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COVID-19 and gastroenterological pathology. Review

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SARS-CoV-2 has led to numerous cases of coronavirus disease (COVID-19) around the world. In addition to fever and respiratory symptoms, some COVID-19 patients also have manifestations from digestive system. On the other hand, patients with chronic diseases of the gastrointestinal tract (GIT) also suffer from coronavirus disease.

Objective — to provide an understanding of the characteristics, possible mechanisms and consequences of gastrointestinal damage caused by SARS-CoV-2 infection, in particular in patients with gastrointestinal tract pathology.

Literature search was carried out using such databases as Scopus, Web of Science. Clinical studies of patients with COVID-19 have shown that gastrointestinal (GI) symptoms such as anorexia, nausea, vomiting, abdominal pain and diarrhea precede or follow respiratory syndromes with a frequency of about 10 to 60 %. Literary sources were studied regarding the relationship of COVID-19 and such gastroenterological pathologies as gastrointestinal bleeding, hepatitis, pancreatitis and inflammatory bowel diseases. Lesions of the digestive system both in patients without chronic pathology and with existing diseases, apparently, are associated with a high concentration of angiotensin converting enzyme 2 (ACE2) throughout the entire GIT, including the intestine, liver, and pancreas. Some studies have shown that the spike (S) SARS-CoV-2 protein has a high affinity for human ACE2, while SARS-CoV-2 mainly enters cells through the ACE2 receptor. In addition, endothelial injury and thrombus inflammation and dysregulated immune responses may contribute to extrapulmonary manifestations of COVID 19. This requires an appropriate correction of the diagnostic search and therapy.

Keywords:
COVID-19, hepatitis, pancreatitis, inflammatory bowel disease, gastrointestinal bleeding, ACE2.

Virus SARS-CoV-2 has led to numerous cases of coronavirus disease 2019 (COVID-19) around the world. In addition to fever and respiratory symptoms, some COVID-19 patients also have gastrointestinal and hepatic manifestations. On the other hand, patients with chronic diseases of the gastrointestinal tract (GIT) also suffer from coronavirus disease.

Objective — to give an idea of the characteristics, possible mechanisms and consequences of damage to the digestive system caused by coronavirus infection, in particular, in patients with an existing gastroenterological pathology.

Lesions of the digestive system both in patients without chronic pathology and with existing diseases, apparently, are associated with a high concentration of angiotensin converting enzyme 2 (ACE2) throughout the entire GIT [40, 41]. Some studies have shown that the spike (S) SARS-CoV-2 protein has a high affinity for human ACE2 [43], while SARS-CoV-2 mainly enters cells through the ACE2 receptor [48]. ACE2 is expressed in most tissues of the human body. ACE2 functions as a typical zinc metallopeptidase, consists of 805 amino acids, and is an integral protein with a single catalytic domain. It has a systemic effect, participating in the renin-angiotensin-aldosterone system (RAAS), and also has a local regulatory effect on pathological changes in several organs, including the heart, kidneys and lungs.

ACE2 is more strongly expressed in type II epithelial cells [17, 49]. Several studies have provided evidence that coronavirus can infect the GIT, as high expression of ACE2 has been found in the epithelial cells of the intestine, esophagus and lungs [15].

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Studies have shown that the expression of ACE2 in the intestines of humans and mice significantly exceeds the expression of ACE2 in the lungs. Clinical studies of patients with COVID-19 have shown that gastrointestinal (GI) symptoms such as anorexia, nausea, vomiting, abdominal pain and diarrhea precede or follow respiratory syndromes with a frequency of about 10 to 60 % [24, 44]. Studies reporting a link between GI symptoms and disease severity are conflicting.

It is also important to consider ACE2 not only as a potential conductor of the SARS-CoV-2 infectious agent into the cell, but also as a regulator of the intestinal microbiota. In ACE2 knockout mice, a decrease in the expression of antimicrobial peptides and an imbalance in the gut microbiota were shown. This imbalance was restored with the introduction of tryptophan [19].

COVID-19 and gastrointestinal bleeding

There have been cases of GI bleeding in patients with peptic ulcer [30]. The development of peptic ulcer disease can be explained by stress resulting from the acute illness, direct gastric epithelial damage caused by COVID-19. It also can be an active mucosal inflammation caused by the cytokine storm. If thromboprophylaxis remains a key point in the management of these patients, the relatively high risk of GI bleeding should alert the clinician in routinely checking for its occurrence by monitoring laboratory parameters and hemodynamic stability. However, given the current effective endoscopic and radiologic tools in managing an active GI bleeding, thromboprophylaxis should not be discouraged.

COVID-19 and hepatitis

In most of the patients with COVID-19, there is an increase in the activity of liver enzymes and bilirubin levels. Against the background of COVID-19, the progression of hepatocellular carcinoma and other chronic liver pathologies increases [5, 15]. At the same time, patients with a severe course of COVID-19 have higher rates of liver dysfunction, and patients with a manifest course of coronavirus infection are more likely to increase the level of liver enzymes compared to patients with a subclinical course of the disease [4, 38]. The prevalence of liver damage in patients with COVID-19 is explained by the fact that the coronavirus through the ACE2 receptors can directly damage cholangiocytes [42]. It is known that ACE2 can also damage perivenular cells, endothelial cells, and, possibly, hepatocytes [4, 6]. According to experimental data, the activity of ACE2, as well as its expression, is significantly increased in hepatocytes and cholagiocytes during hypoxia [35]. In the study of liver biopsies, viral nucleic acids were detected in the liver tissues. Also, the patients showed an increase in hepatocytes, their moderate steatosis, moderate lobular and portal inflammation, increased apoptosis, the presence of acidophilic bodies [3, 10, 34, 38]. Coronavirus infection can cause «reactive hepatitis» due to the development of a systemic inflammatory response and cytokine hyperactivity. Therefore, the disturbanses of the course of chronic diffuse liver diseases develops logically. At the same time, in patients with COVID-19, liver failure was not separately distinguished, including in severe and fatal cases [16, 47]. In the pathogenesis of liver damage, it is necessary to take into account the drug toxicity of high doses of antiviral drugs, antibiotics and corticosteroids, which are usually used for the treatment of the disease. On the other hand, the existing liver damage makes the patient more susceptible to coronavirus infection, and increases the risk of its severe course. It should be noted that patients with decompensated chronic liver diseases themselves are at increased risk of infection due to existing immune dysfunction [1]. Also, against the background of coronavirus infection in patients with chronic liver diseases, reactivation and decompensation of these diseases is possible [4, 38], which is important both for patients after liver transplantation and for patients with autoimmune liver diseases who receive immunosuppressive therapy [3]. There is evidence for further study indicating that immunosuppression may even provide some protection against immunopathological damage that appears to contribute to lung damage in more severe cases [25, 45]. This may be associated with a hyperinflammatory syndrome characterized by a cytokine storm with multiple organ failure [29].

Non-alcoholic fatty liver disease (NAFLD) is often associated with components of the metabolic syndrome, such as diabetes mellitus, hypertension and obesity, which requires these patients to be considered at increased risk for severe coronavirus infection. In patients with COVID-19 infection, the presence of NAFLD has already been associated with a 4-fold increased risk of developing severe COVID-19 [11]. These data relate to patients without diabetes. And, the greater the number of metabolic risk factors, the greater the likelihood of developing a severe course of coronavirus infection. Therefore, patients with NAFLD during the COVID-19 pandemic need active therapy aimed at reducing the degree of steatosis and the stage of fibrosis, and normalizing the activity of liver enzymes. The less the degree of changes in the structure of the liver, the fewer ACE2 receptors in it, the lower the risk of infection and damage by the virus [11].

It is important for the clinician to understand that critically ill patients with COVID-19 may show signs of liver dysfunction [46]. And, on the other hand, patients with liver dysfunction during a pandemic require prophylactic and maintenance therapy.

COVID-19 and pancreatitis

Expression of ACE2 in pancreatic tissue (pancreas) makes it a target for SARS-COV-2. Affection of the pancreas is characterized by subsequent damage to both exocrine and endocrine functions. In a recent study by F. Wang et al. In 52 patients with COVID-19 pneumonia, 17 % of patients had signs of damage to the pancreas, which manifested itself as an increase in the concentration of blood amylase or lipase [9].

Chronic pancreatitis (CP) is not a disease that poses a risk of severity and affects the outcome of coronavirus infection. However, the possibility of developing certain complications in CP significantly changes the clinical situation and affects the severity of the course of COVID-19 infection, forming, in fact, risk factors. This can be both the development of various variants of carbohydrate metabolism disorders, and a violation of the exocrine pancreatic function with the development of trophological insufficiency, the course of which may be accompanied by the emergence of a secondary immunodeficiency state.

The ACE2 receptor is also highly expressed in pancreatic islet cells, so SARS-CoV-2 infection could theoretically cause islet damage, leading to diabetes. According to F. Wang et al., Out of nine patients with pancreatic injury, six had an increase in blood glucose [9]. The mechanisms by which pancreatic damage can occur include direct cytopathic effects of coronavirus and indirect systemic inflammatory and immune-mediated cellular responses leading to organ damage or secondary enzyme elevation [9, 26, 27].

On the one hand, damage to the pancreas can contribute to a «cytokine storm» during COVID-19 (as in acute pancreatitis) and subsequent worsening of acute respiratory distress syndrome. On the other hand, with damage to the pancreas, the same mechanisms of fibrosis can develop as in the lungs [37].

That is, on the one hand, the development of pancreatitis can worsen the immune response to COVID-19, and on the other hand, existing diabetes is a poor prognostic factor for COVID-19. Unfortunately, in the scientific literature there is little data on the development of acute pancreatitis against the background of a new coronavirus infection, which requires further studies of the functional state of the pancreas in COVID-19.

COVID-19 and inflammatory bowel disease

The COVID-19 receptor ACE2 is highly expressed in intestinal epithelial cells from the terminal ileum and to a lesser extent in the colon, where mucosal inflammation in patients with inflammatory bowel disease (IBD) — Crohn's disease (CD) and ulcerative colitis (UC) is frequently detected [13, 18]. ACE2 can act as a co-receptor for nutrient uptake, in particular for aminoacid resorption from food [19]. ACE2 activity in the colon was elevated in non-inflamed colon in IBD as compared with controls and active IBD. The average expression of soluble ACE2 was shown to be increased in patients with IBD (mainly in CD) and a higher ACE2:ACE ratio in plasma was noted in patients with IBD as compared with controls without IBD [12, 13]. We have an expression of cytokines in IBD, it can potentially induce ACE2 expression by cytokine signalling events driving ACE2 promoter activity consistent with the idea that mucosal inflammation may increase expression of ACE2. It was shown higher levels of ACE2 in inflamed areas of intestine in patients (CD) in comparisin with patients with UC [33]. The fusion of SARS-CoV2 with the host cell membrane is critical for uptake in cells and is modulated by the S protein. Activation of the S protein is controlled by host trypsin-like proteases, whose activity is upregulated in IBD. This point may facilitate infection in patients with IBD [22]. All together, these findings suggested the possibility that patients with IBD might be particularly susceptible to COVID-19. From the other hand, there is no evidence that patients with IBD are highly susceptible to COVID-19. A recent study from Wuhan studied 318 patients with IBD (204 UC and 114 CD) during the local outbreak of the disease and did not report any COVID-19 cases [2, 20, 23, 36].

The expression of ACE2 is increased in the inflamed intestine of patients with IBD [33]. Analysis of tissue samples of IBD patients has revealed a significantly higher expression of ACE2 in CD than in UC [33]. Fusion of the coronavirus envelope with host cell membranes is critical for establishing a successful infection. This process is mediated by S-protein [21, 28]. S-protein is activated through a proteolytic cleavage induced by host cell trypsin-like proteases, the activity of which is up-regulated in IBD [8, 31]. An inflamed intestine of IBD patients represents an optimal doorway for the virus.

The use of immunesuppressive therapy for inducing and maintaining remission in IBD has been associated with increased risk of infections because it blocks intracellular signals needed for the host to fight pathogens [14]. On the other hand, it is noted that suppression of the cytokines in IBD could be beneficial also for preventing COVID-19-associated pneumonia. The profile of cytokines documented in patients with severe COVID-19 resembles that seen in the inflamed intestine of IBD patients and during the 'cytokine storm' syndrome, it characterized by activation of T-cells and hyperproduction of interferon-γ, tumour necrosis factor-α, interleukin (IL)-2 and IL-6 [7, 28, 32]. The blockers of IL have been used with success in cytokine storm

syndrome. Preliminary evidence supports the use of IL-6 receptor antagonists in the treatment of COVID-19-associated pneumonia [39].

Conclusions

Thus, given that ACE2, the entrance receptor for the pathogen SARS-CoV-2, is expressed in many extrapulmonary tissues, including the intestine, liver and pancreas, is one of the likely mechanisms of their damage. In addition, endothelial damage and thrombus inflammation and dysregulated immune responses may contribute to the gastroenterological manifestations of COVID-19. This requires an appropriate correction of the diagnostic search and therapy.

Conflicts of interest: none.

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COVID-19 та гастроентерологічна патологія. Огляд літератури

Вірус SARS-CoV-2 спричинив численні випадки захворювання на коронавірусну хворобу 2019 (COVID-19) у всьому світі. Окрім лихоманки та респіраторних симптомів, у деяких хворих на COVID-19 спостерігаються вияви з боку травної системи. На COVID-19 хворіють також пацієнти з хронічними захворюваннями шлунково-кишкового тракту.

Мета — висвітлити особливості, можливі механізми та наслідки ураження шлунково-кишкового тракту, спричиненого інфекцією SARS-CoV-2, зокрема у пацієнтів із патологією шлунково-кишкового тракту.

Пошук літератури проведено у базах даних Scopus і Web of Science. Клінічні дослідження пацієнтів із COVID-19 засвідчили, що шлунково-кишкові симптоми (анорексія, нудота, блювота, біль у животі та діарея) передують або виникають після респіраторних синдромів із частотою від 10 до 60 %. Вивчено літературні джерела щодо зв'язку між COVID-19 і такими гастроентерологічними патологіями, як шлунково-кишкова кровотеча, гепатит, панкреатит та запальні захворювання кишечника. Ураження органів травлення у пацієнтів як без хронічної патології, так і з наявними захворюваннями, імовірно, пов'язані з високою концентрацією ангіотензинперетворювального ферменту-2 (ACE2) у всьому шлунково-кишковому тракті. Деякі дослідження засвідчили, що спайковий (S) білок вірусу SARS-CoV-2 має високу спорідненість з ACE2 людини, а вірус SARS-CoV-2 проникає в клітини переважно крізь рецептор ACE2. Пошкодження ендотелію та запалення тромбу, а також порушення регуляції імунної відповіді можуть спричинити позалегеневі вияви COVID-19. Це потребує відповідної корекції діагностичного пошуку та терапії.

Ключові слова: COVID-19, гепатит, панкреатит, запальні захворювання кишечника, шлунково-кишкова кровотеча, ACE2.

ДЛЯ ЦИТУВАННЯ

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