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SARS-CoV-2 Infection and Gastrointestinal Involvement: The Tip of the Iceberg

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ABSTRACT

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Introduction

The outbreak of the coronavirus disease of 2019 (COVID-19), which evolved into a pandemic, is a life-threatening condition that has now officially recorded one million confirmed deaths in the United States as of May 2022 [1]. In the last two years, a lot of attention has been placed worldwide on the finding of effective treatments. COVID-19 is the cause of an enveloped, non-segmented, single-strand RNA virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that attacks the body cells to cause infection in the respiratory system [2]. The SARS-CoV-2 spike protein binds to the cell's angiotensin converting enzyme 2 (ACE2) receptors. ACE2 receptors are widespread in human tissues, explaining the multiorgan dysfunction reported in patients [2]. ACE2 receptors are highly abundant in the gastrointestinal (GI) tract and evidence of SARS-CoV-2 replication and inflammatory response to the GI infection have been reported in COVID-19 patients [2]. Additionally, COVID-19 vaccinated people develop multisystemic symptoms that could be associated with the diversity of the immune response to the viral protein [3]. The pathogenesis of SARS-CoV-2 infection is not totally understood. It is not clear the role of the viral replication in the GI tract and the effects of the immune response against the cells infected with SARS-CoV-2. This article explores the current knowledge about the GI system involvement in the COVID-19, the post-acute COVID-19 syndrome (PACS) and the COVID 19 vaccine side effects that lead to diverse gastrointestinal manifestation and disease severity outcomes.

The acute period or COVID-19, that lasts approximately four weeks [4], is driven initially by replication of SARS-CoV-2 in the cells, that seems to last longer in GI tract cells [5], and then by an exaggerated immune/inflammatory response to the virus that damages tissues [2,6], COVID-19 is a primary respiratory transmitted illness that presents with fever, fatigue, cough, shortness of breath, muscle or body aches, headache, sore throat, congestion or runny nose, loss of taste or smell, nausea, vomiting and diarrhea [7]. GI manifestations are reported in 11.4-61.1% of individuals with COVID-19(6), and are different across the literature reviewed in frequency, presentation [8,9], onset time [10] and clinical outcome [9]. The majority of COVID-19-associated GI symptoms are mild and self-limiting. Also, acute pancreatitis, acute appendicitis, intestinal obstruction, bowel ischemia, abdominal compartment syndrome are described with less frequency [8]. The presence of viral nucleocapsid protein has been verified in almost the entirety of the GI lumen, such as gastric, duodenal and rectal glandular epithelial cells, apart from the esophagus [2,5,6] and the high prevalence of viral shedding in stool, particularly after viral RNA negativity in respiratory specimens, have led to the idea of a possible viral fecal-oral transmission [5]. Only interaction between SARS-CoV-2 and

ACE2 receptors might be enough to disrupt the normal function of ACE2 pathway and result in diarrhea and inflammation [11] but the pathophysiology of the infection in the GI tract seems to be more complex. One study reported that fecal calprotectin (FC) and serum calprotectin (SC) might have the potency to assess the prognosis in COVID-19 patients, but increased FC and SC did not feature GI symptoms or even diarrhea in COVID-19(9). Also, elevated FC suggested an inflammatory response in the gut, which was significantly correlated with IL-6 [12]. Furthermore, in the GI tract the microbiota that colonizes it plays a variety of important physiological roles in the body, through multiple recognized axes (brain, lung, estrogen) [4,13], and is altered during SARS-CoV-2 infection. COVID-19 patients had significantly reduced bacterial diversity, a significantly higher relative abundance of opportunistic pathogens (*Streptococcus, Rothia, Veillonella and Actinomyces*), and a lower relative abundance of anti-inflammatory symbionts compared to non-infected [10,14]. The persistent dysbiosis produces barrier dysfunction, translocation of bacterial products, hyperinflammation and immune dysregulation [14]. Ultimately, prolonged and disorganized inflammation is also an important cause of autoimmune response and has been described in other viral infections and autoimmune disorders [13,15,16]. After the acute period and during at least one year post infection, some individuals develop long-term sequelae or post-acute COVID-19 syndrome (PACS) [17]. PACS also known as long-COVID is part of the post-acute infection syndromes group, characterized by an unexplained failure to recover from an infectious disease [15]. The majority of manifestations in PACS are systemic, neurological, cardio-respiratory, and gastrointestinal [4]. The gastrointestinal-related symptoms in these patients include loss of appetite, nausea, weight loss, abdominal pain, heartburn, dysphagia, altered bowel motility and irritable bowel syndrome [4]. The syndrome may develop not only in COVID-19 hospitalized patients and evidence indicates that it can develop regardless of the severity of the original symptoms. Common features are viral persistence, a continuous dysbiosis, and aberrant immunological response with a persistent inflammation that can lead to autoimmunity [4,15,16].

Despite the benefits of the SARS-CoV-2 vaccination in the control of the pandemic, the immune response to the virus antigen and autoimmunity have been linked to some rare serious adverse events [3]. Sides effects are usually less serious than developing COVID-19 or complications associated with coronavirus infections, mostly being mild to moderate and have lasted no longer than a few days [18]. Typically, pain at the injection site, fever, fatigue, headache, muscle pain, chills, nauseous and diarrhea are the most frequently reported [18,19]. It is not clear if the side effects observed after vaccination are due to the produced antibodies against the viral spike protein (more studied antibodies) or anti-idiotype antibodies that resemble the spike protein structure [3]. This same mechanism that could be involved in the off-target vaccine effects could also explain the autoimmune response during the acute period of the infection [3].

Currently the main therapeutic effort for COVID 19, such as antiviral and vaccines, have their main effect early in the viral infection, while immunosuppressive and anti-inflammatory therapies focus on targeting later stages of COVID-19 have been centered in the pulmonary manifestations [8]. The GI tract plays a significant role throughout the course of the disease; therefore, this has recently prompted the exploration of several therapies directed to the control in the GI tract of SARS CoV-2 infection, the immune response and the microbial dysbiosis. [10]. A recent trial explored the possibility of oral-fecal transmission and oropharyngeal tissues as reservoirs for SARS-CoV-2, by testing the effects of Niclosamide treatment on fecal shedding of the virus, but the results were not significant between the study groups [5]. The effect of berberine, that acts inhibiting key factors in cell signal transduction on intestinal function in patients with severe SARS-CoV-2 infection, was also explored in a clinical trial to target the inflammatory response by balancing the intestinal microenvironment during severe Covid-19 [20]. Lastly, other studies, exploring the correlation between intestinal microbiota and COVID-19, recommend including probiotics and prebiotics in the patient's therapy regimen, which could reduce inflammation and improve disease conditions by modulating the immune system, infected patients [10].

COVID-19 is the first disease event since the beginning of the XX century to demand an urgent global healthcare response, that disrupted everyday life on earth in 2019. Since this moment, a lot of effort has been put into getting the knowledge to develop the required tools to control the coronavirus pandemic worldwide, but our knowledge of the disease is still limited because it is an evolving situation that continues to challenge healthcare professionals and societies. There is still controversy in most of the aspects related to this viral infection in the GI tract that therefore requires further research.

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