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Review Article

COVID-19 and Gastrointestinal Disorders: Possible Pathomechanism of SARS-CoV2 Infection in Inflammatory Bowel Disease Patients

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Abstract

COVID-19 infection has become a global pandemic and has hit almost all countries in the world. SARS CoV2 virus can cause mainly respiratory infection called COVID19, but can also influence another organs, like gastrointestinal system. One of the comorbidities related to the digestive organs is Inflammatory Bowel Disease (IBD) which is the most common inflammation in the large intestine. The prevalence rate of IBD has recently increased (approximately 400 cases per 100,000 person/years in 2020) mainly related to low fiber diet, smoking, alcohol consumption, obesity and the influence of environmental factors, such as air pollution. The mechanism of the relationship between COVID19 infection and IBD is still not widely known. Several theories explain that genetic factors, direct infection with the SARS-CoV2 virus, inflammation, the influence of the gut microbiota, and COVID19 therapy are suspected of having effect on the worsening of IBD. Through this article, the author would like to describe some of the pathomechanism reviews of the influence of COVID19 infection on patients who have experienced IBD. By knowing the right pathomechanism, it is hoped that medical personnel can handle cases of patients with IBD who experience COVID-19 infection and can further reduce the morbidity and mortality rates.

Keywords: COVID19; IBD; Direct Infection; Inflammation; Dysbiosis; Hypercoagulation

Introduction

After emerging in December 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread rapidly across the globe, leading to high morbidity and mortality. As March 20, 2022, WHO reported that globally there have been 468 million confirmed cases with more than 6 million deaths. COVID-19 was originally considered a respiratory disease, and the majority of patients exhibit typical respiratory symptoms, among which fever, dry cough, and dyspnea are the most prominent symptoms [1,2].

Some evidence indicates that the gastrointestinal tract (GIT), including the stomach, small intestine, large intestine, liver, and pancreas, might also be affected by SARS-CoV-2. Notably US reported a history of nausea and vomiting as symptom and sign of COVID19 was found on admission and then diarrhea on day 2 after admission [1]. With an incidence of 18.6%, gastrointestinal (GI) features included anorexia (26.1%), diarrhea (13.5%), vomiting (6.0%), and nausea (7.5%) in a study involving 25,210 patients [3]. The GI tract in SARSCoV2 infection became inflammed and cause bleeding. This phenomenon will impact on the immune system in intestine and can be connected with lungs and other organs [4] Inflammatory bowel disease (IBD) is one of gastrointestinal disease with criteria: chronic, precancerous, and often relaps. Clinical outcome of COVID19 infection has been shown by the inflammatory bowel disease (IBD) and was reported by a study from Italy. Worsening outcome caused by active IBD was suspected has association with old age and comorbidities [5] The pathogenesis of IBD remains to be determined, but may be related to interactions among multiple pathogenic factors, including disease susceptibility gene variants, environmental stimulations, abnormal gut microbial, immune factors and some agents like; toxins and pollutans [6] Recent study

reports that hypercoagulation state among patients with Covid-19 can has correlation with inflammatory bowel disease too [7,8].

Pathophysiology of IBD

Based on the increasing incidence of IBD, so this disease became a global healthcare problem. Inflammatory bowel disease (IBD) has been a global healthcare problem with a sustained increasing incidence. The worldwide incidence of IBD has increased over the past several years, especially in the rapidly developing countries in Asia [9]. IBD can be divided by two major forms depends on histopathological features: Crohn's disease (CD) and ulcerative colitis (UC) [7]. The characteristic of CD is non continuous (called skip lesions) and can cause transmural inflammation especially in terminal ileum or perianal region of colon. The presence of pathogenic factors such as abnormal gut microbiota, dysregulation of immune respons, environmental changes, and involvement of genetic factors are some factors associated with the pathogenesis of IBD [10,11].

One of the gene variants include the clearest linkages is for IBD-1, a susceptibility locus in the pericentromeric region of chromosome 16,30. Benzimidazole diamides was identified as gene and protein which has function as selective inhibitors of the nucleotide binding oligomerization domain 2 (NOD2). NOD2 is also known as caspase activation and recruitment domain 15 (CARD15). Research has proved that there were strong association in replication process between CD and NOD2 gene at genome wide level. Some genes like CARD9, IL1R 2, REL, SMAD3 and PRDM1 were suspected can interfere the immune function in IBD [3,12]

Environmental factors, such as air pollution, chemical factors or free radicals are believed to have strong association with pathogenesis of IBD. Some risk factors were considered to be involved in IBD, such as: low fiber diet, drugs, cigarette, and psychological factors which can induced stress. Cigarette smoking has been established to become one of environment trigger for IBD patients [10] The other hand, air pollution nowadays can role as an oxidative stress which can cause inflammation in CD and UC. The association between air pollution and IBD are this substance can trigger the expression of leucocytes (especially PMN) and plasma cytokines [3].

Around 1150 bacterial species roughly and about 160 species individually, mentioned as gut microbiomes lived in human gut. Two kinds of gut microbiota which have role in production of epithelial metabolic substrates are Firmicutes sp and Bacteriodetes sp. In patients with CD there are contrast form of gut microbiota compared with healthy subjects, the level of Firmicutes and Bacteroidetes decreased, meanwhile enterobacteria will be increased [12]. Research suggests that genetic alterations result in varied immunoregulatory responses to the same bacteria. For example, exposure to Bacteroides vulgatus in an IL-10- deficient mouse results in only minimal inflammation, whereas the same bacterium causes a high expression of inflammation in a human leukocyte antigen-B27 b2 transgenic model. Thus, in patients with IBD, it is likely that different bacteria are responsible for the inflammatory effect in different individuals [13].

The established pathophysiology of IBD is inflammation process which include the involvement of some cytokines, chemokines and Tcells [14] Many studies had proved that some cytokines, like IL-1, IL-6, IL-10, IL-17 and IL-18 will overexpressed in IBD patients. The IL-6 and IL-17are proinflammatory cytokines that activates STAT-3 which stimulates strong chronic immune inflammatory response. One kind of immunosuppressive cytokine (or anti-inflammatory cytokine) is IL-10 which has therapeutic effect for IBD [10]. IL-8 production will increased in UC patients. Intestinal inflammation in CD by immune system are mediated by Th1 cells, induced by IL-12, and will produce a high amount of IFN-γ, whereas Th2 cells release IL-4, IL-5 and IL-13 [7,8]. An abnormal Th1 immune response is thought to inflame intestinal in CD. There is a new theory that Th17 cells has role in gut inflammatory response in IBD [3]. Inflammation in IBD gut tissue will also release IL-17 and Th17-related cytokines [14]. Compared with healthy patients, the expression of IL-17 and level of IL-17A and IL-17mRNA level were higher in IBD patients [2].

Pathomechanism of COVID19 infection in inflammatory bowel disease

Although there are no exact reports about the percentage patients with IBD who obtained COVID-19 infection, the real evidence reports these population whose suffer from COVID19 will be more harmful. There are several pathomechanism about the correlation of IBD with SARS-CoV infection, like direct infection of SARS-CoV which bonds with ACE2 receptors, inflammation process with the involvement of adaptive immunity, role of gut microbiota, involvement of hypercoagulation, and the influence of some COVID19 drugs with IBD patients.

Direct infection and the role ACE2 receptors

There are strong association between digestive symptoms and the process of COVID19 disease [3]. As already discovered that

SARS CoV2 virus can spread after bonding with ACE2 receptors, and these receptors are highly expressed in GI tract too. Angiotensin converting enzymes (ACE2) are expressed by epithelial cells not only in respiratory tract, but also in kidney, blood vessels and intestine, which the expression is the highest. In ulcerative colitis (UC) the expression of ACE2 receptors will be increased probably associated with inflammation processes [5,15].

Pathogenesis of SARS CoV2 virus depends on the specific "spike" glycoprotein and this protein is activated through the tryp sin like protease, the transmembrane protease serine 2 (TMPRSS2) that mediates fusion of the coronavirus envelope with the host cell membrane [30]. These glycoprotein was upregulated in IBD (Figure 1) [15].

Enterocyte dysfunction after binding of SARSCoV2 with ACE2 receptors will cause an alteration of intestinal permeability. About 40% incidence of diarrhea has been proven also happened in severe acute respiratory syndrome (SARS) patients. Intestinal problems were also associated with the severity of the infection [14].

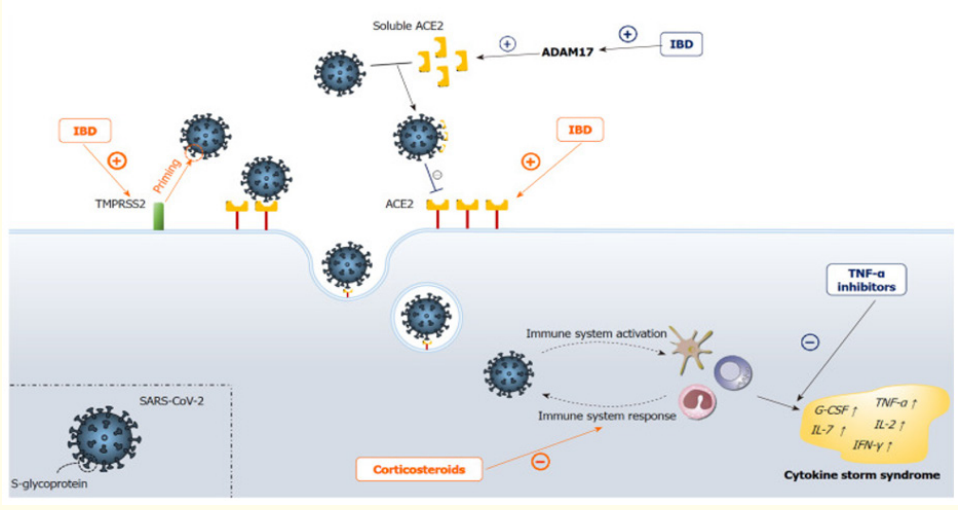

Figure 1: Associated pathway between intestinal severe acute respiratory syndrome coronavirus 2 infection with proposed inflammatory bowel disease effects. The blue lines represent inflammatory bowel disease (IBD)/IBD approach-mediated reduction in either coronavirus disease 2019 (COVID19) acquisition or poor outcomes of it, whereas the red lines represent IBD/IBD approach-mediated increase in risk for COVID-19 acquisition or poor outcomes. IBD: Inflammatory bowel disease; ADAM17: A disintegrin and metalloproteinase 17; TNF-α: Tumor necrosis factor-alpha; ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane protease serine 2; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; IL: Interleukin; G-CSF: Granulocyte-colony stimulating factor; IFN-γ: Interferon-γ (Kumric,2021).

The mechanism of direct infection by SARS-CoV2 infection has to be supported by the inflammation process and the alteration of gut microbiota (intestinal dysbiosis) which are connected one another.

Inflammation process and the role immune cells

There are many evidence that covid 19 infection has strong connection with innate and adaptive immune cell activation in the infected host [14]. The local accumulation of neutrophils at the site of the infection are caused by release of mediators and chemokines by infected cells. The inflammation and mucosal damage in intestinal tract will trigger gastrointestinal symptom. There is a loss of intestinal barrier integrity and gut microbes that can activate innate and adaptive immune cells to release proinflammatory cytokines into the circulatory system, leading to systemic inflammation [5].

Cytokines and chemokines are well established mediators of the immune system and many novel antiviruses are based on this mediators. The excessive or large amount production of proinflammatory cytokines in response of COVID19 infection is called cytokine storm. Cytokine storm has already proved by many studies that has strong association with ARDS and multiorgan failure in COVID-19 [16]. Activated macrophages and other lymphocytes as innate immune cells will surge proinflammatory cytokines and chemokines

(IL-6, TNF- α, IL-8, MCP-1, IL-1 β, CCL2, CCL5, and IF) and usually have delayed respons in COVID-19. The recruitment and activation of adaptive immune cells like T cells, neutrophils and NK cells along with further production are induced by these cytokines and can damage the intestinal tissue (Figure 2) [17] Some studies also reports that IBD patients whose got COVID19 infection can also experience cytokine storm syndrome especially before treated with biologic agents such as bevacizumab, vedolizumab or tocilizumab which is known as anti-IL-6 in COVID19. Those immunotherapies which have immunosuppression effect can decrease the risk of hyperinflammatory response and may be considered to overcome the cytokine storm and have beneficial effect for IBD patients [18].

Analysis of inflammation markers in serum showed elevated levels of procalcitonin, C reactive protein, D-dimer and ferritin in COVID-19. Compared with milder cases in COVID-19, serum levels of TNF, IL-2R, IL-6, Il-8 and IL-10 were much higher in severe cases, while IL 1beta levels and the number of IFN gamma producing CD4 and CD8 T cells remained unchanged [10]. The expression of ACE2 are triggered by mucosal inflammation and this incidence can drived by IFN-gamma, one kind of cytokines expressed in IBD [14].

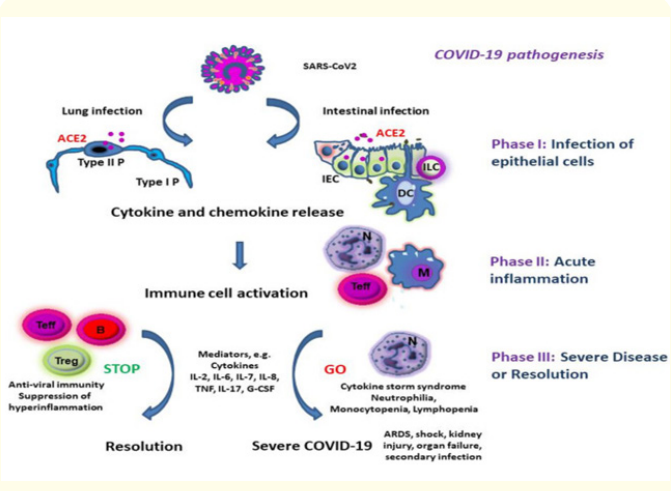

Figure 2: Hypothetical pathogenesis of COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infects ACE2 expressing epithelial cells in the lung and/or the intestine. Some mediators who are expressed by SARS-CoV2 on ACE2 receptors will produced and activate immune cell. Activation of overwhelming immune cells in COVID19 infection can cause severe complication, like acute respiratory distress syndrome (ARDS), shock and multiorgan failure B', B lymphocytes; IEC, intestinal epithelial cell; ILC, innate lymphoid cell; M, monocyte/macrophage; N, neutrophils; Teff, effector T cells; Treg, regulatory T cell; Type I P, type I pneumocytes; Type II P, type II pneumocytes (Neurath,2020).

The role of gut microbiota in IBD and COVID19 infection

The composition of the human gut microbiota which are very variable are believed can have involvement in development of infectious disease in human. The balance composition of gut microbiota(symbiosis) in healthy human is recognized as crucial pattern for maintaining a normal GI tract [5] The pathophysiology of patients with confirmed IBD has been proved to have correlation with gut microbiomes. Although there are many theories explain about the alterations of gut microbial communities of patients with IBD, so far the association between microbial factors and inflammation are not clearly yet [3,19].

Studies show that IBD with active disease is strongly associated with an overall increased prevalence of proteobacteria (i.e., bacterioides) and drop in intestinal species richness, more specifically a significant drop in firmicutes [5]. Novel studies reveal there is association between IBD and decreased of butyrate producing Faecali bacterium prausnitzii (firmicutes) as the group of Clostridia cluster IV species and the increasing prevalence of the AIEC will increase rate of E coli in ileal CD [20,21].

Intestinal and lung microbiome flora in COVID 19 are very amazed caused by this colonization has diverse numbers and about 235 variety of bacterias with important role and has already described above that the homeostasis of the body is the basic of physiological function. The disorders of viral balance of GI tract in COVID-19 infection will lead to further impact of dysbiosis [3]. The development and function of immune system are influenced not only by the process of inflammation itself but also by the microbiota. Emerging experimental and epidemiological evidences indicated there is crucial cross-talk between the intestinal microbiota and the lungs which was termed 'gut-lung axis' or another terminology 'brain-gut-lung axis (Figure 3) [22].

Changes in the composition and function of the GI tract could further influence the respiratory tract through the common mucosal immune system with the largest being the intestinal immune system. There is strong association between dysbiosis in respiratory tract and functional disorders with digestive tract and that is known as gut-lung axis [3,15].

Furthermore, there is connection between gut dysbiosis with inflammation in IBD with COVID19 patients. The release of intestinal cytokines into the circulatory system and increasing the systemic inflammation of COVID 19 are triggered by microbial products and

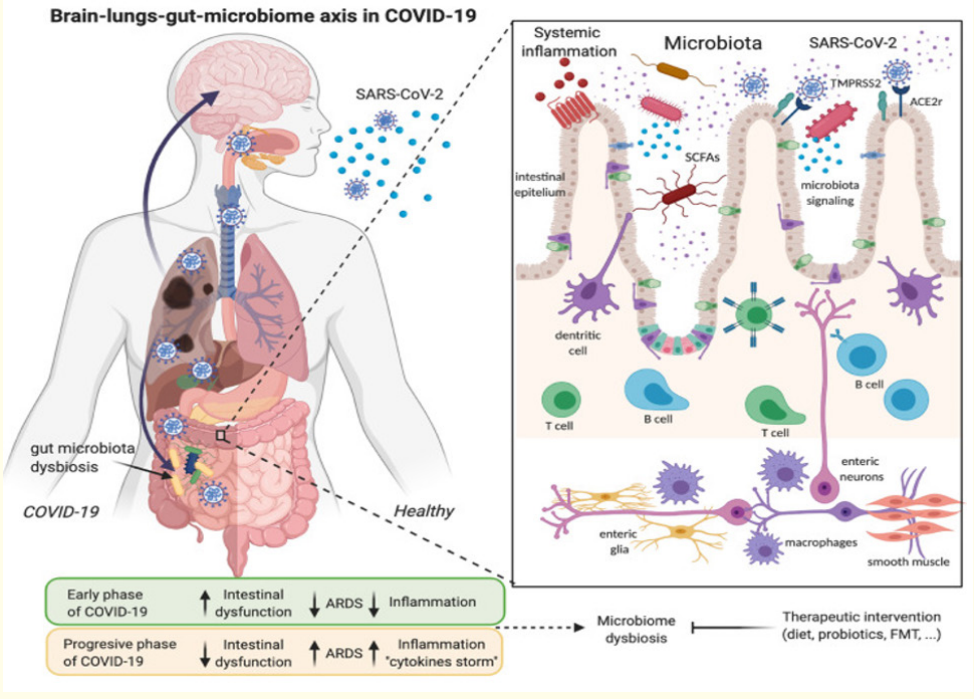

Figure 3: The interaction of SARS-CoV2 infection with lung-gut-brain axis and dysbiosis can be seen with this illustrative model.. Some organs like: esophagus, lungs, liver, kidneys, brain, colon, or small intestine epithelium can express Angiotensin Converting Enzyme II (ACE2) receptors and transmembrane serine protease 2 (TMPRSS2). After binding with ACE2 receptors, SARS CoV2 virus will activated and induce inflammation, especially diarrhea. Because these tissues above are target of SARS CoV2, so in the early phase of infection moreover with high viral load can become serious intestinal problems. After the microbiome dysbiosis altered T and B cells of intestinal immune system, directly the enteric system will send inflammatory signals to current circulatory or other organ, including brain. The continuous phase where acute respiratory distress syndrome (ARDS) appears, the intestinal symptoms will decrease, otherwise the inflammation from the cytokines storm increases considerably. This is called the second phase of COVID19 (Villapol,2020).

cytokines which can cause microbial dysbiosis [5]. Hence, inverse correlation between healthy subjects and COVID19, whereas in COVID19 infection there are abundance of Coprobacillus, Clostridium ramosum, and Clostridium hathewayi and lack of Faecalibacterium p rausnitzii (an anti inflammatory bacterium [9].

Hypercoagulability and COVID19 in IBD settings

Thromboembolism-related complication is common in severe COVID-19 patients. After binding with ACE2 receptor, SARS CoV2 virus directly infect the endothelial cells, cause diffuse inflammation spreadly. The exact mechanism of hypercoagulability and thromboembolism in COVID 19 disease is still not yet known for certain. According to Virchow's triad, there are association among vascular endothelial injury, hypercoagulability and blood stasis in the pathophysiology of thromboembolism [8] The association between COVID19 infection with risk of Venous Tromboembolism (VTE) still not well recognized yet [13]. In intensive care unit (ICU) setting evidence reported that incidence of venous tromboembolisme (especially deep vein thrombosis) were increased. Because of hypercoagulation is more severe in ICU so the incidence of pulmonary embolism (PE) are higher in COVID19 patients [8].

The progression and severity of infla mmatory bowel disease (IBD) was proved to be associated with effect of inflammation and thrombosis. About 1% until 7% venous thromboembolism (VTE) complication was found in patients with IBD. The evidence reported that VTE risk will about 3 times greater in patients with IBD compared with normal population [23] Reported by many metanalysis that the increased risk of VTE patients with IBD were depended on the phases of IBD [24]

Basic theory of thrombosis in IBD is similar with other organs [24]. It has been established that the theory of thrombosis is caused by imbalance between prothrombotic and antithrombotic mechanism. Chronic vasculitis which marked by focal arteritis and fibrin deposition are specific characteristics of multifocal vascular infarcts in intestine microcirculation. These findings supported that there were thrombosis process in IBD [25]. Based on the same mechanism, in COVID19 settings, this patients with IBD with COVID19 infection will tend to have possibility of venous or arterial thrombosis [13].

There are some hereditary and acquired factors which will increase thrombosis risk of patients with IBD, and the acquired risk is divided into common and IBD-related risk factors (Table 1).

Hereditary Factors	Acquired Factors	
	Common Risk	IBD Related
Factor V Leiden mutation Deficiencies of protein C, protein S, and antithrombin Methylene tetrahydrofolate reductase gene mutation PAI-1 gene polymorphism Prothrombin G20210A gene mutation Factor XIII gene mutation	Advanced age Long air travel Obesity Smoking Hypertension Metabolic syndrome Pregnancy	Inflammation (active) Immobilization Surgery Malignancy Dehydration Corticosteroid therapy Central venous line Hyperhomocysteinemia Antiphospholipid Ab

Table 1: Hereditary and Acquired Factors That Increase Thrombosis Risk in IBD.

Conclusion

The relationship between COVID19 infection in IBD patients and various possible pathophysiology between them has been described. In general, there is no different between the mechanism of COVID-19 infection in both normal patients and those with comorbidities, in this case is IBD. The large number of ACE2 receptors in the gastrointestinal tract will strengthen the bond between the SARS-CoV2 virus and ACE2 receptors and will activate the inflammatory process mediated by innate and adaptive immunity. This mechanism will lead to the activation of Thelper1, Thelper2 and Thelper17 lymphocytes, proinflammatory cytokines and chemokines. The effect of COVID19 on the large intestinal tract will also exacerbate intestinal dysbiosis that has been disrupted in IBD conditions. The existence of hypercoagulable conditions due to thrombosis which will aggravate the condition of patients with IBD is also a mechanism that needs to be considered. Further novel researches are needed to support the pathomechanism between COVID19 infection and IBD problems, so we can treat these complicated patients more accurately.

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