The interplay between oral-gut microbiome and bone health: a comprehensive review

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Abstract

This review encapsulates a holistic exploration of the interconnected realms of the gut microbiome (GM), bone health, interleukins, chronic periodontitis, and COVID-19. It begins by elucidating the intricate relationship between GM and bone health, detailing the composition, functions, and influential factors shaping this dynamic ecosystem. The narrative seamlessly transitions into the intersection of GM and bone metabolism, highlighting nutrient absorption, microbial metabolites, specific bacteria, and immune system modulation. Experimental evidence solidifies the significant impact of GM on bone health, showcasing the dynamic role of microbial metabolites and specific bacterial strains. The analysis then delves into the complex relationship between interleukins, chronic periodontitis, and COVID-19, emphasizing genetic intricacies and immune responses dictating susceptibility and severity in viral infections. Chronic periodontitis emerges as a gateway to understanding systemic dysbiosis, with genetic variants, dysbiosis, and therapeutic strategies providing insights into risk assessment and potential interventions. The proposed paradigm shift in therapeutic strategies focuses on the negative impact of dysbiosis, immune system dynamics, and endocrine balance, offering a novel approach to managing degenerative and infectious diseases. In conclusion, this review navigates through the complexities of human physiology, weaving a narrative that connects diverse elements into a holistic understanding, providing a foundation for ongoing research and emphasizing the need for continued exploration into the intricate interplay of genetics, immune responses, and systemic health.

Keywords: gut microbiome; oral microbiome; bone health; bone metabolism; interleukins; chronic periodontitis; covid-19; probiotics; prebiotics.

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Introduction

The human body functions as a complex interplay of various systems and organs, with recent research shedding light on the intricate relationship between GM and bone health (1). The GM, an extensive community of microorganisms in the gastrointestinal tract, has been recognized for its pivotal role in influencing several physiological processes crucial for maintaining overall health (2). This examination delves into the multifaceted connections between GM and bone health, exploring the composition and significance of GM, the fundamentals of bone health, and the emerging evidence pointing towards a mutualistic relationship between the two (3–9).

Overview of the GM

The GM is a complex and dynamic ecosystem residing in the gastrointestinal tract, comprising trillions of microorganisms, including bacteria, viruses, fungi, and archaea (10–21). This microbial community is pivotal in maintaining overall health and homeostasis within the human body (22).

Composition

The GM's composition is diverse and varies between individuals. It is shaped by numerous factors, including genetics, diet, age, lifestyle, and environmental exposures (23–26). The predominant phyla in the GM include Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Each individual's microbiome is unique, resembling a fingerprint that reflects their distinct genetic makeup and life experiences (27–29).

Functions

The functions of GM are multifaceted. It actively participates in digestion and nutrient absorption, breaking down complex carbohydrates and producing enzymes that the human body cannot generate independently (30,31). Additionally, the GM contributes to the synthesis of certain vitamins, such as B vitamins and vitamin K, which are essential for various physiological processes (32).

Immune System Regulation

The GM plays a crucial role in training and modulating the immune system. It helps distinguish between harmful pathogens and beneficial microorganisms, contributing to the development of a well-balanced and responsive immune system (Figure 1) (33,34). An imbalanced GM has been associated with immune-related disorders and inflammatory conditions (35).

Metabolism and Energy Homeostasis

The GM influences host metabolism and energy regulation. It can extract additional energy from nutrients, affecting the host's overall energy balance (36). Imbalances in the GM composition have been linked to conditions such as obesity and metabolic disorders, emphasizing its role in maintaining metabolic homeostasis (37,38).

Influence of External Factors

Various external factors impact the GM. Dietary choices, antibiotic use, lifestyle, and environmental exposures can alter the composition and diversity of the microbiota (39). A diet rich in fiber and diverse nutrients promotes microbial diversity, contributing to a resilient and healthy GM (Figure 2) (40,41).

Gut-Brain Axis

An intriguing aspect of the GM is its communication with the central nervous system, forming the gut-brain axis (42). This bidirectional communication involves neural, hormonal, and immunological pathways, influencing gastrointestinal function and cognitive and emotional processes (43). Disruptions in the GM have been associated with mental health disorders, highlighting the intricate link between the gut and the brain (44).

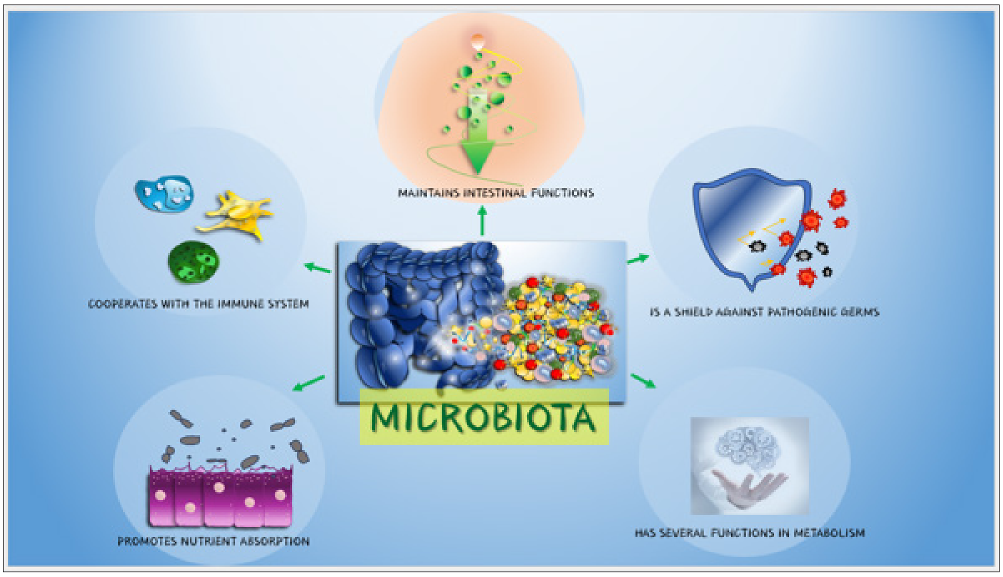

Figure 1. Functions of the GM in the human body.

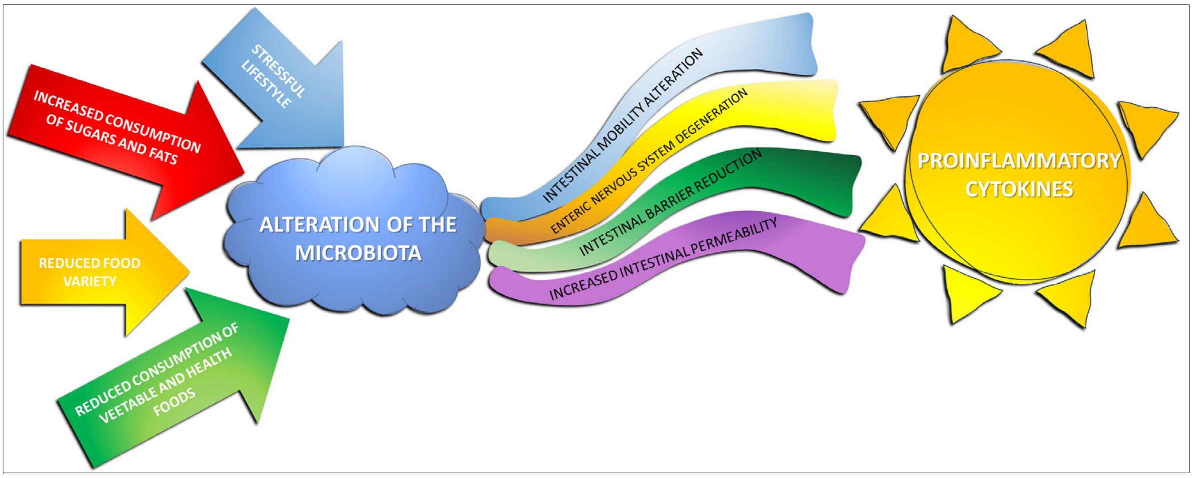

Figure 2. A stressful lifestyle and improper diet can alter GM with gut consequences and inflammatory response by cytokines.

Interconnectedness with Overall Health

The GM's impact extends beyond the gastrointestinal system, influencing various aspects of overall health (45). Imbalances in GM have been implicated in conditions such as inflammatory bowel disease, allergies, autoimmune disorders, and even systemic diseases like cardiovascular disease (46).

In conclusion, the GM is a fascinating and essential component of human biology, with its intricate interactions influencing various physiological processes. Understanding the composition, functions, and factors influencing the GM is crucial for unlocking its potential to maintain health and prevent a spectrum of diseases (47,48). Ongoing research continues to unveil the complexities of this dynamic ecosystem, opening avenues for personalized medicine and innovative therapeutic interventions (49).

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 (50–53). The maintenance of optimal bone health is crucial for overall well-being, and it involves a dynamic balance between bone formation and resorption throughout one's life (54,55)..

Structure and Function

Bones comprise a dense matrix of collagen fibers and mineralized calcium and phosphorus crystals, forming a strong and flexible framework (56–60). This structure not only supports the body's weight but also protects organs and facilitates movement (61). Bone marrow, found within bones, is responsible for hematopoiesis, the production of blood cells (62–76)..

Bone Cells

Two primary types of cells govern bone health: osteoblasts and osteoclasts. Osteoblasts are responsible for synthesizing and depositing new bone tissue, contributing to bone formation (77). In contrast, osteoclasts break down and resorb bone tissue, allowing for remodeling and the release of minerals back into the bloodstream (78,79).

Bone Remodeling

Bone remodeling is a continuous and dynamic process that occurs throughout life. It involves the removal of old or damaged bone tissue by osteoclasts and the subsequent replacement with new bone tissue by osteoblasts (80). This process is crucial for maintaining bone strength, adapting to mechanical stress, and repairing micro-damages within the bone structure (81,82).

Importance of Calcium and Vitamin D

Calcium and vitamin D are pivotal for bone health (83). Calcium is a fundamental mineral that provides structural integrity to bones, and adequate levels in the bloodstream are necessary for various physiological functions (84). Vitamin D facilitates the absorption of calcium from the intestines, promoting its incorporation into bones. Calcium and vitamin D deficiency can lead to weakened bones and an increased risk of fractures (Figure 3) (85,86).

Interconnection between vitamin K2 and vitamin D

Vitamin K2 K2 intervenes directly in the fixation of calcium in bones. Vitamin K2 delivers vitamin D into the circulation to support the activity of D in calcium fixation (87,88). In the presence of dysbiosis, the level of vitamin D below 30 ng/mL leads to the certainty of severe osteoporosis and influences bone regeneration, the repair of fractures, in short, in the various areas of medicine and implantology and the process of bone atrophy, which is much more rapid and violent the lower the vitamin D level (89). To be healthy, the vitamin D level must always be above 60 ng/mL constantly, and whenever it falls below 50 ng/mL, the organism suffers severely, and the more the level falls below 50 ng/mL, the more the general condition of the organism suffers (90–92). As the D level falls, the bones suffer from severe calcium deficiency (93–109).

Factors Affecting Bone Health

Several factors influence bone health throughout one's life. During childhood and adolescence, proper nutrition, physical activity, and adequate calcium intake are

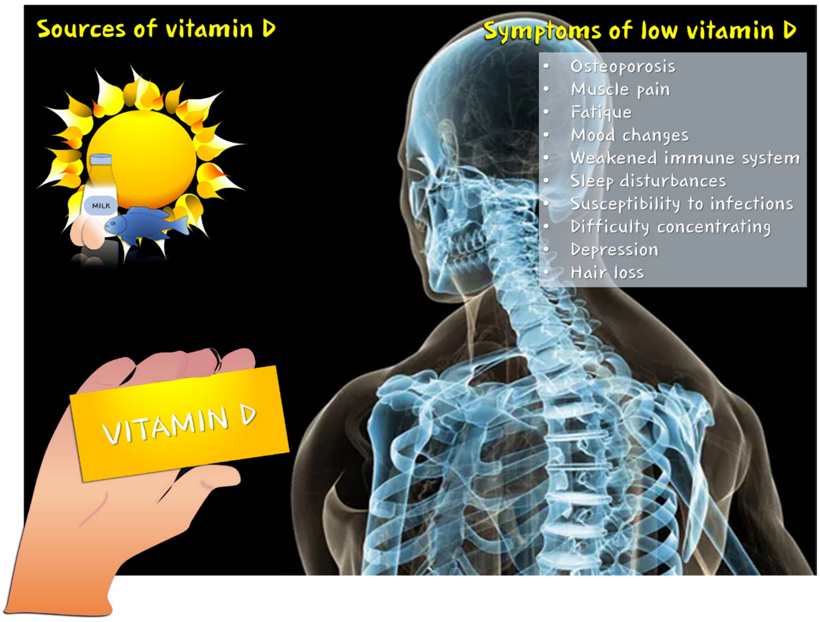

Figure 3. The importance of vitamin D (sources and symptoms of its deficiency).

critical for achieving optimal peak bone mass (110,111). Aging, hormonal changes, and lifestyle factors such as smoking, excessive alcohol consumption, and sedentary behavior can negatively impact bone density and increase the risk of conditions like osteoporosis (112).

Osteoporosis
Osteoporosis s a common bone-related condition characterized by reduced bone density and increased susceptibility to fractures (113). It often occurs in postmenopausal women due to hormonal changes but can affect men and women of all ages (114–116). Osteoporosis is a major public health concern, emphasizing the importance of preventive measures and interventions to maintain bone health (117)..

Exercise and Physical Activity
Weight-bearing exercises, resistance training, and physical activity play a crucial role in maintaining bone health (118–120). These activities stimulate bone formation, enhance bone density, and improve overall bone strength. Regular exercise also helps maintain joint flexibility and balance, reducing the risk of falls and fractures (121).

Preventive Measures and Treatment

Preventive measures for maintaining bone health include a balanced diet rich in calcium and vitamin D, regular physical activity, and lifestyle modifications (122). In cases where bone health is compromised, medical interventions such as medications, hormone therapy, and dietary supplements may be recommended (123–127). Early detection and management of bone-related conditions are essential for preserving bone strength and preventing complications (128–130).
In conclusion, bone health is integral to overall well-being and requires a holistic approach encompassing proper nutrition, physical activity, and lifestyle choices (131–133). Understanding the intricate processes of bone formation and resorption, along with the factors influencing bone health, empowers individuals to take proactive measures to preserve their skeletal integrity throughout life (134).

GM and Bone Metabolism
The relationship between GM and bone metabolism is an evolving area of research, uncovering intricate connections between the gastrointestinal tract's microbial inhabitants and the maintenance of skeletal health (135–137). This section explores how GM influences nutrient absorption, particularly calcium and vitamin D, and the role of microbial metabolites, such as short-chain fatty acids (SCFAs), in modulating bone metabolism (138)

Nutrient Absorption
One of the crucial contributions of GM to bone metabolism lies in its influence on nutrient absorption, particularly calcium and vitamin D. Calcium, a fundamental mineral for bone health, is absorbed in the small intestine (139). The gut helps regulate the solubility and bioavailability of calcium, impacting its absorption (140). Additionally, vitamin D, synthesized in the skin or obtained through diet, undergoes further activation in the liver and kidneys, processes influenced by the GM (141–143). Efficient absorption of both calcium and vitamin D is essential for optimal bone mineralization and overall skeletal integrity (144–161).

Microbial Metabolites and Bone Health
The GM's fermentation processes yield various metabolites, with SCFAs emerging as key players in the gut-bone axis (162–166). SCFAs, including acetate, propionate, and butyrate, are produced through the microbial fermentation of dietary fibers (167,168)These metabolites not only contribute to energy metabolism but also impact bone cells. Research suggests that

SCFAs can influence osteoclast and osteoblast activity, the cells responsible for bone resorption and formation, respectively (169–171). The balance between these processes is crucial for maintaining bone homeostasis (172).

Specific Bacteria and Bone Health

Recent studies have identified specific bacterial strains associated with positive or negative effects on bone health (173–175). For instance, some species within the Lactobacillus and Bifidobacterium genera have been linked to increased calcium absorption and improved bone density (176). On the other hand, dysbiosis, an imbalance in the GM composition, has been associated with conditions like inflammatory bowel disease, which may impact bone health negatively (177–181). Understanding the role of specific bacteria in bone metabolism offers potential targets for therapeutic interventions (182).

Immune System Modulation

The GM's influence extends to immune system regulation, affecting bone health (183–185). Inflammatory responses can influence bone metabolism, and the gut microbiota plays a role in modulating immune function (186–188). Dysregulation of the immune system, often associated with imbalances in the GM, can contribute to conditions such as osteoporosis and rheumatoid arthritis (21,189–203)..

Bile Acids and Bone Health

Bile acids, essential for lipid absorption, also contribute to the gut-bone axis (204–206). The GM influences bile acid metabolism, and certain bile acids have been implicated in bone metabolism (207–209). These acids can act as signaling molecules, affecting bone cells and contributing to the regulation of bone homeostasis (210).

Hormonal and Neural Pathways

The gut and bone communication involves intricate hormonal and neural pathways (211–213). Hormones such as leptin, ghrelin, and serotonin, which play roles in both gut function and bone metabolism, mediate this crosstalk (214–218). The gut-brain-bone axis reflects the interconnectivity of these systems, emphasizing the holistic nature of bone health (219).

Understanding the dynamic interplay between GM and bone metabolism holds promise for developing targeted interventions to promote skeletal health (220–222). 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 (223)

Experimental Evidence of the Impact of GM on Bone Health

Scientific investigations utilizing both animal models and human trials have provided compelling experimental evidence supporting the notion that GM significantly influences bone health (224). These studies have offered insights into the complex interplay between the gut microbiota and bone metabolism, shedding light on mechanisms, microbial metabolites, and potential therapeutic interventions (225–243).

Animal Models

Germ-Free Mice Studies: Experimental evidence often relies on germ-free mice, which are bred and raised in sterile conditions without any exposure to microorganisms (244–246). Comparisons between germ-free mice and conventionally raised mice have revealed distinct bone density and structure differences. Germ-free mice often exhibit altered bone phenotypes, emphasizing the impact of the absence of a microbiota on skeletal development (247).

Microbiota Transplantation Studies: Transplanting gut microbiota from donor mice to germ-free mice has been a crucial experimental approach (248–250). These studies demonstrated that the introduction of a diverse and healthy microbiota positively affects bone health in recipients (251–253). Conversely, transplanting microbiota from diseased or imbalanced donors may lead to compromised bone density and structure (254).

Human Trials

Probiotics and Bone Health: Clinical trials exploring the effects of probiotics on bone health have provided encouraging results (255–257). Probiotics, which are beneficial microorganisms, can modulate the GM (258–260). Certain strains of probiotics have been associated with increased calcium absorption and improved bone density in both animal models and human subjects (261).

Short-Term Antibiotic Use and Bone Density: Studies investigating the impact of short-term antibiotic use on GM and bone health have revealed noteworthy findings (262). Antibiotics, while effective in treating bacterial infections, can disrupt the balance of the gut microbiota. Such disruptions have been linked to reduced bone density and altered bone metabolism in experimental settings (263).

Identification of Specific Bacterial Strains

Akkermansia muciniphila and Bone Health: Research has identified specific bacterial strains associated with positive effects on bone health (264). For example, Akkermansia muciniphila, a mucin-degrading bacterium, has been linked to enhanced bone density (265). Experimental studies involving the supplementation of A. muciniphila have demonstrated positive effects on bone health, highlighting the potential role of specific microbes in promoting skeletal integrity (266).

Role of Butyrate-Producing Bacteria: Bacteria that produce SCFAs, particularly butyrate, have garnered attention for their impact on bone metabolism (267). Experimental evidence suggests that butyrate-producing bacteria contribute to bone health by influencing the activity of osteoblasts and osteoclasts, the cells responsible for bone formation and resorption (268).

Microbial Metabolites

SCFAs and Bone Remodeling: The production of SCFAs by the gut microbiota, especially acetate, propionate, and butyrate, has been linked to bone remodeling (269). SCFAs can influence osteoclast and osteoblast activity, thus regulating the delicate balance between bone resorption and formation (270–272). Animal studies have demonstrated that SCFAs contribute to maintaining optimal bone density (273).

Indole and Bone Health:

Another microbial metabolite, indole, has been implicated in bone health (274). Experimental evidence suggests that indole may positively influence bone density by modulating the differentiation and activity of bone cells (275–277). These findings underscore microbial metabolites' diverse and dynamic role in bone metabolism (278).

In conclusion, a wealth of experimental evidence from both animal models and human trials supports the significant impact of GM on bone health (279). These studies have unraveled complex mechanisms, identified specific microbial strains, and highlighted the role of microbial metabolites in influencing bone metabolism (280–282). This knowledge provides a foundation for further exploration and the development of targeted interventions to optimize the gut-bone axis for improved skeletal health (283).

Exploring the Interconnected Landscape of Interleukins, Periodontitis, and COVID-19: A Comprehensive Analysis

The intersection of interleukins, chronic periodontitis, and COVID-19 unveils a fascinating landscape of genetic intricacies, immune responses, and systemic implications. As we delve into this complex tapestry, it is essential to contextualize the broader understanding of susceptibility and varied responses to the SARS-CoV-2 virus (284–286). The provided speech emphasizes the multifaceted factors influencing SARS-CoV-2 infection and the highly variable responses observed in individuals, with a particular focus on genetic predisposition, immune defenses, and pre-existing conditions (287).

Genetic Predisposition and SNPs: Unveiling Susceptibility and Severity

The investigation into single nucleotide genetic polymorphisms (SNPs) serves as a genetic gateway to deciphering individual responses to COVID-19. SNPs associated with COVID-19 susceptibility and severity provide a lens through which we can examine the nuanced genetic landscape (288–292). Genomic variations, especially those about immune-related genes, play a pivotal role in shaping an individual's response to viral infections (293). The genetic makeup of hosts significantly influences disease progression, and understanding these genetic nuances is paramount for personalized medicine approaches in managing COVID-19 (294–297). In the pursuit of unraveling the genetic underpinnings, the study focuses on key interleukin genes, including IL1β, IL1RN, IL6, IL6R, IL10, IFNγ, TNFα, ACE2, SERPIN3, VDR, and CRP (298). These genes are not only integral to proinflammatory and immunomodulatory responses but are also considered crucial in the progression and complications of COVID-19. The genetic variations in these key genes set the stage for a diverse array of immune responses and contribute to the observed heterogeneity in disease outcomes (299).

Immune Responses and Lymphocyte Dynamics in COVID-19

Moving beyond genetics, the speech draws attention to 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 of COVID-19 (300). 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 (301–305). The study suggests that the levels of these cell subsets could serve as independent predictors of the disease's severity, paving the way for a more nuanced understanding of immune dynamics in COVID-19 (306).

Systemic Implications and Multi-Organ Involvement in COVID-19

As we traverse the systemic implications of COVID-19, thewe traverse the systemic implications of COVID-19, the speech illuminates the multi-organ involvement observed in infected individuals, particularly affecting the lungs, kidneys, and heart (307). Pre-existing comorbidities, including cardiovascular, respiratory, and renal disorders, coupled with severely low vitamin D, extremely high IL-6, and low glomerular filtration rate (eGFR), contribute to the overall complexity of the disease (308).

The immune-mediated responses, characterized by an overexpression of proinflammatory cytokines like IL-6, gain prominence as potential culprits in exacerbating COVID-19 severity (309–313). Noteworthy is the interconnected web where reduced vitamin D levels, age-related factors, and the presence of metabolic disorders of inflammatory and autoimmune origin intertwine with immune responses, contributing to the observed multi-organ involvement (314,315).

Chronic Periodontitis: A Gateway to Understanding Systemic Dysbiosis

The The narrative extends to chronic periodontitis (CP), a multifactorial disease intricately linked to oral health and systemic immune responses (Figure 4) (316–318). CP is not confined to its oral manifestations but is positioned as part of a more complicated systemic disease often co-existing with obesity and metabolic syndrome (MetS) (319). The association between metabolic syndrome and periodontal inflammation, driven by the elevated presence of lipopolysaccharide (LPS) triggering an immune response, underlines the broader clinical implications of CP (320).

The study bridges the gap between genetics, oral

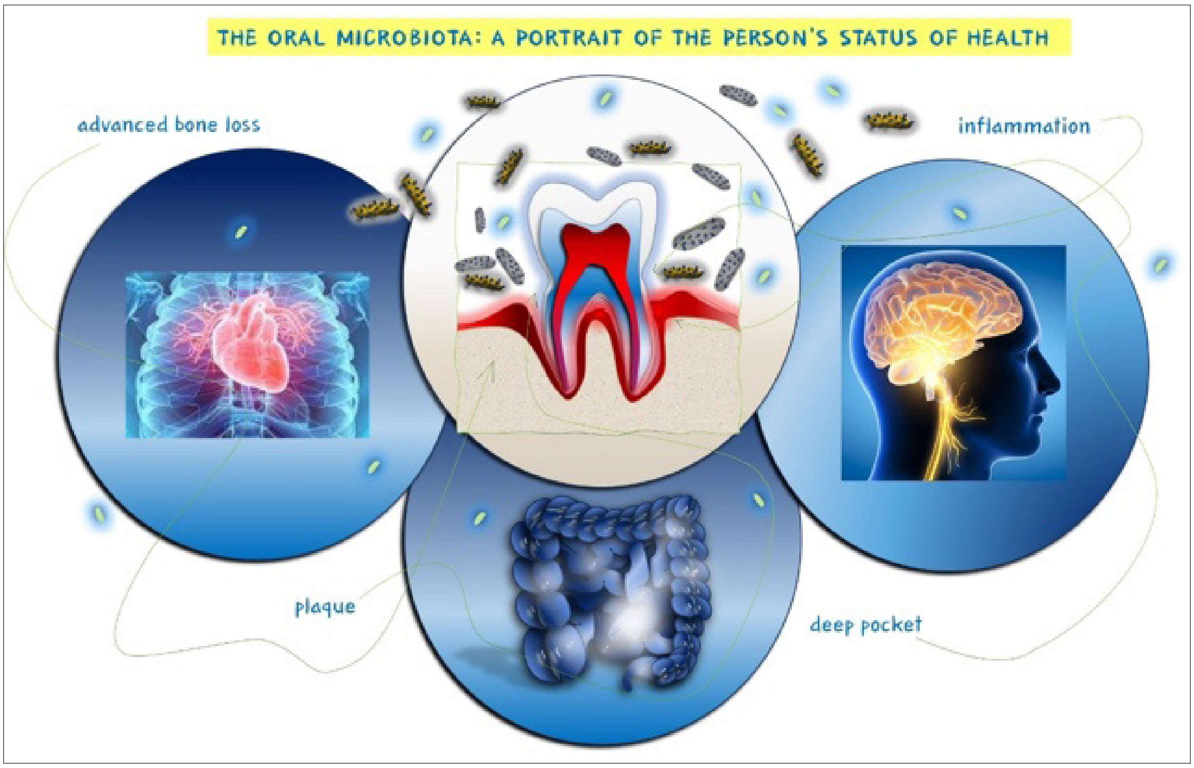

Figure 4. Correlation between oral microbiota and CP, a multifactorial disease related to the overall health of the individual.

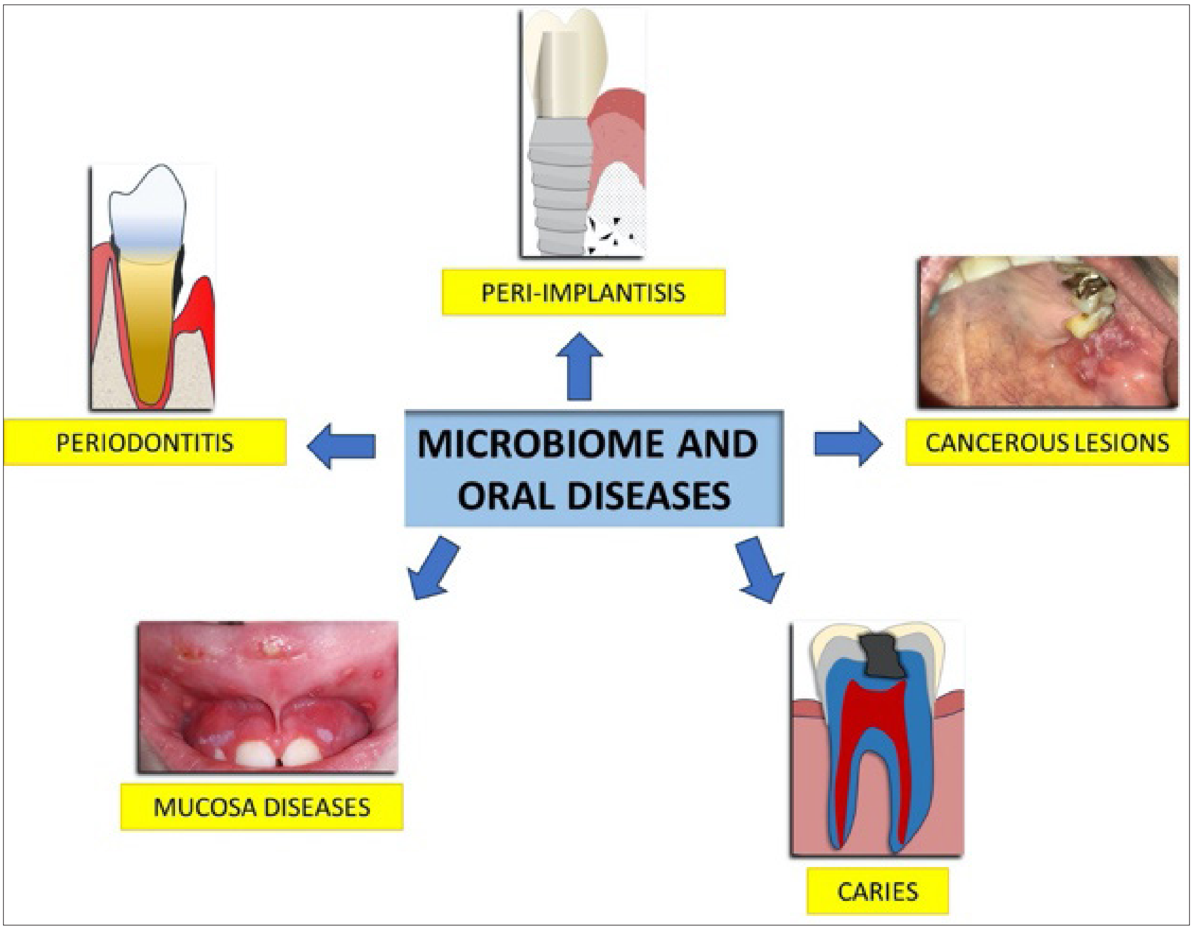

Figure 5. A generic view of possible oral diseases caused by alterations in the microbiome.

dysbiosis, bacteremia, and CP (Figure 5). 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 high presence of pro-inflammatory cytokines, including TNF-α, GM-CSF, and IL-6, released from adipose tissue in individuals with MetS and CP, paints a vivid picture of the intricate connections between systemic and oral health (321).

Genetic Variants, Dysbiosis, and Therapeutic Strategies

The exploration of genetic variants, particularly in the interleukin-10 gene, sheds light on their association with IL-1α, IL-1β-RN, COLIA1, and VDR genes in chronic periodontitis—a condition often found in patients with COVID-19 (322,323) . This association, coupled with the presence of specific bacterial strains, underscores the complexity of the oral-systemic axis (324–326). The genetic landscape, oral dysbiosis, and bacteremia collectively contribute to the intricate dance of susceptibility and progression in chronic periodontitis (327). The speech concludes by proposing a paradigm shift in therapeutic strategies for degenerative and infectious diseases, including COVID-19. Understanding the negative impact of dysbiosis, coupled with insights into immune system dynamics and endocrine balance, emerges as a potential therapeutic strategy (328). 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 (329–331). In this evolving understanding landscape, the study makes a significant contribution by systematically observing the correlation between genetic variants and interleukin/cytokine gene polymorphisms in chronic dysbiosis-related conditions (332). The call for further research, more extensive genetic information, and a representative sample size underscores the need to explore the intricate interplay of genetics, immune responses, and systemic health in the context of COVID-19 and chronic periodontitis (293).

Mechanisms of Interaction between the GM and Bone Cells

The intricate communication between the GM and bone cells involves a variety of mechanisms, signaling pathways, and interactions that contribute to the regulation of bone metabolism (333). Understanding these mechanisms is essential for unraveling the complex interplay between the microbial inhabitants of the gastrointestinal tract and the cells responsible for bone formation and resorption (334).

Influence on Nutrient Absorption:

- The GM plays a pivotal role in nutrient absorption, particularly calcium and vitamin D (335–337). Calcium is crucial for bone mineralization, and vitamin D facilitates its absorption (338). Microbial metabolites, such as short-chain fatty acids (SCFAs), modulate calcium solubility, impacting its absorption in the intestines (339).

Production of Microbial Metabolites:

- SCFAs, including acetate, propionate, and butyrate, are byproducts of microbial fermentation in the gut (340–342). These metabolites can directly influence bone cells. For example, butyrate has been shown to stimulate osteoblast activity, promoting bone formation (343).

Regulation of Immune Responses:

- The GM influences immune responses, and this modulation can impact bone health. Dysregulation of the immune system may lead to increased inflammation, affecting bone metabolism (344,345). Proinflammatory cytokines produced in response to an imbalanced GM can influence osteoclast activity, leading to bone resorption (346).

Bile Acid Metabolism:

- Bile acids, essential for fat absorption, undergo metabolism by the GM (347–349). Certain bile acids have been implicated in bone metabolism, acting as signaling molecules that influence bone cells (350). The microbiome's impact on bile acid metabolism thus indirectly affects bone health (351).

Hormonal Signaling:

- Hormonal signaling pathways, including the gut-brain-bone axis, play a crucial role in the crosstalk between the GM and bone cells (352–354). Hormones such as leptin, ghrelin, and serotonin, involved in both gut function and bone metabolism, mediate communication between these systems (355).

Neural Pathways:

- Neural pathways connecting the gut and bone contribute to the bidirectional communication between these systems (356–358). Sensory nerves in the gut can relay signals to the central nervous system, influencing the release of neurotransmitters that impact bone cells (359)

Regulation of Inflammatory Responses:

- The GM modulates inflammatory responses in the gastrointestinal tract, which can extend to affect bone health (360–362). Chronic inflammation may disrupt the delicate balance between bone formation and resorption. Microbial-derived factors can influence immune cells, leading to altered bone metabolism (363).

SCFAs and Bone Remodeling:

- SCFAs, particularly butyrate, have been shown to impact bone remodeling. Butyrate, in particular, can stimulate the differentiation and activity of osteoblasts, promoting bone formation (364–366). SCFAs may also regulate the receptor activator of nuclear factor-kappa B ligand (RANKL)/osteoprotegerin (OPG) pathway, a key regulator of osteoclast differentiation and activity (367).

Indirect Effects on Hormones and Growth Factors:

- The GM can indirectly influence hormones and growth factors involved in bone metabolism (368–

370). For example, modulation of insulin-like growth factor-1 (IGF-1) and transforming growth factor-beta (TGF-β) by the microbiome may impact bone cell function (371).

Modulation of Wnt Signaling Pathway:

- The Wnt signaling pathway is critical for bone formation (372–374). Experimental evidence suggests that the GM can modulate this pathway, influencing the differentiation and activity of osteoblasts and osteocytes (375).

Understanding these mechanisms provides insight into how the GM exerts its influence on bone cells (376–378). It also highlights the complexity of the gut-bone axis and the potential for targeted interventions aimed at optimizing bone health by modulating the GM. As research in this field progresses, more specific interactions and pathways are likely to be uncovered, paving the way for innovative therapeutic strategies (379).

Factors Influencing the Gut-Bone Axis

The intricate interplay between the gut and bone, often called the gut-bone axis, is influenced by many factors that span dietary choices, lifestyle, medications, and environmental exposures (380). Understanding these factors is crucial for comprehending how the GM impacts bone health and identifying potential avenues for intervention (381,382).

Diet and Nutrient Intake:

- Calcium and Vitamin D: Adequate calcium and vitamin D intake is essential for bone health (383–385). The GM influences the absorption of these nutrients in the intestines, with a balanced diet supporting microbial diversity and optimal nutrient utilization (386).
- Fiber and Prebiotics: Dietary fibers and prebiotics serve as fuel for beneficial gut bacteria (387–389). A diet rich in fiber promotes microbial diversity, contributing to a healthier GM, which, in turn, may positively impact bone health (390).

Antibiotic Use:

- Antibiotics, while crucial for treating bacterial infections, can significantly impact the GM (391–393). Broad-spectrum antibiotics may disrupt the microbial balance, potentially affecting bone metabolism. Prolonged or frequent antibiotic use can lead to dysbiosis and altered nutrient absorption (394).

Lifestyle Factors:

- Physical Activity: Regular exercise and weight-bearing activities positively influence bone health (395–397). Physical activity may contribute to a diverse GM, and the gut-bone axis may be modulated through the release of factors influenced by exercise (398).
- Smoking and Alcohol Consumption: Smoking and excessive alcohol consumption have been associated with negative effects on bone health (399–401). These lifestyle factors can influence the GM composition, potentially impacting bone metabolism (402).

Age and Hormonal Changes:

- Bone health is influenced by age-related changes, with hormonal shifts being particularly impactful (403–405). Postmenopausal women, for example, experience a decline in estrogen levels, leading to increased bone resorption (406–408). Hormonal changes may also influence the GM, creating a complex interplay between aging, hormones, and bone health (409).

Medications:

- Proton Pump Inhibitors (PPIs) and Antacids: Medications that alter gastric acidity, such as PPIs and antacids, may influence calcium absorption in the gut. This can potentially impact bone health over prolonged use (410).
- Antibiotics and Medications Affecting GM: Besides antibiotics, other medications can affect the GM composition (411–413). For example, certain drugs used in the treatment of inflammatory bowel disease may have implications for both the GM and bone health (414).

Stress and Mental Health:

- Stress and mental health conditions can impact the gut-brain axis, influencing the GM and potentially affecting bone metabolism. Chronic stress may contribute to inflammatory responses that could impact bone health (415).

Disease States:

- Inflammatory Bowel Disease (IBD): Conditions like IBD, characterized by chronic inflammation in the gastrointestinal tract, can disrupt the GM and impact nutrient absorption (416–418). This may contribute to compromised bone health (419).
- Celiac Disease: Celiac disease, an autoimmune condition triggered by gluten consumption, can lead to nutrient malabsorption and impact bone density (420–422). Changes in the GM are also observed in individuals with celiac disease (423).

Genetic Factors:

- Individual genetic makeup can influence both the GM composition and bone health (424–426). Genetic factors may determine how an individual responds to dietary interventions, medications, and other environmental influences that shape the gut-bone axis (427).

Environmental Exposures:

- Microbiome Development in Early Life: Early life environmental exposures, including mode of delivery during childbirth and feeding practices in infancy, influence the development of the GM (428–430). This early microbial imprinting may have long-lasting effects on bone health (431).

Dietary Additives and Preservatives:

- Certain additives and preservatives in processed foods may have unintended consequences on the GM (432–434). If disruptive to microbial balance, these substances may impact nutrient absorption and potentially influence bone metabolism (435).

Understanding these multifaceted factors provides a comprehensive view of the gut-bone axis. Interventions targeting these factors, such as dietary modifications, lifestyle changes, and personalized approaches, promise to optimise the gut-bone axis and promote skeletal health throughout life (436).

Clinical Implications and Therapeutic Interventions

The growing understanding of the interplay between the GM and bone health has significant clinical implications, offering potential avenues for therapeutic interventions to optimise skeletal well-being (437–439). The following points explore the practical applications of this knowledge and propose potential strategies for clinical management (440).

Probiotics and Prebiotics:
- Clinical Applications: Probiotics, live microorganisms with proven health benefits, and prebiotics, substances that promote the growth of beneficial bacteria, represent promising interventions (441–443). Specific strains of probiotics have shown the potential to positively influence bone health (444).
- Therapeutic Approach: Supplementation with probiotics or including prebiotics in the diet could be explored as a therapeutic approach to modulate the GM and, subsequently, positively impact bone metabolism (445).

Personalized Medicine:
- Individualized Approaches: Considering the variability in GM composition among individuals, personalized approaches may be crucial (446–448). Tailoring interventions based on an individual's microbial profile and genetic makeup could enhance the effectiveness of therapeutic strategies (449).
- Microbiome Analysis: Advanced techniques such as metagenomic sequencing could be employed to analyze an individual's GM composition, allowing for personalized interventions that consider the unique microbial landscape (450).

Dietary Recommendations:
- Nutrient-Rich Diets: Promoting diets rich in calcium, vitamin D, and prebiotic fibers supports both bone health and a diverse GM (451–453). Dietary choices that foster microbial diversity can contribute to the production of beneficial metabolites (454).
- Fermented Foods: Including fermented foods in the diet, such as yogurt and kefir, can introduce probiotic microorganisms (455–457). These foods may contribute to a healthy GM and support bone health (458,459).

Exercise and Physical Activity:
- Bone-Strengthening Activities: Encouraging weight-bearing exercises and resistance training can positively impact bone health. Physical activity may influence the GM and contribute to a holistic approach to maintaining skeletal integrity (460).
- Combined Lifestyle Interventions: Integrating exercise regimens with dietary modifications may offer a synergistic effect, addressing both the GM and bone health concurrently (461).

Antibiotic Stewardship:
- Awareness of Consequences: Healthcare providers should be mindful of the potential impact of antibiotics on the GM and bone health (462–464). Antibiotic stewardship programs could emphasize the importance of judicious antibiotic use to minimize unintended consequences on skeletal well-being (465).
- Probiotic Supplementation during Antibiotic Use: Considering probiotic supplementation during and after antibiotic courses may help mitigate disruptions to the GM and support bone health (466).

Clinical Monitoring and Biomarkers:
- Biomarkers for Gut-Bone Axis: Developing specific biomarkers that reflect the status of the gut-bone axis could aid in clinical monitoring. Biomarkers may include microbial signatures, metabolite levels, or markers indicative of bone turnover (467).
- Regular Assessments: Routine assessments of bone health, including bone mineral density measurements and biomarker monitoring, could be integrated into clinical practice to identify individuals at risk and tailor interventions accordingly (468).

Patient Education:
- Promoting Gut-Bone Health Awareness: Patient education programs can raise awareness about the link between the GM and bone health (469–471). Empowering individuals with knowledge about lifestyle choices, dietary habits, and the importance of microbial diversity fosters active participation in bone health maintenance (472).

Pharmacological Interventions:
- Targeted Medications: Developing pharmacological interventions that specifically target the GM or its metabolic products could open new avenues for therapeutic strategies (473–475). Research into drugs that modulate microbial activity may provide innovative approaches to influence bone metabolism (476).

Multi-disciplinary Approaches:
- Collaboration Across Specialties: A multi-disciplinary approach involving gastroenterologists, endocrinologists, nutritionists, and bone health specialists is essential. Collaboration can facilitate comprehensive assessments, considering both gut and bone health parameters (477).
- Integrated Care Plans: Integrating gut health considerations into existing care plans for conditions like osteoporosis or inflammatory bowel disease can enhance overall patient outcomes (478).

Research and Clinical Trials:
- Translational Research: Further translational research is needed to bridge the gap between preclinical findings and clinical applications. Clinical trials exploring the efficacy of GM-targeted interventions

on bone health will contribute to evidence-based practices (479).

- Longitudinal Studies: Conducting longitudinal studies that track changes in the GM and bone health over time can provide valuable insights into the causal relationships and long-term effects of interventions (480).

Recognizing the clinical implications of the gut-bone axis opens doors to innovative therapeutic strategies [481]. From personalized medicine to lifestyle interventions, a holistic approach that considers both the GM and bone health holds promise for enhancing patient outcomes and preventing skeletal-related disorders. Continued research and clinical trials are pivotal for translating these insights into effective, tailored clinical interventions (482-483-484).

Conclusion

The intricate relationship between the GM and bone health represents a fascinating frontier in biomedical research. As we unravel the mechanisms governing this interplay, opportunities for therapeutic interventions to enhance bone health emerge (485). Continued research is essential to elucidate the specific bacterial strains, metabolites, and pathways involved in the gut-bone axis. Integrating this knowledge into clinical practice can revolutionize preventive and therapeutic strategies for bone-related conditions, ultimately contributing to enhanced overall health and well-being (486,487).

Abbreviations

CP	Chronic Periodontitis
Egfr	Glomerular Filtration Rate
GM	Gut Microbiome
Mets	Metabolic Syndrome
LPS	Lipopolysaccharide
OPG	Osteoprotegerin
RANKL	Receptor Activator Of Nuclear Factor-Kappa B Ligand
SCFAs	Short-Chain Fatty Acids
SNPs	Single Nucleotide Genetic Polymorphisms
TGF-β	Transforming Growth Factor-Beta

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