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The Role of the Microbiome and Nutritional Therapy in Critical COVID-19

Dysbiosis has been closely related to inflammation and severe-to-critical COVID-19, a reason why nutritional therapy could be important in the prevention and management of critical disease.

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Introduction

Infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease (COVID-19), involves the recognition of the cell's angiotensin converting enzyme 2 (ACE2) receptor through its Spike protein. ACE2 is not only expressed in the respiratory tract, but also in the gastrointestinal tract, especially enterocytes of the ileum and colon (An et al. 2021). The interactions between enterocytes, ACE2 receptors and the gastrointestinal microbiome are believed to be involved in health and disease, possibly leading to gastrointestinal symptoms in patients with COVID-19 (Pan et al. 2020). Since SARS-CoV-2 RNA has been identified in stools of patients with COVID-19, viral infection of enterocytes could play a role in its pathogenesis (Xiao et al. 2020). Understanding the role of intestinal dysbiosis and nutritional therapy in patients with COVID-19 could be important to improve management of patients with critical disease.

Human Microbiome and SARS-CoV-2 Infection

SARS-CoV-2 has been detected in nasopharyngeal and oropharyngeal swabs, and faecal samples of patients with COVID-19 (Xiao et al. 2020). Increased ACE2 expression has been associated with facilitation of viral infection, impaired immune responses, and intestinal dysbiosis during SARS-CoV-2 infection (Aguirre García et al. 2021). Alterations in the intestinal microbiome may influence lung immunity, response to respiratory infections, and development of concomitant gastrointestinal and respiratory symptoms (Chunxi et al. 2020). This link would be of importance since COVID-19 patients with gastrointestinal (GI) symptoms experience greater respiratory distress compared with patients without GI involvement (Mao et al. 2020). Furthermore, chronic conditions which are often associated with intestinal dysbiosis (i.e. obesity, diabetes mellitus, cardiovascular diseases and other age-related disorders) (Durack and Lynch 2019) are associated with greater risk of experiencing severe-to-critical COVID-19 and short-term mortality (Mancilla-Galindo et al. 2020; Vera-Zertuche et al. 2021).

Dysbiosis and Inflammation in COVID-19

Dysbiosis refers to any changes in the composition of the microorganisms which shape the human microbiome, with respect to that found in healthy individuals (Petersen and Round 2014). Therefore, dysbiosis may occur in different forms, including reduced microbial diversity, loss of beneficial microbes, or increased relative abundance of pathogens. Like the chicken-and-egg dilemma, directionality and causality of dysbiosis in the context of COVID-19 remains to be determined since it is not

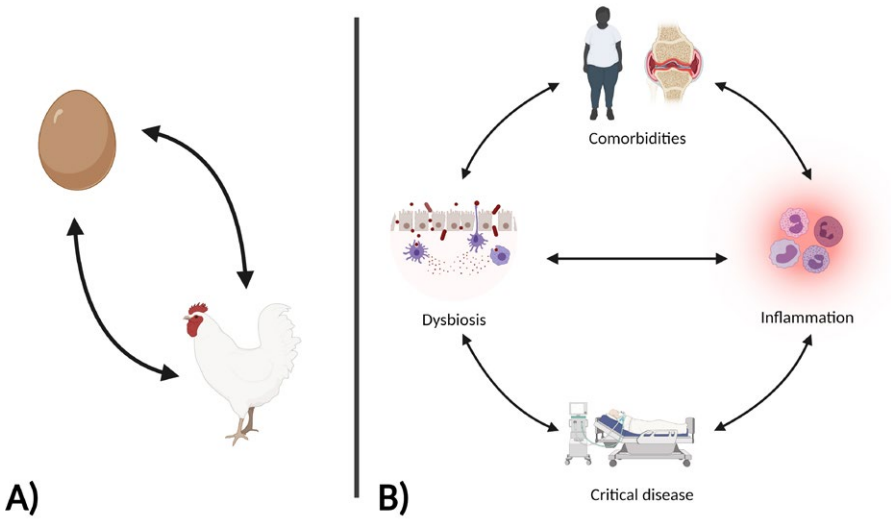

Figure 1. Like the A) chicken-and-egg dilemma, the B) dysbiosis-and-COVID-19 dilemma remains unsolved since there are numerous factors which interplay during viral infection of which causality and directionality have not been elucidated. Created with BioRender.com.

clear yet if dysbiosis puts patients at risk of disease progression, if altered immune responses favour dysbiosis, if dysbiosis promotes inflammation, or if dysbiosis is an incidental finding in severe-to-critical COVID-19 since patients with comorbidities are inherently at increased risk of adverse outcomes. We depict interactions involved in the dysbiosis-and-COVID-19 dilemma in **Figure 1**, which do not necessarily have to be unidirectional but could be bidirectional.

There are various ways by which the microbiome could have its interplay with the immune system and other organs. For instance, metabolites, such as short chain fatty acids (SCFAs), play an important role in modulating immune responses (Gonçalves et al. 2018). These SCFAs can efficiently minimise exaggerated inflammatory responses through T helper (Th) cells, regulatory cells and Th17 effector cells (Li et al. 2018). Furthermore, intestinal dysbiosis is correlated with a lower production of metabolites from intestinal bacteria such as butyrate, leading to increased intestinal permeability (Mosca et al. 2016). Consequently, the integrity of the intestinal barrier is compromised, which facilitates translocation of microbial products, activating the immune system and triggering inflammatory responses. This could be associated with favouring the increased proinflammatory cytokine signature (IL-6, IL-10, and TNF-α) found in patients with severe-to-critical COVID-19 (Del Valle et al. 2020).

Risk Factors

During the patient's stay in the Intensive Care Unit (ICU), there are numerous factors which may promote dysbiosis in critical patients. These include glucose and electrolyte alterations, the use of exogenous opioids, sedatives, catecholamines, and muscle relaxants, poor oral hygiene, invasive devices, body positioning, transport and mobilisation of patients, among others (Bao et al. 2020; Fernández-Barat et al. 2020). Mechanical ventilation in itself promotes airway stress, which affects mucociliar activity and clearance of secretions, with inexistent or diminished cough reflex, which favour overgrowth of opportunistic and pathogenic microorganisms (Dickson 2016).

Comorbidities

Conditions like obesity, cardiovascular disease, hypertension, diabetes, rheumatoid arthritis, and cancer have been associated with higher levels of proinflammatory cytokines and decreased intestinal barrier function, which increases the risk of infection and intestinal dysbiosis (Aguirre García et al. 2021).

Antibiotics

Antibiotics are important therapeutics often used in patients at the ICU which have the potential of reducing mortality, although their irrational use is not uncommon (Ali et al. 2019; Mancilla-Galindo et al. 2021). Use of antibiotics in patients with COVID-19 has been reported to be high (three quarters of patients regardless of receiving ambulatory or hospital care) (Langford et al. 2021). The use of antibiotics is associated with important changes in the GI microbiome with the consequent increase in susceptibility to GI infections by nosocomial pathogens (Dickson 2016). Thus, regeneration of the intestinal microbiota during and after hospitalisation in patients exposed to antibiotics could be considered as part of their rehabilitation.

Sedatives, analgesics, relaxants and inotropes

Increasing evidence has pointed out that sedatives, analgesics, opioids, and muscle relaxants may be involved in favouring dysbiosis. For example, opioid receptors are found not only in the central nervous system but also in the GI tract, thereby having influence on the host-microbe relationships. Also, inotropes have been associated with increased relative abundance of pathogens in the gut. Thus, prescription of these drugs in the ICU must be well founded without forgetting that their prolonged or irrational use may have a negative impact in the microbiome (Rueda-Ruzafa et al. 2020).

Opportunistic Pathogens and COVID-19

A recent study showed that faecal samples from COVID-19 patients tested positive for SARS-CoV-2 up to 6 days after clearance of the virus from the respiratory tract (Zuo

et al. 2020a). In addition, these faecal samples had an increased abundance of bacterial pathogens: *Collinsella aerofaciens, Collinsella tanakaei*, *Streptococcus infantis*, and *Morganella morganii*. Among these species, *C. aerofaciens* is associated with loss of integrity of the intestinal epithelium by increasing the expression of the proinflammatory cytokine IL-17 and chemokines CXCL1 and CXCL5 (Kalinkovich and Livshits 2019). Similarly, higher levels of *Klebsiella, Streptococcus*, and *Ruminococcus gnavus* in COVID-19 patients have been associated with increased proinflammatory cytokines (IFN-γ, TNF-α) and Th1 cell activation (Zuo et al. 2020b).

Opportunistic pathogens (*Streptococcus, Rothia, Veillonella, Erysipelatoclostridium*, and *Actinomyces*), along with bacteria which favour inflammation (*Coprobacillus, Clostridium ramosum, Clostridium hathewayi*) have also been found to be increased during the course of COVID-19 (Zuo et al. 2020a). The number of common opportunistic pathogens of the genus *Enterococcus*, phylum *Firmicutes* such as *E. faecalis*, and Enterobacteriaceae family, which includes *Escherichia coli* and *Klebsiella pneumoniae*, have also been found to be increased in critically ill COVID-19 patients, whereas faecal samples that had low or no SARS-CoV-2 traces were reported to have a higher abundance of SCFAs-producing bacteria like *Parabacteroides merdae, Bacteroides stercoris, Alistipes onderdonkii*, and *Lachnospiraceae bacteria* 1_1_57*FAA* (Tang et al. 2020).

In summary, early evidence has shown that SARS-CoV-2 is associated with dysbiosis, possibly by favouring changes on the microbiome through yet uncharacterised mechanisms.

Bowel Dysfunction

GI symptoms during SARS-CoV-2 infection are usually mild and non-specific, including nausea, vomiting, diarrhoea and abdominal pain (Kariyawasam et al. 2021). Patients with GI symptoms present fever, shortness of breath and body aches more often. As mentioned earlier, the presence of GI symptoms has been associated with greater disease severity, hospitalisation, ICU admission, and intubation (Reintam Blaser et al. 2020). In critically ill patients, gastrointestinal dysfunction is highly prevalent and associated with adverse outcomes. A study in patients with acute respiratory distress syndrome found an increased occurrence of potentially serious GI complications like ileus and mesenteric ischaemia, as well as high risk of GI thrombosis due to increased clotting activity (Helms et al., 2020). Inflammation of the endothelium and increased cell death have been described for GI tissues from patients with COVID-19 (Stahl et al. 2020; Varga et al. 2020).

> **“early evidence has shown that SARS-CoV-2 is associated with dysbiosis, possibly by favouring changes on the microbiome through yet uncharacterised mechanisms”**

Probiotics and Prebiotics

The use of probiotics (live microorganisms able to provide potential health benefits), prebiotics (nutrients that stimulate growth or activity of beneficial microorganisms) and synbiotics (combination of probiotics and prebiotics) have been used to treat intestinal dysbiosis with the intention of allowing proliferation of protective bacteria, potentially attenuating inflammation (Hemarajata and Versalovic 2013). These products may have protective effects by enhancing epithelial barrier function, improving intestinal diversity, and preventing colonisation with opportunistic pathogens. The use of probiotics in critically ill patients could improve outcomes in patients with COVID-19 (Walton et al. 2021), although randomised controlled trials evaluating them should be performed. Nonetheless, the Chinese National Health Commission has advocated for the use of probiotics to treat patients with severe COVID-19 to mitigate intestinal dysbiosis and possibly reduce bacterial translocation and secondary infections ((Tian and Rong 2020). Currently there are multiple lines of research involving probiotics which will allow to elucidate their utility in critical patients.

The Role of Nutritional Support in Dysbiosis

Omega 3

The effect of Omega-3 polyunsaturated fatty acids (omega-3 PUFAs) like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish oil, have the potential to attenuate the inflammatory response related to metabolites released by macrophages (cytokines, chemokines, prostaglandins and leukotrienes) (Gutiérrez et al. 2019), by contributing to the synthesis of eicosanoids and specialised lipid mediators such as resolvins and protectins which lower inflammatory activities. The daily intake of Omega-3 PUFAs produces an increase in SCFAs, resulting in a protective effect for the intestinal microbiome (Watson et al. 2018). In a small randomised study where 1000 mg of omega-3 (400 mg EPA, 200 mg DHA) were administered for 14 days after admission to the ICU, patients had greater survival compared with the control group (Doaei et al. 2021). Therefore, omega 3 PUFAs could be used in critical patients to improve outcomes, although further prospective studies are warranted.

Enteral nutrition

Enteral nutrition (EN) remains the preferred method of nutritional therapy when oral ingestion fails since it promotes GI stimulation. The lack of contact with nutrients in the GI tract of critically ill patients is an important factor associated with intestinal dysbiosis. Resulting alterations of the intestinal mucosa could lead to atrophy of

lymphoid tissue and functional deterioration of the immune system, as well as bacterial proliferation and translocation (Szefel et al. 2015). For this reason, nutritional intervention therapy could play an essential role to prevent such complications. The use of early enteral nutrition has been associated with better immune function, less bacterial translocation, and greater mucosal integrity (Zaher 2020).

The intestinal microbiota is normally preserved through food and its dietary components in adequate proportions and concentrations. Thus, EN should contain protein, a moderate amount of carbohydrates, and the use of fibre once the intestine has recovered functionality, to produce SCFAs that may confer anti-inflammatory benefits (Martindale et al. 2020). With this in mind, inadequate dietary composition of EN may also alter the composition of the intestinal microbiota and increase the growth of opportunistic pathogens (Zaher 2020), whereas overfeeding produces gastrointestinal complications when there is risk of refeeding syndrome (i.e. haemodynamically unstable patient).

Diet as a protective factor

When diets are low in fibre and high in fat and/or carbohydrates, intestinal dysbiosis is more frequent. The intestinal microbiota is responsive to both acute exposures and long-term dietary exposures, with an ability to respond rapidly in a matter of hours (Thaiss et al. 2016). Therefore, eating habits including daytime, duration, and frequency of meals influence the composition and functionality of the intestinal microbiota (Thaiss et al. 2014).

Conclusion

The human microbiome may influence how the immune system responds to viral infections. Dysbiosis has been closely related to inflammation and severe-to-critical COVID-19, although more research is needed to understand the directionality and potential causality of these associations. Nutritional intervention can be helpful to reduce the risk of presenting dysbiosis through regular consumption of foods, nutrients and bioactive molecules with potential anti-inflammatory effects, to promote a healthy microbiome in the absence of critical disease. Nutritional therapy is also of primary importance in critically ill patients with COVID-19.

Conflict of Interest

None. ■

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