® Postepy Hig Med Dosw (online), 2020; 74: 498-503
e-ISSN 1732-2693

www.phmd.pl
Review

Received: 26.06.2020
Accepted: 02.09.2020
Published: 26.11.2020

Gastrointestinal symptoms in the course of COVID-19

Objawy ze strony układu pokarmowego w przebiegu COVID-19

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Summary

COVID-19 is an infectious disease caused by novel coronavirus SARS-CoV-2, a betacoronavirus comprised of single-stranded ribonucleic acid (RNA), the first time reported in December 2019 as pneumonia with unknown etiology in Wuhan City in China. It is a very important current problem for public health worldwide. A typical clinical course includes dyspnoea, dry cough and fever. In the presented paper we conducted the literature review and described the most important facts within the current state of knowledge about symptomatology and pathophysiology of gastrointestinal dysfunction in the course of COVID-19. Data about prevalence of gastrointestinal symptoms in the course of COVID-19 show wide divergence in the cited literature. Generally, the most common reported digestive symptoms were loss of appetite, nausea and vomiting. Liver injury in the course of COVID-19 is also an important and not well understood problem. The virus has high affinity to cells containing angiotensin-converting enzyme 2 (ACE2) protein. Digestive symptoms of COVID-19 may be associated with ACE2 expression in epithelial cells in upper oesophagus, ileum and colon. Previous scientific reports have elucidated the role of ACE2 in modulating intestinal inflammation and diarrhoea.

Keywords: **COVID-19, diarrhoea, abdominal pain, liver injury, angiotensin-converting enzyme 2**

GICID 01.3001.0014.5459
DOI: 10.5604/01.3001.0014.5459
Word count: 4 754
Tables: 1
Figures: 1
References: 69

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Abbreviations: **ACE2** – angiotensin-converting enzyme 2; **COVID-19** – Coronavirus Disease 2019; **MERS** – Middle East Respiratory Syndrome; **RT-PCR** – reverse transcriptase polymerase chain reaction; **SARS** – severe acute respiratory syndrome; **SARS-CoV** – severe acute respiratory syndrome coronavirus; **SARS-CoV-2** – severe acute respiratory syndrome coronavirus 2.

INTRODUCTION

Coronaviruses, a family of viruses, are divided into three genera: alpha, beta and gamma. Coronaviruses belong to the subfamily coronavirinae, within the family of *coronaviridae*, within the order or superfamily of nidovirales. Coronavirus infections occur in domestic and wild animals as well as in humans [58]. Although most coronavirus infections occur in form of a common cold, some coronavirus species can cause acute respiratory distress syndrome such as SARS and MERS [3, 24].

COVID-19 was first reported in December 2019 as pneumonia with unknown etiology in Wuhan City in China in patients, most of whom had visited a market with fish, poultry and wild animals such as bats, snakes, marmots [39]. The disease is caused by SARS-CoV-2, a betacoronavirus comprised of single-stranded ribonucleic acid (RNA) [40]. SARS-CoV-2 shows a similarity of the SARS-CoV genome of 82% and a similarity of the MERS-CoV genome of 50% [67].

Typical symptoms of COVID-19 include fever (83% to 98% of patients), dry cough (76% to 82%), and fatigue or myalgias (11% to 44%), but less characteristic symptoms have been described, which makes the diagnostic process more difficult and may increase the risk of further virus transmission. The most common findings in laboratory tests include lymphopenia (70%), prolonged prothrombin time (58%), and elevated lactate dehydrogenase (40%) [11]. Radiological tests, especially chest computed tomography, are also useful in diagnosis [34].

COVID-19 is currently one of the most important public health problems. It generates a significant economic burden for countries worldwide [18, 23]. Efforts are ongoing around the world to develop effective COVID-19 pharmacotherapy and vaccine [66]. Currently, the use of such drugs as lopinavir [65], ribavirin [14], remdesivir [26], tocilizumab [64], chloroquine and hydroxychloroquine [16], intravenous immunoglobulin therapy [62], and corticosteroids [27] has been considered. Results of the first-in-human trial of COVID-19 vaccine have been presented on 22 May 2020 [69].

A better understanding of the pathophysiology and symptomatology of the new disease plays a crucial role in formulating correct diagnostic, prophylaxis, and therapeutic methods. The purpose of this article is to describe the current state of knowledge about pathophysiology, epidemiology, and symptomatology of gastrointestinal dysfunction in the course of COVID-19.

SYMPTOMATOLOGY AND EPIDEMIOLOGY

According to scientific report from Luo et al. from 1.183 patients with confirmed SARS-CoV-2 infection, 16% had initially only gastrointestinal symptoms: loss of appetite (98%), nausea (73%), vomiting (65%), diarrhoea (37%) and abdominal pain (25%) [41]. Pan et al. have published results from an observational study including 204 patients with recognized COVID-19, from which 103 persons have symptoms from gastrointestinal tract. Ninety-seven patients (47%) had both digestive and respiratory symptoms. Six patients (3%) had digestive symptoms without respiratory symptoms, from which five patients had fever. In the group of patients with digestive symptoms, lack of appetite (78.64%), diarrhoea (33.98%), vomiting (3.88%) and abdominal pain (1.94%) were documented [47].

Lin et al. have presented results from a retrospective, single-centre study. They have analysed 95 cases of SARS-CoV-2 infection confirmed by RT-PCR treated at the Fifth Affiliated Hospital of Sun Yat-sen University in China from 17 January to 15 February 2020. Fifty-eight patients had gastrointestinal symptoms (in 11 patients occurred on admission, in remaining 47 patients developed during hospitalization). Thirty-one patients developed hepatic function impairment during hospitalization. The most important digestive symptoms were diarrhoea (23 patients), anorexia (17 patients) and nausea (17 patients). What is noteworthy, diarrhoea and liver impairment during hospitalization were significantly associated with antibiotic treatment. In 65 patients (42 with and 23 without gastrointestinal symptoms), SARS-CoV-2 was present in faeces, but according to authors' analysis there is no significant association between the presence of viral RNA in the stool and the severity of gastrointestinal symptoms. Interestingly, SARS-CoV-2 RNA has been detected in material taken during endoscopy from oesophagus, stomach, duodenum, and rectum, especially in patients in severe clinical condition [37].

Cheung et al. have performed a meta-analysis of 60 studies comprising 4.243 patients with COVID-19 from six countries (China, South Korea, Singapore, Vietnam, United States, United Kingdom) to assess the epidemiology of symptoms of gastrointestinal manifestations in the course of SARS-CoV-2 infection. They have stated that gastrointestinal symptoms occur in 17.6% patients with COVID-19. The pooled prevalence of loss of appetite was 26.8%, of diarrhoea 12.5%, of nausea and vomiting taken together 10.2%, and of abdominal pain 9.2%. An important conclusion from this meta-analysis is the observation that the prevalence of severe disease was more common in patients who had gastrointestinal symptoms than those who did not (17.1% vs 11.8%). The authors noted the high heterogeneity of the data in the included studies, mainly in terms of loss of appetite, diarrhoea, and nausea/vomiting, to a less extent regarding abdominal pain. In 48.1% of patients, the virus RNA was detectable in the stool. Interestingly, in 70.3% of this group, the virus was present in the stool even when the test for the presence of the virus in the respiratory tract was negative [9]. What is noteworthy, Ling et al. have noticed that viral presence in the stool lasted longer in patients treated with corticosteroids [38].

Chen et al. have published results from retrospective, single-centre analysis of 99 cases of pneumonia caused by SARS-CoV-2 infection. In 43 patients, features of liver injury

Table 1. Data from meta-analysis evaluating manifestations of gastrointestinal and liver involvement in patients with COVID-19 [43]

Manifestation of digestive system	Prevalence [%]
Loss of appetite	21
Diarrhoea	9
Nausea and vomiting	6
Abdominal pain	3
Liver injury	19
Increased AST	21
Increased ALT	18
Increased total bilirubin	6
Decreased albumin	6

in laboratory tests defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) activity above the normal range have been reported. One patient presented severe liver injury with ALT 7590 U/L and AST 1445 U/L. Total bilirubin blood concentration was increased in 18% of patients [8]. Generally, elevated blood levels of aminotransferases according to different studies occur in 14% to 53% of patients suffering from COVID-19 [15, 22, 27, 61, 63, 67, 68].

Dysphagia is a significant problem in patients after treatment for COVID-19 [12]. Two main mechanisms leading to dysphagia associated with COVID-19 in severely ill patients have been elucidated in the literature. Dysphagia commonly occurs in patients after mechanical ventilation in association with endotracheal intubation. The frequency of dysphagia after extubation in trials included into systematic review prepared by Skoretz et al. ranged from 3% to 62% [50]. Goyal et al. have published a clinical report describing the first 393 patients hospitalized in New York due to COVID-19. A total of 130 patients (33.1%) developed respiratory failure and invasive mechanical ventilation was necessary [19]. The second mechanism is direct influence of SARS-CoV-2 on the central nervous system. It was evidenced that coronaviruses are neurotropic [35]. SARS-CoV particles have been found in human neurocytes [20]. It is likely that SARS-CoV-2 can also access the human nervous system and cause its injury [53]. It is also postulated that similar mechanism could explain anosmia and ageusia in the course of COVID-19 [55].

Mao et al. have prepared a systematic review and meta-analysis including data from 6.686 patients (35 studies). A total of 6.064 patients reporting gastrointestinal symptoms participated in 29 studies. In 12 studies (1.267 participants), liver injury was reported. Interestingly, the authors have noticed that patients with severe COVID-19 were more likely to present with abdominal pain (OR 7.10 [95% CI 1.93–26.07]; p = 0.003) compared with those with non-severe disease. No significant difference has been found between patients with severe and non-severe disease in loss of appetite, diarrhoea, or nausea or vomiting. The prevalence of gastrointestinal manifestations among patients suffering from COVID-19 was presented in Table 1 [43]. What is noteworthy, gastrointestinal symptoms are one of the reasons for the increased risk of malnutrition, as found in COVID-19 patients, especially among the elderly people [33].

Wang et al. have reported that in the group of 52 patients with pneumonia in the course of COVID-19, incidence of pancreatic injury defined as elevated blood activity of amylase or lipase was 17%. Clinical symptoms of severe pancreatitis have not occurred [57].

Studies in children have documented gastrointestinal symptoms in COVID-19 in this population as well. A higher proportion of children with vomiting has been reported than that of adults [54].

PATHOPHYSIOLOGY OF GASTROINTESTINAL SYSTEM DYSFUNCTION

The SARS-CoV-2 virion consists of nucleocapsid containing genomic RNA and phosphorylated nucleocapsid protein (N) inside a phospholipid bilayer covered by the spike glycoprotein trimmer (S) and the hemagglutinin-esterase (HE). Among the S proteins in the viral envelope, there are molecules of the membrane protein (M) and the envelope protein (E). The size of the genome is 29.9 kb [28].

The virus uses densely glycosylated spike protein (S glycoprotein) to enter host cells. The virus has a high affinity to cells containing angiotensin-converting enzyme 2 (ACE2) protein [59]. The place of ACE2 in the renin-angiotensin-aldosterone system is presented in Figure 1.

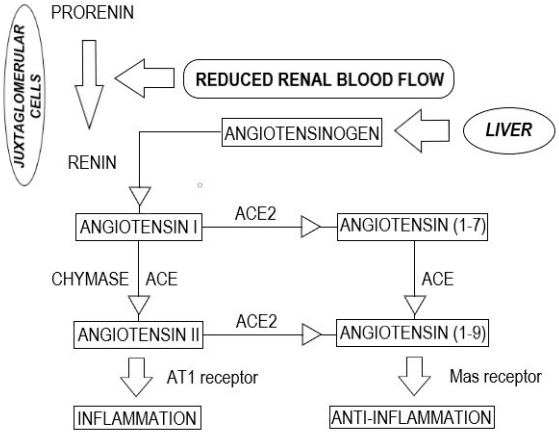

Fig. 1. Basics of renin-angiotensin-aldosterone-system (RAAS) and the role of ACE2 [13, 46, 48]

S glycoprotein of SARS-CoV-2 binds to ACE2 with a 10-20-fold higher affinity than SARS-CoV [60]. TMPRSS2 protease activity plays a crucial role in S glycoprotein priming, which is significant for virus spread [25]. ACE2 is highly expressed in type II alveolar cells in lung [5]. Digestive symptoms of COVID-19 might be associated with ACE2 expression in epithelial cells in upper oesophagus,

ileum, and colon [21]. It has been shown that the high expression of ACE2 increased the expression of genes involved in viral replication, which may enhance the ability of the virus to enter the host cells [32]. It is well established that ACE2 has activity of kininase and it is responsible for bradykinin (BK) degradation [49]. Bradykinin is a peptide mediator, which plays an important role in vasodilation and inflammatory response [1]. Biological effects of bradykinin on the cellular level is mediated by two types G protein-coupled receptor, B1 and B2. Signal transduction mechanisms involve a change in the activity of phospholipase C, phospholipase A2, prostaglandins, and finally alterations in calcium ion cytoplasmic concentration [17]. It has been postulated that SARS-CoV-2 interaction with ACE2 on the cell surface leads to downregulation of ACE2 expression and function, which is associated with decreased inactivation in B1 receptor potent ligand des-Arg9-BK. This might explain local pulmonary angioedema in the course of SARS-CoV-2 infection [56]. It has been reported that ACE2 plays an important role in modulating intestinal inflammation and diarrhoea [36]. It has been shown that ACE2 expression is elevated in the colon during experimental model of colitis induced by dextran sulphate sodium (DSS) [30] and ACE2 inhibitor reduces severity of illness [6]. Presumed mechanism of diarrhoea in the course of COVID-19 is associated with alteration in intestinal permeability and malabsorption induced by interaction of SARS-CoV-2 with ACE2 [10].

A significant term associated with the severe course of COVID-19 is cytokine storm, which should be understood as the overproduction of such inflammatory cytokines as TNF, IL-1β and IL-6. Cytokine storm can lead to vascular hyperpermeability, multiorgan failure, and eventually death when the high cytokine concentrations persist for a sufficiently long time [29]. The pathogenesis of liver injury in patients with SARS-CoV-2 infection remains poorly understood and further studies are necessary. Liver damage in patients with COVID-19 might be caused by the virus replication in liver cells [67].

It is also possible that the liver impairment is associated with drug hepatotoxicity. Ong et al. have noticed that liver injury developed in all patients in their cohort during the course of COVID-19 was associated with the use of lopinavir and ritonavir and it normalised with cessation [45].

Taken together, several possible mechanisms of liver injury in the course of COVID-19 are discussed in the literature:

- liver damage as the consequence of severe inflammatory response to SARS-CoV-2 infection [44];
- ACE2 is expressed in biliary epithelial cells and liver injury may be the consequence of direct infection by SARS-CoV-2 [7];
- liver damage caused by hypoxia induced by respiratory insufficiency in the course of COVID-19 [52];
- drug-induced hepatotoxicity [4];
- activation or exacerbation of previously existing (perhaps non-diagnosed) liver disease caused by SARS-CoV-2 infection [42].

CONCLUSION

Although COVID-19 has been considered mainly as a respiratory tract infection, in some cases leading to acute respiratory distress syndrome, our review shows that gastrointestinal symptoms are also important in the symptomatology of this new and yet not well understood disease.

Gastrointestinal manifestations have also been reported during the course of SARS and MERS [2, 31]. Considering the molecular and clinical similarities between SARS-CoV, MERS-CoV and SARS-CoV-2, gastrointestinal manifestations of SARS-CoV-2 infection is not completely unexpected.

Gastrointestinal symptomatology of COVID-19 and possible faecal-oral way of virus transmission should be considered when qualifying patients for endoscopic examinations during the pandemic. Endoscopic procedures should be performed with personal protective equipment in conditions of negative pressure rooms [51].

Further studies concentrating on role of gastrointestinal tract in pathophysiology of COVID-19 and significance of digestive symptoms in diagnosis are necessary. During the coronavirus pandemic, we should pay attention to less common symptoms such as abdominal pain and diarrhoea without symptoms of respiratory tract infection. Especially patient with diarrhoea should be tested for SARS-CoV-2 infection to control the potential of fecal-mediated spread of this virus.

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The authors have no potential conflicts of interest to declare.