33, 34]. It infects enterocytes lining the small intestine and leads

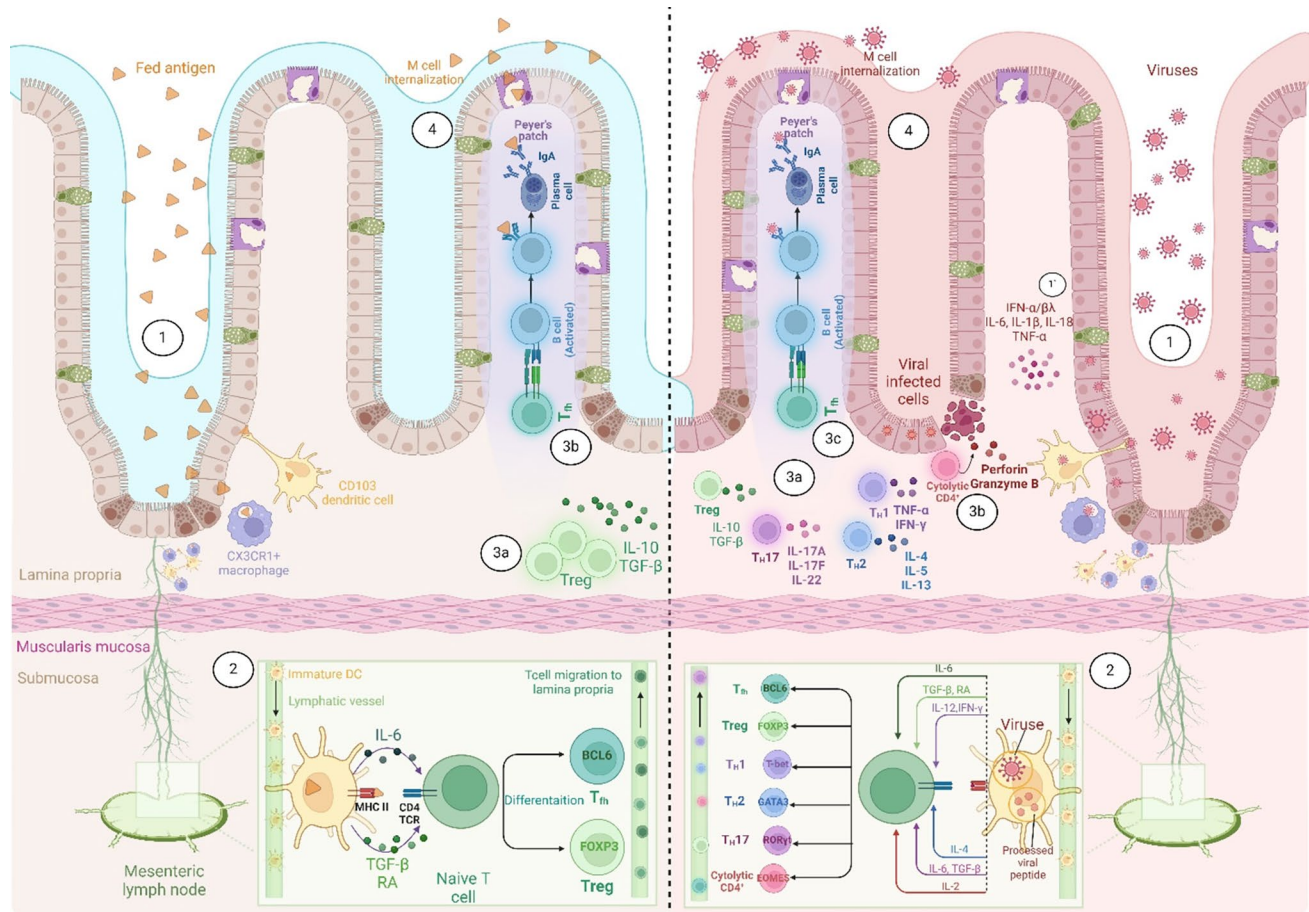


Fig. 1 Comparative Overview of Oral Tolerance and Intestinal Immune Responses during Viral Infection. Left panel: 1) Antigens that are ingested make their way to the small intestine, where they are captured by CD103-expressing dendritic cells. At the same time, CX3CR1+ macrophages extend their dendrites through the intestinal epithelium to sample antigens from the lumen and transfer these antigens to CD103+ cells for transportation to the mesenteric lymph nodes (MLN). Particulate antigens are taken up by M cells positioned above Peyer's patches [19, 20]. 2) Dendritic cells loaded with antigens then migrate to the mesenteric lymph nodes, where they present the antigens to naïve CD4⁺ T cells. During this process, DCs secrete transforming growth factor-beta (TGF-β) and retinoic acid (RA), which stimulate the expression of the Treg master transcription factor Foxp3 and equip newly differentiated Tregs with gut-homing receptors CCR9 and α4β7, they may secrete IL-6 to induce the expression of the Tfh master transcription factor BCL6. Subsequently, antigen-specific Tregs and Tfh cells return to the lamina propria of the small intestine. 3a) At this stage, Tregs can produce anti-inflammatory

cytokines such as IL-10 and 3b) Tfh cells can activate B cells, converting them into plasma cells that produce IgA [21, 22]. 4) IgA can bind to and neutralize food allergens, thereby enabling oral tolerance to food [23]. Right panel: 1) The early detection of viruses by innate immune cells is facilitated by pattern recognition receptors, including intracellular sensors for DNA and RNA, 1') which triggers an interferon and cytokine response that alerts neighboring cells and recruits leukocytes. 2) Dendritic cells in the lamina propria migrate to the mesenteric lymph nodes, where they present viral antigens to virus-specific T cells. 3a) Once activated, T cells travel to the intestinal tissue to promote antiviral immunity by secreting cytokines or through exerting cytotoxic effects. 3b) Cytotoxic CD 4+ T cells can lead to the destruction of infected cells by releasing perforin and granzyme B. 3c) B cells activated in Peyer's patches undergo class switching to IgA and differentiate into plasma cells, supported by follicular T helper cells. 4) The intestinal plasma cells then produce secretory IgA, which serves to neutralize viruses present in the mucosal environment [24, 25].

to gastroenteritis known as "stomach flu" [35]. Although *Rotavirus* was discovered in 1973 by Ruth Bishop and her colleagues, its impact on human health has been underestimated, especially in developing countries [36]. Studies have linked rotavirus infection, as an environmental modulator, to CD initiation or progression. In this regard, Stene et al. proposed that a high frequency of rotavirus infections may have a role in increasing the risk of CD development in

genetically predisposed childhood who carried CD-related HLA risk alleles [37, 38]. Of interest, Zanoni et al. by screening a random peptide library found that in active CD a subset of anti-transglutaminase IgA antibodies recognized the rotavirus major neutralizing protein VP-7 and suggested a potential role of *rotavirus* infection in CD pathogenesis initiation [39]. VP-7 is a major glycoprotein of the rotavirus

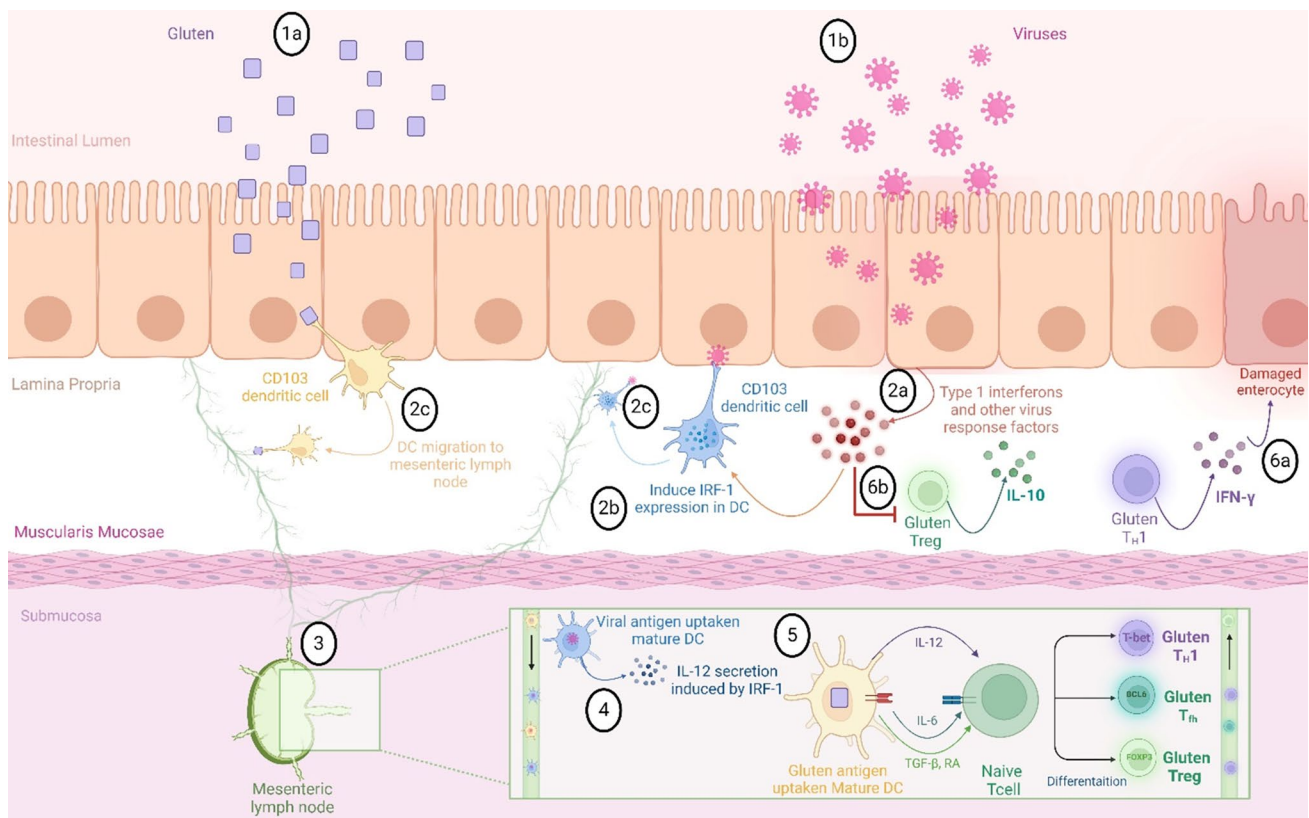


Fig. 2 A Proposed Model for the Induction of Celiac Disease by Viruses. 1a) Upon entry, gluten antigens are captured by dendritic cells (DCs). 1b) Viruses, such as the T1L reovirus strain T1L, manipulate antiviral responses to establish persistent infections, leading to 2a) the release of type 1 interferons and other mediators that 2b) enhance the expression of interferon regulatory factor-1 (IRF-1) in dendritic cells within the lamina propria. 2c) Both DCs that have taken up gluten and those that have captured viral antigens migrate into the lymphatic vessels. 3) In this cytokine-rich inflammatory

environment, antigen-laden dendritic cells travel to the mesenteric lymph nodes. 4) By promoting IRF-1 expression, virus-activated DCs secrete increased levels of IL-12. 5) The presence of IL-12 in the mesenteric lymph nodes activates gluten-specific inflammatory T cells (Th1). 6a) These T cells, in turn, secrete IFN- γ , which damages enterocytes. 6b) Additionally, the type 1 interferons induced during T1L infection suppress regulatory T cells, promoting the expansion of Th1 immunity to gluten, a critical element in the pathogenesis of celiac disease [26]

outer layer that elicits class I MHC-related cytotoxic T lymphocyte response.

Reovirus and celiac disease

Reovirus (respiratory and enteric orphan viruses) is a double-stranded RNA virus of the Reoviridae family and is thought to mainly infect adults [40, 41]. *Reovirus* has three serotypes including T1, T2, and T3 and its infection is usually mild or subclinical, so it does not cause significant disease in humans [42, 43]. *Reovirus* entrance is through the respiratory or fecal–oral route and one of its replication sites is the intestinal epithelium [44]. Recent studies have considered reoviruses to be an environmental modifier for CD development. In a study conducted by Bouziat et al., it has been suggested that this seemingly harmless virus can cause inappropriate immune activation and intestinal immune homeostasis disruption,

leading to gluten intolerance and CD development [45]. In another study, by infecting mice with reovirus strains, it has been reported that the T1L strain of reovirus stimulates inflammatory signals as compared to mice infected with T3D-RV (a T3D reassortant harboring the S1 and L2 genetic segments of T1L) [46]. Their data suggested that reoviral infection may trigger CD in susceptible patients.

Adenovirus and celiac disease

Adenovirus is a double-stranded DNA virus of the Adenoviridae family with a prevalence of around 14% in young children under the age of three. Infection with adenovirus is associated with respiratory (usually) or gastrointestinal (occasionally) problems and many patients are asymptomatic and their infections are self-limiting [47, 48]. Adenoviruses are transmitted via fecal–oral route, respiratory droplets,

touching contaminated surfaces, etc. There are more than 50 different adenoviral serotypes in humans (Human adenovirus 1–57; HAdV-1 to HAdV-57), divided into seven different species (Human adenovirus A, B, C, D, E, F, and G) [49, 50]. Some adenovirus serotypes, such as HAdV-40 and HAdV-41, are linked to gastroenteritis in children [51]. Studies also have identified infection with *Adenovirus* type 12 (Ad12), which is commonly isolated from the intestine, as a trigger for CD development [52]. In this regard, it has been reported that there is a molecular mimicry between alpha-gliadin protein and the early region E1b protein of human Ad12 [53]. Moreover, a significant increase in the anti-Ad12 antibody titers was observed among CD patients relative to controls [53, 54]. Lähdeaho et al. also showed higher IgG antibody levels against nonhomologous Ad40 E1b peptide in celiac and dermatitis herpetiformis patients in comparison with controls [55]. However, later studies did not confirm the role of adenovirus in increasing the risk of CD. For instance, Mahon et al. performed a PCR method for finding adenovirus 12 DNA encoding the E1B-58 kDa in small intestinal biopsy samples of patients with CD, ruling out the link between persistent adenovirus 12 infection and CD pathogenesis [56]. Tarish et al. also found that the level of anti-adenovirus IgG did not increase in CD patients and was not correlated with IFN- α level in their studied subjects. Accordingly, they concluded that CD may not be caused by past adenovirus infection [57].

Enterovirus and celiac disease

Enterovirus is a single-stranded positive-sense RNA virus of the Picornaviridae family known as a major cause of human infectious illnesses. It mainly affects individuals younger than 20 years, especially infants and children under 4 years [58]. *Enterovirus* includes ten species of enteroviruses (A to J) and three rhinovirus species (A to C) [59]. Enteroviruses are frequently found in an infected person's respiratory secretions and stool and are spread through fecal–oral and respiratory routes or contaminated objects [59]. *Enterovirus* infection clinical outcomes vary from mild respiratory sickness to myocarditis and severe neonatal sepsis-like disease [60]. Studies linked Enterovirus A and B infection to CD development [61]. For instance, Lindfors et al. in their metagenomic study showed that repeated exposure to enterovirus along with higher gluten consumption increased the risk of CD autoimmunity in genetically susceptible children between 1 and 2 years of age [62]. Kahrs et al. also in their longitudinal study reported an association between a higher prevalence of *enterovirus* during early childhood and later onset of CD [61]. Likewise, a recent study conducted by Oikarinen et al. suggested that enterovirus infection may trigger subsequent intolerance to gluten and is associated

with CD development [63]. It is noteworthy that an association between enterovirus infection during pregnancy and subsequent CD development in childhood has not been proven [64].

It has been explained that enterovirus infection is associated with lower Foxp3 expression in Tregs (as an important factor for Tregs development) along with increased Th1 immunity results in autoimmune response induction [65].

Moreover, Chen et al. study showed that the frequencies of Th17 cells (which are important in CD pathogenesis) were significantly increased in peripheral blood samples of children infected with enterovirus relative to controls and suggested that the Th17 lineage may be considered an important mediator during this viral infection [66]. Decreased activation of CCL22 (C–C Motif Chemokine Ligand 22), which is associated with Th2 deviation, is also reported in enterovirus infection [65].

Rhinovirus and celiac disease

Rhinovirus is another single-stranded positive-sense RNA virus of the Picornaviridae family that belongs to the Enterovirus genus [67]. *Rhinovirus* is divided into three categories (RV-A, B, and C) based on their surface glycoproteins and its infection is known as the most important cause of the common colds in children and adults [68]. *Rhinovirus* transmission occurs by aerosol routes or direct contact [69, 70]. It is known that rhinoviruses replicate in the respiratory tract at relatively low temperatures and due to the high temperature of the gastrointestinal tract and the presence of gastric acid in that area, they do not have the ability to replicate there [71]. However, there is evidence suggesting that many viral respiratory infections can cause gastrointestinal symptoms in children [72]. In this regard, Simre et al. found that rhinoviruses were slightly more common in nasal swab samples of children with CD than controls, but not in their fecal samples. Based on the possibility of certain rhinovirus species, such as species C, replicating at higher temperatures and the expression of main *rhinovirus* receptor intercellular adhesion molecules-1 (ICAM-1) in the intestinal mucosa in CD, they suggested that rhinovirus infection by increasing the expression of ICAM-1 can cause leukocyte (including gluten-specific T cells) migration toward infection site, thus triggering an immune response to gluten leads to CD [73]. Ruotula et al. showed that rhinovirus infection in infants before the age of one year is associated with increased Foxp3 expression in Treg cells and decreased Th1- and Th2-related cytokines, which suggested upregulation of immunoregulatory mechanisms after rhinovirus infection [65].

Astrovirus and celiac disease

Astrovirus is a positive-sense, single-stranded RNA virus (like the Picornaviridae) of the Astroviridae family [74]. Human astroviruses are classified into eight serotypes and infection with this virus generally causes acute gastroenteritis most commonly in children (usually under 2 years), which is self-limited and is accompanied by watery diarrhea, nausea, fever, anorexia, etc. [75–77]. In a study conducted by Mousavi Nasab et al. in 2020, human astrovirus was the most frequently detected virus in Iranian children with gastrointestinal infections [78]. In another study by Sayed Othma et al. in 2022, astrovirus was among the most frequently identified viruses in the stool samples of children with gastroenteritis, which was mostly reported in warm weather [79]. *Astrovirus* is transmitted fecal–orally and through contaminated food, water, and surfaces [80]. Interestingly, Smits et al. using (real-time) PCR method found a strain closely related to *Astrovirus* VA1 in the stool of a 4-year-old male with new onset CD [81].

Hepatitis viruses and celiac disease

Liver disorders, such as autoimmune liver disease, viral hepatitis, and nonalcoholic fatty liver disease (NAFLD), are known as CD-associated disorders [82]. There are five major hepatitis viruses (A, B, C, D, and E), each of which is in a distinct viral family that affects the liver and causes inflammation. HAV and HEV are spread through the fecal–oral route and can cause acute infections that are generally cleared by the host immune system [83]. HBV (transmitted through sexual activity, contaminated injecting equipment sharing, etc.) and HCV (transmitted through blood products) are known as the major causes of chronic hepatitis that can progress to hepatocellular carcinoma [83]. HDV, which is transmitted through contact with contaminated blood or other body fluids, is dependent on HBV infection for replication and can cause acute or chronic liver disease [83]. It has been hypothesized that HCV and HBV may be associated with gluten intolerance and the development of CD [84].

Hepatitis B (HBV) is a double-stranded DNA virus and a member of the Hepadnaviridae family [85]. There are little data about the link between HBV infection and CD and their relationship seems to be controversial. Previous studies pointed out a lower HBV vaccination response in CD patients than in the general population [86–89]. This unresponsiveness to HBV vaccination can be linked to HLA molecules, including HLA-B8, DR3, and DQ2 homozygotes and defects in their normal immune response [88, 89]. According to the Noh et al. study, unresponsiveness to the HBV vaccine was observed among adults who were HLA-DQ2 positive

(homozygous or heterozygous) [89]. On the contrary, Nemes et al. and Ertem et al. found similar seroconversion after hepatitis B vaccination in patients who were vaccinated after adherence to the dietary treatment and healthy controls [90, 91]. Ertekin et al. also found significantly higher anti-HB titers in CD patients under GFD than in CD subjects without GFD adherence [92]. These studies suggested the effect of patients' gluten intake at the time of vaccination on the vaccine-induced immune response [93]. These hypotheses are still debated and due to the representation of serious problems following hepatitis B vaccination unresponsiveness, new vaccination strategies like the use of boosters and/or higher doses of HBV vaccine were proposed for this group of patients [93].

Hepatitis C (HCV) is a positive-strand RNA virus belonging to the Flaviviridae family [94]. The presence of the HLA-DQ2 haplotype in subjects with HCV can be considered an effective factor in CD and HCV co-occurrence [95]. Furthermore, interferon therapy, particularly with IFN- α , is a recognized therapeutic strategy for chronic HCV infection. However, this treatment can potentially induce or exacerbate autoimmune disorders and has been implicated in the onset of CD [95]. This phenomenon is attributed to an imbalance in Th1/Th2 cell responses, which is crucial for the activation of CD and can be triggered by IFN- α [96].

Marconcini et al. in their retrospective study reported a higher prevalence of anti-gliadin antibodies among HCV subjects related to controls, which was not statistically significant [97]. Ruggeri et al. also observed positive anti-endomysial antibodies (AEA) in 2% of HCV patients (who had positive tTG antibody results) [98]. However, some studies denied the association between these two diseases or the increased prevalence of CD in patients with HCV. For instance, in their study on a group of CD patients with HCV, Garg et al. found that while these two disorders can occur simultaneously, they are not causally linked [95]. Garbovan et al. in their study concluded that the prevalence of CD in chronic HCV patients has decreased over time [99]. Hernandez et al. study also did not show an increased incidence of CD in patients with HCV infection [100].

Coronavirus disease and celiac disease

Coronavirus disease (COVID-19) is a positive-sense single-stranded RNA virus of Coronaviridae family [101]. Coronavirus causes mild to fatal respiratory tract infections and also can infect the gastrointestinal tract through angiotensin-converting enzyme 2 (ACE2) receptor [102]. ACE2 is a receptor that is expressed on pneumocytes and other cells like absorptive enterocytes and its expression is reduced following villous atrophy, which happens in CD [103]. It affects both children and adults, but its clinical symptoms

are milder in children [104]. *COVID-19* modes of transmission include airborne, respiratory droplets, and fecal–oral routes [105]. Lebwohl et al. in their cohort study conducted in Sweden showed that there was no significant increase in the risk of severe disease outcomes, hospitalization, or death attributed to *COVID-19* in CD patients [106]. Asri et al. also in their study compared CD and *COVID-19* patients and concluded that the high level of anti-inflammatory mediators in active CD patients may protect them from developing severe *COVID-19* [13]. In their questionnaire-based study conducted via telephone and email with 101 CeD patients in Turkey, Gokden et al. found that patients on a gluten-free diet did not face any additional risk of *COVID-19* susceptibility compared to the non-CD population [107]. A small cohort study conducted by Italian researchers on 21 patients with refractory celiac disease (who have persistent or recurrent symptoms despite strict GFD adherence for more than 12 months) reported no cases of *COVID-19* among them [108]. An interesting hypothesis in this regard is the protective role of HLA-DQ2/DQ8 haplotype (as CD predisposing factors) against *COVID-19* infection [109]. On the contrary, the role of *COVID-19* in disrupting gut integrity has been suggested as an effective factor in the development of celiac disease [110]. Cakir et al. found that the pandemic *COVID-19* period is associated with an increased number of CD patients per year [110]. Similarly, Trovato et al. reported that previous *COVID-19* exposure may lead to the development of celiac disease in genetically predisposed subjects [111].

Norovirus and celiac disease

Norovirus has a single-stranded positive-sense RNA and belongs to the Caliciviridae family [112]. It is a highly contagious virus, transmitted through direct person-to-person contact, contaminated food, surfaces, etc. [113]. *Norovirus* is distributed throughout the small intestine and is known as one of the most common causes of gastroenteritis [114]. Its human strain is classified into three genogroups (GI, GII, and GIV) and can infect all age groups, but older people and immunocompromised patients have high risks of a severe form of the infection [115–117]. Although previous studies did not evaluate the potential association between the norovirus and CD, some studies reported its accompanance with enteropathy [118]. Woodward et al. detected norovirus in fecal samples of common variable immunodeficiency (CVID) patients with malabsorption, who had duodenal villous atrophy [119]. It has also been reported that norovirus can break oral tolerance and promote pro-inflammatory T cell responses to dietary antigens in murine models resulting in food intolerance [120]. However, Simre and co-workers in their prospective study on stool and nasal swab samples of children with CD (before the diagnosis)

and their matched controls, showed no marked difference in terms of infection with viruses like norovirus between their studied groups [73].

Herpesvirus and celiac disease

The Herpesviridae family consists of large double-stranded DNA viruses that cause various diseases in humans and animals [121]. This family is divided into three subfamilies: Alphaherpesvirinae, Betaherpesvirinae, and Gammaherpesvirinae. Alphaherpesvirinae includes herpes simplex virus (HSV)-1 (HHV-1), HSV-2 (HHV-2), and varicella-zoster virus (VZV or HHV-3). Betaherpesvirinae features human cytomegalovirus (HCMV or HHV-5) and human herpesviruses 6A, 6B (HHV-6A, HHV-6B), and 7 (HHV-7). The Gammaherpesvirinae subfamily comprises Epstein–Barr virus (EBV or HHV-4) and Kaposi’s sarcoma-associated herpesvirus (KSHV or HHV-8) [122]. Cytomegalovirus and herpes simplex virus are the two main herpesviruses that can cause ulcerative disease in the gastrointestinal tract. While this disease can affect healthy individuals, it is more prevalent and severe in immunocompromised patients [123]. Research involving animal models has demonstrated an association between infections caused by gastric herpesviruses and the symptoms of functional gastrointestinal disorders (FGIDs). Furthermore, herpesviruses are posited to contribute to the development of fibromyalgia (FM), a chronic pain condition frequently observed in conjunction with FGIDs [124]. Human herpesviruses rank among the most prevalent infectious agents in the gastrointestinal tract and have been implicated in oncogenesis as well as a range of gastrointestinal disorders [125].

Clinical observations indicate a heightened risk of herpesviruses in patients with CD, although comprehensive studies are sparse [126]. Chatterjee et al. [127] investigated the risk of herpes zoster (HZ) in adults with CD, focusing on those aged under and over 50. A retrospective cohort design was used, analyzing data from patients with CD and matched controls over ten years. Results indicate no significant increase in HZ risk for those under 50, while those aged 50 and above showed a modestly higher risk. The findings suggest that routine early vaccination for HZ in CD patients is not warranted, recommending vaccination starting at age 50 instead. Ludvigsson et al. [128] investigated the association between CD and an increased risk of HZ. Analyzing data from 29,064 CD patients and 144,342 matched controls in Sweden, researchers found that 0.53% of CD patients developed HZ compared to 0.35% of controls. The hazard ratio indicated a 1.62-fold increased risk of HZ in CD patients, particularly notable in those aged 60 and older. Overall, CD was linked to a higher risk of HZ, although the absolute risk remains low.

A study involving 21 patients found that tissue transglutaminase antibody levels increased in two patients (9.5%) during CMV infection, while no such increase was observed in control patients who tested negative for CMV via PCR and IgG [129]. Jansen et al. examined the relationship between CMV and TG2A in 4,420 children, revealing that those with extremely high TG2A levels (ten times the normal range) were less frequently infected with CMV, suggesting a potential protective effect.

A 24-year-old woman presented with severe symptoms including watery diarrhea, weight loss, and electrolyte imbalances. Diagnostic tests revealed celiac disease, characterized by flat mucosa and increased intraepithelial lymphocytes, alongside HSV esophagitis. This case is notable for the acute presentation of celiac crisis, likely triggered by her HSV infection, which led to life-threatening malnutrition [130].

While emerging studies indicate a potential link between herpesviruses and celiac disease, further research is necessary to clarify the nature of this association and its implications for clinical management and treatment strategies.

Preventable viral infections by vaccination

Vaccine effectiveness in the general population has demonstrated high efficacy in both clinical trials and real-world settings, as evidenced by various statistical models [131]. Chodick et al. [132] reported a lower vaccine effectiveness in immunosuppressed patients, with rates of 71% compared to 90% in the general population. While the importance of vaccinations in the prevention of infectious diseases is well established, the immunogenicity of vaccines in individuals with CD remains uncertain [131].

Most studies examining the efficacy and immunogenicity of vaccines in individuals with CD have predominantly focused on the immunological response to the HBV vaccine, with limited data available regarding other vaccinations [133]. A meta-analysis published in 2015 showed that patients with CD have a statistically significant lower rate of protective HBsAb titer compared to non-affected controls [134]. These data were confirmed by similar results found in other studies [90, 135–137]. Consequently, a large number of patients with CD may be nonresponders to HBV vaccination [133]. However, Zingone et al. [138] assessed HBsAg and HBsAb titers in three groups of 163 celiac disease (CD) patients—group A (57 gluten-exposed), group B (46 gluten-free), and group C (60 infants)—along with 48 healthy controls (group D). The study found that all CD patient groups exhibited an inadequate response to hepatitis B vaccination compared to controls.

Sari et al. [139] investigated the immunogenicity of the inactivated HAV vaccine in 33 children with CD compared to a sex- and age-matched control group of 66 healthy children. They evaluated seroconversion rates at 1 and 7 months postvaccination and found that the immune responses were comparable, with nonresponder rates of 21.2% for CD patients and 22.6% for controls after 1 month, and 3% vs. 1.6% after 7 months. In contrast, a study by Urganci et al. [140] involving 16 pediatric CD patients showed a significantly lower immunological response compared to 50 healthy controls over a 7-year follow-up, with nonresponder rates of 75% versus 100%.

Vaarala et al. [141] conducted a nationwide cohort study to investigate the impact of rotavirus vaccination on the risk of CD in Finnish children born between 2009 and 2010. By comparing vaccinated and unvaccinated children, the researchers aimed to assess whether vaccination influences the incidence of this autoimmune condition. The study found no significant difference in the risk of CD between the two groups during a follow-up period of 4–6 years. These findings indicate that oral rotavirus vaccination is safe for individuals at risk for CD. Moreover, Hemming-Harlow et al. reported that *rotavirus* vaccination can reduce CD autoimmunity risk in childhood and adolescence [142].

Studies investigating the immune response to COVID-19 vaccines among patients with CD who received viral vector or mRNA formulations have indicated that the humoral responses targeting the spike protein of SARS-CoV-2 are comparable to those observed in healthy controls [143, 144]. In this regard a retrospective cohort study assessed the effectiveness of the BNT162b2 mRNA COVID-19 vaccine in preventing SARS-CoV-2 infection in patients with CD. The study involved 5,381 vaccinated CD patients and 14,939 matched controls. The analysis revealed no significant difference in the risk of breakthrough infections between the two groups. These findings indicate that COVID-19 vaccination is effective for patients with CD, showing effectiveness similar to that of the general population [145].

In summary, while vaccination is critical in preventing infectious diseases, the varied immune responses observed among patients with CD highlight the necessity for further research to determine the immunogenicity of vaccines beyond HBV, ensuring optimal protection for this population.

Conclusion

In the present study, we tried to discuss current information on the association between CD and various viral infections. The high susceptibility of CD patients to several serious infections underscores the importance of such studies. Although

strict adherence to a gluten-free diet is usually helpful for improving CD patients' symptoms, some subjects do not respond completely to the diet, that sometimes need immunosuppressive therapy to relieve their complications. Given that different viral infections can trigger or worsen gastrointestinal symptoms in these patients, our study serves as a catalyst for the healthcare system to focus more on assessing the viral infection history of CD patients (particularly those who do not respond to the gluten-free diet). This enhances the search for effective preventive strategies and promotes patient education regarding important risk factors. Adopting appropriate treatment for suspected viral infections may allow physicians to minimize the virus's impact on disease outcomes. Moreover, further research on the possible role of unstudied/less studied viruses in CD pathogenesis might guide future approaches to prevention.

Acknowledgements This study was supported by the Celiac Disease and Gluten-Related Disorders Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Author contributions N.A. and M.R.N. were involved in conceptualization. Investigation was done by N.A. and S.M. M.R.N. and S.R.M. helped in project administration. Supervision was done by M.R.N. M.J. helped in visualization. N.A., S.M., and M.J. contributed to writing—original draft. M.R.N. and M.R.T. contributed to writing—review and editing.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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