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PERSPECTIVE

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# COVID-19 and celiac disease: A pathogenetic hypothesis for a celiac outbreak

## Abstract

**Background:** A growing body of evidence supports the intestinal trophism of SARS-CoV-2, with ciliated cells and intestinal enterocytes being target cells because of the high expression of ACE2 and TMPRSS2. Indeed, COVID-19 promotes a "cytokine storm" in the intestinal mucosa: the resulting epithelial damage leads to increased barrier permeability, allowing the passage of gliadin in the intestinal lamina.

**Methods:** Based on current literature, we hypothesize the role of COVID-19 as a potential trigger factor for celiac disease in predisposed patients.

**Conclusions:** Genetically predisposed patients could be more likely to develop celiac disease following SARS-CoV-2 infection, making COVID-19 a candidate culprit for a potential outbreak of celiac disease in the forthcoming future.

## 1 | PERSPECTIVES

The outbreak of the new coronavirus disease (COVID-19) caused by the coronavirus SARS-CoV-2, which quickly escalated to a pandemic, has changed the approach to healthcare. Lockdown and restriction measures have been advocated as potential strategies to contain the infection or, in other words, to "flatten the curve." However, the potential burden of the SARS-CoV-2 infection and the resulting disease is an open question, with no data currently available on the development of systemic disorder or on long-term consequences. We aim to highlight the potential risk of an "outbreak" of celiac disease (CD) among genetically predisposed subjects following SARS-CoV-2 infection, based on several pathogenetic mechanisms which could promote the onset of CD.

SARS-CoV-2 is a positive-sense single-stranded RNA virus with a crown-like appearance of spike proteins (S proteins) that project from the envelope. The S protein is used by the SARS-CoV-2 to invade host cells through the angiotensin-converting enzyme 2 (ACE2)[1]: cells with high expression of this enzyme are identified as target cells, and ACE2 promotes viral invasion, thus allowing the amplification and activation of inflammation at the local level. While mainly involved in the renin-angiotensin-aldosterone system (RAAS), ACE2 is expressed in many other tissues, prevalently on epithelial cells, and particularly on epithelial cells of the respiratory tract; therefore, providing a rationale for the interstitial pneumonia observed in COVID-19 patients. Finally, the use of ACE2 by the virus affects the transport of neutral amino acids, inducing a selective malabsorption of tryptophan, responsible first for dysbiosis and subsequently for COVID-19 diarrhoea.[2]

Additionally, priming of the spike protein by the serine protease TMPRSS2 is necessary for SARS-CoV-2 to invade host cells.[1] Ciliated cells and the brush border of intestinal enterocytes, especially in proximal and distal enterocytes, express ACE2 and TMPRSS2,[3] making the gut a candidate target for SARS-CoV-2 infection, also supported by direct evidence of the viral replication in intestinal epithelial cells. Infection by SARS-CoV-2 might, therefore, cause mucosal damage, resulting in increased permeability because of impairment of the intestinal barrier. This would, therefore, result in translocation of microbial components, including MAMPs (microbial-associated molecular pattern), that promote an inflammatory immune response by TLR-expressing cells of the mesentery fat (mostly macrophages and adipocytes) and in this way can reach systemic circulation.[4] These findings, therefore, strengthen the hypothesis that intestinal cells could contribute to increase viremia of SARS-CoV-2.

At the intestinal level, the chemokine profile featured in COVID-19 closely mirrors the immune response of CD and intestinal bacterial translocation,[5] with the activation of T-helper 17 lymphocytes, responsible for the production of high levels of proinflammatory cytokines—IL-17, GM-CSF, IL-21 and IL-22. Cardinale et al suggested that bacterial translocation might occur as an early consequence of the intestinal damage resulting from the COVID-19 "cytokine storm," which involves systemic endothelial dysfunction and vascular impairment mediated by IL-6.[6]

Increased intestinal permeability has been brought into play in the pathogenesis of several autoimmune diseases because this specific permeability causes abnormalities in traffic of parcels that can trigger specific autoimmune responses.[7]

The alteration of the intestinal barrier is one of the major players in the pathogenesis of CD. CD is an autoimmune systemic disorder elicited by gliadin in genetically predisposed individuals (HLA DQ2 and DQ8). Alteration of the intestinal barrier is essential to the passage of gliadin from intestinal lumen to lamina propria—transition

  

that can occur either by the passage between the barrier or by transcellular transport. This passage is the first step for the development of CD, indeed the binding of deamidated gluten proteins (DPG) to antigen-presenting cells (APC) occurs in lamina propria. More in detail, APCs express the disease-associated HLA-DQ molecules which specifically bind gluten-derived peptides modified by the enzyme tissue-transglutaminase (tTG); subsequently, the APCs present these peptides to intestinal T cells, eliciting a T response which triggers the production of antibodies and secretion of pro-inflammatory cytokines. This response mechanism results in mucosal atrophy and is involved in the clinical manifestations of CD.[8]

Differently from other autoimmune diseases, CD is the only autoimmune disease whose trigger (gluten) is known, but several other environmental co-factors implicated in its development are to date unknown.[8]

Although gluten is the main external trigger of CD, gluten ingestion does not fully explain CD pathogenesis by its own. For CD development, the immune system must be activated at the level of the lamina propria and the content of the intestinal lumen has to traverse the intestinal barrier. Tight junctions (TJs), consisting of several proteins such as claudins, occludins and junctional adhesion molecule (JAM), regulate the permeability of the intestinal epithelium.[9]

Indeed, in CD patients, TJs have discontinuities, appear dilated (saccular or fusiform), show a reduced number of strands, and destruction of pentalaminar structures is observed,[10] with marked improvements following gluten-free diet (GFD). Furthermore, increased expression of zonulin has been reported in CD patients, possibly resulting in increasing epithelial permeability following zonulin-induced rearrangement of cytoskeleton and disruption of TJs.[11] In this way, the damage occurring in the epithelial barrier of COVID-19 patients could contribute to the development of CD.[12]

During the COVID-19 pandemic, prevalence of infection in CD patients has been described in adults[13] and children[14]; new diagnostic approaches for CD have been proposed,[15] and lower diagnosis rate[16] and worse clinical status[17] have been described, but no hypothesis on the future of CD are present in literature.

In addition, based on the increased risk of β-cells autoimmunity in patients with a recently respiratory infection, as proven by the TEDDY study,[18] a connection between SARS-CoV-2 and the development of type 1 diabetes has been recently hypothesised.[19] In the same way, in the light of the altered intestinal permeability because of COVID-19 and of the activation of the overlapping cytokine pattern of CD, the presence of an upcoming peak in the incidence of celiac disease after SARS-CoV-2 infection could be hypothesised. Based on this hypothesis, COVID-19 could be considered an additional risk factor for the development of autoimmune diseases, particularly CD, in predisposed subjects. In conclusion, more studies are warranted to investigate the possible pathogenic role of SARS-CoV-2 in the development of celiac disease and its incidence in infected individuals.

## DISCLOSURES

The authors declare no conflicts of interest for the present study.

## AUTHOR CONTRIBUTIONS

CMT and SO conceived the study. CMT and NP drafted the manuscript which was then revised by SO and MM. All authors approved the final version of the manuscript.

## DATA AVAILABILITY STATEMENT

No data to share for the present Perspective paper.

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