

The COVID-19 Vaccination Debate: CoV-2 in Celiac Disease: A Pathogen or just along for the Ride?

Aaron Lerner*

Chaim Sheba Medical Center, the Zabudowicz Center for Autoimmune Diseases, Tel-Hashomer, Israel

*Corresponding author: aaronlerner1948@gmail.com

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Abstract SARS-CoV-2, the virus that causes COVID-19, impacts human health all over the world with high morbidity and mortality. Many chronic diseases predispose the patients to be infected, including autoimmune diseases. Despite theoretical and rare exceptions, celiac disease is not a high-risk condition for COVID-19 infection. The present review expands on those potential circumstances that put the CD patients at risk for COVID-19.

Keywords: celiac disease, Coronavirus 2, SARS-CoV-2, COVID-19, risk

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1. Introduction

SARS-CoV-2, the virus that causes COVID-19, impacts human health worldwide spanning rapidly over 200 countries. According to the WHO report (as for 10, January, 2021), the reported number of infected people mount to 88,383,771 and the death toll to 1,919,126. The contagious pandemic causes a severe disease, resulting in high morbidity and excess mortality, mainly among the elderly and other vulnerable populations. It interrupts routine health services, disrupts trade, economy, travel, education and many other societal behaviors with a negative toll on people's physical and mental health [1]. Intriguingly, the name SARS directs the end target organ to the upper respiratory ways and lungs, but it appears that the gastrointestinal tract is heavily affected and symptomatic too [2,3,4]. In fact, the risk for the major intestinal inflammatory diseases, such as inflammatory bowel disease and celiac disease (CD) to attract covid-19 infection is highly debatable [5,6]. The present review focuses and updates on CD as a high-risk condition for covid-19 infection.

1.1. SARS-CoV-2 is an Auto-immunogenic Virus

Autoimmune diseases (ADs) emerge from the interplay between genetic predisposition and environmental factors, resulting in immune dysregulation and hyperstimulation, finally targeting various end organs. This endogenous-exogenous interplay was coined in the far past, by Shoenfeld Y et al as "The Mosaic of Autoimmunity" [7,8]. Viruses are a major player and multiple ADs are associated or actively initiate them [9,10]. Zooming back

to the current Pandemic, SARS-CoV-2, got recently the title of "the autoimmune virus" [11]. In fact, 17 ADs and 13 various autoantibodies associated with COVID-19 infection, were reported and the list is expanding [11]. The authors describe the association with HLA gene polymorphism in genetically susceptible human subjects, the shared peptides between SARS-CoV-2 virus and Human antigens, alluding to molecular mimicry, and as an integral part ASIA syndrome [11]. From a pathophysiological aspect, in both conditions there is an immune hyper stimulation, but the cytokine storm is much more prevalent during covid-19 deterioration [12,13].

1.2. CoV-2 Affects Celiac Disease Target Organ: the Bowel

In contrast to its scientific name SARS-Cov-2, directing the target organ to the respiratory tract, the human gastrointestinal tract is also affected [2,3,4]. Symptoms wise, 8-11.4% of affected patients had at least one symptom like diarrhea, nausea or vomiting [14,15]. Notably, in another study originating Wuhan, Shina, the percentage of patients with diarrhea reached 49.5% [16]. The Cov-2 induced diarrhea spends all along human life cycle and may present without any respiratory complains [17]. Interestingly, the proportion of patients with diarrhea in the later stage of the Chinese epidemic increased when compared with the pre-epidemic stage. Of note, gastrointestinal bleeding and abdominal pains were described, but the most common complaint was anorexia [17,18]. A higher proportion of patients with diarrhea had viral RNA in stool than patients without diarrhea. Elimination of the virus from the nose and throat preceded the enteric elimination [19,20]. Even a/hypo-symptomatic Cov-2 infected infant can excrete it in their stool without any diarrhea [21]. The Cov-2 surface protruded spike

protein need to meet its host cell receptor, the angiotensin-converting enzyme 2 (ACE2), in order to infect and penetrate into the cell [22]. It appears that ACE2 is highly expressed along the enteric tract. It is presented on the esophageal epithelium, in the small bowel enterocytes from the ileum and in the colon's colonocytes [19]. This means that the closed proximity between the lumenally residing Cov-2 virus and its specific receptor creates optimal condition to infect, penetrate, replicate and damage the host cells and finally be excreted and transmitted via the stools [2,3,4,16,17,19,20,21]. Pathologically, SARS-CoV-2 induces inflammation in all the human gut's segments. Lymphocytic infiltration in the esophageal squamous epithelium, stomach edema, plasma cells and lymphocytic infiltrations and enteric mucosal necrosis, degeneration and cellular shedding, were reported [17,23]. The virus itself and its nucleocapsid proteins were depicted in the cytoplasm of stomach, duodenal and colonic epithelium, in addition to the fecal excreted samples [17,24,25]. It is concluded that Cov-2 virus infect, overcomes the intestinal protective barrier mechanisms, penetrates and damage the intestinal mucosa and activates the local immune system [26].

2. Might Gluten Enhance and Gluten Free Diet Attenuate Cov-2 Gastrointestinal Effects?

More and more information is accumulating regarding the detrimental effects of gluten intake. The topics of gluten side effect and the benefits of gluten withdrawal were extensively reported [27,28,29]. In fact, gluten increases intestinal permeability, induces dysbiome, it is pro-inflammatory, pro-oxidative, pro-apoptotic and impacts epigenetics. It is immunogenic, cytotoxic and decreases cell viability and differentiation [27]. All those detrimental effects might potentiate the intestinal damage of covid-19. On the contrary, gluten free diet might alleviate the damage and not only in non-celiac ADs [27,28,29,30]. Most recently, Haupt-Jorgensen and Buschard reported on the potential protective effects of gluten elimination in covid-19 infections [31]. It appears that gluten withdrawal induced some anti-inflammatory cytokine profile in mice, and lowered the pro-inflammatory cytokine IL-1beta levels in healthy subjects. It improves intestinal permeability and might protect lung functions by alleviating hemosiderosis and potentially reduce the cytokine storm associated with the Cov-2 infection. Interestingly, when Covid-19 infection is compared, the fare East had a much lower incidence than the Western countries. The same is correct for gluten intake, since rice is the major staple food in Asian countries. The authors concluded that the reduced intake of gluten in Asia should be considered as partly protective for COVID-19 [31].

3. Celiac Patients' Potential Risks for CoV-2 Infections

Most of the celiac patients are asymptomatic and the ratio diagnosed/undiagnosed patients is around 1/7. The

same holds for covid-19, where asymptomatic patients are prevalent, mainly in the younger ages. According to the current knowledge, CD is not a risky condition to get infected with the CoV-2 virus, but parts of the CD population might be in high risk. Table 1 summarizes the shared aspects and potential circumstances that put the CD patients at risk for covid-19. It can be concluded that multiple and well-defined conditions might put the celiac patients at increased risk for covid-19 infection and complications. It should be stressed that most of the CD patients that adhere to **gluten free diet and don't have the associated high-risk morbidities** for covid-19 infection, are safe and their risks are comparable to the general population.

Table 1. Shared aspects and potential circumstances that put the CD patients at risk for covid-19

High-risk in CD	Covid-19	References
IgA deficiency	High-risk	[32,33,34]
Elderly	High-risk	[35,36]
Pulmonary diseases	High-risk	[37,38]
Smoking	High-risk	[39,40]
Obesity	High-risk	[41,42,43]
Cardiovascular diseases	High-risk	[44,45]
Hypercoagulability	High-risk	[46,47,48]
Immune dysregulation/hyperactivation	High-risk	[49,50,51]
Immunosuppression in refractory CD	High-risk	[52,53]
Immune deficiency conditions associated with celiac disease.	High-risk	[54,55,56]
Pre -cancerous disease	High-risk	[57,58]

4. Scientific Facts and Reality in the Celiac-CoV-2 Relationship

In reality, up to the end of 2020, no increase incidence of Covid-19 was described in CD populations. (Italy, secure-celiac, beyond CD). Regarding ADs in general, among patients hospitalized with COVID-19, individuals with ADs and those on chronic immunosuppressive therapy did not have an increased risk of adverse events, at least in New York city [59]. The same holds for CD. An uneventful course in refractory CD patients, during covid-19 outbreak, was observed in Italy when they got suitable therapies and anti- anxiety measures [60]. When telemedicine was applied, only moderate impact was found in CD patients during the covid-19 epidemic. Most patients were happy with the remote consultation [61]. When a real life "snapshot" of a cohort of CD patients during the SARS-CoV-2 outbreak in Italy was evaluated, no confirm COVID-19 diagnosis was detected in 138 patients [62]. It seems that in many CD centers, the following measures were taken to minimize the risk: postponing any non-urgent out-patients visits, encouraging remote telemedicine consultations, ordering and interpreting laboratory examination by email and postponing gastroscopies indefinitely, when possible [62]. Various gastroenterological and endoscopical societies recommended full anti-infection precautions, during the procedures [63,64,65,66,67,68]. In fact, the endoscopists are at increased risk to be infected. SARS-CoV-2 RNA is present in the feces of the infected patients. Colonic biopsy samples positivity has been consistently documented. Stool's viral shedding is more

prolonged then in respiratory compartments' secretions [69] and potential fecal-oral transmission was most recently suggested [70,71]. Above all, a plethora of other viruses and bacteriophages are part of the enteric microbiome and affect the microbiota/dysbiota balance in health and disease [72], but the Cov-2 virus effects on the normal microbiome are far from being explored.

The Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-Celiac) registry is an international, pediatric and adult database to monitor and report on outcomes of COVID-19 occurring in pediatric and adult patients with CD. Up to the end of 2020, 99 cases of CD with covid-19 were registered, with a total death rate of 2% [73]. As for the CD patient's organization, Beyond Celiac is the leading catalyst for a CD cure in the USA [74]. The actual messages for the CD populations are that there is no direct evidence that CD patients are at increased risk of developing severe consequences of COVID-19, but there is theoretical concern based on studies of other infections. Based on the purely hypothetical and not yet proven association between CD and the virus, it is not justified to take any additional precautions separate from those recommended to the general population [75].

5. Conclusions

During the 21st century, human civilization has witnessed three major epidemics caused by Coronaviruses, however COVID-19 has the greatest transmission and mortality rate. Described as "the autoimmune virus" [11], It is associated with numerous ADs and autoantibodies, but as for today, not with CD. The CD patients should not take additional precautions, but follow those recommended to the general populations. However, facing additional associate diseases, comorbidities or immunosuppression, they should be under medical supervision.

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