

# COVID-19 and celiac disease: a review

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**Abstract:** The aim of this review is to broadly cover how the COVID-19 pandemic has affected individuals with celiac disease, including perceived risk, risk of contraction or severe infection, considerations regarding vaccination, access to gluten-free food during the pandemic, and possible long-term changes to the practice of celiac disease management spurred by the pandemic. While initially there was increased perceived risk about COVID-19 in the celiac disease population, studies have found that individuals with celiac disease are not at an increased risk of contracting or having a severe course compared to the general population. There is not yet evidence that COVID-19 infection will lead to an increase in celiac disease incidence, though more research on this topic with longer-term follow-up is necessary to make this determination. Limited access to in-person visits led to an increase in telemedicine, which was adopted swiftly by this patient population and may offer improved access in the long term. In summary, individuals with celiac disease do not appear to be at an increased risk of contracting COVID-19 or having a more severe disease course.

**Keywords:** Celiac Disease, COVID-19

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## Introduction

In the early days of the COVID-19 pandemic, there was urgent concern to identify risk factors for severe outcomes from infection.<sup>1</sup> As the months progressed, a greater understanding of some of these risk factors arose, including older age, diabetes, hypertension, and heart disease.<sup>2</sup> Individuals who are immunocompromised such as those with HIV or taking immunomodulatory therapy for autoimmune diseases have been shown to possibly be at increased risk of having a severe course of COVID-19.<sup>3</sup> Throughout the pandemic, investigators have sought to understand whether people with celiac disease have an increased risk of severe COVID-19 outcomes.<sup>4</sup> Beyond this question, the pandemic has brought change to the management of celiac disease; for instance, lockdowns led to the utilization of new technologies to deliver health care throughout this period. In this review of the literature, we seek to assess the manifold ways that the COVID-19 pandemic has impacted the celiac disease population. Risk of contracting COVID-19, immunity after vaccination, access to gluten-free food during the pandemic, and change in diagnostic

practices in the celiac disease population will be discussed.

## Attitudes and beliefs regarding risk of contracting COVID-19

Despite early concerns about COVID-19 impacting patients with celiac disease more than the general population, current consensus is that there is no elevated risk of developing symptomatic COVID-19 in this patient population. At the beginning of the pandemic, there was little known about the risk of contracting COVID-19. A global study by Zhen *et al.*, conducted during the months of March–June 2020, surveyed 10,737 individuals with celiac disease across 10 countries to evaluate risk and perception of risk of contracting COVID-19. Many participants reported they had poor knowledge of how celiac disease impacts COVID-19 susceptibility and stated that their information about COVID-19 primarily stemmed from the internet. This study reported that 56.1% of participants felt that they were at an increased risk or were unsure if they were at an increased risk of contracting COVID-19. Older age, male

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sex, and strict adherence to a gluten-free diet were associated with a lower perception of risk, while individuals with other comorbidities (such as heart disease and diabetes) reported having higher perception of risk.<sup>1</sup> A study in Italy conducted in March 2020 indicated that within the celiac disease population, older individuals and those with other chronic conditions were more likely to have higher perceived risk of COVID-19 infection.<sup>5</sup> It has been hypothesized that increased perceived risk led to individuals with celiac disease-related symptoms to not seek out medical care during the pandemic out of fear of contracting COVID-19.<sup>6</sup> As the early months of the pandemic progressed and physicians and patients developed a better understanding of COVID-19, a decrease in perception of risk due to celiac disease was acknowledged.<sup>1</sup>

#### **Risk of contraction of COVID-19 and risk of severe infection in patients with celiac disease**

It was hypothesized that those with autoimmune conditions, such as type 1 diabetes and celiac disease, may be at an increased risk of contracting COVID-19. In addition, there was concern that these individuals may have more severe consequences of COVID-19 infection.<sup>1</sup> Celiac disease has been associated with increased complications in certain respiratory infections such as pneumococcal pneumonia<sup>7</sup> and influenza,<sup>8</sup> as well as increased mortality due to respiratory causes.<sup>9</sup> Autoimmune conditions have different mechanisms of placing individuals at an increased risk of severe infections. One mechanism is through treatment with immunosuppressant medication; another relates to the pathophysiology of the disease that confers an increased risk of infection. Increased mucosal permeability and hyposplenism in celiac disease may be the mechanism for increased risk of pneumococcal sepsis.<sup>10</sup>

Early studies indicated that patients with autoimmune diseases who are not prescribed immunosuppressive drug regimens do not have increased susceptibility to COVID-19.<sup>4</sup> A retrospective cohort study in Italy found no significant risk of developing COVID-19 among individuals with celiac disease when compared to the general population.<sup>11</sup> A large international survey conducted in the early months of the pandemic found that individuals with celiac disease had a similar risk of contracting COVID-19 as the

general population.<sup>12</sup> Compared to the general population, individuals with celiac disease mounted a similar humoral immune response to infection.<sup>13</sup> This further supports the hypothesis that there is no increased risk of contracting COVID-19 in individuals with celiac disease.

Studies conducted prior to the availability of COVID-19 vaccines found that hospitalization rate and fatality rate were similar among individuals with celiac disease when compared to the general population.<sup>14-16</sup> A population-based study in Sweden indicated no increased risk of hospitalization for COVID-19 in patients with celiac disease compared to matched controls.<sup>15</sup> In contrast, a similar population-based study in Sweden study showed that individuals diagnosed with inflammatory bowel disease were at an increased risk of hospitalization due to COVID-19.<sup>17</sup> Initial studies in the United States did not find increased COVID-19-related morbidity or mortality for patients with celiac disease.<sup>16</sup> One study found that COVID-19 infection in patients with celiac disease was predominantly mild. One possible explanation for this is that individuals diagnosed with celiac disease are often younger than the general population.<sup>18</sup> Individuals with celiac disease likely do not need to take additional precautions beyond the recommendations for the general public.

Few studies investigated whether there are celiac disease-specific risk factors for severe COVID-19 outcomes. In an international healthcare practitioner registry of patients with celiac disease who developed COVID-19, increased age and presentation with GI symptoms were associated with greater risk of severe COVID-19.<sup>19</sup> A small study in Italy analyzed whether individuals with refractory celiac disease (characterized by villus atrophy and recurrent malabsorption even after adhering to a gluten-free diet for more than year) are at an increased incidence of severe COVID-19 infections. The study, which included 21 patients with refractory celiac disease, did not find a higher incidence of COVID-19, though larger studies need to be conducted in this subset to gain a greater understanding of their risk profile.<sup>20</sup>

In individuals with untreated celiac disease, there is a rise in pro-inflammatory cytokines associated with villus atrophy.<sup>21</sup> Nevertheless, a population-based study indicated that, among patients with celiac disease who undergo a follow-up biopsy, those with persistent villus atrophy do not have an

increased risk of severe infections compared to those with mucosal healing.<sup>22</sup> The pathogenesis of celiac disease involves antigen presentation to CD4<sup>+</sup> T cells. T cells play an integral role in response to viral infection. It has been hypothesized that there is a potential impact in antiviral response of individuals with celiac disease because HLA-DQ2 may have decreased ability to present viruses to the same degree as other class-II molecules. In contrast, one group of investigators has suggested that HLA-DQ2 and HLA-DQ8, two of the HLA haplotypes most commonly found in patients with celiac disease, may be protective against COVID-19.<sup>23</sup>

### Vaccination

Vaccination against COVID-19 has been shown to be highly effective in reducing the risk of severe infection. There was initial concern that individuals with celiac disease may not mount a strong immune response to the COVID-19 vaccine. This concern was related to prior studies indicating that children with celiac disease have decreased response to the hepatitis B vaccine. One study found that the difference in hepatitis B vaccine response was not based on adherence to a gluten-free diet, but rather was likely due to the haplotypes associated with celiac disease.<sup>24</sup> A study conducted in February 2021 indicated that almost one-quarter of individuals with celiac disease were hesitant about the COVID-19 vaccine because of vaccine-related risks due to celiac disease.<sup>25</sup> There was also initial concern that if there is a decreased response to the vaccine, then individuals with celiac disease would need COVID-19 vaccine boosters sooner than the general population. However, a study in Norway analyzing antibodies to the spike protein after receiving the COVID-19 vaccine indicated that individuals with celiac disease mounted similar humoral responses as the general population.<sup>26</sup>

### Access to gluten-free food and maintaining a gluten-free diet

As COVID-19 spread globally in early 2020, many households purchased large quantities of products with a long shelf life, greatly impacting access to certain products. In addition, there was limited access to restaurants due to severe lockdowns in many countries. This placed a particular burden on individuals with celiac disease given their dietary restrictions. Gluten-free products are often more expensive than their gluten-containing

counterparts.<sup>27</sup> Studies in various countries analyzed individuals' perceived risk and anxiety of adhering to a gluten-free diet in the early months of COVID-19.<sup>28-30</sup> For individuals with gastrointestinal diseases, lack of access to personal products such as toilet paper during the early months of the pandemic likely caused increased psychological distress.<sup>31</sup> Studies conducted in Brazil and Australia during the pandemic did not indicate that individuals with celiac disease experienced decreased quality of life during the pandemic.<sup>29,30</sup> Some subgroups, such as those using antidepressants and those not adhering to a gluten-free diet, did report a worsening quality of life during this time period.

It was reported that individuals with celiac disease reported higher levels of food insecurity than the population as a whole.<sup>28</sup> Food insecurity must be considered in patients with celiac disease given the high cost of maintaining a gluten-free diet. One study of families in the United States found an increase in intentional consumption of gluten-containing products due to decreased availability of gluten-free food.<sup>32</sup> A study in Turkey reported that individuals more recently diagnosed with celiac disease had greater difficulty adhering to a gluten-free diet.<sup>6</sup> In Chile, individuals reported that loss of jobs, food shortages, and increasing costs of gluten-free products all played a significant role in the difficulty in adhering to a gluten-free diet.<sup>33</sup> Conversely, a study in Italy indicated that the majority of individuals with celiac disease were not worried about obtaining gluten-free food in the early days of the pandemic. A significant number of respondents in one study reported an improved adherence to a gluten-free diet. Eating at restaurants with friends and family is one of the main sources of gluten contamination in those on a gluten-free diet. Patients reported having more time to cook at home during the pandemic and they ordered from restaurants significantly less than before the pandemic. One possible explanation of increased adherence is that decreased access to gluten-free processed foods led to more individuals cooking with naturally gluten-free products.<sup>34</sup>

The pandemic highlighted two important ways that environmental circumstances can affect the gluten-free diet. Given the lack of access to dining during strict lockdown, some individuals reported greater adherence to a gluten-free diet.<sup>29</sup> Conversely, other individuals with celiac disease reported greater

difficulty in affording gluten-free food and reported greater barriers to adhering to a gluten-free diet.<sup>33</sup>

### **Telehealth and developments in the diagnosis and management of celiac disease and future application in a non-pandemic state**

The early weeks of the pandemic saw a sudden and marked increase of telemedicine.<sup>35</sup> In a survey conducted in Italy, a majority of individuals with celiac disease felt that they could trust tele-visits and appreciated this new option of receiving health care from their own homes.<sup>5</sup> Patients reported that they appreciated that they did not need to take significant time out of their day to go to a clinic. Patients also reported that they appreciated the anonymity of telemedicine.<sup>36</sup> While few studies analyzed telemedicine in celiac disease before the pandemic, one such study indicated that patients were satisfied with tele-visits and a majority wished to continue with online consultations.<sup>37</sup> In India, a similar pattern was also acknowledged. An overwhelming majority preferred to have an online appointment rather than a physical one.<sup>38</sup> Barriers to telemedicine include language barriers, difficulty using technology, and lack of telephone or internet access.<sup>36</sup>

Since the mainstay of treatment in celiac disease is adopting a gluten-free diet, nutritional counseling is essential. Telehealth allowed individuals with celiac disease to receive nutritional counseling during the pandemic. In addition, one of the primary disadvantages of telemedicine is the physical examination, which is usually less relevant to nutritional counseling than to a medical evaluation. Telehealth will likely allow for greater access to dietitians in areas with fewer healthcare resources. Telehealth has also allowed for increased access to quality gastrointestinal care during the pandemic. Given its popularity, telemedicine will likely continue to play a greater role in medicine as technologies continue to improve.<sup>39</sup> Utilization of telemedicine may allow for specialized care to reach a broader patient population.

The pandemic also influenced the way that celiac disease is diagnosed in some circumstances. In 2020, in an effort to minimize exposure to COVID-19, the British Society for Gastroenterology published a non-biopsy-based protocol for diagnosis of celiac disease. Laboratory results including elevated IgA tissue transglutaminase level 10 times the upper limit of normal or greater appears to be

highly correlative with villus atrophy on endoscopy. According to those guidelines, individuals younger than 55 years with a highly elevated IgA tissue transglutaminase (tTG;  $\geq 10$  times the upper limit of normal) and a positive endomysial antibody can be considered as having a confirmed diagnosis of celiac disease.<sup>40</sup> A non-biopsy approach to the diagnosis of celiac disease in adults is not widely adapted outside of this context, but this may be changing. A multicenter study found that a highly elevated tTG IgA (10 times the upper limit of normal) in adults has a positive predictive value of 95%.<sup>41</sup> Moreover, 2023 guidelines issued by the American College of Gastroenterology now list serologic criteria for an 'after the fact' diagnosis of celiac disease in adults unable or unwilling to undergo intestinal biopsy.<sup>42</sup> Lack of access to endoscopy during the early days of the COVID-19 pandemic led to adaptations in diagnostic criteria for celiac disease that likely will continue to be adopted in future non-pandemic eras.

The pandemic may have also accelerated the use of self-monitoring health technology. In recent years, home-based assays that detect gluten in urine have become available. Gluten immunogenic peptides (GIP) are found both in the stool and in the urine and such technologies may allow for detection of non-adherence to a gluten-free diet.<sup>43</sup> Such tests may play a role in monitoring celiac disease *via* telemedicine.<sup>44</sup> A study in Italy utilizing GIP detection in the urine indicated that it can be a useful tool to evaluate compliance with a gluten-free diet. Another benefit of this approach is that it can be done at home and can reassure symptomatic celiac disease patients who are concerned about inadvertent gluten exposure.<sup>45</sup> Conversely, testing such as this may provide increased anxiety for patients who are concerned about inadvertent exposure. Careful consideration should be utilized when discussing the potential benefits and other consequences of using at-home monitoring of celiac disease with modalities such as GIP testing.

### **COVID-19 risk for future development of celiac disease**

There likely was a significant decrease in diagnosis of celiac disease in patients during the early months of the pandemic due to a decrease in clinic appointments and a significant decline in non-emergent medical services. As such, there may be a significant increase in celiac disease

incidence in the coming years due to a catch-up effect after this lag of diagnosis during the pandemic.<sup>46</sup> One case report described a young child having severe complications such as failure to thrive and intussusception due to undiagnosed celiac disease.<sup>47</sup> Delayed diagnosis of celiac disease during the pandemic may thus lead to reports of more advanced symptoms of celiac disease.

A theoretical risk of an increased incidence of celiac disease as a consequence of COVID-19 has also been hypothesized. Viral infections have been reported to trigger increased immune reaction to dietary antigens.<sup>48</sup> Development of celiac disease has been associated with viral gastrointestinal infections, and early reports of COVID-19 included significant abdominal symptoms such as vomiting and diarrhea.<sup>49</sup>

COVID-19 invades host cells by utilizing angiotensin-converting enzyme (ACE), more specifically, ACE2. Cells with increased expression of this protein are more likely to have viral invasion. This is particularly relevant to celiac disease, given that intestinal enterocytes express ACE2, and there is a predisposition for viral replication in these enterocytes, leading to an increased inflammation in these cells.<sup>50</sup> It has been hypothesized that a breakdown in the gut barrier plays a role in the pathogenesis of celiac disease in those

with a genetic predisposition.<sup>51</sup> This leads to the theory that inflammation in intestinal epithelial cells may lead to COVID-19 playing a role in an increased incidence of celiac disease. Despite this theoretical concern and plausible mechanism, evidence that COVID-19 infection can trigger celiac disease has not yet accumulated in the epidemiologic literature.

It has also been hypothesized that vaccination could lead to an increase in autoantibodies that are commonly found in autoimmune disease.<sup>46</sup> A recent study of 121 individuals indicated that individuals with baseline autoantibodies did have an increase in autoantibody production, a phenomenon seen with other vaccines. Nevertheless, this study indicated that there was no increase in induction of autoantibodies for celiac disease from mRNA vaccines.<sup>52</sup> Thus, while an increase in diagnosis in celiac disease is possible in the coming years, this may be due in large part to missed diagnosis during the pandemic rather than COVID-19 (or COVID-19 vaccination) triggering celiac disease.

## Conclusions

Studies on the intersection of COVID-19 and celiac disease have addressed risk perception, outcomes, immune response to vaccines, and adapting to the pandemic (see Table 1). Overall,

**Table 1.** Selected studies on the intersection of COVID-19 and celiac disease.

Date of final publication	Authors	Title	Description
June 2020	Penny, <i>et al.</i> <sup>41</sup>	BSG interim guidance: COVID-19-specific non-biopsy protocol for those with suspected coeliac disease	A non-biopsy approach for individuals with suspected celiac disease, established by the British Society of Gastroenterology. This change was in response to the difficulty of undergoing elective endoscopy in the early months of the pandemic. They proposed that individuals with suspected celiac disease and IgA tissue transglutaminase (tTG) level of $\geq 10$ times the upper limit of normal should have EMA testing and if positive, should be considered to have celiac disease.
February 2021	Lebwohl, <i>et al.</i> <sup>15</sup>	Risk of severe COVID-19 in patients with celiac disease: a population-based cohort study	A population-based cohort study seeking to establish if individuals with celiac disease were at an increased risk of severe COVID-19. The study did not find that those with celiac disease are at an increased risk of hospitalization, ICU admission, or death from COVID-19.
March 2021	Zhen, <i>et al.</i> <sup>1</sup>	Risk perception and knowledge of COVID-19 in patients with celiac disease	Global survey measuring the risk perception of contracting COVID-19 in patients with celiac disease. This study found high levels of perceived risk that may have an overall negative impact on patients, particularly on mental health, in the early days of the COVID-19 pandemic.
June 2021	Gasbarrini, <i>et al.</i> <sup>11</sup>	COVID-19 in celiac disease: a multicentric retrospective cohort study	A global cross-sectional study aiming to determine if patients with celiac disease are at an increased risk of contracting COVID-19. The study found that the odds of contracting COVID-19 is similar between patients with celiac disease and the general population.
February 2023	Ibsen, <i>et al.</i> <sup>26</sup>	Immune responses to SARS-CoV-2 vaccines in celiac disease	A study of serum antibodies of individuals with celiac disease to analyze humoral response to COVID-19 vaccines. The study indicated that individuals with celiac disease mounted a similar humoral response to vaccination.

individuals with celiac disease do not have an increased risk of contracting COVID-19 or having a more severe course with the virus. Despite initial concerns to the contrary, this population mounts an adequate immune response to mRNA vaccines. The pandemic required the healthcare system to formulate new ways for technology to integrate into everyday patient care. Telemedicine is a well-received technology for this patient population and offers a way to expand access to celiac disease sub-specialists to patients outside of urban settings.

### Declarations

#### *Ethics approval and consent to participate*

Not applicable.

#### *Consent for publication*

Not applicable.

#### *Author contribution(s)*

**Brandon S. Cohen:** Conceptualization; Project administration; Resources; Writing – original draft; Writing – review & editing.

**Benjamin Lebwohl:** Conceptualization; Project administration; Resources; Supervision; Writing – original draft; Writing – review & editing.

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#### *Availability of data and materials*

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