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The Interplay of Microbiota, Long COVID, and Musculoskeletal Pain: A Narrative Review

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Abstract

Context: Long COVID, a condition that persists after the acute phase of COVID-19, poses a significant burden, with 10 - 45% of recovered patients experiencing persistent symptoms. Among these, approximately 46% report musculoskeletal pain. This narrative review explores the potential connections between gut microbiota, Long COVID, and musculoskeletal pain, aiming to introduce new therapeutic avenues and preventive strategies for managing musculoskeletal symptoms in Long COVID patients.

Evidence Acquisition: A comprehensive search was conducted using Google Scholar, Lens.org, and ConnectedPaper.com to identify relevant articles published between 2019 and 2024. Keywords related to microbiota, Long COVID, and musculoskeletal pain were used. Articles were selected based on predefined inclusion and exclusion criteria, and their quality was assessed. Data from the selected articles were synthesized to provide an overview of the interplay between microbiota, Long COVID, and musculoskeletal pain.

Results: Recent research highlights the significant role of gut microbiota in modulating immune responses and systemic inflammation. Dysbiosis has been linked to the severity and progression of COVID-19 and the persistence of Long COVID symptoms. Individuals with Long COVID often experience new-onset musculoskeletal manifestations, such as joint pain, myalgia, and chronic musculoskeletal pain. Additionally, gut dysbiosis has been associated with conditions like lower back pain and knee osteoarthritis. This suggests that the relationship between gut dysbiosis and musculoskeletal problems in general may also extend to musculoskeletal pain in Long COVID patients, indicating broader implications for musculoskeletal outcomes. Therapeutic strategies targeting the gut microbiota, such as probiotics, prebiotics, and dietary interventions, have shown promise in managing these symptoms and improving overall health outcomes.

Conclusions: The evidence underscores the importance of understanding the microbiota-musculoskeletal nexus in Long COVID. Gut dysbiosis contributes to systemic inflammation, exacerbating musculoskeletal symptoms in Long COVID patients. The associations between gut dysbiosis and other musculoskeletal conditions emphasize the need for microbiota-targeted therapeutic strategies. Future research should focus on elucidating the mechanisms linking gut dysbiosis to musculoskeletal pain, exploring the gut-brain axis, and developing personalized approaches to modulate the microbiota. Advancing our understanding of this nexus can pave the way for innovative therapeutic strategies to address the complex health challenges posed by Long COVID and other musculoskeletal conditions.

Keywords: Gut Microbiota, Long COVID, Musculoskeletal Pain, Dysbiosis, Probiotics, Prebiotics

1. Context

The COVID-19 pandemic has revealed numerous health issues beyond acute respiratory symptoms. Among these is the phenomenon of "Long COVID"—a condition characterized by persistent symptoms lasting weeks to months after the initial infection (1). Reports indicate that pain in the joints, bones, ears, neck, and back is more common one year after infection (2), with about 46% of Long COVID patients experiencing musculoskeletal pain, including chronic pain, myalgia, and arthralgia (3). While much attention has been given to respiratory and cardiovascular symptoms, the impact of Long COVID on musculoskeletal health remains a compelling area of study (4).

Recent research suggests that the gut microbiota, a complex ecosystem of microorganisms residing in our intestines, may play a pivotal role in regulating immune responses, inflammation, and overall health (5). An imbalance in the gut microbiota, known as dysbiosis, is characterized by a reduction in beneficial bacteria and an increase in pathogenic species, which can lead to various health problems (6). Factors such as antibiotic use, diet, lifestyle, and genetic predispositions can influence this imbalance. Dysbiosis has been linked to many diseases, including metabolic disorders, autoimmune diseases, and gastrointestinal conditions, highlighting its widespread impact (6).

In this narrative review, we explore the potential connections between Long COVID, gut microbiota, and musculoskeletal pain. We examine how dysbiosis might contribute to joint discomfort, exacerbate existing musculoskeletal conditions, or even trigger new symptoms. By investigating the complex interaction between viral infections, immune responses, and microbial communities, we aim to uncover new therapeutic and preventive strategies for managing musculoskeletal pain in Long COVID patients.

2. Evidence Acquisition

A comprehensive search was conducted using Google Scholar, Lens.org, and ConnectedPaper.com to identify relevant articles published between 2019 and 2024. Keywords such as "microbiota," "Long COVID," and "musculoskeletal pain" were used. Articles published in peer-reviewed journals between 2019 and 2024, studies on microbiota and Long COVID, and research on the impact of microbiota on musculoskeletal pain were included. Exclusion criteria were articles not available in English and studies that did not specifically address Long COVID or musculoskeletal pain. Data from the selected articles were synthesized to provide an overview of the interplay between microbiota, Long COVID, and musculoskeletal pain.

3. Results

3.1. The Gut Microbiota: A Key Player in Long COVID

Long COVID remains a complex puzzle for researchers, but it has been suggested that gut microbiota plays a role not only during the acute phase of COVID-19 but also in the development of Long COVID (7). Substances produced by gut microbiota, particularly short-chain fatty acids (SCFAs), play a crucial role in how these microorganisms interact with the host's body, significantly impacting the immune system (8). Signals from gut microbiota help regulate the immune system and protect tissues during severe viral respiratory infections (9). The gut and lung microbiota interact in a relationship known as the gut-lung axis (GLA). Changes in the gut microbiota or their metabolites can disrupt the immune system, weakening its ability to fight off respiratory viruses like SARS-CoV and SARS-CoV-2 (9).

Infection with SARS-CoV-2, the virus responsible for COVID-19, can disrupt the gut microbiota, leading to an imbalance known as dysbiosis (10, 11). Patients with Long COVID often show a decrease in beneficial bacteria, such as those producing SCFAs like Faecalibacterium prausnitzii and Roseburia intestinalis, and an increase in potentially harmful bacteria like *Klebsiella pneumoniae* and *Klebsiella quasipneumoniae* (12, 13). This dysbiosis can lead to a disrupted gut barrier, exaggerated inflammation, immune dysregulation, enhanced cytokine storms, and significant metabolic changes in the body (14, 15). Dysbiosis has also been linked to the progression of COVID-19, delayed viral clearance, and prolonged gastrointestinal symptoms (16).

Recent research suggests a potential link between persistent dysbiosis and the severity and duration of symptoms in Long COVID patients (2, 17), indicating that ongoing dysbiosis may contribute to the persistence of these symptoms (18). Additionally, systemic inflammation resulting from gut dysbiosis can affect various organs, contributing to the multi-systemic nature of Long COVID (12). Studies have shown that the gut microbiota of COVID-19 patients who do not develop Long COVID is restored within six months after the initial infection, while those with Long COVID exhibit persistent gut dysbiosis (2).

The persistent imbalance in the gut microbiota of Long COVID patients can lead to immune dysfunction and chronic inflammation, contributing to the pathogenesis of Long COVID (2). Patients with persistent dysbiosis and prolonged symptoms often have higher levels of inflammatory microbiota, such as *Prevotella* and *Veillonella* (19), and increased levels of genera like Dialister and Bacteroides (20). The use of antibiotics during acute infection has been found to reduce gut microbiota richness, even months after recovery (20).

Vitamin D deficiency has also been linked to dysbiosis, which can alter the composition of the microbiome and affect gut barrier integrity (21). This deficiency has been associated with COVID-19 severity and mortality, suggesting a potential role in Long COVID (22). However, more research is needed to establish the precise role and direct effect of vitamin D supplementation on Long COVID symptoms.

These findings highlight the potential role of microbiota in Long COVID (2) and suggest that targeting the gut microbiota could be a potential therapeutic approach for managing Long COVID (12, 20). Further research is necessary to establish causality and develop effective therapeutic strategies (2).

3.2. Inflammation, Immune Responses, and Musculoskeletal Health

3.2.1. How gut Dysbiosis Impacts Systemic Inflammation

Gut dysbiosis, characterized by an imbalance in the composition of gut microbiota, significantly influences systemic inflammation. Research has shown that dysbiosis can compromise the integrity of the intestinal epithelial barrier, allowing immunogenic substances, such as lipopolysaccharides, to enter the bloodstream and provoke excessive inflammation (23). Additionally, studies have identified gut microbiota dysbiosis and elevated systemic inflammatory cytokine levels in patients with late-life depression, indicating a link between gut microbiota changes and inflammation in this condition (24). Moreover, alterations in gut microbial composition due to factors such as dietary one-carbon metabolites, including vitamin B12, have been found to influence gut permeability and systemic inflammation, exacerbating myeloid lineage differentiation bias and promoting an innate inflammatory response (25). These findings collectively highlight the significant impact of gut dysbiosis on systemic inflammation and the complex relationship between gut microbiota and inflammatory processes.

3.2.2. Implications for Musculoskeletal Pain in Long COVID Patients

In COVID-19 patients, an imbalance in gut bacteria, known as gut dysbiosis, can lead to widespread inflammation. This disruption in gut health might be linked to musculoskeletal pain in those with Long COVID. Studies have shown that gut dysbiosis in patients who have recovered from COVID-19 is associated with long-term symptoms, including musculoskeletal pain, fatigue, and digestive issues (26). This imbalance can cause gut microbes and their metabolites to enter the bloodstream, inducing systemic inflammation that may impact distant organs, such as the musculoskeletal system (27).

Moreover, chronic musculoskeletal pain in Long COVID patients has been associated with central sensitization and elevated levels of pro-inflammatory cytokines, indicating the role of chronic inflammation in exacerbating musculoskeletal conditions (28, 29). Combined with reduced physical activity, these factors can significantly impact overall function, psychological health, and quality of life (28, 30).

3.3. Broader Implications of Dysbiosis on Musculoskeletal Pain

3.3.1. Association Between Lower Back Pain and Dysbiosis

Beyond the implications for Long COVID patients, gut dysbiosis has also been linked to musculoskeletal pain in other contexts. Studies have shown that people with lower back pain (LBP) often have altered gut microbiota, with an increased presence of certain bacteria like *Adlercreutzia*, *Roseburia*, and members of the *Christensenellaceae* family (31).

The proposed gut-disc axis suggests that this imbalance in the microbiome might influence the degeneration of intervertebral discs, a common cause of LBP. This could occur through mechanisms such as the translocation of bacteria into the bloodstream, regulation of the immune system, and nutrient absorption (32). Typically, the blood-disc barrier protects the intervertebral disc from systemic infections and inflammation, but dysbiosis may compromise this protective barrier (33).

While these findings point to a potential role of the gut microbiome in LBP, more large-scale studies are needed to validate these associations and explore new treatments targeting the gut-disc axis.

3.3.2. Association Between Knee Pain and Dysbiosis

Similarly, recent studies suggest that gut microbiome dysbiosis might be linked to knee pain, including conditions like knee osteoarthritis (OA). One study found that a higher presence of Streptococcus species was associated with increased knee pain, possibly due to local joint inflammation (34). Additionally, research by Jiang et al. observed changes in gut fungal microbiota and the relationships between fungi and bacteria in individuals with knee synovitis (35). However, Sanchez Romero et al. reported only a weak correlation between certain microbial taxa or their products and the severity of OA symptoms, including knee pain (36).

It is proposed that chronic low-grade systemic inflammation, potentially influenced by gut microbiome dysbiosis, may contribute to a metabolic OA phenotype. While these findings suggest a possible gut-joint axis in OA-related pain, the exact mechanisms

remain unclear (37). More high-quality research is needed to establish a definitive relationship between gut microbiome composition and OA pain (36, 37).

Overall, the persistence of these symptoms for more than two years after a COVID-19 diagnosis underscores the chronic and debilitating nature of Long COVID. This highlights the importance of developing strategies to manage and alleviate these musculoskeletal manifestations in affected individuals (38). By understanding how gut dysbiosis contributes to systemic inflammation and musculoskeletal pain, we can gain valuable insights for creating targeted interventions and management plans for Long COVID patients.

3.4. Unraveling the Microbiota-Musculoskeletal Nexus: Dysbiosis, Inflammation, and Joint Health

Gut microbiota dysbiosis has been recognized as a contributing factor to the onset and progression of various viral diseases, including COVID-19 and its post-infection manifestations, such as musculoskeletal symptoms (39). This dysbiosis is associated with immune dysregulation, chronic neuroinflammation, and mitochondrial dysfunction in Long COVID (40).

Studies have shown that individuals with Long COVID frequently experience new-onset musculoskeletal issues like joint pain, myalgia, and chronic musculoskeletal pain (28, 29, 41, 42). These symptoms are often accompanied by widespread pain, weakness, reduced function, depression, anxiety, and lower quality of life, indicating a state of central sensitization and pro-inflammation (28).

Furthermore, the role of gut microbiota in neurological symptoms in COVID-19 and Long COVID has been emphasized, suggesting a possible link between gut dysbiosis and the neurological manifestations of Long COVID. This underscores the need to investigate the gut-brain axis to better understand the progression and severity of the disease (12). Additionally, the chronic inflammation observed in Long COVID may contribute to joint discomfort, highlighting the necessity for further research to elucidate the mechanisms linking chronic inflammation to musculoskeletal symptoms in Long COVID (43).

3.5. Microbiota Modulation Strategies: Therapeutic Perspectives

Probiotics and prebiotics have shown considerable promise as therapeutic agents for managing Long COVID symptoms, including musculoskeletal manifestations, by influencing the gut microbiota and immune responses (44-46). The gut microbiota plays a crucial role in regulating immune function and overall health, and an imbalance in this microbiota may contribute to the development of Long COVID (2). Studies suggest that probiotics can help reduce inflammation and oxidative stress, thereby improving COVID-19 symptoms and potentially enhancing vaccine effectiveness (45).

Furthermore, interventions that target the microbiome, such as probiotics, prebiotics, and dietary changes, may help reduce autoimmune reactions associated with Long COVID. This highlights the importance of modulating the microbiota to improve long-term outcomes for COVID-19 survivors (46). Overall, utilizing probiotics, prebiotics, and dietary interventions to influence gut microbiota shows promise in managing musculoskeletal symptoms and addressing the broader health impacts of Long COVID. Personalized approaches that consider factors like the specificity of strain and dosage are essential for maximizing the effectiveness of these interventions (44).

4. Conclusions

The potentially complex interplay between gut microbiota, Long COVID, and musculoskeletal pain underscores the necessity of understanding how these elements interact. The evidence presented in this narrative review highlights the significant role of gut microbiota in regulating immune responses and systemic inflammation. An imbalance in this microbiome has been observed in Long COVID patients (2, 46), which may exacerbate musculoskeletal symptoms in these individuals. The associations between gut dysbiosis and conditions such as lower back pain and knee OA further illustrate the wide-ranging impact of microbiota imbalances on musculoskeletal health.

However, this narrative review has several limitations. Firstly, it is constrained by the availability of existing literature in English. Secondly, many studies in this area are still in their early stages, and there is a paucity of large-scale, long-term research. Additionally, the review relies on published studies, which may be subject to publication bias, making it challenging to draw definitive conclusions. Lastly, the rapidly evolving nature of COVID-19 research means that new findings may emerge that could alter the current understanding of these interactions.

Future research should focus on elucidating the underlying mechanisms linking gut dysbiosis to musculoskeletal pain induced by Long COVID. Large-

scale, longitudinal studies are needed to better understand the causal relationships between microbiota alterations, Long COVID, and musculoskeletal pain. Investigating the specific mechanisms through which microbiota influence musculoskeletal pain in Long COVID patients could provide valuable insights for innovative therapeutic strategies to address the complex health challenges posed by Long COVID.

Therapeutic strategies targeting the gut microbiota, including probiotics, prebiotics, and dietary interventions, show promise in managing Long COVID symptoms such as musculoskeletal pain and enhancing overall health outcomes for Long COVID survivors.

Footnotes

Authors' Contribution: Study concept and design, study supervision, L. S.; acquisition of data, M. s., and M. S. M.; analysis and interpretation of data, L. S., R. H.; critical revision of the manuscript; all authors, study supervision, L. S.

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