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REVIEW

Viruses and celiac disease: what do we know ?

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Abstract
The aim of this review is to provide a comprehensive overview about the link between viruses and celiac disease. A systematic search on PubMed, Embase, and Scopus was conducted on March 07, 2023. The reviewers independently selected the articles and chose which articles to include. The review is a textual systemic review, and all relevant articles were included based on title and abstract. If there was a disagreement between the reviewers, they came to a consensus during deliberation sessions. A total of 178 articles were selected for the review and read in full; only part of them was retained. We found studies between celiac disease and 12 different viruses. Some of the studies were done only on small groups. Most studies were on pediatric population. Evidence for an association was found with several viruses (trigger or protective). It seems that only a part of the viruses could induce the disease. Several points are important to keep in mind: firstly, simple mimicry or that the virus induces a high level of TGA is not sufficient to promote the disease. Secondly, inflammatory background is necessary to induce CD with virus. Thirdly, IFN type 1 seems to have an important role. Some of the viruses are potential or known triggers like enteroviruses, rotaviruses, reoviruses, and influenza. Further studies are needed to better understand the role of viruses in celiac disease to better treat and prevent the disease.

Keywords Virus · Coeliac · Celiac · Gluten

Introduction

Celiac disease (CD) is one of the most prevalent digestive diseases, affecting 1% of the population [1]. CD is a complex autoimmune disease caused by the loss of oral tolerance to gluten in patients with genetic susceptibility, expressing the human leukocyte antigen DQ2 or DQ8 [2]. Since the 1950s, the general pathogenesis of CD has been more and more understood. However, the exact pathogenesis is not understood. Celiac disease causes an inappropriate adaptive immune response to gluten-derived peptides. It causes an intestinal inflammation with an increase in IFN-γ which is associated with a TH1 response [3]. Research indicates that a single trigger is not sufficient to trigger the disease, but several factors are needed [4]. Many studies have tried to identify environmental factors and triggers, including infections, antibiotics, the season of birth, microbiome, age of gluten introduction, breastfeeding, vaccinations, diet [5–7], and more. Understanding the exact mechanisms and identifying all the possible triggers can help in prevention and early disease diagnosis. Viruses are already known to be implicated in autoimmune disease [8, 9]. Considering that, research has also progressed in understanding the relationship between CD and viruses, which might be potential triggers [10]. Except for the reovirus [11], there is no pathogenesis relationship directly proved between coeliac and viruses, but there are several facts that let us think that the reovirus is not the only virus involved in the disease. For example, gliadin, a part of the gluten protein [12], can have a role in the disease. A-gliadin 31–43, an undigested gliadin peptide, is considered the main peptide responsible for the innate immune response in celiac disease patients [13]. It mimics and enhances the innate immune response to viruses, interferes with endocytic trafficking, and activates the IFN-α pathway in patients with CD. This peptide cooperates with a viral ligand to activate the TLR7 pathway in the intestine, similar to the viral ligand LOX [14]. However, simple mimicry is not sufficient to explain the pathogenesis of the CD, which also needs an activator [1]. Another article

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summarizes how HLA-DQ2/8 could orchestrate a CD4 + T cell response against gluten; they showed that IFN-α and IL-15 are upregulated (with a virus as possible inducer) and may precipitate a pro-inflammatory Th1 response and finally promote the emergence of autoimmune disease [3]. The pro-inflammatory environment can be exogenous, such as food and viruses. Low-grade inflammation of the CD epithelium is present even before intestinal damage [15]. One of the factors that also could play a role is the adenosine deaminase acting on RNA 1 (ADAR1). This RNA editing enzyme is important to prevent self-RNAs or viral RNAs from triggering auto-inflammatory responses, most notably the type I IFN production pathway. Reduced expression of ADAR1 was seen in untreated CD. Downregulation of ADAR1 could also triggers unwanted inflammation [16]. Another link between viruses and CD is the anti-transglutaminase antibodies (TGAs). Transglutaminase 2 (TG2) catalyzes transamidation reaction. More and more viral and cellular proteins with which virus interact have been found to be modified by TG2, suggesting a novel function for TG2 in viral pathogenesis [17]. More than that, a study analyzed the level of TGA in non-celiac children suffering from infectious diseases (several virus antibodies were checked). They showed that high anti-transglutaminase could be found in children without CD suffering from infectious disease and may trigger the CD [18]. However, in this article, the TGA was not checked before, and maybe the children were TGA positive before the infection.

In the last years, a lot of research has been done to understand the pathogenesis of the CD and to understand the role of viruses in the disease. In this review, we summarize the knowledge about the relation between CD and viruses and discuss each virus separately for a clearer understanding. We include pathophysiological, epidemiological, and clinical data. We then conclude and advise further research.

Search method

This review was based on a comprehensive literature search at PubMed using the MeSH terms: ((CELIAC OR COELIAC OR GLUTEN) AND VIRUS). The same terms were used in Embase and Scopus.

The search was carried out on March 07, 2023, and 611 articles were selected in PubMed. The reviewers chose only the articles from the last ten years to specifically discuss the latest findings, and 320 articles were selected. In Embase, 828 articles were found, and in Scopus, 1638 articles were found. If relevant, studies performed on animals were included. The reviewers independently decided which articles to select based on the title and abstract. They debated on articles not selected by all reviewers. They finally chose to read the full 178 articles. They systematically checked the references to include significant references from other data sources. Some of the articles that they added were published more than ten years before.

Limitations

There are several limitations in this review. First, the reviewers selected only the articles in English. Second, the search was performed on PubMed, Scopus, and Embase but not on other databases such as Google Scholar or Web of Science.

Third, most of the studies were done on few patients, usually on children.

Forth, the reviewers decided to not include all articles with the same conclusion (for example, the hepatitis B vaccine in patients with CD).

Five, the search in Embase and Scopus was sorted by best match. Only the 400 first articles of those databases were checked (articles after 400 were not relevant based only on title, not abstract). Six, except for the relevant article found in the references, the reviewer included only the articles published in the last ten years.

Results

Cytomegalovirus [CMV]

A study conducted on 21 patients showed that TGA was rises in two patients (9.5%) during infection of CMV but was not found in patient control (PCR and IgG negative) for CMV [19]. Jansen et al. studied the relationship between CMV and TG2A on 4420 children. They showed that patients with very high TG2A (10 times the normal range) were less often infected than other patients by CMV [20], showing a putative protective effect. However, the immune system is not completely mature at this age (at age of 6), and this relationship must be taken with caution. The Generation R study is a prospective, population-based cohort study from fetal life through early adulthood. It was designed to identify early environmental and genetic causes of normal and abnormal growth, development, and health [21]. Interestingly, a study conducted on 1068 patients of the Generation R showed alterations in Vδ1 + and CD57 T cells, which were present with subclinical CD. Indeed, if the CMV serology was negative, there were almost two-fold fewer Vδ1 + and 2.7 fold more CD57 + cells than in the control. Considering that CMV promotes Vδ1 + and that there is an inverse association between subclinical CD and Vδ1 + in the blood [22], it is possible that CMV is protective against CD. However, because the molecules that activate the Vδ1 + and CD57 + cells are unknown, a direct link cannot be established. Moreover, several cofounders can explain this association, such as HIV [23]. It is also interesting to notice that both CMV and CD are related to poor

socioeconomic status [24]. However, this may only reflect a diverse viral and microbial exposure [25]. A study on 80 gastrointestinal biopsies did not find nucleic acids for CMV [26]. In a study based on sera from 297 healthy subjects and 90 patients diagnosed with CD, a higher prevalence of positive serologies was found in the control group (67.7 vs. 54.4%, $P < 0.01$), that may reflect a protective effect [27]. In summary, the connection of CMV to CD is not clear. Small studies based on CMV serology and diagnostic of CD do not support a link between them. Conversely, larger studies based on TG2A and Vδ1 + tend to show a protective effect of CMV.

Epstein–barr virus [EBV]

The same study that we reported earlier about TGA and CMV also showed that the TGA is inversely associated with combined infection of EBV with CMV and seems to protect against CD [20]. However, it could very well be that CMV alone may protect against CD. Conversely, EBV may aggravate a simple CD to a refractory disease. In an article [28] that is based on PCR of duodenal biopsy of 17 patients, EBV was found in 70% of patients with the refractory disease compared to only 16% in usual CD. Supposedly, EBV may re-instruct activation of pro-inflammatory cells and not allow the epithelium to recover. It was also shown that TGA could develop during EBV infection (in 25% of the 20 patients) [19] and cause a possible increase in the risk to develop CD. A study on 80 gastrointestinal biopsies find nucleic acids of EBV in 8/40 of CD patients' mucosa and only 4 of control group samples [26], but considering the low percentage, it is not possible to conclude that EBV triggers the disease. The study cited earlier based on 387 sera also showed a high prevalence of IgM antibodies against EBV but a lower prevalence of IgG antibodies in the CD group. The anti-EBV nuclear antigen IgG was higher in healthy controls (77.8 vs. 90.2%) and anti-EBV capsid antigen IgG (78.9 vs. 88.9%) [27]. The place of EBV is not clear. It may be a cause of CD (suppressed if there is CMV) or protective, but the studies done are only on a few patients. The EBV may play a role in patients in refractory CD without triggering it.

Enterovirus

A study in a birth cohort of 41 children showed a potential link between enterovirus and CD. In this study, enterovirus infection was checked based on viral seroconversion after a proven CD biopsy [29]. This link is also supported by other studies based on stool exposition to the virus, one based on 220 children [30] and the other on 83 children [31]. Sarmiento et al. showed that transglutaminase could develop during infection of several viruses, and TGA was highest during infection, especially with echovirus 16. The enterovirus might cause inflammation in the small intestine and upregulate tissue TGA in inflamed sites [19]. Another fact that possibly links enterovirus and CD is zonulin, which is a tight junction regulator. Zonulin is higher in CD patients and correlates with the density of enterovirus in the small bowel mucosa of CD patients with severe atrophic changes [32]. Interestingly, enterovirus is possibly associated with parechovirus to cause CD [33]. Research shows that to lower the risk of CD, we should introduce a gluten-free diet for preventive purposes in subjects genetically at-risk during enterovirus infection [4]. A case–control study on 29 children (3 to 6 months old) based on swabs or stool samples and blood samples at CD diagnostic was performed. The study did not support a causal link between enterovirus and CD [34]. Recently, an analysis performed on 2005 stool samples found 222 stools samples positive for parechovirus. Viruses were detected by PCR in monthly stool samples (collected from 3 through 3 years of age). TGA was retrospectively tested in blood sample taken earlier. It showed a higher frequency of parechovirus before developing TG2 antibodies, mainly if the parechovirus was associated with enterovirus. They conclude that parechovirus infections are associated with the development of CD in genetically at-risk children [33]. In conclusion, there seems to be a link between enterovirus and CD as triggers. Several studies based on seroconversion or stool samples support this link. More than that, a higher TGA and zonulin and gluten-free diet during infection can support a pathophysiologic phenomenon.

Hepatitis A virus [HAV]

There are two publications on the efficacity of the HAV vaccination in CD patients. Both were done in the same country, but the two conclusions are contradictory. The first checked 95 patients and concluded that there is no difference between the general population and CD. But the P was over 0.05 [35]. The second one, which studied the response on 80 patients, concluded that the response is lower in CD patients [36].

Hepatitis B virus [HBV]

A meta-analysis of 1447 participants was done about the failure of the HBV vaccination in celiac disease patients. A lower percentage of responders was found in the CD group [37]. It seems that genetic background is a crucial factor. A particular combination of functional IFN—single nucleotide polymorphism may be associated [38]. It is probably not the only cause as gluten itself may play a role [39, 40]. Recently, it was shown that adherence to a gluten-free diet does not influence the HBsAb concentration in patients with CD [41]. Based on these data, it has been recommended to implement new vaccination strategies, for example, controls to all new CD diagnoses [42–44]. Some suggest using the

high-mobility group box 1, a protein that acts as an architectural chromatin-binding factor, to evaluate an immune impairment, leading to HBV vaccination failure [45]. One article suggests that the lack of response to the vaccination may predict autoimmune disease later in the patient's life. They recommended carefully following those patients and advise that more research is needed to verify the existence of potential IL-18 and IFN-γ gene polymorphisms to utilize as biomarkers of latent autoimmunity [46]. A small study on 60 patients also supports that HBV can cause CD, but it may be a consequence of the treatment by INF -α and not because of the virus itself [47]. A cross-sectional study did not show an increased risk of HBV infection in CD patients [48]. In summary, 5 to 10% of patients with CD do not respond to the HBV vaccine. Non-responsiveness to the vaccine can possibly be predictive of future autoimmune diseases. HBV may be a trigger.

Hepatitis C virus [HCV]

It is known that TGA can be higher during the infection of HCV [19]. Indeed, HCV is associated with autoimmune diseases [49]. Moreover, CD is at least twice as common in cirrhotic patients [50]. In this article, they reviewed the prevalence of CD markers in patients with cirrhosis. They also showed that gluten-free diet improves liver tests in HCV patients. Another study [51] showed that patients with TGA before starting treatment for HCV with interferon were more susceptible to developing CD during the treatment. An interferon-free therapy or gluten-free based can be considered if the TGA is positive before beginning the treatment. However, because of the lack of a link between the two diseases, the screening of CD cannot be recommended [52]. Several studies have failed to find a relationship between HCV or polyethylene glycol Interferon-α and CD. For example, a study based on a proven liver biopsy of 210 patients with HCV and serological markers [53] did not show a clear link. A retrospective study based on 245 patients with CD suggests that the lack of normalization of one or both aminotransferases after one year of gluten-free diet in CD patients may indicate the coexistence of liver disease, including HCV [54]. Research about the relationship between CD and HCV in transcriptional regulatory networks revealed a selected combination of genes covering a wide range of functions triggering the inflammation like NFKB1, STAT3, IRF1, interleukin, or chemokines [55]. They compared 321 genes of CD and 1032 genes of HCV to find a common pathway. Based on computer data, 11 transcription factors were identified as hallmark molecules. In summary, the link between HCV and CD is not well established. Studies are contradictory, but it seems that the HCV (or the Interferon) plays a role in the development of CD in patients with a positive serological marker.

Hepatitis D virus [HDV]

A study made on 52 cirrhotic patients and 44 non-cirrhotic patients infected with HDV [56]. TTG IgA was positive in two cirrhotic groups and one non-cirrhotic group. TTG IgG among was positive for three patients with delta hepatitis-related cirrhosis. No patients had positivity for TTG IgG in the non-cirrhotic group. Two cirrhotic patients had histopathologically confirmed CD. They conclude that celiac seromarkers may increase the rate of early identification of advanced cirrhosis. TTG in high-risk populations can identify individuals in the earliest stages of infection. Based on that study, the rate of CD patients with TTG IgG and cirrhosis with HDV seems to be higher, but the HBV may also be a trigger of CD and it seems that the CD is more prevalent in patients with cirrhosis [50]. A study on more patients to confirm those finding is needed.

Influenza

A positive association between influenza and CD was found in a significant retrospective study on 2.6 million people in Norway. It seems that suffering from influenza increases the risk of later CD, but this causality should be carefully examined because of confounders and bias [57]. Patients affected by CD seem to be more at risk of being admitted to the hospital because of influenza. [58]. The link between severe flu and CD may be explained because the interaction between osteopontin and CD103 leads to an autoimmune disease [59]. Indeed, osteopontin is a complex cytokine and adhesion protein commonly found in extracellular matrix molecules. Its production has been associated with several pathological conditions, including autoimmune diseases and CD [60]. It is also known that osteopontin has been shown to exacerbate pulmonary damage during a flu. This supposedly shows that patients with CD may have a more severe flu due to the interaction between osteopontin and CD103 because this can finally reduce the CD8 T cell response. In a study on 22,521 patients, the vaccine against the flu was compared to saline or vaccine without adjuvant. The vaccine did not seem to be related to CD [61]. A prospective study on vaccination against influenza among 14 children with CD and age-matched healthy controls showed that the protective antibody titers are comparable to the two groups [62]. In summary, the influenza virus is a potential cause of CD.

Norovirus

Noroviruses are single-stranded RNA viruses that infect host organisms via the fecal–oral route and are a leading cause of gastroenteritis in the USA [63]. Bouziat et al. showed that the acute CW3 VP1 strain of murine norovirus induces TH1 immunity to dietary antigens. The loss of tolerance

to dietary is mediated by the dendritic cell (especially the 103 + CD11b- CD8 α +, which takes most of the dietary OVA). These dendritic cells are activated and begin a TH1 response to dietary antigen [64]. Based on an earlier article [11], they showed that the norovirus and the reovirus T1L induce a common transcriptional signature in the mesenteric lymph nodes, which is associated with a loss of tolerance. They went further and checked the role of the interferon regulatory factor 1 (IRF1), which is upregulated in the site where the response to a dietary antigen is determined. They showed that mice with an IRF1 -/- have a skewed dendritic cell population but failed to induce activation and IL12 production in 103 + CD11b- CD8 α + dendritic cells [64].

Reovirus

The most important step of the last years was made by Bouziat et al. They used two recombinant human viruses and transgenic mice with genetic predisposition for celiac disease. The reovirus Lang strain caused CD disease but the Dearing strain did not. More precisely, they showed that the reovirus TL1 (Lang type), an asymptomatic virus, blocks the differentiation of pTregs and promotes TH1 immunity to dietary antigen at sites where responses to oral antigens are initiated. This study found an upregulation of the IRF1, which is also upregulated in the mucosa of children with CD. They also showed that mesenteric lymph node dendritic cells from T1L-infected mice failed to promote TH1 cell differentiation without IRF1 expression. To support the fact that there is a relationship between reovirus and CD, they took mice expressing the HLA-DQ8, infected it and assessed the presence of TGA2 [11]. Another study focused on the relation between reoviruses and the gut [65]. They conclude that T1L could subvert the apoptosis pathway to stimulate the inflammatory pathway, break the immunological tolerance to dietary protein, and promote pro-inflammatory phenotypes in dendritic cells. They identified the M2 gene (which encodes for an outer-capsid protein) as a potential gene that dictates intestinal pathogenesis. Brown JJ et al. explain that the reovirus can break tolerance after peroral inoculation. The reovirus T1L subverts the antiviral responses to establish prolonged infection, triggering the release of type 1 interferons and other virus response factors (not defined). This mechanism induces IRF-1 expression in lamina propria. In this inflammatory context, dendritic cells phagocytose new food antigens (such as gluten or gliadin), go to the mesenteric lymph nodes, and finally activate gluten-specific inflammatory T cells (TH1). Upregulation of type 1 interferon during T1L infection inhibits regulatory T cells and leads to expansion of TH1 immunity to gluten in the development of celiac disease [66]. In another study, 100 samples (50% CD patients) were tested to detect anti-reovirus antibodies. This study describes an association between reoviral infections and CD and an upregulation of the type 1 IFN pathway. It seems that type 1 IFN may contribute to explain the LOT in a subset of IL15-negative patients. This study also suggests that viral infections may trigger a pro-inflammatory response in the small intestinal mucosa, which leads to the break of tolerance toward oral antigens [67]. NK cells also have a role in the loss of tolerance. Indeed, depletion of NK cells impairs T1L-induced loss of tolerance to newly introduced food antigen in mice [68].

Respiratory syncytial virus [RSV]

A retrospective study in Sweden on 3835 children found an association between RSV infection and later CD. They did not look for the mechanism, but their hypothesis is lack of vitamin D, or as in several other viral infections, TGA can be produced temporarily [69]. A cohort study on 1,351,265 children (with 1195 exposed to palivizumab) examined if palivizumab treatment can increase the risk of autoimmune disease [70]. They showed an insignificant increase in the risk of CD.

Rotavirus

Previous studies showed a link between rotaviruses and CD [71–73]. VP7 is a protein of the outer layer of rotavirus. They analyzed the gene array and showed that purified anti-rotavirus VP7 antibodies modulate genes involved in apoptosis and inflammation and alter the epithelial barrier integrity in intestinal epithelial cells, all typical of CD features. In addition, a prospective study on almost 2000 children with genetic susceptibility for CD indicated that a high frequency of rotavirus infection might increase the risk of CD [74]. The molecular mimicry as a trigger of CD is not precise and still lacks evidence [75]. However, vaccinations against the rotavirus seem to be safe and may even protect against CD [76, 77].

Others virus

The link between CD and other viruses like adenovirus, HHV-6, and rhinovirus [26, 34, 78] has not been shown. It is not clear if patients with CD are more susceptible to suffer from COVID [79–83], maybe if untreated [84]. But a future outbreak of CD may be possible [85]. The immune response to the vaccine is the same than in healthy controls [86, 87]. considering the molecular pathophysiological mechanisms of SARS-CoV-2, a zonulin antagonist may be used as treatment [84]. We can notice other potential viruses: retrovirus [88], human polyomavirus 2, Enterobacteria phage mEpX1, and Enterobacteria phage mEpX2 [89]. A study based on gene signatures revealed a possible between several autoimmune diseases, including CD and several other viruses:

influenza A, human T-lymphotropic virus type 1, and herpes simplex infection [90]. Rubella may be protective: sera of anti-rubella IgG were higher in the control group (87.8% vs 94.9%) and may demonstrate a possible protective role against CD in a study on 297 healthy subjects and 90 patients [27].

Virome

The virome is the collection of all viruses that are found in or on humans. The human gut contains the most abundant viruses. Patients with CD showed a statistically significant viral dysbiosis by metagenomic analysis [31]. A study based on PCR of stool (21 pathogens including bacteria, parasites, and viruses) showed that patients with CD have significantly fewer viral and parasitic pathogens [91]. Another study on 11 healthy patients showed that gluten-free diet can lead to change in the virome. This study also showed that lower initial diversity of the human gut virome leads to a more pronounced effect of the diet on the virome [92]. Enteric viruses play a role in the homeostatic equilibrium of the microbiome [93], for example, in gut phageome. Then, the virome can also indirectly cause or protects CD. The microbiome is an important target for therapeutic potential in celiac disease [94].

Conclusion

Viruses are probably an important factor in the onset of CD, but certainly not the only one. Moreover, the frequency of clinical viral infection is not associated with an increased risk of CD [95], which emphasizes the importance to understand separately the viruses. We should keep in mind several points: first, simple mimicry or that the virus induces a high level of TGA is not sufficient to promote the disease, even with a genetic background. Second, inflammatory background is necessary to induce CD with virus. Third, IFN type 1 (including interferon α) seems to have an important role. Viral infections often induce type 1 interferon response, which can break oral tolerance and precipitate the development of CD in mice like reovirus. It may explain why treatment with interferon-α can lead to CD in humans, as we see with HBV and HCV. However, the undigested gliadin peptide P31-43 can activate the IFN-α pathway in patients with CD and may by itself promote inflammation. Moreover, intraluminal delivery of p31-43 induces morphological changes in the small intestinal mucosa of normal mice consistent with those seen in CD [96]. Fourth, reovirus (Lang type) causes a response in the intestine, which can alter the immune system selectively to bring a different immune system response against a food protein. It is interesting that rotaviruses are one of the eight genera of the Reoviridae and are considered potential triggers. Five, the role of triggers or protectors of most viruses and vaccinations is not clearly established, some of them are potential triggers like enteroviruses, rotaviruses, reoviruses, and influenza. Six, the viruses may play an indirect role in the CD by influencing the bacteria/microbiome.

There are probably several viruses that can lead to CD, and maybe several activation pathways leading to a loss of dietary tolerance. Moreover, it is well known that viruses lead to polyclonal activation [97]. All those findings may explain why the sensitivity (the symptoms) against gluten is not similar in all patients. Indeed, in some patients, the complaint is diarrhea, and in others, anemia, neurocognitive impairment [98], etc. This also allows for possibility of several supposed pathogeneses or causes.

In summary, it seems that in humans, viruses alone do not lead to CD. The combination of virus, gliadin (which can on itself lead to inflammation), and other causes of inflammation (like IFN-α) may cause CD in patients with a specific background. It would be interesting to continue research, especially on the enteroviruses, rotaviruses, reoviruses, and influenza, which have epidemic and pathogenesis support.

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Declarations

Competing interests The authors have no conflicts of interest to disclose.

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