REVIEW

OPEN

The interaction between gut microbiome and bone health

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Purpose of review

This review critically examines interconnected health domains like gut microbiome, bone health, interleukins, chronic periodontitis, and coronavirus disease 2019 (COVID-19), offering insights into fundamental mechanisms and clinical implications, contributing significantly to healthcare and biomedical research.

Recent findings

This review explores the relationship between gut microbiome and bone health, a growing area of study. It provides insights into skeletal integrity and potential therapeutic avenues. The review also examines interleukins, chronic periodontitis, and COVID-19, highlighting the complexity of viral susceptibility and immune responses. It highlights the importance of understanding genetic predispositions and immune dynamics in the context of disease outcomes. The review emphasizes experimental evidence and therapeutic strategies, aligning with evidence-based medicine and personalized interventions. This approach offers actionable insights for healthcare practitioners and researchers, paving the way for targeted therapeutic approaches and improved patient outcomes.

Summary

The implications of these findings for clinical practice and research underscore the importance of a multidisciplinary approach to healthcare that considers the complex interactions between genetics, immune responses, oral health, and systemic diseases. By leveraging advances in biomedical research, clinicians can optimize patient care and improve health outcomes across diverse patient populations.

Keywords

bone health, bone metabolism, chronic periodontitis, coronavirus disease 2019, gut microbiome, interleukins, oral microbiome, prebiotics, probiotics

INTRODUCTION

Recent research highlights the complex relationship between gastrointestinal microorganisms (GMs) and bone health. The GM plays a crucial role in maintaining overall health by influencing physiological processes (Fig. 1). This study explores the composition and significance of GM, the fundamentals of bone health, and emerging evidence suggesting a mutualistic relationship between the two [1].

OVERVIEW OF THE GASTROINTESTINAL MICROORGANISM

The GM is a complex ecosystem containing trillions of microorganisms, including bacteria, viruses, fungi, and archaea, which are crucial for maintaining overall health and homeostasis in the human body. The GM's composition varies between individuals and is influenced by factors such as genetics, diet, age, lifestyle, and environmental exposures. The predominant phyla include Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. GM plays a multifaceted role in digestion, nutrient absorption, and vitamin synthesis. It also plays a

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KEY POINTS

- Personalized medicine approach: Understanding genetic predispositions and immune responses to coronavirus disease 2019 (COVID-19) can improve personalized patient care by tailoring treatment strategies based on individual genetic profiles, potentially improving treatment efficacy and patient outcomes.
- Early detection and intervention: Genetic variants and biomarkers linked to chronic periodontitis and COVID-19 offer early detection and intervention opportunities, enabling clinicians to identify high-risk individuals and implement preventive measures.
- Integration of oral and systemic health: Chronic periodontitis is a systemic disease that requires a holistic approach to healthcare, involving routine dental screenings and assessments to identify early signs and potential systemic implications.
- Targeted Therapeutic Strategies: Researchers are exploring the role of gut microbiome, interleukins, and immune responses in bone metabolism and COVID-19, aiming to develop targeted therapeutic strategies for improved bone health and chronic periodontitis management.
- Evidence-based practice: The review underscores the significance of evidence-based healthcare practices, emphasizing the need for rigorous research and clinical trials to validate findings and ensure high-quality patient care.

crucial role in training and modulating the immune system, helping distinguish between harmful pathogens and beneficial microorganisms. Imbalances in GM composition have been linked to conditions like obesity and metabolic disorders. External factors, such as diet, antibiotic use, lifestyle, and environmental exposures, can alter the GM's composition and diversity [2]. A diet rich in fiber and diverse nutrients promotes microbial diversity, contributing to a resilient and healthy GM. The GM's communication with the central nervous system forms the gut-brain axis, influencing gastrointestinal function and cognitive and emotional processes [3]. Disruptions in the GM have been associated with mental health disorders. GM's impact extends beyond the gastrointestinal system, influencing various aspects of overall health. Understanding the GM's composition, functions, and factors is essential for unlocking its potential to maintain health and prevent diseases [4].

BONE HEALTH

Bones are the structural foundation of the human body, providing support, protection for vital organs, and serving as a reservoir for essential minerals. Maintaining optimal bone health is crucial for overall well being, and it involves a dynamic balance between bone formation and resorption throughout one's life. Bones consist of a dense matrix of collagen fibers and mineralized calcium and phosphorus crystals, forming a strong and flexible framework that supports the body's weight, protects organs, and facilitates movement. Bone marrow, found within bones, is responsible for hematopoiesis, the production of blood cells. Two primary types of cells govern bone health: osteoblasts and osteoclasts. Osteoblasts synthesize and deposit new bone tissue, contributing to bone formation, while osteoclasts break down and resorb bone tissue, allowing for remodeling and the release of minerals back into the bloodstream. Bone remodeling is a continuous and dynamic process that occurs throughout life, involving the removal of old or damaged bone tissue by osteoclasts and the subsequent replacement with new bone tissue by osteoblasts [5–7]. Calcium and vitamin D are pivotal for bone health, as they provide structural integrity to bones and facilitate the absorption of calcium from the intestines. Vitamin D deficiency can lead to weakened bones and an increased risk of fractures. Vitamin K2 intervenes directly in the fixation of calcium in bones, delivering vitamin D into the circulation to support its activity. Several factors affect bone health throughout one's life, including proper nutrition, physical activity, adequate calcium intake, aging, hormonal changes, and lifestyle factors such as smoking, excessive alcohol consumption, and sedentary behavior. Osteoporosis is a common bone-related condition characterized by reduced bone density and increased susceptibility to fractures, and early detection and management of bone-related conditions are essential for preserving bone strength and preventing complications [8–12].

GASTROINTESTINAL MICROORGANISM AND BONE METABOLISM

The relationship between GM and bone metabolism is a growing area of research, revealing the intricate connections between the gastrointestinal tract's microbial inhabitants and the maintenance of skeletal health (Fig. 2). GM plays a crucial role in nutrient absorption, particularly calcium and vitamin D, and the role of microbial metabolites, such as short-chain fatty acids (SCFAs), in modulating bone metabolism. The gut helps regulate the solubility and bioavailability of calcium, impacting its absorption. Additionally, vitamin D, synthesized in the skin or obtained through diet, undergoes further activation in the liver and kidneys, processes

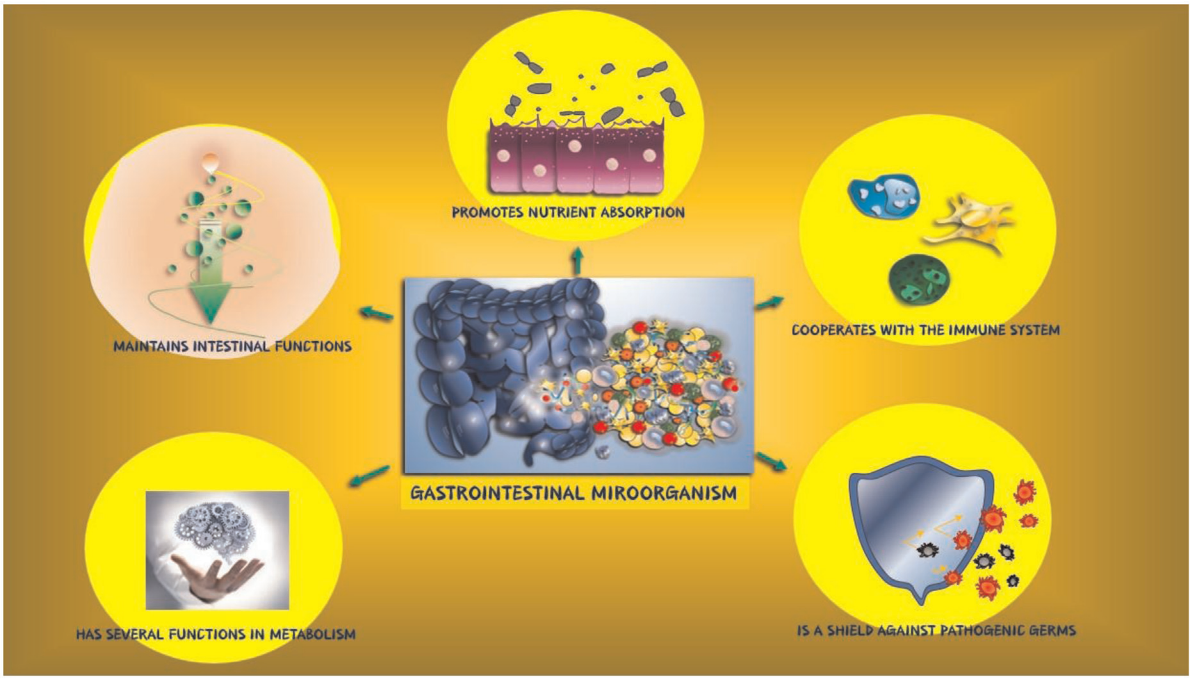

FIGURE 1. Gastrointestinal microorganisms play a key role in preserving the overall well being of the body, as they influence several physiological processes.

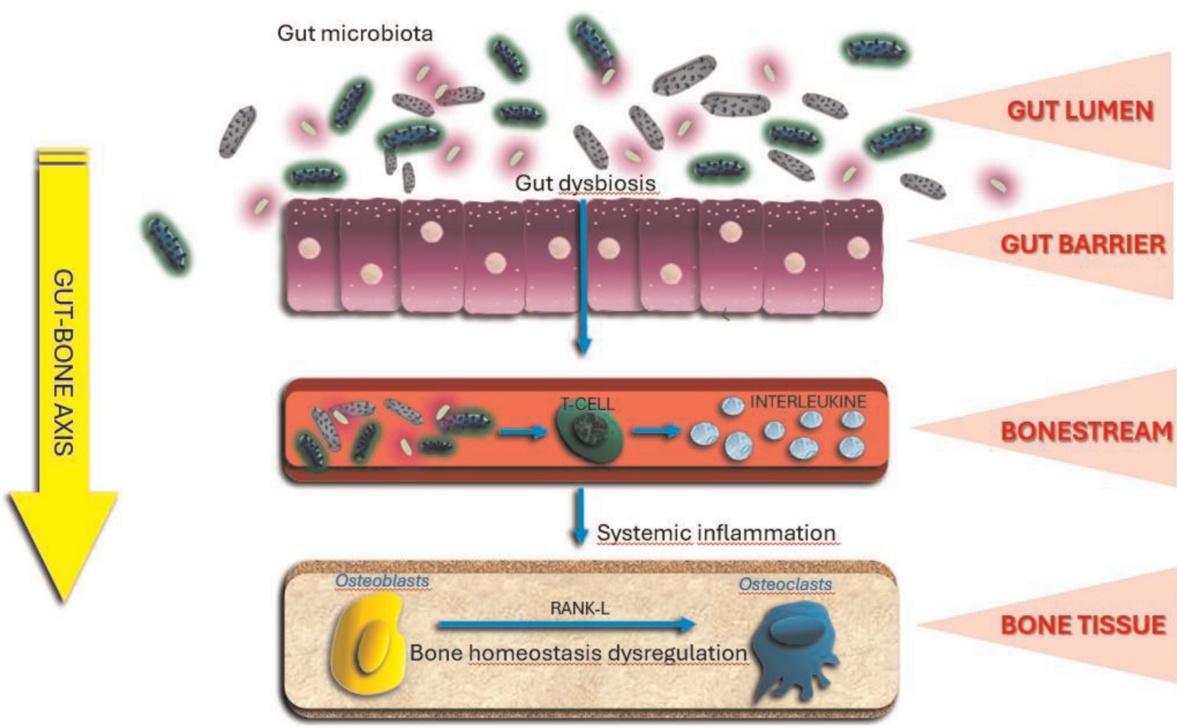

FIGURE 2. Correlation gut microbiota and bone health.

influenced by the GM. Efficient absorption of both calcium and vitamin D is essential for optimal bone mineralization and overall skeletal integrity. GM's fermentation processes yield various metabolites, with SCFAs emerging as key players in the gut-bone axis. These metabolites not only contribute to energy metabolism but also impact bone cells, influencing osteoclast and osteoblast activity, the cells responsible for bone resorption and formation. The balance between these processes is crucial for maintaining bone homeostasis. Recent studies have identified specific bacteria associated with positive or negative effects on bone health, such as Lactobacillus and Bifidobacterium genera, while dysbiosis, an imbalance in the GM composition, has been associated with conditions like inflammatory bowel disease [13▪▪,14–16]. Understanding the role of specific bacteria in bone metabolism offers potential targets for therapeutic interventions. GM's influence extends to immune system regulation, affecting bone health. Inflammatory responses can influence bone metabolism, and the gut microbiota plays a role in modulating immune function. Dysregulation of the immune system, often associated with imbalances in the GM, can contribute to conditions such as osteoporosis and rheumatoid arthritis. Understanding the dynamic interplay between GM and bone metabolism holds promise for developing targeted interventions to promote skeletal health. As research in this field advances, it may pave the way for innovative therapies and personalized strategies aimed at optimizing the gut-bone axis for enhanced overall well being [17–19].

EXPERIMENTAL EVIDENCE OF THE IMPACT OF THE GASTROINTESTINAL MICROORGANISM ON BONE HEALTH

The genetically modified (GM) diet significantly impacts bone health, as evidenced by both animal models and human trials. These studies reveal the complex interplay between gut microbiota and bone metabolism, shedding light on mechanisms, microbial metabolites, and potential therapeutic interventions. Germ-free mice, raised in sterile conditions without exposure to microorganisms, have been used as experimental models to study the impact of germ-free mice on bone density and structure. Microbiota transplantation studies have shown that introducing a diverse and healthy microbiota positively affects bone health in recipients, while transplanting from diseased or imbalanced donors may lead to compromised bone density and structure [20–24]. In human trials, probiotics have been found to modulate the GM, with certain strains associated with increased calcium absorption and improved bone density. Short-term antibiotic use has also been linked to reduced bone density and altered bone metabolism [25–33]. Specific bacterial strains have been identified as having positive effects on bone health, such as Akkermansia muciniphila, which has been linked to enhanced bone density. Butyrate-producing bacteria have been found to contribute to bone health by influencing the activity of osteoblasts and osteoclasts, responsible for bone formation and resorption [34–43]. Microbial metabolites, such as acetate, propionate, and butyrate, have been linked to bone remodeling and maintaining optimal bone density. Indole, another microbial metabolite, has been implicated in bone health, potentially positively influencing bone density by modulating the differentiation and activity of bone cells. In conclusion, the extensive experimental evidence from both animal models and human trials supports the significant impact of the GM diet on bone health, providing a foundation for further exploration and targeted interventions to optimize the gut-bone axis for improved skeletal health [44–46,47▪▪,48–52].

EXPLORING THE INTERCONNECTED LANDSCAPE OF INTERLEUKINS, PERIODONTITIS, AND CORONAVIRUS DISEASE 2019: A COMPREHENSIVE ANALYSIS

The intersection of interleukins, chronic periodontitis, and coronavirus disease 2019 (COVID-19) presents a fascinating landscape of genetic intricacies, immune responses, and systemic implications. Understanding the multifaceted factors influencing SARS-CoV-2 infection and the highly variable responses observed in individuals is essential for personalized medicine approaches in managing COVID-19. The investigation into single nucleotide genetic polymorphisms (SNPs) serves as a genetic gateway to deciphering individual responses to COVID-19. Genomic variations, especially those per-tinting to immune-related genes, play a pivotal role in shaping an individual's response to viral infections. The genetic makeup of hosts significantly influences disease progression, and understanding these genetic nuances is paramount for personalized medicine approaches in managing COVID-19 [53–63]. Key interleukin genes, including interleukin (IL)1β, IL1RN, IL6, IL6R, IL10, interferon gamma (IFNγ), tumor necrosis factor alpha (TNFα), Angiotensin-converting enzyme 2, Serine protease inhibitor 3, Vitamin D receptor, and C-reactive protein, are integral to proinflammatory and immunomodulatory responses and are considered crucial in the progression and complications of

COVID-19. The study also highlights the dynamic immune responses observed in COVID-19. Lymphocytes, pivotal players in the immune system, exhibit a notable decline in patients with COVID-19. The immune landscape, as reflected in the alteration of lymphocyte subsets, establishes a significant association with the inflammatory status in COVID-19. Neutrophils, T-killer cells, T-active cells, T-suppressor cells, and T-CD8$^+$CD38$^+$ cells emerge as crucial actors in the immune response to COVID-19 and COVID-like individuals. The intricate dance of immune cells, especially T-lymphocytes and B-lymphocytes, takes center stage in predicting the severity of COVID-19 and the potential efficacy of therapeutic interventions [63–73]. The systemic implications of COVID-19 are illuminated, particularly affecting the lungs, kidneys, and heart. Preexisting comorbidities, coupled with severely low vitamin D, extremely high IL-6, and low glomerular filtration rate (eGFR), contribute to the overall complexity of the disease. The immune-mediated responses, characterized by an overexpression of proinflammatory cytokines like IL-6, gain prominence as potential culprits in exacerbating COVID-19 severity. Challenges in chronic periodontitis (CP) include the complex relationship between oral health and systemic immune responses. Specific genetic profiles, particularly those involved in bone metabolism (VDRs, COLIA1) and immune responses (IL-10, TNF-α, IL-1α, 1β, 1RN), play a crucial role in CP susceptibility. The study proposes a paradigm shift in therapeutic strategies for degenerative and infectious diseases, including COVID-19, by understanding the negative impact of dysbiosis, coupled with insights into immune system dynamics and endocrine balance. The association between genetic variants of interleukin-10 and other key immune-related genes holds promise for risk assessment in systemic diseases linked to chronic dysbiosis [74–81,82▪▪,83,84▪▪,85▪▪].

MECHANISMS OF INTERACTION BETWEEN THE GASTROINTESTINAL MICROORGANISMS AND BONE CELLS

The interaction between GM and bone cells involves various mechanisms, signaling pathways, and interactions that regulate bone metabolism. GM plays a pivotal role in nutrient absorption, particularly calcium and vitamin D, which are crucial for bone mineralization. Microbial metabolites, such as SCFAs, modulate calcium solubility, impacting its absorption in the intestines. Microbial metabolites, such as acetate, propionate, and butyrate, are byproducts of microbiol fermentation in the gut and can directly influence bone cells. GM also influences immune responses, which can impact bone health. Dysregulation of the immune system may lead to increased inflammation, affecting bone metabolism [86–94]. Bile acid metabolism by the GM indirectly affects bone health. Hormonal signaling pathways, including the gut-brain-bone axis, play a crucial role in the crosstalk between the GM and bone cells. Neural pathways connecting the gut and bone contribute to the bilateral communication between these systems. Sensory nerves in the gut can relay signals to the central nervous system, influencing the release of neurotransmitters that impact bone cells [95–106,107▪]. GM can indirectly influence hormones and growth factors involved in bone metabolism, such as modulating insulin-like growth factor-1 (IGF-1) and transforming growth factor-beta (TGF-β). The Wnt signaling pathway is critical for bone formation, and the GM can modulate this pathway, influencing the differentiation and activity of osteoblasts and osteocytes. Understanding these mechanisms provides insight into how GM exerts its influence on bone cells and the potential for targeted interventions to optimize bone health [19,108–116,117▪▪].

FACTORS INFLUENCING THE GUT–BONE AXIS

The gut-bone axis is a complex interplay between the gut and bone, influenced by various factors such as diet, lifestyle, medications, and environmental exposures. Adequate calcium and vitamin D intake is crucial for bone health, while a balanced diet supports microbial diversity and optimal nutrient utilization. Fiber and prebiotics fuel beneficial gut bacteria, contributing to a healthier GM [118–126,127▪▪]. Antibiotic use can significantly impact the GM, potentially affecting bone metabolism. Lifestyle factors like regular exercise and weight-bearing activities can modulate the GM composition, potentially impacting bone metabolism. Age-related changes, particularly hormonal shifts, can also influence bone health. Medications like proton pump inhibitors (PPIs) and Antacids can affect calcium absorption in the gut, potentially impacting bone health over prolonged use. Other medications, such as those used in the treatment of inflammatory bowel disease, may have implications for both the GM and bone health. Stress and mental health conditions can also impact the GM and potentially affect bone metabolism. Disease states like inflammatory bowel disease (IBD) and Celiac Disease can disrupt the GM and impact nutrient absorption, potentially leading to compromised bone health. Genetic factors can determine how an individual responds to dietary interventions, medications, and other environmental influences that shape the gut-bone axis. Environmental exposures, including early life microbiome development, can have long-lasting effects on bone health. Dietary additives and preservatives in processed foods may have unintentional consequences on the GM, potentially impacting nutrient absorption and potentially influencing bone metabolism [128–138].

CLINICAL IMPLICATIONS AND THERAPEUTIC INTERVENTIONS

The growing understanding of the relationship between GM and bone health has significant clinical implications, offering potential avenues for therapeutic interventions to optimize skeletal well being. Probiotics and prebiotics, live microorganisms with proven health benefits, represent promising interventions that could be explored as a therapeutic approach to modulate the GM and positively impact bone metabolism. Personalized medicine is crucial due to the variability in GM composition among individuals, and advanced techniques such as metagenomic sequencing can be employed to analyze an individual's microbial profile and genetic makeup. Dietary recommendations include nutrient-rich diets rich in calcium, vitamin D, and probiotic fibers, as well as fermented foods like yogurt and kefir. Exercise and physical activity can also positively impact bone health by encouraging weight-bearing exercises and resistance training [139–148]. Antibiotic stewardship programs should emphasize the importance of judicious antibiotic use to minimize unintended consequences on skeletal well being. Probiotic supplementation during antibiotic courses may help mitigate disruptions to the GM and support bone health. Clinical monitoring and biomarkers can aid in clinical monitoring, and routine assessments of bone health can identify individuals at risk and tailor interventions accordingly. Patient education programs can raise awareness about the link between GM and bone health, and pharmacological interventions targeting the GM or its metabolic products could open new avenues for therapeutic strategies. Multidisciplinary approaches involving gastroenterologists, endocrinologists, nutritionists, and bone health specialists are essential for comprehensive assessments and integrated care plans. Further translational research is needed to bridge the gap between preclinical findings and clinical applications, and longitudinal studies can provide valuable insights into causal relationships and long-term effects of interventions. Recognizing the clinical implications of the gut-bone axis opens doors to innovative therapeutic strategies, from personalized medicine to lifestyle interventions, enhancing patient outcomes and preventing skeletal-related disorders [149,150▪].

CONCLUSION

The relationship between GM and bone health is a significant area of biomedical research. Understanding the mechanisms governing this interaction can lead to therapeutic interventions for bone health improvement. Further research is needed to understand specific bacterial strains, metabolites, and pathways involved in the gut–bone axis, which can revolutionize preventive and therapeutic strategies for bone-related conditions.

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Conflicts of interest

There are no conflicts of interest.

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