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Potential role of microbiome in liver injury during COVID-19: Further research is needed

Tovani-Palone MR *et al*. Microbiome *vs* liver injury during COVID-19

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Abstract

Although different researches have associated coronavirus disease 2019 (COVID-19) with the occurrence of liver injury, the hepatic injury route during the COVID-19 course is not yet fully understood. In order to better understand the mechanisms of the disease, the human gut microbiota has been the subject of extensive discussion in the context of the COVID-19 pathophysiology. However, there is to date very little evidence about the risks of liver injury due to COVID-19 in many specific populations. Further research in this field could allow the discovery of new personalized treatment strategies aimed at improving the microbiota composition, thereby reducing COVID-19 severity and its complications in different populations. In this article, we discuss basic mechanisms of SARS-CoV-2 infection, recent evidence on the relationship between COVID-19, gut microbiome and liver injury, as well as propose recommendations for further research.

Key Words: COVID-19; Gut microbiota; Coronavirus; Gut microbial-host-immune axis; Gut-lung axis; Liver injury

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Core Tip: Although different researches have associated coronavirus disease 2019 (COVID-19) with the occurrence of liver injury, the hepatic injury route during the COVID-19 course is not yet fully understood. Further research is needed to better

understand the impacts of changes of the gut microbiota and immunology of COVID-19 on specific populations.

TO THE EDITOR

The gut-liver axis is a well-described bidirectional relationship where a mutual interaction between gut and liver microbiota occurs that has attracted much attention in the context of coronavirus disease 2019 (COVID-19). This close anatomical and functional relationship between the gut and its microbiota, and liver function, results from an interaction between genetic and environmental factors, including diet, medicine use and diseases[1]. Although the human gut microbiota is recognized to have an important role for immunity and protection against pathogens, its diversity is decreased in old age, which is the age group with the highest mortality from COVID-19[2]. If on the one hand this suggests a potential protection of balanced gut-liver axis against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which should be of interest to prevent and reduce the number of fatal cases of COVID-19; on the other any imbalance of this microbiome should affect immunity as well as viral activity against SARS-CoV-2[3]. Moreover, different studies have also reported the occurrence of liver injury to varying degrees in COVID-19 patients, which could be associated with important changes in both the gut-liver axis microbiota and responses at the cellular and molecular level[4,5]. However, research on the risks of liver injury due to COVID-19 in many specific populations is still scarce. Here we discuss basic mechanisms of SARS-CoV-2 infection, recent evidence on the relationship between COVID-19, gut microbiome and liver injury, as well as propose recommendations for further research.

Cellular entry of SARS-CoV-2 and general implications

There is a consensus among most scientists that the cellular entry of SARS-CoV-2 mainly occur *via* high-affinity interactions between the receptor-binding domain of the SARS-CoV-2 spike protein and the angiotensin converting enzyme 2 (ACE2) receptor, in

addition to other molecules[3-9]. This receptor has been identified in different and important organs, including , the surface of respiratory tract epithelium, epithelial cells of the upper esophagus, enterocytes of the ileum and colon, in the heart, testicles, cells of smooth muscles, the endothelium of pancreatic, brain and kidney blood vessels[4], and in bile duct epithelial cell and liver[5]. The resulting downregulation of ACE2 activity may lead to an increase in angiotensin 2 through ACE. This is due to the fact that the decrease in ACE2 is associated with a lower conversion of angiotensin to angiotensin 1-7 vasodilator. Thus, there is a gradual tendency towards an increase in plasma concentrations of angiotensin I and angiotensin II, causing an imbalance in the renin-angiotensin system as well as a consequent deregulation of systemic homeostasis[6,8].

COVID-19 and gut

According to general statistics, about half of COVID-19 patients are expected to have at least one of these gastrointestinal symptoms: Diarrhea, nausea, vomiting, and abdominal pain[4,5]. Different research has shown that the ACE2 receptor is the main gateway for SARS-CoV-2 into epithelial cells of the gastrointestinal tract. This receptor is in turn highly expressed on epithelial cells in the small intestine. In addition to the decrease in ACE2 receptor expression due to the invasion of SARS-CoV-2, important changes in the gut microbiota involving different microorganisms (dysbiosis) may also occur, affecting above all the function of the intestinal barrier and the permeability and homeostatic balance of metabolites in the gut lumen[8,9].

It is also hypothesized that SARS-CoV-2 infection of epithelial cells in the gut, especially in the small intestine, could result in malnutrition as well as potentiate the associated dysbiosis, leading to impaired gut barrier function and systemic inflammation. This in turn may create a positive feedback loop for increased translocation of gut microbes into the systemic circulation and potentiation of inflammation, culminating in systemic inflammation and cytokine storm that may contribute to both worsening gut and systemic damage as well as to increase the

COVID-19 severity[8,9]. Therefore, in addition to the classic gastrointestinal disorders and symptoms of COVID-19, accessory digestive organs such as the liver can be affected, as a result of the worsening of the infection[4].

COVID-19 and liver injury

Although COVID-19 has been associated with liver injury by innumerous researchers, the hepatic injury route during the COVID-19 course is not yet fully understood. It is believed that such injury is due to specific pathogenic mechanisms of the virus or even the use of hepatotoxic drugs[3,4]. Among the different etiological hypotheses described in the literature in order to advance knowledge about this topic the following stand out: (1) Liver injury resulting from a direct virus cytopathic effect by lysis or by inducing apoptosis; (2) immune-mediated liver injury, source from pro-inflammatory cytokines [interleukin (IL)-1, IL-6, tumor necrosis factor], chemokine, and inflammatory cells produced against the SARS-CoV-2; (3) liver injury resulting from viral-induced cytotoxic T cells (CD8); (4) liver injury due to the use of drugs including antivirals, anti-inflammatory drugs, anticoagulants, antibiotics, and which are used underlying chronic diseases during the SARS-CoV-2 infection; (5) liver injury caused by hypoxia resulting from pneumonia[4,5]; and (6) liver injury resulting from gut vascular barrier and dysbiosis due to indirect effect of toxic compound of opportunistic microorganisms[5].

COVID-19, gut microbiome and liver injury

More specifically, researchers in this field believe that the occurrence of prolonged gut microbiome dysbiosis in COVID-19 patients may be associated with two important phenomena: Shedding of fecal virus into the environment and disease severity. Evidence for this pathophysiological mechanism is based on the hypothesis that dysbiosis may lead to epithelial inflammation and increase in ACE2 expression. Given that ACE2 plays a key role in dietary amino acid homeostasis, patients can be severely affected. In this connection, SARS-CoV-2 binds to ACE2, leading to microflora imbalance. This is because the possible downregulation of ACE2 may reduce the

secretion of antimicrobial peptides and in turn lead to increased pathogen survival and gut dysbiosis[5]. It is also worth noting that some drugs used to treat COVID-19, such as corticosteroids, have been shown to interact with the gut microbiome. This is also true for chloroquine, which has been equivocally administered to many patients[3,5] as well as different medicinal herbs[10].

Despite this, in the current context of the ongoing pandemic, although a large amount of research has been published on liver injury due to COVID-19[4,5] there is to date very little evidence about the risk of this type of injury in many specific populations. Important research has demonstrated a greater vulnerability to alterations in the composition of the gut microbiota in different populations. This is true for example for the population of individuals with cleft lip and palate[11] and Hashimoto's thyroiditis[12]. Therefore, knowing more about interactions between the human microbiota and the host cytokine pathway should be of great relevance in this connection. One of the justifications for carrying out further research in this field includes the need to discover new personalized treatment strategies to improve the composition of the gut microbiota in order to more effectively reduce the severity of COVID-19 and its complications[3,5]. This in conjunction with healthy lifestyle could have positive impacts on both COVID-19 prevention and treatment[13,14].

CONCLUSION

Finally, in view of the development of new COVID-19 vaccines, another important point to take into account is that the microbiome may affect the immune response of vaccines. This is due to the fact that the immunogenicity can be impaired with dysbiosis[5]. Moreover, faced with a probable endemic situation of COVID-19 in the world, further microbiological and immunological research may be critical to evidence more robustly the impacts of changes on the balance of the human microbiota and immunology related to COVID-19, in order to achieve better predictions in the fight against possible new SARS-CoV-2 variants.

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