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Research Article

Microbiota in the Era of COVID-19. Correlation and Benefits

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Abstract

Background: SARS-CoV-2 is considered one of the most widely spread viral infections globally. The relation between diminished gut microbiota and susceptibility to Corona virus 2019 infection is well correlated. We aimed to investigate of the correlation between gut microbiota imbalance and the development of several diseases including COVID-19 with suggestion of routes for restoring this imbalance in affected patients especially geriatric ones.

Discussion: Resulting immune disruption from COVID-19 infection can alter gut microbiota leading to dysbiosis and increases gut permeability leading to progression of secondary bacterial infections and bacterial pneumonia. Besides, dysbiosis may lead to development of inflammatory bowel diseases, cardiovascular diseases, and autoimmune diseases. Diet changes and supplementation can positively affect dysbiosis state.

Conclusion: Diets like cereals, fruits, vegetables, and whole grain cereal are main contributor in restoring gut microbiota balance, on the other hand, diets containing high fat content are unfavorable due to their negative effect on microbiota diversity. Moreover, massive use of antibiotics is not recommended and was proven to affect gut microbiota abundance and balance leading to several inflammatory diseases. Finally, probiotics and prebiotics are proven to regulate bacterial balance and reduce probability of bacterial and viral infections.

Keywords: COVID-19; Gut Microbiota; Antibiotics; Probiotics; Prebiotics; Crohn's Disease

Abbreviations

COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; TMPRSS2: Type II Transmembrane Serine Protease

Background

In December 2019, SARS-CoV-2, which is also called new coronavirus disease 2019 (COVID-19), appeared in Wuhan (China), which is the main cause of COVID-19 infection [1]. On September 13th 2020 the number of COVID-19 cases reached to about 28,637,952 confirmed cases all over the world with about 917,417 associated deaths, as per COVID-19 weekly epidemiological update from WHO [2].

Many questions were raised regarding mood of transmission, signs and symptoms, vaccination, and therapeutic choices for treatment of COVID-19 which are still unanswered, continuous investigations are ongoing to answer these unknowns regarding. In order to protect public health and limit viral spreading among individuals, many protective and restrictive measures are applied

including; social distancing, wear face masks, minimizing public appearances, confining social gatherings, use of cellphones and networking communication means [3].

For complete SARS-CoV-2 infection process, spike protein of the virus recognizes ACE2 receptor via type II trans-membrane serine protease (TMPRSS2) which both proteins need to be co-expressed in the viral cell for invasion of host cell. Investigations found that ACE2 and TMPRSS2 are mainly co-expressed in lung tissue, epithelial cells, gland cells in esophagus, and enterocytes in ileum and colon [4].

Studies showed that cardiopulmonary disease might be associated with ACE2 through changes in the gut or lung microbiomes [5] and GIT symptoms are prevalent in about 3.34 to 11.4% of COVID-19 patients, including, vomiting and diarrhea, and are more predominating in critically ill patients [6]. There is a suggestion that the digestive tract might be a site of viral replication and activity, supported by the presence of viral RNA and living viruses in stool samples [7].

Human gastrointestinal tract hosts a vast numbers of gut microbiota which has a remarkable effect on the host during homeostasis and disease. Establishment of microbiota during early childhood is affected by different factors, including diet which is the main contributor in development and shaping of gut microbiota across life time [8].

Interestingly, maintaining of immune, metabolic homeostasis, and protecting against pathogenic infections is attained by the presence of intestinal bacteria, on the other hand, pathogenesis of many inflammatory diseases and infections has been related to altered gut microbiota dysbiosis [8].

There is a correlation and a balanced interaction between gut microbiota and immunity which is fundamentally taking part in homeostatic functions. Moreover, gut microbiota plays a basic function in the growth and maturation of immunity, meaning while, the immune system contributes in shaping microbiota composition and functions. Whenever a disturbances or alterations occurred in this balance a human disease occurs [9].

It was evidenced that disruption in intestinal microbiota occurs by aging during which various types of gut microbiota decreases and a sort of an imbalance state occurs in microbiome composition (dysbiosis) causing immune dysfunction and generalized inflammation. Imbalance of microbiome composition has been correlated with various chronic comorbidities as asthma, arthritis, obesity, and diabetes mellitus type 2 [10], thus, people above 65 years old have recorded a higher mortality rate from COVID-19 than those less than 65 years old [11].

Discussion

Correlation of COVID-19 with Microbiota

In a healthy individual, lung microbiota shows a low microbial density and high microbial diversity of interacting microbiota. Streptococcus, Prevotella, and Veillonella are the most predominant microorganisms. Lung microbiota contributes in prevention of infection, inflammation, immunity development, and immune cells activation. During lung diseases dysbiosis occurs and, therefore, an increased growth of one microbial species with reduction of microbial diversity occurshttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC7405772/-b0110 [12].

Evidences from studies shows that microbiome in gut and lung are altered in COVID-19 infected patients which may have crucial effect on immunity and COVID-19 disease severity [13]. It was shown that COVID-19 patients had a remarkable reduction of bacterial diversity and a significant high abundance of opportunistic pathogens as Streptococcus, Actinomyces, Veillonella, and Rothia, and a low abundance of beneficial organisms indicating that gut microbial interacts with SARS-CoV-2 [14].

Moreover, a pilot study showed that in COVID-19 patient, the gut microbiome opportunistic pathogens, *Clostridium hathewayi*, and *Actinomyces viscosus*, *Bacteroides nordii*, becomes more abundant and beneficial commensals, as, *Eubacterium ventriosum*, *Lachnospiraceae taxa*, *Faecalibacterium prausnitzii*, Roseburia becomes depleted [15].

It is well known that bacteria in lungs have an important role in COVID-19 course of disease and investigations showed that microbiota on respiratory tract surface can act as a barrier which prevents attachment of a virus to the host cells. Besides, microbiota prime lung immunity. Also, gut microbiota exerts the same mechanism in protection against flu viral infections [16].

Animal experimental results on mice showed that upon application of a respiratory normal flora, *Corynebacterium pseudodiphtheriticum* via nasal route, an increased in TLR3 antiviral response against RSV and enhanced production of IL-6, TNFα, IFNγ, and IFNβ occurred [17].

Clinical picture of COVID-19

Severe and critically ill patients with COVID-19 commonly have lymphopenia which rarely occurs in mild symptoms cases. Bilateral ground-glass opacity, consolidation, and local or bilateral patchy shadowing are mainly found in chest computed tomography features [18].

Concerning laboratory investigations, it was found that there is an elevation in liver enzymes, lactate dehydrogenase, C-reactive protein, neutrophil-to-lymphocyte ratio (NLR), derived NLR ratio (d-NLR), and platelet-to-lymphocyte ratio which can be indicative of an inflammatory storm. Increased D-dimer is also one of the lab findings in covid-19. In critical ill patients, D-dimer value is elevated, blood lymphocytes decreased, high amylase and coagulation disorders are found [19].

Gut-lung axis in COVID-19

It was found that COVID-19 causes immune response disruption and an increase in pro-inflammatory cytokines and lymphocytopenia in case of severe SARS-CoV-2 infections. Cytokine storm is the end result of increased cytokine and chemokine production which in turn will lead to severe acute respiratory syndrome and multiple organ failure [20].

Viral infections as influenza can induce immune responses resulting in alterations in gut microbiota leading to dysbiosis and increasing gut permeability which consequently causes a secondary infection and bacterial pneumonia [21].

It is worthy to mention that, the elevated levels of circulating pro-inflammatory cytokines resulting from viral infections are able to alter gut microbiota and cause an intestinal integrity disturbance, where, the increased intestinal inflammation in turns lead to high gut permeability allowing bacterial antigens and toxins to enter systemic circulation leading to more worsening septic state of COVID-19 patients [22]. A conducted study on critically ill patients in an ICU showed that multiple organ failure has found to be associated with increased intestinal permeability [23].

Massive amounts of antibiotics use can alter gut microbiota resulting in dysbiosis and increase susceptibility to new infections and inflammatory disorders. Diarrhea associated with antibiotic use is one of the most common side effects that results from an imbalance in gut microbiota. Moreover, diarrhea in hospitalized patients can cause *Clostridium difcile* associated diarrhea [4].

Microbial movement from gut via systemic circulation to the lungs as a result of reduced intestinal barrier integrity will be followed by a secondary infection. Also, it was reported that sepsis and acute respiratory distress syndrome occurred as a result of possible gut barrier dysfunction and secondary bacterial infection [24]. Moreover, gut and respiratory tract are linked with modulate immune responses. Occurrence of dysbiosis in gut microbiota lead to disease pathogenesis in respiratory tract [25].

In a study performed it was found that individuals suffering from chronic lung diseases as asthma and chronic inflammatory lung disease are accompanied by GI tract diseases like inflammatory bowel syndrome, intestinal mucosa and permeability alterations [26]. About 50% of inflammatory bowel syndrome patients of adults reported to have an impaired lung function although they have no respiratory disease history [27].

Infectious viruses could move from infected lung to distant organs via systemic circulation, where, pathological modifications in the digestive system tissues indicating that immune cells infected by viruses could circulate and invade the enteric cells resulting in gastrointestinal damage, suggesting that coronavirus could move to systemic circulation after lung tissue damage and migrate to intestinal cells through circulatory and lymphatic system [4].

Diminished microbial diversity as a risk factor for different diseases

Although gut microbiota within an individual is considered stable throughout adult life, in geriatric individuals its diversity decreases and dysbiosis increases which is associated with cognitive deficits, depression, inflammatory markers, a decrease in Firmicutes to Bacteroidetes ratio (F/B ratio) [3].

Inflammatory bowel diseases

Bacterial and fungal gut microbiota composition disturbances have been involved in different forms of inflammatory bowel diseases, as Crohn's disease (CD) and Ulcerative Colitis (UC)

characterized by a loss of microbiotas diversity and development of specific bacterial groups like *Enterobacteriaceae* [18].

Mice experiments showed that growth of *Enterobacteriaceae* has been correlated to new-onset of CD and intestinal inflammation improvement occurred upon reducing the number of *Enterobacteriaceae* [29]. On the other hand, loss of microbiota as *Faecalibacterium prausnitzii* has been related to CD recurrence, where, trials indicated that reduction of inflammation (colitis) occurred after supplementation of mice with *Faecalibacterium prausnitzii* which raise a suggestion on the anti-inflammatory role for this enteric microbiotas [28].

Moreover, it was identified that the supernatant of *Faecalibacterium prausnitzii culture* contains bioactive anti-inflammatory molecule which might contribute in the reduction of intestinal inflammation. Besides, it was found that alleviation of intestinal inflammation in mice was noticed upon boosting them with *Lactococcus lactis* which express *Faecalibacterium prausnitzii* anti-inflammatory molecule [30].

Cardiovascular diseases

Large component of western diet contains choline and carnitine, where, their microbial metabolism has shown to increase the risk of CVS disease [31], where, both metabolic process results in trimethylamine (TMA) production which is oxidized via hepatic route to trimethylamine-*N*-oxide, an amine oxide, correlated with the development of atherosclerosis [32].

Trimethylamine (TMA) production is catalyzed by microbial TMA lyase which on inhibition contributes in the reduction of atherosclerosis development, investigation showed that supplementation of mice with *A. muciniphila* protected them against development of atherosclerosis. In fact, mice bearing high levels of microbial TMA lyase are highly liable to diet-induced atherosclerosis, thus, dietary changes or direct supplementation with microbiota might provide an effect either alone or in combination with therapies to prevent progression of cardiovascular diseases [28].

Autoimmune diseases

When microbiota mimic molecular human antigens, a potential reprogramming of immune system may occur, it results in autoimmune tissue damage [33]. There is a proposal that Type 1 diabetes mellitus (T1DM) pathogenesis may be attributed to variation in microbial lipopolysaccharide immunogenicity, evidenced by a study performed on infants of Northern Europe, Finland and Estonia who exhibited a high prevalence of T1DM compared to Russian ones in the early 3 years of life. Besides, Finnish and Estonian infants were noticed to be enriched with *Bacteroides* spp. especially *Bacteroides dorei* [34].

There was a positive correlation observed between the abundance of *Bacteroides* spp and serum insulin autoantibody levels which can be attributed to the special shape of lipopolysaccharide from *Bacteroides* that repressed immune activation induced by *E. coli* lipopolysaccharide suggesting that it may interfere with normal immune development and increase vulnerability of autoimmune diseases [34].

Rheumatoid arthritis (RA) is a chronic auto-immune disease in which auto-antibody production and destruction of bone in multiple joints occurs. Recent studies showed that before onset of arthritis, immunoglobulin-A (IgA) anti-citrullinated protein antibody (ACPA) was detected suggesting mucosal origin of rheumatoid arthritis like oral cavity and gut. In periodontal diseases, *Porphyromonas gingivalis* bacterium may be correlated with progression of rheumatoid arthritis [35].

Investigations of microbiota composition in subjects with rheumatoid arthritis at early stage or fibromyalgia showed that the *Bacteroides fragilis*, *Bifidobacterium*, and *Eubacterium rectale* are reduced in rheumatoid arthritis patients [35].

Simultaneous diseases

When Gut dysbiosis occurs as a result of increased Firmicutes/Bacteroidetes ratio and elevated levels of facultative anaerobes *Escherichia/Shigella*, a leak in gut occurs that contributes to pathogenesis of *autism* via increasing systemic metabolites that alter the neuroimmune and neuroendocrine systems, which in turn affect the brain and neurodevelopment [36].

COVID-19 infection

It was reported that SARS-CoV-2 can bind to human ACE2 receptors to enter the host cell which are highly expressed in the intestine and play a role in regulation of amino acid transport, microbialecology, and inflammation in gut. Investigations showed that *Bacteroidetes* species contributes in down regulation of ACE2

expression in murine colon, thus contributing with a beneficial effect in alleviating COVID-19 severity. On the other hand, *Firmicutes* species showed variable effects in modulating ACE2 expression that is associated with increased COVID-19 infection severity [37].

Despite that different studies showed variable findings, *Bacteroides, Clostridium, and Lactobacillus* appear to be recurrently altered in elderly individuals. Lack of capacity to quell infection, compromised immune system, and reduced microbiome diversity, are main leading causes for higher mortality rates in COVID-19 elderly patients especially those above 80-years old [3].

Antibiotics and abundance of pathogenic microbiome in COVID-19

Antibiotic-naïve patients with COVID-19 showed high levels of opportunistic pathogens including *Clostridium hathewayi, Bacteroides nordii*, and *Actinomyces viscosus*. A study found that antibiotic therapy in COVID-19 patients was related to a more diverse microbiome and a change of the gut microbiota away from a healthy microbiome [37].

Three bacterial members from *Firmicutes phylum* which are; *genus Coprobacillus*, species *Clostridium ramosum*, and *Clostridium hathewayi*, were from the main bacteria associated with increased COVID-19 disease severity. Both *C. ramosum* and *C. hathewayi* have been associated with human infection and bacteremia. Moreover, investigations showed that *Coprobacillus bacterium* strongly up-regulate colonic ACE2 expression in the murine gut that contributes in increased severity of COVID-19 infection [37].

Reports from WHO showed that macrolide antibiotic including azithromycin is being widely used in therapeutic protocols of COVID-19 treatment [38]. Antibiotics combination of β-lactams with macrolides or fluoroquinolones were used in COVID-19 therapeutic protocols as well. In addition, Piperacillin and tazobactam combination considered as the most commonly used for ICU patients [39].

Dietary and supplements effect on modulation of gut microbiota

Dietary and supplements nutrients can affect gut microbiota diversity. Polyphenols like flavonoids, phenolic acids, stilbenes, and lignans from cereals, fruits, vegetables, tea, and coffee possess an antioxidant, anti-inflammatory, and anti-carcinogenic effects. *In vitro* investigation suggested that polyphenols can inhibit potential pathogenic organisms like *H. pylori*, *Staphylococcus* sp. and aid the growth of potential beneficial bacteria, like *Bifidobacteria* and *Lactobacillus.* Thus, polyphenols could contribute in modulation of human gut microbiota [40].

Vitamins are essential in very small amounts for supporting normal physiological functions, one of their most important roles is being co-factors for enzymes. Primary source of vitamins comes from diet owing to inability of human bodies to synthesize all vitamins to meet daily needs. Certain vitamins like vitamin K, and vitamin B, are synthesized by gut microbiota [41].

It was reported that administration of retinoic acid (vitamin A active metabolite) lead to a remarkable increase in *Lactobacillus* sp. during a norovirus infection which exerted an antiviral action against norovirus leading to the postulation that the high amount of *Lactobacillus* in the gut was contributing partially for norovirus inhibition [42].

Some B vitamins have been demonstrated to help in bacterial colonization and to alter bacterial pathogenicity. Vitamin B12 supplementation was reported to improve Bacteroides thetaiotaomicron colonization in mouse gut [40].

Vitamin C is the most important antioxidant obtained from dietary sources as fruits and vegetables via intestinal absorption. In an assessment for a group of individuals with stable cystic fibrosis, it was found that vitamin C intake was positively correlated with Firmicutes and its lower taxa (*Clostridium*) and negatively associated with Bacteroidetes [40].

Minerals like zinc is essential for modulating the beneficial gut microbiota and maintaining epithelial integrity, moreover, selenium supplementation from dietary sources with an amount ranged from 0.1 μg/g to 2.25 μg/g increased the gut microbial diversity [40].

High fat intake was shown to have adverse effects on intestinal microbiome and it was proved that diets high in total and saturated fat content have an unfavorable impact on abundance and diversity of microbiota [43]. It has been observed that 40% fat consumption in healthy young individuals is connected with undesirable alterations in gut flora [40].

A chronic deficiency of dietary fiber could lead to a reduction in the diversity of gut microbiota [44], while diet containing high-fiber as whole grain cereal, soluble corn fiber, barley kernel-based bread increases the fecal abundance of beneficial microbiota as *Bifidobacterium*, *Lactobacillus*, *Akkermansia*, *Roseburia*, *Bacteroides*, *Fecal bacterium*, and *Prevotella* [40].

How to reduce COVID-19 severity through gut microbiota?

Bifidobacterium, Faecalibacterium, Ruminococcus, *and Prevotella* are the main microbiota species that are highly found in a healthy individual's gut which is associated with low systemic inflammation. Probiotics are living micro-organisms or beneficial bacteria for the health of the host modulating the composition and function of the intestinal microbiota [45].

Prebiotics are a formulations of nutrients which on metabolization support the overgrowth of probiotic bacteria. Examples of prebiotics include maize fibre, inulin, and polydextrose were shown to enhance gut flora, digestion, and immunity, particularly in geriatric population [46]. The use of prebiotics and probiotics to regulate the intestinal flora could be an effective in reducing the risk of bacterial and viral infections [45]. Furthermore, reduction of antibiotics use as a supportive therapy in management of COVID-19 is favorable to avoid its negative impact on gut microbiota balance [47].

Probiotic strains like lactobacilli and bifidobacteria generate bacteriocins that are efficient against harmful bacteria and viruses. *Lactobacillus* sp. enhances gut immunity by producing antiviral substances such as mucins and mucus in the intestine. Furthermore, it regulates innate and adaptive antiviral immunity via interactions with dendritic cells, monocytes or macrophages, and lymphocytes [48].

It is recommended that capsules or powder dosage forms of *Bifidobacterium* sp., *Lactobacillus acidophilus*, or *Saccharomyces boulardii*, combination of *Lactobacillus* sp., *Bifidobacterium* sp. and *Streptococcus thermophiles* be included via oral or enteral route in management protocols of COVID-19 [49].

Conclusion

Gut microbiota may exhibit a sort of imbalance as a result of different factors that can negatively affect health state and increase individual's infection susceptibility. Geriatric individuals by nature are more vulnerable for gut microbiota imbalance and progression for several diseases and one of them is COVID-19.

Diets reach in phenolic compounds like cereals, fruits, vegetables and fibers are main contributor in restoring gut microbiota balance. Diets containing high fat content are unfavorable due to their negative effect on microbiota diversity. Unnecessary use of antibiotics is not recommended as it was proven to affect gut microbiota abundance and balance leading to several inflammatory diseases. Probiotics and Prebiotics are proven to regulate bacterial balance and reduce probability of bacterial and viral infections.

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