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Influence of Intestinal Inflammatory Diseases on Gastrointestinal Symptoms in Patients with COVID-19 †

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Abstract: COVID-19 is characterized by pulmonary involvement, which has generated a large number of hospitalizations and studies worldwide, motivating researchers in their search of a possible treatment and in the development of vaccines for the disease. However, other symptoms related to SARS-CoV-2 have been less relevant pertaining to studies published to date. Thus, there is a need to establish a relationship between patients with inflammatory bowel diseases and the symptoms of the gastrointestinal tract caused by COVID-19, since the involvement of the gastrointestinal tract affects up to 53% of patients who contract SARS-CoV-2. In this perspective, the present study was an integrative review carried out at the Virtual Health Library and PubMed based on the health descriptors: gastrointestinal diseases and COVID-19, applying the Boolean operator "AND" between them. The selection criteria used were the eligibility criteria: articles in Portuguese, English, and Spanish, published between December 2019 and July 2020. Individuals with inflammatory bowel diseases, even with greater expression of ACE2, are not at increased risk of symptoms or worsening. Thus, based on the relationship between pre-existing symptoms and the symptoms of the new COVID-19, health professionals, based on their clinical experiences, will be able to compose prophylactic measures and manage patients with COVID-19 and gastrointestinal symptoms more effectively.

Keywords: COVID-19; gastrointestinal symptoms; intestinal inflammatory diseases; gastrointestinal tract

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1. Introduction

Coronaviruses (CoVs) are viruses enveloped with a single positive strand RNA genome. Among those that infect humans, there is SARS-CoV-2, the agent responsible for COVID-19—a respiratory and infectious disease. It was found in bronchoalveolar lavage samples obtained from patients with pneumonia of unknown cause in the city of Wuhan, Hubei province, China, in December 2019 [1,2].

COVID-19 can cause respiratory failure, sepsis and septic shock, thromboembolism and/or multiple organ failure, including acute liver or heart damage. To date, Brazil has recorded more than 270,000 deaths and more than 11 million confirmed cases [3]. In this context, it is a severe respiratory syndrome in which its transmission occurs mainly via droplets or contact with contaminated objects and surfaces [4,5].

The mechanism of entry of the virus into the cell depends on the binding of the angiotensin-converting enzyme 2 (ACE2) receptor and its spike (S) protein. The ACE2 enzyme receptor, which is very present in the gastrointestinal tract, can cause direct or indirect damage to it, due to a generalized inflammatory response [6,7]. In this perspective, despite being a respiratory disease, the symptoms are varied, so the health team must be attentive, since the patient may present various symptoms, such as cough, fatigue, fever, muscle pain—common to the infection—as anorexia, diarrhea, abdominal pain,

vomiting, nausea [8,9]. Therefore, establishing relationships between patients' pre-existing diseases and their relationship with COVID-19 can reveal which individuals are prone to develop certain symptoms. Therefore, the study has the guiding question: "What is the possibility among individuals with inflammatory bowel diseases to develop gastrointestinal symptoms when contracting COVID-19?"

It is essential for medical practice and prevention programs to be aware of the likelihood that individuals will manifest any specific symptom during COVID-19 infection associated with the gastrointestinal tract. In addition, due to the lack of information on the topic, the present study aims to seek an intrinsic link between inflammatory bowel diseases and the appearance of gastrointestinal symptoms among those infected with SARS-CoV-2.

2. Methodology

A systematic search of the literature was carried out through the Virtual Health Library (VHL) and PubMed. For that, the descriptors in health sciences (DeCS) were used: gastrointestinal diseases, COVID-19; as well as the Boolean operator "AND" between descriptors.

For the selection of articles, the following eligibility criteria were applied: articles in Portuguese, English, and Spanish, published from December 2019 to July 2020, since in this period, the first publications that reported gastrointestinal symptoms in patients with COVID-19 occurred, with the full texts available. For exclusion: publications of the review genre and case reports, works that did not include in the title and abstract, the theme of the proposal and duplicate articles.

The search was carried out by two researchers on the same day, using the aforementioned descriptors on different computers and connections, in order to reduce the risk of bias in the selection of articles. In addition, in case of discrepancy between the results obtained by the researchers, a third researcher assisted in the elaboration of the search, thus minimizing the chance of errors.

3. Results and Discussion

Knowing that the ACE protein supports the infection, it is important to assess whether their expression in the GIT is directly related to the expression of symptoms. Lee et al. (2020) studied the co-expression of TMPRSS4 (serine protease), which promotes viral entry into human intestinal epithelial cells in combination with TMPRSS2. They reported "predominant co-expression of ACE2 and TMPRSS2 in the enterocytes of the lower GI tract, with progenitor and stem-like epithelial cells demonstrating highest proportions of ACE2, TMPRSS2, and TMPRSS4 co-expression, especially in the small intestine". Thus, the proportions of cells that expressed ACE in the gastrointestinal tract were compared; it was observed that the upper GI tract (esophagus, stomach, duodenum) has an expression 13 times smaller than the lower gastrointestinal tract (ileum, colon, rectum) [10].

In view of this finding, the correlation between ACE expression and TMPRSS may not be directly involved with the symptoms presented at the clinic of these patients, since the most commonly observed were in the upper gastrointestinal tract. However, the importance of proteins for the entry mechanism and pathophysiology is emphasized. Thus, more studies should be carried out in order to better understand this correlation.

In the meantime, it is also necessary to evaluate patients with pre-existing intestinal diseases that predispose greater expression of the protein. Thus, the study by Monteleone et al. [11] pointed out that patients with Crohn's disease (CD) and patients with ulcerative colitis (UC), the main inflammatory bowel diseases (IBDs) in humans, are possibly associated with an increased risk of complications, such as infections, due to immunosuppressive drug therapy and/or the chronicity of intestinal inflammation that increases the expression of ACE2. In the same study, patients with Crohn's showed ACE2 expression 1.3 times greater than that of the control, in addition to increased expression of TMPRSS2 (1.25 times greater), in contrast to ulcerative colitis with ACE expression (1.27 times less) and TMPRSS (1.5 times less) than in the control samples. However, the study by Cao et al. [8] did not

show any interference in the history of gastrointestinal comorbidities in the appearance of symptoms and infection.

Thus, although patients with Crohn's present more expression of ACE2, this does not support an increased risk of infection in patients with previous inflammatory bowel diseases, since, according to Guerra et al. [12], only 82 of the 805 patients (10.2%) with inflammatory bowel disease were diagnosed with COVID-19, with 51.2% having Crohn's; the prevalence of gastrointestinal symptoms was the same in patients without previous diseases 41 (50%). Thus, as demonstrated by Lee et al. [10], a greater expression of these proteins does not directly reflect a greater involvement in these tissues.

4. Conclusions

The evidence shows that the increased expression of ACE does not corroborate an increased risk in patients with inflammatory bowel diseases; therefore, it does not fit the risk profile. However, the importance of further research is highlighted in order to elucidate the association between the ACE protein and the manifestation of symptoms.

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