COVID-19 and gut microbiota: An unexplored link

INTRODUCTION

Microorganisms colonise the human body in large amounts, and the diversity of such microbes is evident by the fact that it is different amongst individuals as well as ethnic groups. Despite the fact that the role of the human microbes has to be fully understood, it is thought to be linked to number of diseases, such as inflammatory bowel disease (IBD), type 2 diabetes mellitus (T2DM), Parkinson's disease and colorectal cancer.[1] In March 2020, the World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease 2019 (COVID-19) as a global pandemic. COVID-19 is a respiratory illness which can express itself in a variety of ways that range from asymptomatic or moderate disease with cough and fever to severe pneumonia with acute respiratory distress syndrome (ARDS). A cytokine cascade, which includes interleukin (IL), granulocyte colony-stimulating factor (G-CSF) and tumour necrosis factor (TNF), is known to induce ARDS. Intensive care unit (ICU) patients with COVID-19, including ARDS, exhibited higher levels of pro-inflammatory cytokines such IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIp1A and TNF than non-ICU patients, according to prior research. These inflammatory cytokines were correlated with a specific pattern of the gut microbiome.[2]

POTENTIAL CONNECTION BETWEEN COVID-19 AND GUT MICROBE

Bacteria, archaea (anaerobic eukaryotic microbes), viruses and fungus are amongst the 1014 microorganisms that comprise the human gut microbiota. Bacteroidetes, Proteobacteria, Firmicutes and Actinobacteria are the four phyla that dominate gut microbes in healthy people. Bacteria from the groups, Lachnospiraceae, Rikenellaceae, Prevotellaceae, Ruminococcaceae and Bacteroidaceae, are found in abundance in the colon. Through its metabolic, protective and trophic functions, the gut microbiota plays an important role in human health.[1] While we provide the bacteria with a home and food, the microorganisms support us by regulating various physiological functions such as nutritional digestion as well as providing protective immunity against infections. Any alteration in the gut microbiota, often known as 'gut dysbiosis', has been linked

to a variety of diseases and disorders, such as inflammatory bowel disease (IBD) and T2DM, amongst others.

The gut microbes have been found to influence pulmonary health via critical cross-talk between the gut microbes and the lungs known as the 'gut–lung axis'. The gut–lung axis is considered to be bidirectional, which means that the endotoxins and the microbial metabolites may influence the lung through blood, and lung inflammation can affect the gut microbiota. This offers the intriguing prospect that new SARS-CoV-2 might affect the gut microbiome as well. In fact, a change in the makeup of the gut microbiota has been linked to respiratory infections in multiple studies. Pneumonia and ARDS are two significant clinical symptoms of COVID-19, especially in elderly and immune-compromised patients.[2]

The efficiency of lung immunity is known to be influenced by the makeup of a balanced gut microbiome. Germ-free mice with no intestinal microbes have been demonstrated to have a reduced capacity to remove pathogens from the lungs. The disruption of gut microbes caused by extensive antibiotic usage can have a similar impact, as evidenced by population studies linking increasing use of quinolones, macrolides, cephalosporins and penicillins to a higher risk of lung cancer. Intriguingly, influenza virus infection increases Enterobacteriaceae while decreasing lactobacilli and lactococci in the gut microbes in mice.[2,3]

The presence of gastrointestinal (GI) signs and symptoms throughout the duration of the disease, as well as viral RNA in faeces has been observed. Pilot research was also done, which found signs of long-term 'silent' GI infection even in the absence of GI symptoms. By viral ribonucleic acid (RNA) metagenomic sequencing, 7 of 15 patients with COVID-19 exhibited stool positive for SARS-CoV-2 in this investigation.[4] Three individuals had active virus infection for up to 6 days after the clearance of SARS-CoV-2 from their respiratory samples. Bacterial species such as *Morganella morganii*, *Collinsella aerofaciens*, *Streptococcus infantis* and *Collinsella tanakaei* were found in high numbers in faeces samples with high SARS-CoV-2 infectivity as well as better functional ability for nucleotide *de novo* production, amino acid biosynthesis and glycolysis. SARS-CoV-2 infectivity was low to non-existent in bacteria

that produce short-chain fatty acids, such as *Bacteroides stercoris*, *Alistipes onderdonkii*, *Parabacteroides merdae* and *Lachnospiraceae bacterium* 1 1 57FAA.[3]

Precisely, SARS-CoV-2 requires the presence of transmembrane protease serine-2 and angiotensin-converting enzyme-2 receptor in enterocytes from the colon and ileum to enter and infect the cells. It is possible that all these GI symptoms are caused by SARS-CoV-2 infection in the enterocytes.[3] It is also possible that the gut–lung axis phenomena is at work, and that these GI abnormalities in COVID-19 are just a side consequence of the substantial pulmonary changes, or that SARS-CoV-2 is infecting enterocytes, leading to gut dysbiosis and enhanced lung damage. The gut microbiota of elderly people is frequently less organised. COVID-19 infection is more severe in the elderly, which might indicate a relationship between a less diversified microbiota and COVID-19 infection. However, we need further research and clinical studies to confirm this hypothesis.[1]

A healthy gut microbiota might be crucial in maintaining an ideal immune system to avoid an array of overactive immune reactions that will eventually damage the lungs and important organ systems to avoid the response to pathogenic infections such as COVID-19.[5] In such conditions, having a balanced immune response is critical, as either an overly reactive or unresponsive immune function can exacerbate clinical consequences such as pneumonia and ARDS in a viral illness like COVID-19.[3]

GUT MICROBE, DISEASE SEVERITY AND CYTOKINE STORM

There is growing evidence that being elderly people who are suffering from a chronic inflammatory condition and other chronic medical illnesses could be predisposed to a pro-dysbiotic state.[4] A higher rate of morbidity and death from COVID-19 has also been found in the elderly population, individuals with underlying chronic medical problems and immunosuppressed cancer patients, which is unlikely to be a coincidence. The inflammatory disease is most likely to blame for the severity of COVID-19 illness. Inflammatory cells were found in the lungs of a patient with severe COVID-19 in post-mortem samples, indicating a strong inflammatory reaction.[5] Furthermore, investigations have found that severe COVID-19 patients had higher plasma levels of pro-inflammatory cytokines such IL-1, IL-6 and TNF-alpha.

Further inflammatory stimuli may shift the balance towards a leaky gut in individuals with gut dysbiosis, resulting in a self-perpetuating inflammatory feedback loop[6] [Figure 1]. Two minor investigations, in particular, found a link between severe COVID-19 and gut dysbiosis. Patients with severe COVID-19 had more prominent GI symptoms, as well as greater levels of stool calprotectin (indication of GI inflammation and compromised mucosal integrity).[7] These studies support the idea of immune interaction between the lungs and the gut, which is probably controlled by the gut flora.

In severe/critical patients, the pro-inflammatory cytokines IL-6, IL-10, TNF and interferon (IFN) are elevated during COVID-19 infection. The severity of COVID-19 is thought to be the result of 'cytokine storm'. It is worth noting that some of the cytokines listed above are frequently linked to the gut microbes and play a key role in triggering the cytokine storm.[8-10] Furthermore, the gut bacteria contribute to maintaining the cytokine storm by interacting with Toll-like receptors.
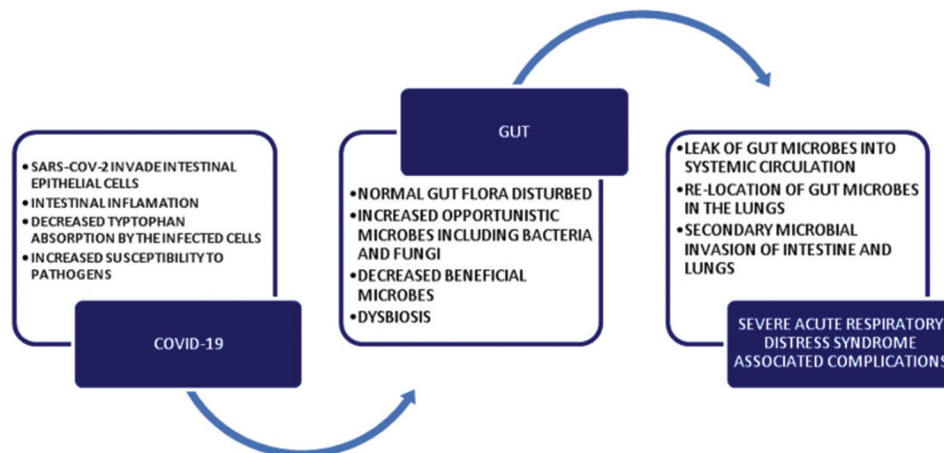

Figure 1: Response of gut microbiota to COVID-19

COVID-19 patients had lower amounts of probiotic bacteria (such as *Lactobacillus* and *Bifidobacterium*).[4] This can be difficult because high *Lactobacillus* spp. levels are linked to higher levels of the anti-inflammatory cytokine IL-10. The cytokine marker IL-10 might be utilised to quickly identify individuals who are at a higher risk of COVID-19 disease worsening after infection. Several gut commensals with recognised immunomodulatory potential, such as bifidobacteria, *Faecalibacterium prausnitzii* and *Eubacterium rectale*, were underrepresented in COVID-19 patients and remained low in samples obtained up to 30 days following resolution of COVID-19. Furthermore, butyrate-producing bacteria, such as *Eubacterium*, *Clostridium butyricum*, *Faecalibacterium prausnitzii* and *Clostridium leptum*, were found to be in lower abundance. Beneficial commensals such as *Eubacterium ventriosum*, Lachnospiraceae taxa, *Faecalibacterium prausnitzii* and *Bacteroides* spp., [e.g. *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, *Bacteroides dorei* and *Bacteroides massiliensis*], and *Roseburia*, were found to be depleted in COVID-19 patients, an observation that correlated with illness severity.[11,12]

During COVID-19 infection, the gut flora dysbiosis causes pathogenic bacteria to take over the commensal bacterial population. Higher levels of *Klebsiella*, *Ruminococcus gnavus* and *Streptococcus* have been linked to an increase in pro-inflammatory cytokines resulting in cytokine storm and activation of T-helper (Th1) cells in COVID-19 patients.[9] As a result, the severity of COVID-19 in the patient group increased. During the course of COVID-19 disease, opportunistic pathogens such as *Streptococcus*, *Actinomyces*, *Veillonella*, *Erysipelatoclostridium* and *Rothia* as well as pro-inflammatory bacteria such as *Erysipelotrichaceae bacterium* 2 2 44A, *Clostridium ramosum*, *Coprobacillus bacterium* and *Clostridium hathewayi*. In critically ill COVID-19 patients with poor prognosis, the frequency of common opportunistic pathogens are from the genus *Enterococcus*, phylum Firmicutes like *Enterococcus faecalis* and the Enterobacteriaceae family, which includes *Klebsiella pneumoniae* and *Escherichia coli* is elevated. This shows that the bacterial makeup of our gut and the presence of infection in our stomach may influence our immune responses during COVID-19.[13]

TAKING CARE OF GUT

Each person's gut microbiota is distinct. Its constitution changes with age, genetics, food and environmental circumstances. In any event, scientists advise eating a nutritious diet high in vegetables, cereals and fruits to support the gut microbial functioning.[10] The use of pre- and probiotics to replenish gut microbiota before, during and after SARS-CoV-2 infection is also mentioned in the scientific literature, in addition to a balanced diet.[14] They can both decrease GI symptoms caused by COVID-19 and eventually secondary infections by stimulating the growth of beneficial microorganisms in the intestine.[7] A healthy diet and probiotic supplementation, on the other hand, cannot undermine the importance of vaccinations and certified medical treatments, which are still the best ways to protect ourselves against COVID-19.

The importance of gut microbiota in various respiratory diseases is well understood. Furthermore, the elderly and individuals with a chronic medical condition have borne the brunt of COVID-19's negative results, both of whom are being known to exhibit senescence-driven gut dysbiosis. The evidence supporting gut dysbiosis as a predisposing factor for severe COVID-19 is growing, owing to leaky gut phenomena and the leakage of bacterial products and toxins that results.[15,16] Evidence is accumulating, indicating that the severity of COVID-19 sickness is related to the degree of dysbiosis.[8,17] This necessitates more research into possible preventative and therapeutic targets, such as dietary changes and probiotics. Various pathogenic paths and treatment techniques are being evaluated in a number of current studies. While direct antiviral medicines and vaccines are of paramount importance, the gut–lung axis may yet have therapeutic promise.[1]

This review outlines the relationship between gut microbes and COVID-19 through immunomodulation and also the significance of that relationship. There are ideas that imply a link, such as the 'gut–lung axis', in which the gut microbes may influence lungs or immunomodulatory signals secreted by gut microbes. By creating a high number of immune cells, a healthy gut microbiota can limit the lung infection induced by SARS-CoV-2, whereas dysbiosis of the gut microbiota produces a lesser number of immune cells.[18] Dietary probiotics and prebiotics are important modulators of the gut microbial ecology, and they may be useful in maintaining gut microbiome homeostasis and influencing SARS-CoV-2 infection.[19] Currently, this review discusses a lot of possibilities that might explain the gut microbiota's function in SARS-CoV-2 infection. For these claims to be justified, they must be scientifically validated through multiple research projects on the gut microbiota composition of SARS-CoV-2 patients.[20]

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How to cite this article: Boppana SH, Kutikuppala LV, Pantangi S, Kummara CR, Kandi V. COVID-19 and gut microbiota: An unexplored link. J Clin Sci Res 2023;12:72-5.