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Review Article

The Impact of Gut Microbiome Modulation on Long COVID Symptoms in Patients with Metabolic Syndrome

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Abstract

Stroke remains a leading cause of disability and death in the United States, disproportionately affecting Black, Latinx, and Asian or Pacific Islander populations. Atrial Fibrillation (AF), a prevalent arrhythmia, further elevates stroke risk. This article reviews the impact of culturally tailored prevention programs on health equity, particularly in underserved populations. Evidence from studies highlights the effectiveness of culturally specific education in improving stroke awareness, prevention behaviors, and emergency response in minority communities. Programs that integrate cultural beliefs and address systemic barriers show promise in reducing stroke-related disparities. However, challenges in sustaining long-term behavior change and addressing healthcare access persist. Future research should focus on refining these programs, fostering trust between patients and providers, and overcoming systemic obstacles to improve stroke outcomes for all populations.

Keywords: acutest elevation myocardial infarction; cardiogenic shock; percutaneous coronary intervention; double culprit vessel occlusion

Introduction

The role of the intestinal microbiota in lung disease has been well documented. We also know that respiratory virus infections cause disturbances in the intestinal microbiome [1–3]. Changes caused by COVID-19 infection to the fecal microbiomes, resulting in gut dysbiosis, are attributed to the proliferation of opportunistic pathogens and the depletion of beneficial commensals [4]. We also know that dysbiosis is associated with metabolic syndrome and other metabolic disorders [5,6]. The association of dysbiosis with the development of metabolic syndrome (as well as other metabolic disorders) is characterized by low microbial diversity. Therefore, patients suffering from this condition are more prone to viral and intestinal SARS-CoV-2 infections due to the existing disturbances within the gut microbiome [7]. Chronic gut inflammation has been suggested to result from a specific constitution of the gut microbiome regulated by diet. Plant-based foods may support a gut microbiome capable of inducing an appropriate anti-inflammatory response. In contrast, a pro-inflammatory response is elicited by the gut microbiome of those consuming foods such as wheat, red meat, and alcohol, resulting in chronic gut inflammation [8]. This article will examine the impact of gut microbiome modulation on Long-term COVID symptoms in patients with metabolic syndrome.

Plant-Based Diets on Inflammation

It is essential to understand the impact of plant-based diets on inflammatory processes. Individuals who consume plant-based diets have lower levels of inflammation and plasma C-reactive protein (CRP). Specific antioxidants, such as flavonoids and carotenoids—found in foods like blueberries and strawberries—help reduce inflammation by neutralizing free radicals and modulating cytokine release. A plant-based diet has also been associated with a 50% reduction in the development of metabolic syndrome [10]. In a study comparing vegetarian and omnivore diets, vegetarians were found to have lower levels of gamma-glutamyl transferase (GGT) and ferritin [9]. Socioeconomic status plays a crucial role in determining the realistic achievability of this diet for the general population. Food deserts and low-income status make it difficult for specific populations to access plant-based foods. Future research should emphasize the impact of zip codes and local resources on the feasibility of maintaining a plant-based diet. Plant-based diets are also cardioprotective. They improve cardioprotective factors and reduce major adverse cardiac events (MACE) by lowering LDL cholesterol, increasing insulin sensitivity, and reducing advanced glycation end products contributing to atherosclerotic plaque formation [10]. These effects highlight the potential of dietary intervention as a non-pharmacologic strategy for reducing cardiovascular risk.

Pro-inflammatory Effects of Diets High in Processed Foods, Red Meat, and Alcohol

Processed foods, red meat, and alcohol are pro-inflammatory. These dietary components are associated with elevated levels of pro-inflammatory biomarkers such as C-reactive protein (CRP) and ferritin [11]. Another study similarly reported that high consumption of red meat is linked to increased circulating levels of gamma-glutamyl transferase (GGT) and high-sensitivity CRP (hs-CRP), both of which were found to be reduced in individuals following predominantly plant-based diets [12].

Potential Dietary Intervntions to Restore Microbial Balance

The foods we consume directly impact our ability to ward off infection and disease. Our microbiome continuously adapts to dietary changes through multiple mechanisms, one of which this paper explores in detail. The body's inflammatory response to food—reflected in modifications to biomarkers such as ferritin and gamma-glutamyl transferase (GGT)—differs between populations consuming plant-based diets and those consuming diets high in processed foods or red meat. Further investigation into whether specific dietary patterns can help restore microbial balance is interesting. The gut microbiome is one of the body's primary defense barriers against bacterial invasion and is critical in influencing the development of major diseases [13]. Nutrition can potentially restore gut homeostasis, and future studies should examine how dietary interventions may help prevent diseases such as COVID-19. A study published in Frontiers in Microbiology found that polyphenols—bioactive compounds abundant in plant-based foods—can influence the host by interacting with the gut microbiota to produce bioactive metabolites with anti-inflammatory and antioxidant effects [14]. Understanding how Long COVID affects the microbiome supports the need to promote diets with known anti-inflammatory properties. From a clinical perspective, initiating specific dietary interventions that encourage positive microbiome remodeling may expedite recovery or alleviate symptoms related to metabolic syndrome in patients with long-term COVID-19.

Probiotics, Prebiotics, and Other Microbiome-Modulating Interventions

Probiotics are live microorganisms that provide health benefits to the host when administered in adequate amounts [15]. Common strains such as Lactobacillus and Bifidobacterium have been shown to restore beneficial gut microbiota, particularly following disruptions caused by antibiotic therapy or gastrointestinal infections [16]. The mechanisms through which probiotics support gut microbiome restoration include suppressing pathogenic microbes, enhancing epithelial cell proliferation, and reinforcing the intestinal barrier function [17]. Beyond gastrointestinal health, a balanced gut microbiome may also offer systemic benefits, including protection against respiratory infections through modulation of the immune response [18]. Prebiotics, conversely, are indigestible dietary components that enhance gut health by selectively stimulating the growth or activity of beneficial microorganisms. Compounds such as fructooligosaccharides and galactooligosaccharides specifically promote the proliferation of Bifidobacteria and Lactobacilli, which are integral to maintaining a healthy intestinal environment [19]. In addition to fostering microbial balance, prebiotics help preserve gut barrier integrity and modulate immune function. They also stimulate the production of short-chain fatty acids (SCFAs), particularly butyrate, which serves as an energy source for intestinal epithelial cells and exerts potent anti-inflammatory effects [19]. Fecal microbiota transplantation (FMT) is a promising therapeutic strategy for various health conditions. This procedure involves transferring stool from a healthy donor into a patient's gastrointestinal tract to help restore a balanced and functional microbiome. FMT is increasingly being investigated for its potential benefits in treating gastrointestinal, autoimmune, respiratory, and neurological disorders. The gut-lung axis—the bidirectional communication between the gut and lung microbiomes—offers insight into how gut health influences respiratory outcomes [20]. Several mechanisms have been proposed to explain this connection. For instance, beneficial gut bacteria produce SCFAs, such as butyrate, which exert anti-inflammatory effects. SCFAs also modulate T cell differentiation and promote the development of regulatory T cells (Tregs), both of which are essential for maintaining immune balance and mitigating lung inflammation [21].

Long COVID, also known as Post-Acute Sequelae of SARS-CoV-2 Infection (PASC), encompasses a range of symptoms that persist for weeks or even months following the resolution of acute COVID-19 infection. These symptoms often include fatigue, shortness of breath, brain fog, gastrointestinal disturbances, joint pain, etc. Emerging evidence suggests that gut dysbiosis—an imbalance in the gut microbiome—may contribute to the pathophysiology of long-term COVID-19 by promoting immune dysregulation, chronic inflammation, and disturbances in gut-lung communication. Consequently, gut microbiome modulation has become a potential therapeutic target for managing Long COVID symptoms [22]. Several probiotic strains, including Lactobacillus, Bifidobacterium, and Saccharomyces boulardii, have been studied for their roles in enhancing immune function and gastrointestinal health [23]. These probiotics may alleviate gastrointestinal symptoms associated with long-term COVID-19, such as bloating, diarrhea, and constipation while reducing systemic inflammation and supporting immune function, which is crucial in managing symptoms like fatigue and cognitive impairment. Prebiotics such as inulin and fructooligosaccharides (FOS) have similarly demonstrated their ability to enhance gut health and modulate the immune response. Their use in individuals with long-term COVID may help improve digestive symptoms and promote broader immune resilience.

Maintaining a balanced, microbiome-supportive diet is essential for restoring and preserving gut health. Diets rich in fiber, polyphenols, and fermented foods promote the growth of beneficial gut bacteria and help reduce inflammation. Additionally, supplementation with SCFAs may further support intestinal barrier integrity and immune homeostasis, as SCFAs are known to stimulate regulatory T-cell development, which is vital for modulating inflammation [24].

Gut Microbiome and Metabolic Syndrome

Gut microbiome dysbiosis disrupts the composition and function of the gut microbial community. It is commonly associated with various disease states, particularly chronic and inflammatory conditions. This imbalance may manifest as a decrease in microbial diversity, an overgrowth of pathogenic species, or a reduction in beneficial bacteria—especially those producing key bioactive compounds, such as short-chain fatty acids (SCFAs). SCFAs play a central role in regulating inflammation, maintaining intestinal barrier integrity, and supporting metabolic function, making their disruption a key factor in the pathogenesis of metabolic syndrome [25,26]. Metabolic syndrome (MetS) is characterized by a cluster of interrelated conditions, including insulin resistance, obesity, dyslipidemia, and hypertension. Together, these factors significantly elevate the risk of developing cardiovascular disease, non-alcoholic fatty liver disease, type 2 diabetes, accelerated aging, and immune dysregulation [27,28]. The gut microbiome profoundly influences metabolic processes and overall human physiology through complex mechanisms integrating microbial metabolism, host signaling pathways, and immune regulation—key factors in developing metabolic syndrome (MetS) [29]. One primary mechanism involves the fermentation of dietary fibers into short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate. These SCFAs serve as energy sources for colonocytes and function as signaling molecules and immune modulators [30]. SCFAs regulate glucose homeostasis, lipid metabolism, and energy balance by stimulating the release of gut hormones like glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), enhancing insulin sensitivity, promoting satiety, and influencing energy storage [31]. Butyrate has been shown to mitigate high-fat diet-induced obesity and improve metabolic parameters by activating the adiponectin signaling pathway. It increases the expression of adiponectin receptors (AdipoR1 and AdipoR2) and AMP-activated protein kinase (AMPK) in skeletal muscle, resulting in enhanced mitochondrial function and energy metabolism [32]. Additionally, the gut microbiota contributes enzymes not encoded by the human genome, facilitating the breakdown and transformation of polyphenols, polysaccharides, and bile acids into nutrients, vitamins, and other bioactive compounds [33]. Bile acid metabolism further highlights this relationship. The conversion of primary bile acids into secondary bile acids, which interact with receptors such as FXR and TGR5, is essential for lipid digestion and cholesterol homeostasis, processes often disrupted in MetS [34]. This microbial conversion, carried out by species from the Clostridium, Bacteroides, and Lactobacillus genera, improves insulin sensitivity and lipid profiles [35–37].

Conversely, specific microbial metabolites, such as trimethylamine N-oxide (TMAO) and indole derivatives, are detrimental to health. Elevated TMAO levels promote atherosclerosis by enhancing platelet aggregation, impairing cholesterol metabolism, and stimulating foam cell formation via upregulated macrophage scavenger receptors [38]. TMAO also activates the ER stress kinase PERK, leading to an increase in the production of pro-inflammatory cytokines and reactive oxygen species (ROS), which contributes to endothelial dysfunction [39]. Gut bacteria—particularly from the Ruminococcaceae and Lachnospiraceae families—influence TMAO levels, and this metabolite has been associated with impaired glucose and lipid metabolism, insulin resistance, and dyslipidemia [40]. The gut microbiome communicates directly and indirectly with the host immune system through the production of bioactive metabolites. This interaction results in local effects, such as the maintenance of intestinal barrier integrity through the regulation of gap junctions in the mucosa and systemic effects via metabolites that modulate immune cell function [41–43]. Butyrate, a key microbial metabolite, promotes the differentiation of regulatory T cells (Tregs) by enhancing histone H3 acetylation, a modification essential for immune tolerance and mucosal integrity [44,45]. It also influences innate immunity by inhibiting histone deacetylases (HDACs) in macrophages, resulting in reduced secretion of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and interleukin-12 (IL-12), while enhancing the antimicrobial activity of macrophages [46, 47]. In addition, butyrate modulates the adaptive immune system by promoting the differentiation of IL–10–producing regulatory B cells. Along with propionate, it suppresses IL-12 production in dendritic cells—a mechanism believed to help reduce systemic inflammation [48,49]. When gut microbiome dysbiosis occurs, it can destabilize the intestinal epithelial barrier, leading to increased intestinal permeability and facilitating the translocation of bacterial endotoxins, such as lipopolysaccharides (LPS), into the systemic circulation [50]. This state of metabolic endotoxemia has been associated with the development of insulin resistance, dyslipidemia, obesity, and hypertension, which are all hallmark features of metabolic syndrome [51,29].

Gut Dysbiosis in COVID-19 and Long COVID

Emerging research suggests a significant link between SARS-CoV-2 (COVID-19) infection, gut microbiome dysbiosis, and metabolic syndrome (MetS). During the acute phase of infection, SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors, which are highly expressed on the luminal surface of the gastrointestinal tract, including gastric, duodenal, and rectal epithelial cells. This facilitates viral entry into intestinal epithelial cells [52,53]. Under normal physiological conditions, ACE2 plays a key role in regulating intestinal amino acid transport, supporting antimicrobial peptide production, and maintaining mucosal barrier integrity by promoting the proliferation of intestinal stem cells.

Antimicrobial peptides such as β-defensins are vital to the innate immune defense of the gut. They directly disrupt microbial membranes, modulate immune responses as chemoattractants for immune cells like macrophages and dendritic cells, and enhance epithelial barrier function by upregulating tight junction proteins [54,55]. However, when SARS-CoV-2 binds to ACE2, it disrupts these protective mechanisms, impairing amino acid homeostasis, weakening mucosal integrity, and increasing intestinal permeability. This allows for the greater translocation of bacterial endotoxins, such as lipopolysaccharides (LPS), into the systemic circulation, triggering widespread inflammation [50]. Simultaneously, the gut microbiota undergoes significant alterations. Beneficial commensal bacteria such as Faecalibacterium prausnitzii and Bifidobacterium species are reduced, while opportunistic pathogens like Clostridium and Enterococcus strains increase in abundance [56,57]. This dysbiosis reduces the production of short-chain fatty acids (SCFAs), particularly butyrate, which is essential for maintaining mucosal integrity and regulating inflammation. As a result, local immune responses are disrupted, and systemic inflammation may worsen. Furthermore, serotonin (5-hydroxytryptamine, 5-HT), a neurotransmitter produced by enterochromaffin cells in the gut, is essential in regulating intestinal motility and inflammation. SARS-CoV-2 infection may impair serotonin biosynthesis, further contributing to gastrointestinal dysregulation and inflammation in affected patients [58]. Beyond the acute phase of SARS-CoV-2 infection, persistent alterations in the gut microbiome have been observed in individuals with long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC). In these patients, chronic gut dysbiosis is often associated with low-grade, persistent inflammation, impaired intestinal barrier function, and immune dysregulation [59]. These sustained microbial changes are frequently accompanied by endocrine dysfunctions, including insulin resistance, thyroid abnormalities, and disrupted hypothalamic-pituitary-adrenal (HPA) axis signaling, which collectively contribute to the pathogenesis of metabolic syndrome [27].

One key finding in patients with long COVID is the presence of hypocortisolemia. Yavropoulou et al. reported that individuals experiencing long COVID symptoms, particularly respiratory manifestations, exhibited abnormally low cortisol levels, suggesting HPA axis suppression [60]. Camici et al. further proposed that chronic functional damage to the HPA axis—along with vagus nerve impairment and mitochondrial dysfunction—may play a central role in the pathogenesis of long COVID [61]. They emphasized the need to investigate glucocorticoid receptor sensitivity and potential long-term epigenetic changes induced by the virus. Similarly, Di Filippo et al. highlighted prolonged HPA axis impairment in long-term COVID patients, which may result in mild or subclinical forms of central adrenal insufficiency, contributing to the diverse and lingering symptoms reported [62]. Additionally, reductions in short-chain fatty acid (SCFA) production due to COVID–19–induced gut dysbiosis may disrupt the host's circadian rhythm by altering the expression of circadian genes, such as Per2 and Bmal1, in enterocytes [63]. Circadian rhythm disruption may impair immune regulation and exacerbate microbiome imbalances, creating a self-perpetuating cycle that fuels the gut-brain axis dysfunction observed in patients with long COVID-19. In return, disruption of the circadian rhythm can impair the host's immune system and further exacerbate gut-microbiome dysbiosis, creating a vicious gut-brain axis in long-term COVID-19 patients.

Clinical Implications and Future Research

The potential to modulate the gut microbiome as a therapeutic strategy for long-term COVID is an emerging and promising area of research, particularly given the growing body of evidence implicating gut dysbiosis in the pathogenesis of post-acute COVID-19 syndrome (PACS). Alterations in gut microbial composition have been associated with persistent clinical manifestations, including fatigue, gastrointestinal disturbances, and neuropsychiatric complications. Recent clinical trials and systematic reviews have identified several microbiome-targeted interventions—such as probiotic administration, prebiotic supplementation, and fecal microbiota transplantation (FMT)—as potentially effective in alleviating symptoms related to PACS. Probiotics, in particular, have been shown to enhance microbial diversity and modulate host immune responses, thereby reducing systemic inflammation and improving quality of life among patients with severe COVID-19 [64].

Additionally, prebiotic interventions and dietary modifications that increase fiber intake are effective in reshaping gut microbiota composition and alleviating gastrointestinal symptoms. Importantly, Long COVID has also been shown to directly and indirectly affect cardiomyocytes. SARS-CoV-2 can infect cardiomyocytes, resulting in structural disarray, multinucleation, and elevated troponin I levels. Moreover, the inflammatory environment characterized by high interleukin-6 (IL-6) and interleukin-1β (IL-1β) can lead to contractile dysfunction and arrhythmias. Gut dysbiosis may further exacerbate these cardiac effects by fostering systemic inflammation and metabolic dysfunction, linking gastrointestinal disturbances in Long-term COVID-19 to adverse myocardial outcomes.

Several targeted probiotic strains may offer distinct therapeutic advantages for individuals with Long-term COVID-19. Lactoplantibacillus plantarum LPLDL is recognized for its cardiovascular benefits, particularly its ability to reduce cholesterol levels by modulating bile salt metabolism and decreasing intestinal cholesterol absorption. Similarly, Bifidobacterium lactis HN019 has been shown to improve lipid profiles and reduce inflammatory markers effectively. Clinical studies have shown that the daily intake of fermented milk containing B. lactis HN019 can significantly reduce total and low-density lipoprotein (LDL) cholesterol, as well as pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Other probiotic strains, such as Bifidobacterium longum BB536, have been shown to increase the relative abundance of beneficial bacteria like Faecalibacterium while also elevating levels of key metabolites, including tryptophan and its indole derivatives—both of which are indicative of a healthier gut environment. Faecalibacterium plays a pivotal role in mitigating inflammation and maintaining intestinal homeostasis. At the same time, tryptophan and indole derivatives contribute to gut barrier function, immune regulation, and neurotransmitter synthesis, enhancing gastrointestinal and systemic health [65]. Additional probiotic strains may also provide critical support for microbiome restoration in Long-term COVID patients. For example, Bifidobacterium breve HRVD521 produces butyrate, a short-chain fatty acid (SCFA) with potent anti-inflammatory properties that help fortify the intestinal lining. Lactiscaseibacillus rhamnosus LR6 enhances barrier integrity by producing antimicrobial peptides, while L. rhamnosus HRVD113 strengthens tight junction proteins, thus reducing intestinal permeability and circulating lipopolysaccharides (LPS) levels. Moreover, Limosilactobacillus fermentum LF8 supports gut microbial balance by promoting SCFA production and maintaining digestive homeostasis. Limosilactobacillus reuteri RD830 contributes to gut and oral health by lowering inflammation and inhibiting the proliferation of pathogenic bacteria through competitive exclusion, thereby promoting a more resilient and stable microbiome.

Conclusion

The relationship between gut microbiome dysbiosis, metabolic syndrome, and long COVID is becoming increasingly evident. The disruption of gut microbial balance caused by SARS-CoV-2 infection exacerbates metabolic dysfunction and contributes to persistent inflammation and immune dysregulation in long COVID patients. Given the gut's significant role in modulating immune responses, maintaining metabolic health, and influencing systemic inflammation, targeting the microbiome provides a promising avenue for therapeutic intervention. Restoring gut homeostasis through the use of probiotics, prebiotics, dietary modifications, and fecal microbiota transplantation may help alleviate symptoms associated with long-term COVID-19. These interventions can reduce systemic inflammation, improve metabolic function, and enhance the immune system. The gut-lung axis is also crucial in modulating the microbiome and can impact respiratory health while supporting post-COVID recovery strategies. Despite these promising insights, further research is needed to fully understand the long-term effects of microbiome-targeted therapies in patients with long-term COVID-19. Considering individual microbiome compositions and specific metabolic needs could be a promising approach to providing personalized care that may enhance treatment efficacy. Clinical trials investigating optimal probiotic strains, prebiotic formulations, and dietary interventions for patients with long-term COVID-19 will be essential in refining therapeutic recommendations. Microbiome modulation could be a key factor in addressing the persistent effects of COVID-19 as our understanding of the gut microbiome's impact on health and disease expands. By integrating gut-targeted strategies into clinical practice, we may improve patient outcomes and provide relief for those struggling with the persistent burden of COVID-19. Future research could focus on a multidisciplinary approach that combines gastroenterology, immunology, and metabolic research to understand the potential of microbiome-based treatments fully.

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