REVIEW ARTICLE

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The digestive system microbiome and bone: environmental determinants and health implications – a narrative review

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Abstract

Introduction and Objective. The human microbiome is a system of microorganisms whose composition is unique to each individual. Numerous factors, including environmental and cultural factors, influence its components and their functioning. It appears that the microbiome can influence skeletal health in both positive and negative ways. The aim of the narrative review is to summarize and organize information regarding the oral and gut microbiome, probiotics, and microbiome transplantation in the context of their impact on bone health, as well as to highlight the importance of the environment in these interactions.
Review Methods. Databases such as PubMed and Google Scholar were used to search for literature. 37 articles from 2009–2023 related to the environment, the microbiome and bone health were included in the review.
Brief description of the state of knowledge. Dysbiosis and all pathologies within the oral and intestinal microbiome can contribute to poor bone health by increasing resorption processes, leading to the development of osteoporosis. Microorganisms can disrupt the proper functioning of bone tissue by impairing nutrient absorption, affecting the immune system, and modulating the gut-brain-bone axis. In turn, repairing a disrupted microbiome can be achieved through probiotic supplements and gut microbiome transplantation. Scientific studies demonstrate that these interventions are highly effective in combating these pathologies.
Summary. Environmental and cultural factors significantly impact the development and function of microorganisms in the human body. Any dysbiosis within the microbiome can result in excessive bone resorption and the development of osteoporosis, the effects of which can be mitigated by supplementing with appropriate probiotics or by gut microbiome transplantation.

Key words
microbiome, environment, probiotics, bone health, intestinal microbiome, oral microbiome, microbiome transplant

INTRODUCTION AND OBJECTIVE

The gastrointestinal tract, respiratory system, and skin are areas of the human body characterized by intensive colonization by microorganisms [1]. Due to their richness and diversity, the microorganisms residing in the gastrointestinal tract (commonly referred to as the gut microbiome) attract the most significant interest among scientists and researchers [2]. Microbiomes from various areas of the human body, depending on their composition, may support local or systemic physiological processes, but may also promote the development of many diseases [3]. In the context of bone health, we know that the human microbiome can influence the balance between bone formation and bone loss, both positively and negatively [4, 5]. Therefore, a thorough understanding of the mechanisms underlying these relationships appears to be key to maintaining skeletal health. Osteomicrobiology, a relatively young field of science that studies and systematizes information on the relationship between bone health and the gut microbiome, is proving extremely useful in advancing our understanding of this topic.

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The knowledge available due to recent scientific progress shows that any dysfunctions within the human microbiome may contribute to the development of metabolic bone diseases (including osteoporosis), and interventions aimed at its repair (including supplementation of probiotic bacteria) may reduce the severity or prevent the development of these skeletal diseases [6]. Numerous scientific studies have shown that there is no single, universal microbiome composition shared by every person worldwide. Human microbiomes vary among populations, and numerous environmental and cultural factors influence these differences. These include diets that differ across continents, culturally dependent approaches to hygiene, and medical aspects, such as the attitude of a given population towards antibiotic therapy [3].

The aim of the review is to summarize and organize information on the positive and negative effects of the digestive system microbiome on bone health, and to present the role of environmental factors in these processes.

REVIEW METHODS

The review is based on a literature search of databases such as PubMed and Google Scholar, using key words: 'bone health', 'microbiome', 'environment', 'oral microbiome', 'intestinal microbiome', 'probiotics' and 'microbiome transplant'. 37 articles from 2009–2023, meta-analyses, and reviews related to the environment, the microbiome (including oral and gut microbiomes, microbiome transplants, and probiotics), and bone health, were included. The publications were analyzed according to the PRISMA 2020 checklist [7]. The PRISMA flowchart and a detailed list of the 37 selected studies are available in the supplementary files.

NEGATIVE IMPACT OF THE MICROBIOME ON BONE HEALTH

Oral microbiome and bone health. The oral microbiota consists primarily of facultatively anaerobic bacteria, such as streptococci and actinomycetes, microorganisms that primarily inhabit the superficial layers of the oral cavity. As they descend from these layers into the subgingival environment, oxygen levels gradually decrease. This results in a shift in the microbiota composition to strict anaerobes, primarily Bacteroidaceae spp. and spirochetes [8]. Recent studies have revealed that, in addition to bacteria, the oral microbiota also includes fungi, viruses, parasites, and archaea [9], a complex community of oral microorganisms which forms a biofilm [8]. The lack of symbiosis between biofilm components can accelerate the development of oral pathologies, including caries, gingivitis, and periodontitis. The negative impact of a lack of symbiosis between oral biofilm components is not limited to the oral cavity. These correlations underscore the importance of maintaining harmony in the oral microbiome to maintain overall health [10].

The environmental factors that have had the most significant impact on the evolution of the human oral microbiome have been hygiene practices. Many clinicians and patients, particularly in developed countries, commonly use mouthwashes. The effectiveness and efficacy of some of these products are supported by compelling scientific evidence, but others have questionable reputations. An example of this is chlorhexidine, which can cause oral dysbiosis by killing both pathogenic microorganisms and desirable biofilm components. Furthermore, oral hygiene using chlorhexidine has been associated with the development of bacterial resistance [11].

Periodontal disease is classified as a chronic inflammatory disease [12] which, as mentioned above, may result from a disruption of the symbiosis among components of the oral microbiome [10]. Research indicates that facultatively anaerobic bacteria are primarily responsible for initiating and exacerbating the inflammatory response that causes periodontal disease. These include Treponema denticola and Porphyromonas gingivalis, which inhabit periodontal pockets, and the inflammatory process that begins in these structures may become permanent, leading to the destruction of periodontal tissues, including alveolar bone resorption [13]. The mechanism underlying this condition involves inhibition of osteoblast activity and increased osteoclast function, driven by increased production of proinflammatory cytokines.

Currently, there is insufficient evidence to demonstrate a direct impact of periodontal disease on the development of systemic osteoporosis. However, dentists can use the aforementioned relationships between inflammatory periodontal disease and alveolar bone resorption to estimate the likelihood of local resorption in the maxillary and mandibular bones and, thus, fractures in these structures, when treating patients with severe periodontitis [14].

Intestinal microbiome and osteoporosis. Gaining knowledge about the gut microbiome has been made possible by advances in next-generation sequencing. Today, thanks to this technology, we are constantly expanding our research base and discovering new ways in which the gut microbiome can influence human life and health [15]. The gut microbiota has been shown to constitute an incredibly complex ecological system, comprising bacteria, viruses, fungi, and archaea [15, 16]. Despite this, the most thoroughly and frequently studied element of this ecosystem appears to be the bacterial microbiota, which is due primarily to the vast number of different bacterial species in the gut. In a healthy gut environment, the number of bacterial species exceeds 1,000, with the majority inhabiting the lumen of the large intestine [16].

Human intestinal colonization begins during labour and plays a significant role in protecting the body from potential colonization by pathogenic microorganisms [17]. Scientific research has demonstrated that the mode of delivery significantly influences the composition and functioning of the human intestinal microbiota throughout life. Vaginal delivery is preferred for proper correlation and interaction among its components. During labour, the digestive system of the newborn is exposed to a rich maternal microbiota, which has a long-lasting and positive impact on its developing microbiome [18].

Diet has been shown to be another crucial factor influencing the gut microbiome. Studies have shown that a western diet increases the risk of dysbiosis within the gut microbiome [18]. A diet high in fat causes unfavourable changes in the composition of the gut microbiome, which may lead to the development of intestinal tumours [19]. Dietary fibre, on the other hand, induces favourable changes in the composition of the gut microbiota by increasing the colonization of the gut by bacteria, such as Bifidobacterium and Lactobacillus spp., large amounts of which increase butyrate production and its concentration in the stool. In biomedical terminology, butyrate is referred to as an anticancer compound [18].

The gut microbiome plays a key role in regulating bone mineral density [20], and numerous studies have demonstrated that it can influence bone metabolism by modifying osteoclast activity. The influence of gut microbiota on the nervous system is crucial in this process, as it modulates the synthesis of hormones and neurotransmitters, particularly serotonin. The serotonin signalling pathway is widely recognized as a key regulator of bone formation. A study led by Bliziotes demonstrated that both osteoblasts and osteocytes express serotonin receptors. Furthermore, they found that elevated levels of this neurotransmitter are associated with reduced bone density [21]. This pathological reduction in bone density and weakening of its structure, resulting from osteoclast activity dominating osteoblasts, can increase the risk of fractures and is referred to as osteoporosis [4].

There is a significant and complex correlation between the gut microbiome and the immune system, a relationship that stems from the fact that approximately 70–80% of pathogenic cells originate in the gastrointestinal tract, from where they modulate systemic disease processes [22]. Gut microbiota influences cytokines and the maturation of CD4+ T helper lymphocytes, specifically subtype 17 (Th17). Obligatory RANKL (receptor activator of nuclear factor kappa B) expression is not limited to osteoblasts and osteocytes, but is also observed in more highly activated CD4+ T lymphocytes. These effects are important in the context of osteoporosis due to their association with bone outcomes [23]. Tumour necrosis factor (TNFα) and interleukin 17 (IL-17), produced by Th17 lymphocytes, are key mediators of osteoclastogenesis. When inflammation occurs in the intestine, activated Th17 lymphocytes may migrate to bone tissue where they may, in turn, demonstrate increased TNFα production and RANKL expression. This situation promotes the formation of large numbers of new osteoclasts, and may ultimately contribute to the development of osteoporosis [24].

It has been shown that the gut microbiome influences nutrient absorption. Some of these nutrients, particularly calcium, are essential for proper skeletal development and significantly impact bone mineral density [4]. Impaired absorption of nutrients, such as calcium, dietary fibre, vitamin D and protein, leads to deficiencies in the body which, in turn, impair bone metabolism. This results in reduced bone mineral density, increased bone fragility, and increased risk of fractures [25]. Therefore, a thorough understanding of the mechanisms of nutrient absorption, including calcium, is crucial for preventing osteoporosis. Research has revealed that a gut microbiome rich in Parabacteroides and Clostridium strains increases calcium absorption, while its Lactobacillus plantarum component increases the bioavailability of this element [26].

POSITIVE IMPACT OF THE MICROBIOME ON BONE HEALTH

Probiotics in bone health. The World Health Organization (WHO) defines probiotics as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' [27]. The criteria that microorganisms must meet to be called probiotics include antibiotic resistance and the ability to survive in the human gastrointestinal tract. Probiotic properties are primarily exhibited by bacteria, but also by some fungi, such as Saccharomyces. The natural habitats for probiotic bacteria include the human intestines, urogenital tract, and skin. Furthermore, probiotics are commonly found in dairy products (e.g., yogurt and ice cream) and fermented products (e.g., beer). They can also be found in dietary supplements in various forms, including capsules, powders, and oral solutions. The bacterial strains most commonly used as probiotics are Lactobacillus, Bifidobacterium, Escherichia, and Enterococcus [28]. The growing interest in probiotics is linked to the rapidly developing pharmaceutical industry. As mentioned above, probiotics are available as dietary supplements in various forms, many of which have been introduced internationally [29]. However, it is important to remember that the effects and effectiveness of probiotics vary among individuals. These differences stem from individual relationships between probiotic bacteria and the host, and are influenced by genetic, cultural, and dietary factors [30].

Probiotics regulate the composition of the gut microbiome and strengthen the intestinal barrier [27]. They are extremely useful in reducing intestinal inflammation and improving the absorption of nutrients from the gastrointestinal tract. In addition to their local effects in the intestines, probiotics also exhibit systemic effects [31]. Scientific studies have revealed that supplementation with fermented dairy products produced by the probiotic bacterium Lactobacillus casei 393, positively affects osteoblast proliferation and causes calcium accumulation in these cell cultures, increasing its bioavailability. This indicates the potential of this bacterium in preventing bone loss and osteoporosis [32].

Many studies examining the effects of probiotics on bone health have focused on the bacterium Lactobacillus reuteri 6475, a bacterium that has been shown to produce and secrete anti-osteoclastogenic factors. A study by Britton et al. showed that administering the probiotic bacterium Lactobacillus reuteri to estrogen-deficient mice protected them from bone loss [33]. Furthermore, a research team led by Nilsson conducted a study demonstrating that the probiotic bacterium Lactobacillus reuteri reduced bone loss in elderly women with low bone mineral density. After a one-year clinical trial, the women receiving a probiotic supplement containing Lactobacillus reuteri had a 50% reduction in bone loss, compared to the placebo control group [34]. A follow-up study by Peishun investigated the effects of Lactobacillus reuteri supplementation on bone metabolism in elderly women with reduced bone mineral density. The effect of Lactobacillus reuteri on bone metabolism was associated with changes in amino acid, peptide, and lipid metabolism, including increased butyrylcarnitine (C4). Butyrylcarnitine (C4) is a carnitine ester of butyrate. This compound acts both as a transporter and a reservoir for butyrate, thereby enhancing bone formation and inhibiting bone resorption, and thus positively affecting bone metabolism and health [35].

Although the cited studies demonstrate a positive effect of probiotics on bone health, caution should be exercised when using them. Adverse effects, including sepsis and intestinal ischemia, may occur. Individuals with weakened immune systems and a high degree of intestinal barrier dysfunction are particularly susceptible to these adverse effects [36].

Table 1. Comparison of routes (upper, middle, and lower) for intestinal microbiota transplant implantation in the FMT procedure. Advantages, disadvantages and clinical indications for selecting a specific route.

Route	Transplant description	Disadvantages and advantages	References
Upper gastrointestinal pathway	Microbiome transplantation using oral capsules or nasogastric tubes. Oral capsules consist of microbiota derived from donor stool, glycerol (which acts as a thermoprotective agent), and a coating. They act directly on the stomach or colon, and depending on the preferred distribution site, they differ in the composition of their coatings. An alternative to capsules is nasogastric tube.	**Disadvantages:** – Risk of reflux leading to suffocation – Risk of degradation by the gastric environment – Risk of perforation and bleeding from the upper gastrointestinal tract – Risk that the transplant will not reach the desired location in the gastrointestinal tract **Advantages:** – Ease of performance – Quick procedure – Good patient tolerance – Low cost	[38, 44, 45]
Middle gastrointestinal pathway	Microbiome transplantation using naso-intestinal tube and mid-gastrointestinal pathway-mediated transendoscopic enteral tube (TET). Naso-intestinal tubes are inserted using a guide wire. With properly functioning gastrointestinal motility, such a complex can pass through the pylorus on its own. An alternative to the naso-intestinal tube is mid-gut TET, which involves permanently placing part of the tube in the deep part of the digestive tract, leaving the other end free.	**Disadvantages:** – High costs when repeated gut microbiota transplantation procedures are required – High incidence of side effects (diarrhea/constipation/cramps) **Advantages:** – The use of naso-intestinal tubes reduces the risk of bacterial translocation – Mid-gut TET does not require the use of X-rays or other medical devices	[38, 46]
Lower gastrointestinal pathway	Microbiome transplantation using enemas or colonic TET. Part of the TET tube is placed in the colon using an endoscope and then attached to the intestinal wall using endoscopic clips. The remaining part of the tube is attached outside the anus.	**Disadvantages:** – Risk that the enema contents will not reach the colon and splenic flexure – Risk of serious adverse events, including the risk of intestinal perforation **Advantages:** – The use of an enema is a simple and minimally invasive procedure – Safety of using the colonic TET method in children aged 3-7 and over 7 years of age – Colonic TET is convenient when multiple intestinal microbiota transplants and multiple administrations of drugs to the colon are required	[38, 46, 47]

Microbiome transplant. Intestinal microbiota transplantation (FMT) begins with collecting microbiota from the intestines of a selected donor. In this case, the donor is a healthy individual with a functioning microbiota. The collected material is first centrifuged and then purified, and the prepared transplant transferred to the recipient, a patient with intestinal microbial imbalances [37]. Bacteria can be transferred through the different parts of gastrointestinal tract (Tab. 1). Their transplantation remodels the recipient's intestinal microflora, enabling its proper functioning. This treatment alleviates the symptoms of existing diseases and prevents their progression. Animal studies confirm that this approach can improve bone mineral density in patients with intestinal microbiota abnormalities [38].

The effectiveness of gut microbiota transplantation depends on many factors. These include the appropriate selection of surgical techniques for the transplant, as well as the physiology of the donor and the recipient, and living environments (including housing conditions) [39]. The medical community has popularized gut microbiota transplantation worldwide, which has resulted in a significant increase in the number of patients benefiting from this procedure [40].

Ma et al. used young, healthy rats as the donors of gut microbiota. Their study confirmed the efficacy of FMT in alleviating the symptoms of senile osteoporosis in older rats (recipients). The researchers concluded that the reduction in symptoms resulted from improved gut microbiota composition in the older rat population and improved intestinal mucosal barrier integrity [41]. Wang et al., however, reversed the above-described process. In their study, young, healthy rats were transplanted with the microbiota from older rats with osteoporosis, which led to the development of senile osteoporosis in the transplant recipients. The researchers concluded that the transplantation of abnormal microbiota led to dysbiosis in recipients and weakened the intestinal barrier, contributing to the development of osteoporosis symptoms in the study group [42]. Additionally, a study by Zhang et al. demonstrated that gut microbiota transplantation, leading to its remodelling, reduced bone loss in a population of ovariectomy-induced osteoporotic mice. The factors contributing to this phenomenon included correction of gut microbiota imbalances, increased levels of short-chain fatty acids, improved intestinal barrier function, and reduced production of pro-osteoclastogenic cytokines. The resulting balance in the gut microbiota limited excessive osteoclast proliferation, led to stabilization of bone formation and osteolysis, and subsequently, reduced bone loss in the studied population of osteoporotic mice [43]. The proposed mechanisms linking the microbiome and bone metabolism are presented in Figure 1.

DISCUSSION

The lack of symbiosis between the components of oral biofilm may contribute to the development of periodontal diseases, resulting in local resorption of the maxillary and mandibular bones and their local fractures. In 2016, Huang et al. conducted an observational study, which led them to conclude that among people with good oral hygiene, the sudden development of periodontal disease is an indicator of the risk of osteoporosis progression. They linked the

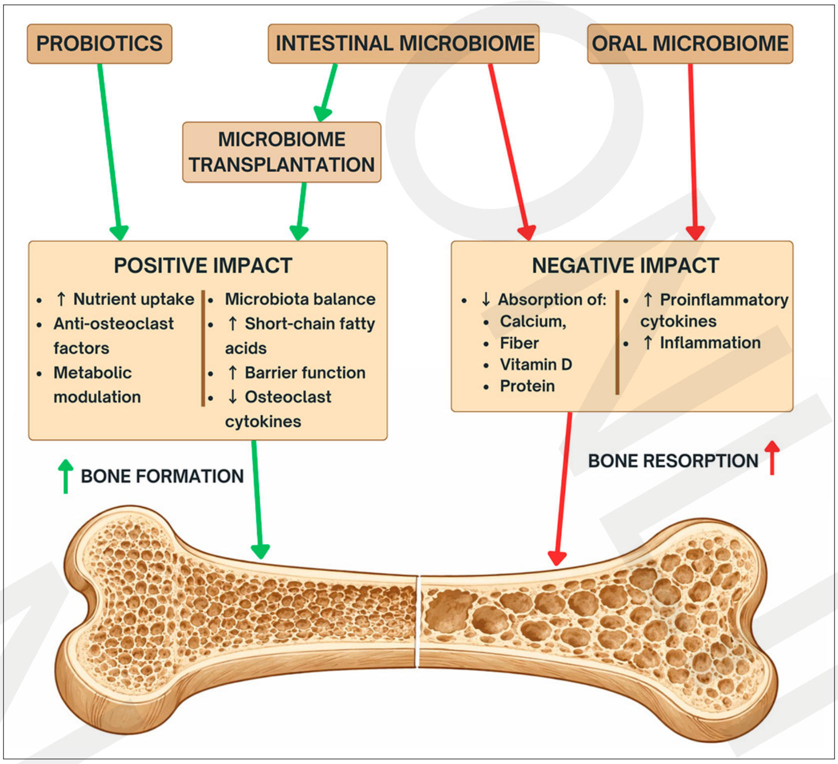

Figure 1. Overview of microbiome influence on bone metabolism

prevention of osteoporosis to maintaining hygienic conditions in the oral cavity [48]. In turn, in 2022, Yu B and Wang CY published a review in which they classified osteoporosis as one of the risk factors for periodontal diseases. However, they emphasized that there is currently insufficient evidence to support the theory that periodontal diseases contribute to a systemic reduction in bone mineral density. Despite this, like Huang et al., they emphasized the importance of dental care in patients with osteoporosis and risk factors for periodontal disease [14].

Depending on its composition and function, the intestinal microbiome may contribute to the development of systemic osteoporosis. The impact of the microbiome on this disease may be related to its influence on the gut-brain-bone axis, modulation of the immune system, and nutrient absorption. In turn, modulation of the disturbed intestinal microbiome through intestinal microbiome transplantation has a positive effect on bone mineral density.

Moreover, probiotics also support bone metabolism. Consuming foods rich in probiotic bacteria and pharmacological supplementation can reduce bone loss and prevent osteoporosis. A 2018 study by Nilsson et al. showed that annual supplementation with L. reuteri bacteria in women aged 78–80 with reduced bone mineral density resulted in reduced bone loss in the study group [34]. In 2021, Li P et al. conducted a follow-up to the Nilsson study, and also obtained results confirming the positive effect of L. reuteri on bone health [35]. In 2024, however, a team led by Gregori conducted a randomized controlled trial involving 239 postmenopausal women and found that L. reuteri supplementation did not change the bone mineral density of the tibia in the study group. Furthermore, the team suggested that supplementation with this bacterium should not be recommended to postmenopausal women for maintaining bone health due to its lack of clinical significance [49].

Due to the conflicting results of the studies conducted, the small number of studies conducted on humans, and the fact that studies have been conducted on a small animal population, it is necessary to conduct new studies in this field. As far as possible, these studies should be conducted on larger human populations and should focus on examining safety, but also efficacy and the duration of the effect obtained. The analysis of existing studies should also be extended.

CONCLUSIONS AND FUTURE DIRECTIONS

Environmental and cultural factors strongly influence the development of the oral and intestinal microbiome, the action and effectiveness of probiotic supplements, and the effectiveness of intestinal microbiome transplantation procedures.

Deterioration in bone health, including the development of osteoporosis, may result from intestinal microbiota imbalance and its impact on nutrient absorption and the activity of osteoclasts. Moreover, dysbiosis in the oral microbiome, by initiating and exacerbating the inflammatory response that causes periodontal disease, contributes to local bone resorption in the jaw, thereby increasing local susceptibility to fractures. This relationship may be extremely clinically relevant for dentists.

Modulation of the composition of the intestinal microbiota through transplantation or supplementation with the probiotic bacterium L. reuteri has great potential to serve as a tool commonly used in clinical practice to reduce bone loss, and prevent the development of osteoporosis.

In order to clearly determine the positive and negative effects of the digestive system microbiome on bone health, it is necessary to conduct more interventional and observational studies and, equally important, to conduct an in-depth analysis of the data already available.

Table 2. Summary of key observational and interventional studies on the microbiome and bone outcomes.

Title	Authors	Year of publication	Type of study	Study size	Subject of the study	Main results	References
Probiotic L. reuteri treatment prevents bone loss in a menopausal ovariectomized mouse model.	Britton RA, Irwin R, Quach D, et al.	2014	Interventional study	No data	Probiotic bacterium L. reuteri	Supplementation of the probiotic bacterium Lactobacillus reuteri in a population of estrogen-deficient mice prevented bone loss in this population.	[33]
Lactobacillus reuteri reduces bone loss in older women with low bone mineral density: a randomized, placebo-controlled, double-blind, clinical trial.	Nilsson AG, Sundh D, Bäckhed F, Lorentzon M.	2018	Interventional study	68 women aged 75 to 80 with low bone mineral density	Probiotic bacterium L. reuteri	One-year supplementation with the probiotic bacterium Lactobacillus reuteri in women aged between 75 and 80 years with reduced bone mineral density reduced bone loss.	[34]
Metabolic Alterations in Older Women With Low Bone Mineral Density Supplemented With *Lactobacillus reuteri*.	Li P, Sundh D, Ji B, et al.	2021	Observational study	269 elderly women with high or very low bone mineral density	Probiotic bacterium L. reuteri	Supplementation with the probiotic bacterium Lactobacillus reuteri inhibits bone resorption and has a positive effect on the metabolism and health of bone tissue.	[35]
Fecal microbiota transplantation mitigates bone loss by improving gut microbiome composition and gut barrier function in aged rats.	Ma S, Wang N, Zhang P, Wu W, Fu L.	2021	Interventional study	32 rats	Fecal microbiota transplantation	Transplantation of gut microbiota from young rats to older and osteoporotic rats resulted in an improvement in the composition of the gut microbiome in the older rat population, ultimately leading to a reduction in bone density loss.	[41]
Gut Microbiota Dysbiosis as One Cause of Osteoporosis by Impairing Intestinal Barrier Function.	Wang N, Ma S, Fu L.	2022	Interventional study	32 rats	Fecal microbiota transplantation	Transplantation of gut microbiota from elderly and osteoporotic rats to young rats resulted in dysbiosis of the recipients' gut microbiome, which ultimately led to the development of senile osteoporosis.	[42]
Fecal microbiota transplantation ameliorates bone loss in mice with ovariectomy-induced osteoporosis via modulating gut microbiota and metabolic function.	Zhang YW, Cao MM, Li YJ, et al.	2022	Interventional study	20 mice	Fecal microbiota transplantation	Fecal microbiota transplantation in a population of mice with ovariectomy-induced osteoporosis led to remodeling of their gut microbiome and reduced bone loss.	[43]

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