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The COVID-19 Vaccination Debate: COVID-19 and Celiac Disease

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Abstract COVID-19 is a novel coronavirus that appears to cause a systemic disorder largely marked by fever and respiratory symptoms as well as diarrhea. The agent gains access to respiratory and gastrointestinal cells through a complex molecular mechanism associated with increased ACE2 receptor expression on brush border membranes of epithelial cells. Because some autoimmune-based disorders, including celiac disease, appear to be at increased risk for viral and community-acquired bacterial infections, a number of preliminary survey studies from different countries, largely web-based or telephone-based, have suggested that COVID-19 infection risk is not increased in celiac disease. However, specific sub-groups of patients with celiac disease have not been thoroughly evaluated. For example, selective immunoglobulin A deficiency or other immune deficiency states with celiac disease may represent a special risk group for COVID-19 and other viral infectious agents.

Keywords: *COVID-19, SARS-COV-2, celiac disease, Immune checkpoint receptors, COVID-19 diarrhea*

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1. COVID-19 and other Coronavirus Agents

COVID-19 (or SARS-CoV-2) is a newly recognized coronavirus initially reported from Wuhan, Hubei Province, China in late 2019. This was mainly associated with a severe form of pneumonia [1]. After global spread to over 100 countries, the World Health Organization declared a pandemic due to a highly infectious single-stranded, positive-sense RNA virus, sometimes fatal [2]. Similarities were noted with the severe respiratory syndrome outbreaks (SARS and MERS) previously recorded from Guangdong Province, China [3,4,5] as well as the Middle East, specifically Saudi Arabia [6]. All of these coronavirus agents may be transmitted largely by droplet-contact transmission and the incubation period is estimated to be days to about 2 weeks [7]. Recently, a so-called "UK Variant" of SARS-CoV-2 has been also noted, perhaps even more highly infectious than the first COVID-19 agent.

To date, millions have been infected globally with COVID-19, while the other 2 agents have been estimated to have infected thousands with death rates for COVID-19 estimated to be about 3 to 4% compared to about 10% to 30% for the other earlier coronavirus agents [7]. For all, the natural animal reservoir appears to be the bat with possibly different intermediate hosts (pangolin?, civets, camel) [7]. Besides non-specific "flu-like" symptoms (eg., fever and chills, headache and myalgias), clinical disease has largely been attributed to respiratory tract involvement (eg., cough, dyspnea, respiratory distress), and, as noted previously in this journal [8,9], however, prominent gastrointestinal symptoms may occur, including diarrhea.

2. Coronavirus Diarrhea

Indeed, all 3 of these recently described agents may cause diarrhea, sometimes profound and associated with nutrient malabsorption. Detailed microscopic studies using immunofluorescence methods and ultrastructural studies used to identify these viruses have documented the agents in intestinal tract epithelium and luminal fecal material, raising the possibility of an alternate oral-anal route for transmission [7,10,11]. Interestingly, some polymerase chain reaction (PCR) studies demonstrated that patient fecal material remained persistently positive, even after respiratory tract viral shedding had ceased, suggesting a possible ongoing source of shedding in fecal material [11].

With COVID-19, evidence for viral host receptor ACE2 in epithelial cell cytoplasm was shown with immunofluorescent staining in gastric and intestinal epithelium of patients with positive fecal studies [11,12,13,14]. In addition, viral nucleocapsid protein could be demonstrated suggesting that the ACE2 receptor was a potentially important route for epithelial cell entry and later assembly of new virions for luminal shedding. Previous studies had also suggested that SARS-CoV could enter gastric and intestinal mucosa by interaction between an envelope anchored spike glycoprotein of the virus and

ACE2 receptors on the apical surface (or brush border microvillus membrane) in gastric and intestinal epithelial cells. Spike protein subunits are thought to mediate both host epithelial cell membrane attachment and fusion. Cellular serine proteases (TMPRSS2), highly expressed in epithelial cells, initiate spike protein cleavage to regulate the process with infectivity dependent on ACE2 binding affinity (SARS-Cov-2 estimated to be 10 to 20 times greater than SARS-Cov) [7,15]. It has also been estimated that the ACE2 receptor is abundantly expressed by a factor of 100 or more compared to respiratory epithelial cells [7]. Some believe that this may lead to altered intestinal permeability and abnormal nutrient absorption [16,17]. Other changes may lead to impaired amino acid and peptide absorption as well as alterations in the gut microbiome [17].

3. Role in Intestinal Diseases

Patients with underlying intestinal diseases may be at increased risk for COVID-19 disease, particularly in patients with inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease. Although intestinal symptoms of diarrhea were initially considered to reflect a more severe illness with COVID-19, more recent studies have suggested that intestinal symptoms may precede or occur independently without any respiratory symptoms. More and more, these patients with inflammatory bowel disease are also being treated with long-term immune suppressive pharmaceutical agents as well as biological agents. Furthermore, some of these patients may be more susceptible to viral infectious agents [18]. There is concern in this patient group for development of severe COVID-19 disease, including an increased COVID-19 mortality, but this hypothesis remains controversial and unproven [19]. It has been suggested that a second form of ACE2 may be present in patients with inflammatory bowel disease, both a membranous ACE2 type as well as a soluble form [19]. In patients with inflammatory bowel disease, a high level of soluble ACE2 may prevent enteric viral interaction with the membranous ACE2 and even lead to a reduction in severity of COVID-19 disease [19,20,21]. Additional studies are needed.

4. Role in Celiac Disease

Information in celiac disease is very limited, in large part, because of the extreme difficulty in conducting direct patient-based clinical research in this environment. As a result most published studies are based on clinical cases and web-based surveys. In addition, much data available is largely related to "in press" publications that have not had the benefit of more extensive peer review of readers. Indeed, Emmi *et al* [22] noted that an Italian cohort with autoimmune disorders and treated with different immune suppressant agents did not appear to have an increased risk of SARS-CoV-2 infection compared to the general population. It was also noted that there was an increased risk of hospitalization with influenza infections in Swedish patients with celiac disease [23] as was the risk of community acquired pneumonia in Italian celiac disease patients [24,25], however, an increased risk of COVID-19 infection could not be confirmed in a telephone survey of 138 Italian adult celiacs on a gluten-free diet [26]. Similar findings were noted in a group of 101 celiac patients based on telephone and email contact [27]. Although the risk of a COVID-19 diagnosis was not increased in Turkish celiacs, access to gluten-free products was significantly reduced [27]. In contrast, a web-based survey of Italian celiacs suggested that adherence to a gluten-free diet was actually improved, particularly in those with prior difficult disease control [28]. In another study using a remote consultation approach based on an email survey of 276 responses in Italian celiacs, there was some concern expressed on gluten-free diet access by elderly patients, females and those with other co-morbidities, but most participants were pleased with this remote consultation mechanism to celiac disease management [29]. Although delay in diagnosis of celiac disease was noted in one report [30], the prevalence rate of COVID-19 in a study from Lombardy [31] was 2.78%, no different from the general population. Clinical features, age, sex, duration, gluten-free diet adherence and mucosal healing did not differ in celiac patients with and without COVID-19. None of their 9 patients (of 324) in this study required hospitalization suggesting that COVID-19 disease course in celiac disease was mild. Similarly, in a series of 21 patients labeled with refractory disease from Milan, contacted after a 2-month period of lockdown, no complicating COVID-19 infections were reported [32].

A recent multi-center survey type study from multiple countries evaluated 18,022 participants, but over 10,000 were self-reported with no biopsy [33]. In this report, the risk of contracting COVID-19 was not increased leading the investigators to conclude that there was no need to assume added precautions to prevent exposure beyond that recommended to the general public.

Although these studies, largely web-based or telephone-based, have not been able to define an increased risk for COVID-19 infection in celiac disease, added studies are needed and there may be specific celiac sub-groups that are at higher risk. For example, adults with celiac disease may also present with concomitant immunoglobulin A deficiency [34]. Importantly, there may be a crucial association between the presence of selective IgA deficiency and COVID-19. Although a gluten-free diet may improve the pathologic features in celiac disease, the diet may also lead to a minimally improved level of IgA in celiac patients with immunoglobulin A deficiency [34]. It seems conceivable that an increased risk for different infectious agents, including COVID-19, may occur in this setting, particularly since small bowel epithelial cells may be seeded with this virus during a systemic infection. Added studies of this particular celiac population group and possible role, if any, of small bowel epithelial IgA may be useful to determine risk of COVID-19.

In conclusion, initial studies have been hindered by limited numbers of confirmed celiac disease patients and further longer term studies are still needed to determine if celiac disease truly represents a concern for increased COVID-19 risk, including patients that fail to expeditiously respond to a gluten-free diet.

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