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REVIEW

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Diets intervene osteoporosis via gut-bone axis

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ABSTRACT

Osteoporosis is a systemic skeletal disease that seriously endangers the health of middle-aged and older adults. Recently, with the continuous deepening of research, an increasing number of studies have revealed gut microbiota as a potential target for osteoporosis, and the research concept of the gut-bone axis has gradually emerged. Additionally, the intake of dietary nutrients and the adoption of dietary patterns may affect the gut microbiota, and alterations in the gut microbiota might also influence the metabolic status of the host, thus adjusting bone metabolism. Based on the gut-bone axis, dietary intake can also participate in the modulation of bone metabolism by altering abundance, diversity, and composition of gut microbiota. Herein, combined with emerging literatures and relevant studies, this review is aimed to summarize the impacts of different dietary components and patterns on osteoporosis by acting on gut microbiota, as well as underlying mechanisms and proper dietary recommendations.

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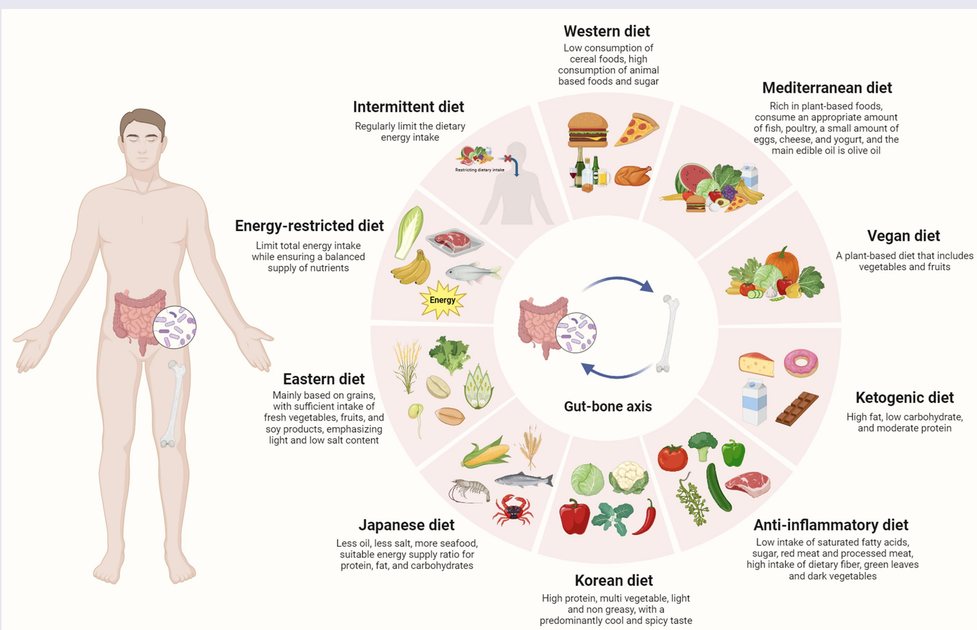

1. Introduction

Osteoporosis is a systemic skeletal disease that seriously endangers the health of middle-aged and elderly individuals, and its severe clinical outcomes mainly include brittle fractures, as well as subsequent disability and death.[1–3] With the accelerating process of global population aging, osteoporosis, including chronic diseases such as hypertension,

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coronary heart disease, and diabetes, has become a pivotal health issue that needs to be faced by whole world.[4,5] According to several previous reports, an osteoporotic fracture occurs every 3 s globally, with approximately 50% of the female and 20% of male suffering from a primary osteoporotic fracture after the age of 50 years, and 50% of patients with a primary osteoporotic fracture may experience a secondary osteoporotic fracture in future.[6,7] Hence, the prevention and treatment of osteoporosis has gradually become a focus of attention for the health of the middle-aged and elderly individuals, and reducing the prevalence of osteoporosis is of great significance for reducing the medical burden, alleviating the pressure on the social medical system, and improving the quality of life of the population.[8]

There are approximately 1×10^{14} bacteria in human gut, and the genome carried by it can be 150 times that of the human genome,[9] The composition of gut microbiota varies significantly in different individuals, which is universally affected by factors such as the host genotype, age, sex, diet, exercise, and living environment.[10,11] Gut microbiota is involved in pivotal physiological processes, such as food digestion, metabolism and absorption of nutrients, energy supplementation, immune modulation, generation of essential vitamins, and the maintenance of gastrointestinal homeostasis,[12,13] and the imbalance of gut microbiota is related to irritable bowel syndrome, colon cancer, obesity, diabetes, osteoporosis, gout, and other intestinal and extraintestinal diseases.[14] Interactions and connections between gut microbiota and its metabolites in multiple organs and tissues of the host are shown in Figure 1. Recently, an enhancing number of studies have suggested that the gut microbiota in patients with osteoporosis and associated animal models is somewhat different from that in healthy individuals, and the severity of bone loss is also associated with alterations in gut microbiota,[15] which also indicates that gut microbiota could be a potential target for the prevention and treatment of osteoporosis. Meanwhile, with continuous deepening of various studies, the research concept of gut-bone axis has gradually emerged,[16] and the cross-linking interactions between multiple organs in host have gradually become a research hotspot. Based on the studies conducted by our research group in the early stages, we showed modulatory influences and implications of gut microbiota on osteoporosis,[17] as well as regulatory effects and repercussions of probiotics and prebiotics,[18] exercise,[19] glucocorticoids,[20] and fecal microbiota transplantation[21,22] on the gut microbiota for prevention and treatment of osteoporosis.

Diet is the most direct connection between the gastrointestinal tract and external environment. Strengthening dietary management is a pivotal measure to modulate the gut microbiota, promote the microbial ecological balance, and consolidate the bone health. A growing number of studies have suggested that diets influence the genes and composition of gut microbiota, and the dominant microbiota of different metabolic substrates vary significantly, thereby affecting the structure and function of the gut microbiota.[23] Meanwhile, the intake of different dietary nutrients (such as protein, fat, carbohydrates, etc.) and the adoption of different dietary patterns (such as the Western diet, Vegan diet, Mediterranean diet, and so on) might influence the gut microbiota and its metabolites, and the alterations of gut microbiota and its metabolites might also affect the metabolic status of the host, thereby adjusting bone metabolism and modulating the occurrence and development of osteoporosis.[24] Hence, based on gut-bone axis, it can be recognized that dietary factors can be involved in the modulation of bone metabolism by altering the abundance, diversity, and composition of the gut microbiota and its metabolites, which further emphasizes the necessity and crucial significance of exploring the close association between the diet, gut microbiota, and osteoporosis. Herein, combined with emerging literatures and relevant researches, this review aims to summarize the effects of different dietary components and patterns on osteoporosis by acting on gut microbiota and its metabolites, as well as the underlying mechanisms and reasonable dietary recommendations, thus renovating the opinions in this research field and providing a reference for future related studies.

2. Inseparable dialogue between gut microbiota and osteoporosis

Gut microbiota is the total collection of microorganisms that colonize the human intestine and feces, which is the largest and most complex ecosystem in the host.[25] The gut microbiota of the

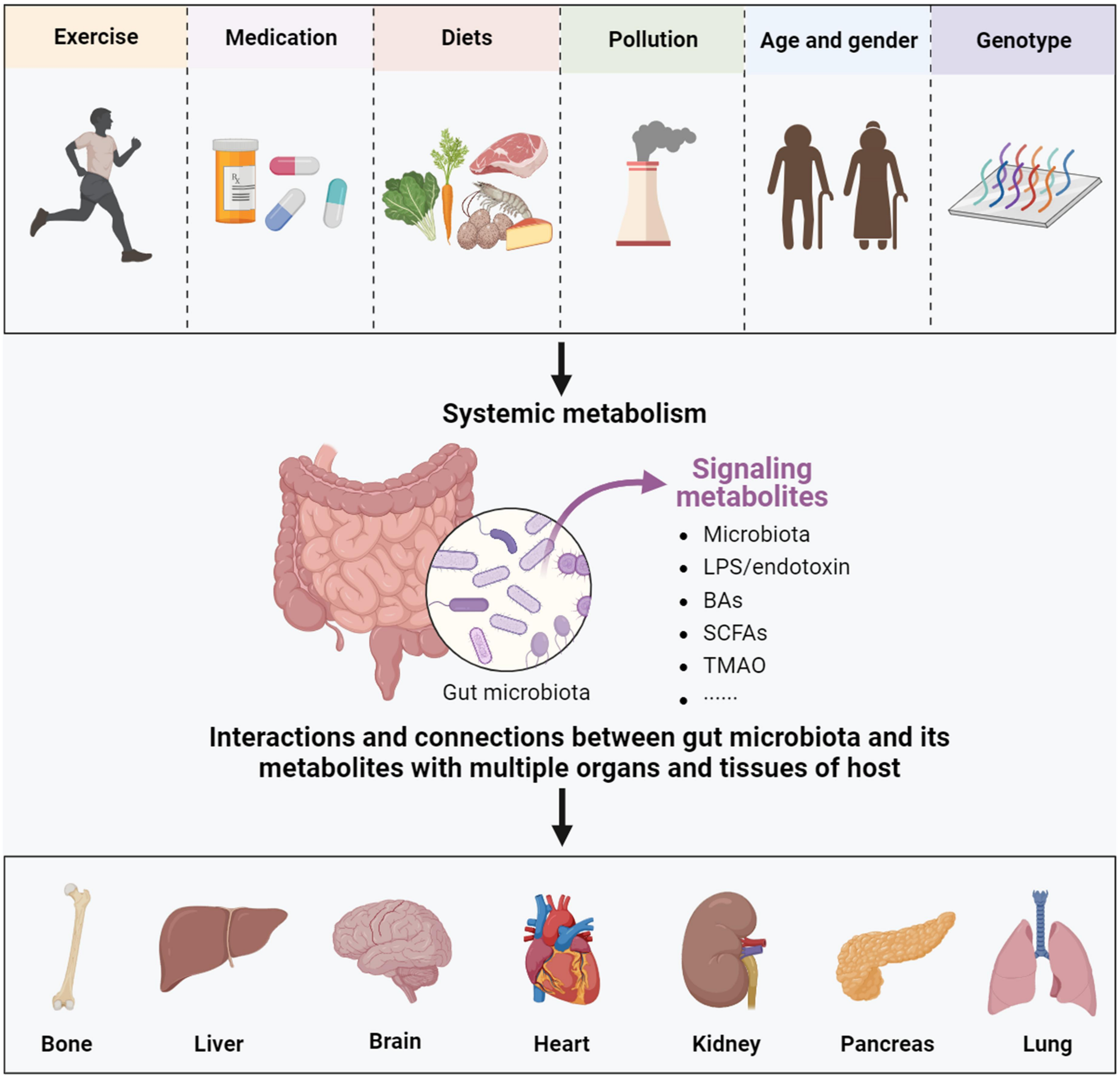

Figure 1. Interactions and connections between the gut microbiota and its metabolites with multiple organs and tissues of host. Several factors, such as exercise, medication, diets, pollution, age and gender, genotype and so on, might affect the gut microbiota and its metabolites of population, and then cause corresponding changes to the bone, liver, brain, heart, kidney, pancreas, lung, and other organs of the host via a variety of regulation approaches. LPS, lipopolysaccharide; BAs, bile acids; SCFAs, short chain fatty acids; TMAO, trimetlylamine oxide.

human body originates from the mother's uterus and birth canal and forms steadily until the age of 3 years.[26] It has a certain self-regulatory ability, assists in maintaining the stability of the intestinal environment, and plays a crucial regulatory role in the nervous, endocrine, immune, and metabolic systems of the human body.[27] Under the physiological conditions, the active modulation of gut microbiota helps to repair intestinal mucosal barrier, improve intestinal permeability, reduce inflammatory reactions, promote nutrient absorption, and participate in the multi-level regulation of bone metabolism.[28] However, under pathological conditions, the accumulation of inflammation in the intestine might result in insufficient calcium absorption and reduced circulating levels of vitamin D and vitamin K, thus resulting in a decrease in bone mass.[29] In addition, as a vital regulator of bone metabolism, the role of gut microbiota in the growth, development, aging, and other pathological alterations of bones should be highlighted.[30] A previous study suggested that malnutrition in infants and young children may result in the disruption of the gut microbiota, disrupt the development and maturation of immune system, and influence the normal growth of the skeletal system.[31] This study also revealed that normal mice transplanted with the gut microbiota of malnourished children exhibited a significant decline in bone mass after a certain period. In a study, the researchers investigated that germ-free (GF) mice exhibited slower weight gain and lower bone mass than normal mice, while GF mice supplemented with *Lactobacillus plantarum* maintained the normal growth rate, which suggested the crucial role of gut microbiota in the progression and development of bone.[32] Therefore, it is of great significance to protect the gut microbiota to support bone health. The gut microbiota and its metabolites may regulate bone growth and bone strength, as well as bone loss and fracture risk, by influencing activity and function of osteoblasts and osteoclasts.

With the updates and iterations of sequencing and omics technologies in recent years, studies on the gut microbiota and osteoporosis are progressing rapidly. In terms of population-based studies, the researchers investigated the China Multi-Ethnic Cohort study and found that high-altitude exposure may decrease bone mineral density (BMD) in adults, thus enhancing the risk of osteoporosis, and the modulation of gut microbiota might be a potential strategy for alleviating the decrease in BMD.[33] The scholars analyzed the gut microbiota of 38 postmenopausal women and indicated that *Bacteroides* and *Rikenellaceae* might be involved in the bone metabolism and fracture risk, and further investigations of the underlying microbiota-related pathways in bone metabolism may reveal treatment strategies and facilitate the prevention of osteoporosis.[34] Researchers also noticed the serum levels of trimethylamine N-oxide (TMAO), a common metabolite of the gut microbiota, in 286 postmenopausal women with hip fractures and found that elevated serum levels of TMAO were associated with a higher risk of hip fracture, suggesting that elevated serum levels of TMAO might contribute to the risk of osteoporosis and fracture in postmenopausal women.[35] In a trial, scholars investigated the additional efficacy of probio-M8, a dairy subspecies of *Bifidobacterium*, as an adjuvant therapy for postmenopausal osteoporosis and noticed that co-administration of Probio-M8 with conventional drugs/supplements was more efficacious than applying drugs or supplements alone in managing postmenopausal osteoporosis, which emphasized the pivotal significance of supplementing probiotics for the prevention and treatment of postmenopausal osteoporosis.[36] In a 1-year randomized, double-blind, and placebo-controlled study, scholars noticed that 100 women with postmenopausal osteoporosis were supplemented with calcium and vitamin D3 tablets and either a hop extract standardized in 8-PN or a placebo for 48 weeks. The results revealed that an 8-PN standardized hop extract can beneficially impacts the bone health of women with postmenopausal osteoporosis.[37] Based on gut-bone axis, dietary nutrients absorbed by the gut through metabolic processes of gut microbiota could further act on the bone, inhibit bone resorption, promote bone formation, and reverse bone loss.[38] Thus, based on the gut-bone axis, it is acknowledged that an enhancing number of studies have demonstrated an inextricable association between gut microbiota and osteoporosis.

3. Potential mechanisms involved in osteoporosis due to the modulation of gut microbiota

After observing and exploring the corresponding correlation in population cohorts, the researchers further delved into the exploration of deep mechanisms, including the modulation of intestinal epithelial barrier function, inflammation and oxidative stress, neuromodulation, immunomodulation, and endocrine modulation.[39] Regarding this, it is worth noting that in the former reviews summarized by our research group in early stages, we have elaborated on potential mechanisms involved in osteoporosis due to modulation of gut microbiota,[17–19] which is presented in details in Figure 2. Specifically, there are multiple mechanisms of modulation of osteoporosis by gut microbiota and its metabolites, including 1) in terms of metabolites, gut microbiota colonized in the intestines of body could produce various metabolites via fermentation, such as short chain fatty acids (SCFAs), indole derivatives, polyamines, adenosine triphosphate, which might have pivotal impacts on bone metabolism.[40,41] Therein, SCFAs are the main energy sources of intestinal epithelial cells and have anti-inflammatory impacts on intestinal mucosa, which can enter bloodstream and participate in the biosynthetic pathways, thus altering the activity of osteoclasts and osteoblasts. SCFAs could also promote the bone formation and indirectly influence bone metabolism by promoting the secretion of insulin-like growth factor-1 (IGF-1) and glucagon-like peptide-1 (GLP-1).[42] 2) Changes of gut microbiota can also result in the disruption of intestinal mucosal barrier function, and enhanced intestinal permeability might cause increased serum lipopolysaccharide (LPS) levels, resulting in metabolic endotoxemia.[43] The increased LPS *in vivo* has been verified to promote bone loss and significantly reduce trabecular volume, lumbar BMD, and vertebral body count in mice models.[44] 3) Gut microbiota is essential for the immune system function and maturation. Recent studies have also suggested a close interaction between immune system and bone metabolism, known as "osteoimmunology", which represents the role of immune cells or immune related factors in modulating the bone metabolism.[45] Intestinal segmental filamentous bacteria (SFB) were verified to enhance the production of interferon-γ (IFN-γ) and interleukin-17 (IL-17), and after the transplantation of SFB in GF mice, the number of Th17 cells increased and the antibacterial effect of epithelial cells was maintained.[46] 4) Due to its impacts on synthesis of cortisol, gut hormones, and neurotransmitters, the gut microbiota is also considered a virtual "endocrine organ" with specific effects on bone metabolism. On one hand, gut microbiota affects bone through the disruption of cortisol pathway, as cortisol and exogenous glucocorticoids can not only reduce the calcium absorption, but also promote the apoptosis of osteoblasts and inhibit the proliferation of osteoblasts. On the other hand, excessive glucocorticoids could also reduce the number of osteoblasts and osteoclasts, prolong the lifespan of osteoclasts, and promote apoptosis of osteoblasts.[47] 5) Gut microbiota can significantly affect the nutrients and heat absorption, thus directly and indirectly affecting bone metabolism. Prebiotic fibers fermented into SCFAs can reduce the pH environment and mineral complexation, such as the formation of calcium phosphate, resulting in more calcium being absorbed to support bone growth or retention.[48]

4. The role of probiotics in managing osteoporosis via its effects on gut-bone axis

Probiotics are a type of active microorganisms that are beneficial to host, which are colonized in the human gut and reproductive system, capable of producing precise health benefits, improving the microecological balance, and exerting beneficial effects.[49] With continuous alterations in the living structure, more and more probiotics are being developed and utilized, which are inseparable for maintaining stable function of body. In addition to food, the application range of probiotics is becoming increasingly wide, and more and more products, such as toothpaste and beer, are adding probiotics.[50] The regulation of probiotics in osteoporosis is an emerging field, and studying how probiotics can improve bone metabolism, prevent, or treat osteoporosis has become a hot research topic, and certain progress has been established.

Current research evidence suggests that supplementing probiotics to restore the balance of gut microbiota and its metabolites is beneficial for bone health. Our former review summarized the contents about the role of probiotics in managing osteoporosis via its effect on gut-bone axis[18]. Specifically, the scholars noticed that the individuals diagnosed with inflammatory bowel disease or related conditions frequently suffered from osteoporosis due to the changes in intestinal microenvironment and consequent dysbiosis, and investigated that *Bifidobacterium lactis* BL-99 could be utilized as a beneficial probiotic preparation to prevent the incidence of osteoporosis in mice with ulcerative colitis owing to its abilities to reshape the gut microbiota and suppress the production of pro-inflammatory cytokines.[51] Researchers noted that supplementation *with Bacteroides vulgatus ATCC 8482* could alleviate the imbalance of gut microbiota in mice with OVX-induced osteoporosis, downregulate the lipopolysaccharide/TLR-4/p-NF-κB pathway, and improve the bone loss and bone microstructure destruction in lumbar spine, which suggested that *Bacteroides vulgatus ATCC 8482* might be a probiotic with the potential to ameliorate postmenopausal bone loss.[52] Recent studies have also revealed that probiotic therapy could inhibit the activity of osteoclasts in ovariectomy (OVX)-induced mice by inhibiting the secretion of IL-6 and intestinal inflammatory response, thus enhancing the bone mass.[53,54]

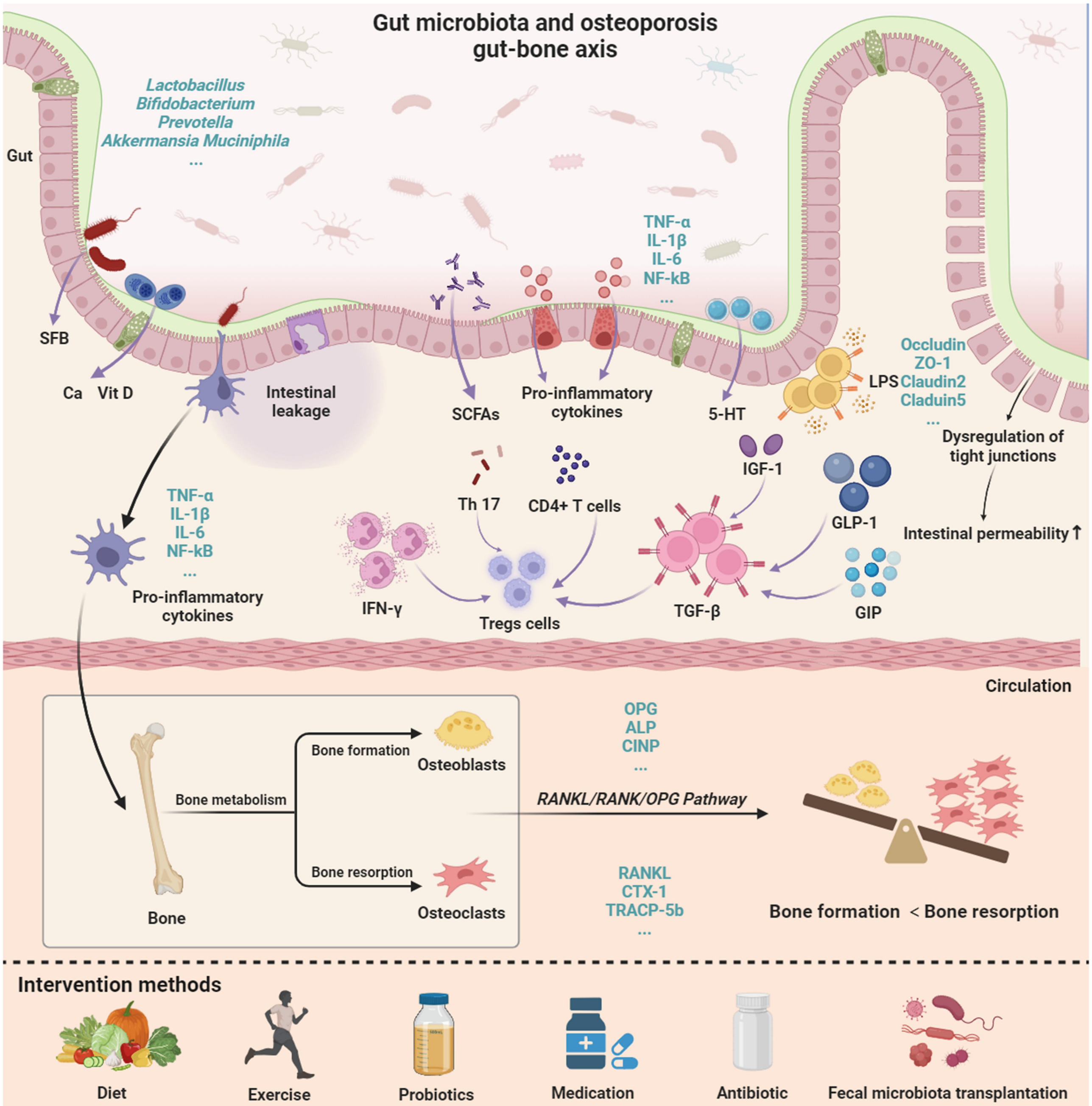

Figure 2. Association between gut microbiota and osteoporosis based on the gut-bone axis. Specifically, gut microbiota can regulate metabolic, immune, and inflammatory states of the body. Meanwhile, it can serve as a pivotal regulatory factor in the bone metabolism, regulating the immune system, affecting the generation of osteoclasts, and exerting regulatory effects on the bone. Studies on the regulation of inflammatory factors and hormones in the gut microbiota have shown that anti-inflammatory factors can reduce bone resorption and prevent bone loss. The constantly emerging researches on probiotics regulating bone metabolism has revealed that the increase of beneficial microbiota can promote the enhancement of bone mass and serve as a potential target for preventing and treating osteoporosis. However, the researches on the relationship between gut microbiota and osteoporosis is still in its infancy, and various studies are needed to further clarify its underlying mechanisms of action. TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6; SCFAs, short chain fatty acids; 5-HT, 5-hydroxytryptamine; NF-kB, nuclear transcription factor-κB; ca, calcium; vit D, vitamin D; SFB, segmented filamentous bacteria; LPS, lipopolysaccharide; GLP-1, glucagon-like peptide-1; IFN-γ, interferon-γ; TGF-β, transforming growth factor-β; GIP, glucose-dependent insulinotropic polypeptide; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor-kB ligand; RANK, receptor activator of nuclear factor-kB; ZO-1, zona occludens 1; ALP, alkaline phosphatase; CINP, N.Terminal propeptide of type I collagen; CTX-1, C-terminal telopeptide of type I collagen; IGF-1, insulin-like growth factor-1; TRACP-5b, tartrate-resistant acid phosphatase 5b.

However, current researches on the probiotics for the prevention and treatment of osteoporosis mostly focuses on animal experiments, with few clinical trials reported. A population-based trial revealed that the co-administering *Bifidobacterium animalis subsp. lactis Probio-M8* with conventional drugs/supplements was more efficacious than conventional drugs/supplements alone in managing post-menopausal osteoporosis.[36] In a double-blind, placebo-controlled study, women from the population who were 75 to 80 years old and had low BMD were randomized to orally receive 10^{10} colony-forming units of *Lactobacillus reuteri ATCC PTA 6475* daily or the placebo, and the results revealed that supplementation with *Lactobacillus reuteri ATCC PTA 6475* may be a novel approach to prevent osteoporosis.[55] Moreover, in a randomized controlled trial, scholars demonstrated that supplementation of *Lactobacillus reuteri ATCC PTA 6475* has potentials to prevent a deterioration of the gut microbiota and inflammatory status in older women with low BMD, which may have beneficial effects on the bone metabolism.[56] Thus, it could be acknowledged that an enhancing number of scholars are starting to probe into deep mechanisms of the modulation of gut microbiota and its metabolites from perspectives of probiotic supplementation, and probiotics have also been a potential candidate for the prevention and treatment of osteoporosis.

5. Influences of different dietary nutrients on osteoporosis by acting on the gut microbiota and its metabolites

The composition and contents of nutrients in different kinds of food significantly affect the composition and abundance of the gut microbiota, which in turn influences bone metabolism and regulates osteoporosis.[57] Therefore, some microorganisms directly utilize certain nutrients as the source of growth material, and the high intake of this kind of nutrient might result in an enhancement in bacterial abundance and act on bone metabolism.[58] For example, microorganisms such as *Streptococcus*, *Bacillus*, *Propionibacterium*, *Staphylococcus*, *Bacteroides*, and *Clostridium* could utilize the protein as a nitrogen source, and higher dietary protein intake could also increase its abundance and diversity.[59] In addition, it is also recognized that the alterations in the physiological environment caused by daily dietary intake can influence the selection of microbial communities.[60] Taking dietary fat intake as an example, a diet rich in fat may promote bile secretion to facilitate the digestion of lipids, and bile acids have detrimental effects on the cell membrane of bacteria, which enables bile acids to exert a strong selection pressure on microbial groups and cause these gut microbiota-related metabolites to play a negative role in the metabolic modulation of osteoporosis.[61] Figure 3 presents and elucidates the effects of dietary nutrients on osteoporosis by acting on gut microbiota and its metabolites.

5.1 Dietary protein and amino acids

Nutritional factors have a crucial impact on osteoporosis, with low calcium intake, vitamin D deficiency, high phosphorus and sodium diets, heavy alcohol consumption, and carbonated beverage consumption being universally considered risk factors for osteoporosis, and adequate protein intake is conducive to bone health.[62,63] Dietary protein intake by human body can alter the electron receptors in the respiratory chain through bacterial fermentation, methanation, decarboxylation reactions, and sulfur reduction.[64,65] For example, sulfur-containing amino acids, such as methionine and cystinine, can generate hydrogen sulfide under the sulfur reduction of sulfate-reducing bacteria, and amino acids and peptides can produce amines through decarboxylation reactions under the action of *Clostridium difficile*.[66] These metabolic end products alter the growth microenvironment of bacteria and enable bacteria to obtain certain growth advantages, thus altering the composition and abundance of the gut microbiota.[67] Meanwhile, studies have reported that the number of *Bacteroides*, *Prevotella*, *Treponema*, *Fusobacterium*, *Clostridium perfringens*, *Bacillus*, and *Sarteria* in the gut microbiota of individuals on high-protein diets is enhanced compared with that of individuals on conventional diets, whereas the number of *Firmicutes* decreases.[68,69] This alteration has also been verified to be consistent with the reversal of osteoporosis. Researchers revealed that the main metabolites of protein, amino acids, and peptides fermented by gut microbiota are SCFAs, such as acetic acid, propionic acid, and butyric acid,

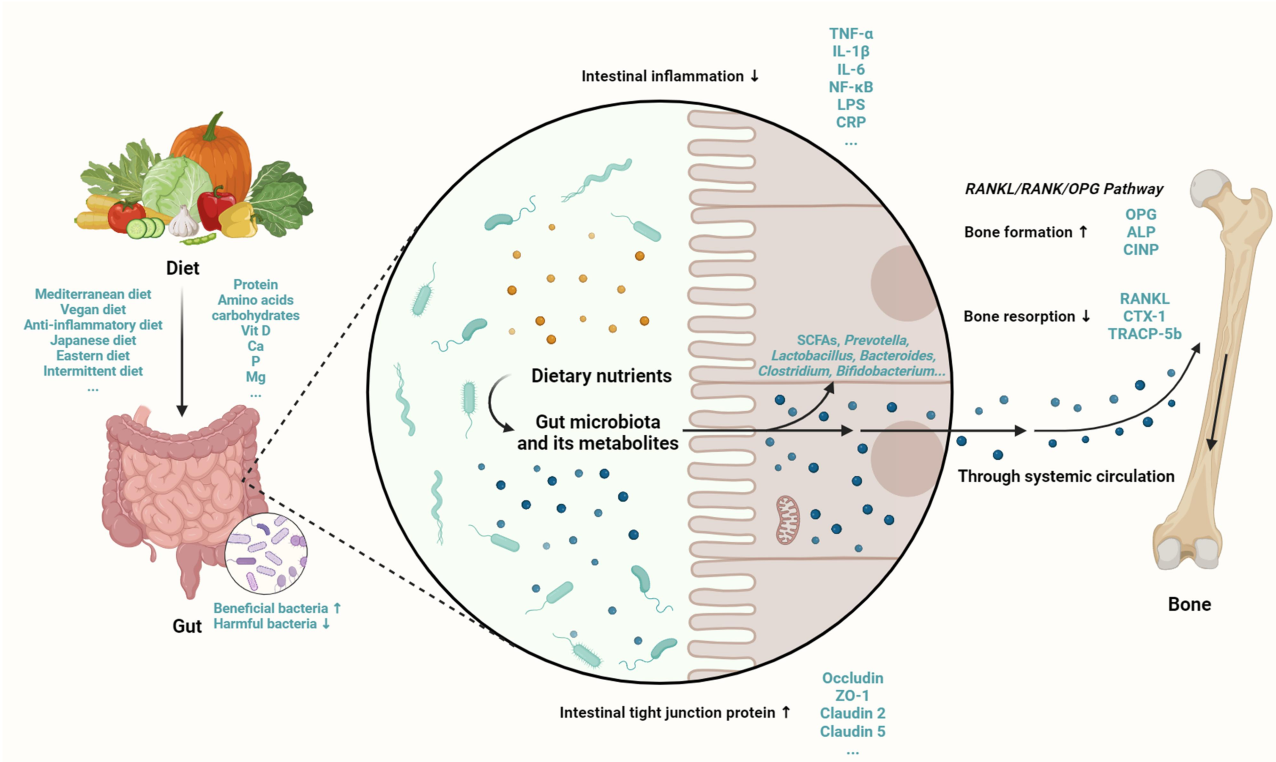

Figure 3. The effects of dietary nutrients on osteoporosis by acting on gut microbiota and its metabolites. Under the domination of various dietary patterns, gut microbiota is closely related to the synthesis and absorption of essential nutrients, such as protein, vit D, ca, P, and mg, which affect the intestinal mucosal barrier function, intestinal inflammation, metabolites, etc., thereby participating in the modulation of the balance between bone formation represented by osteoblasts and bone absorption represented by osteoclasts via systemic circulation. SCFAs, short chain fatty acids; vit D, vitamin D; ca, calcium; P, phosphorus; mg, magnesium; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6; NF-kB, nuclear transcription factor-κB; LPS, lipopolysaccharide; CRP, C-reactive protein; OPG, osteoprotegerin; ALP, alkaline phosphatase; CINP, N.Terminal propeptide of type I collagen; RANKL, receptor activator of nuclear factor-kB ligand; RANK, receptor activator of nuclear factor-kB; CTX-1, C-terminal telopeptide of type I collagen; ZO-1, zona occludens 1; TRACP-5b, tartrate-resistant acid phosphatase 5b.

and further participate in the modulation of bone formation and bone resorption by acting on the above SCFAs.[70] Scholars revealed that intestinal anaerobic bacteria can synthesize the acetic acid from the glycine, threonine, glutamic acid, lysine, ornithine, aspartic acid, and butyric acid from the threonine, glutamic acid, and lysine, whereas propionic acid is mainly synthesized via threonine metabolism.[71] More importantly, the modulation of SCFAs, including the acetic acid, propionic acid, and butyric acid, has been universally reported to be closely associated with the occurrence and development of osteoporosis.[72] Meanwhile, *Clostridium entericum* can utilize the branched chain amino acids (valine, leucine, and isoleucine) to synthesize branched chain fatty acids, and branched chain amino acids and SCFAs are also the potential regulatory factors for metabolic diseases such as osteoporosis, obesity, type 2 diabetes, and so on.[73]

5.2 Dietary fat

Dietary fat is an effective source of energy for the body. Previous studies have suggested that both the quality and quantity of dietary fat intake might influence the composition and abundance of gut microbiota.[74] The unsaturated fatty acids change the composition and abundance of gut microbiota by enhancing ratio of *Bacteroidetes* to *Firmicutes* [75]. *N*-3 polyunsaturated fatty acids (*N*-3 PUFA) can result in beneficial alterations in gut microbiota, including the addition of *Bifidobacterium*, *Lactobacillus*, *Streptococcus*, *Vibrio desulphuricum*, and *Akkermania mucophilus*.[76,77] High intake of saturated fatty acids and trans fatty acids (mainly present in Western diet) enhances risk of cardiovascular and bone metabolism-related diseases, reduces the abundance of *Bacteroides*, *Prevotella*, *Lactobacillus*, and *Bifidobacterium*, and enhances the abundance of *Firmicutes*, which may lead to systemic inflammation, bone metabolism disorders, and osteoporosis.[78] In addition, current studies on the effects of dietary fat on gut microbiota and osteoporosis have mainly focused on the high-fat diets (HFD). Scholars revealed that long-term HFD could result in decreased bone mass, with microbiota dysbiosis, leaky gut, and systemic inflammation, while the administration of *Fructo oligosaccharides* (FOS) or *Galactooligosaccharides* (GOS) could significantly enhance the biodiversity and the SCFAs concentrations of gut microbiota in the HFD-fed mice, and reverse high gut permeability and inflammatory cytokines, ultimately protecting against the HFD-induced osteoporosis.[79] The researchers analyzed the characteristics of gut microbiota and serum metabolomics in mice with HFD-induced osteoporosis and explored potential correlations. These results suggested that HFD-induced bone loss was accompanied by the expansion of bone marrow adipose tissue and inhibition of bone formation.[80] A total of 32 bacterial genera were identified to be significantly correlated with bone loss, and 145 serum metabolites were identified as differential metabolites related to HFD. A former study indicated that probiotic *Lactobacillus paracasei HII01*, prebiotic *xylooligosaccharide*, and synbiotics had similarly beneficial effects to improve jawbone microarchitecture in HFD-fed rats by ameliorating osteoclast-related bone resorption and potentiating bone-formation activities.[81] Scholars also indicated that exercise can prevent several negative effects of HFD on the bone health of male individuals, and the changes in gut microbiota induced by exercise (reducing the ratio of *Firmicutes* to *Bacteroidetes*) might exhibit an emerging mechanism contributing to exercise-induced benefits for the bone health.[82] The scholars also summarized that HFD has a crucial effect on bone structure and health, and the imbalance of gut microbiota, deterioration of the intestinal barrier, inflammatory response, oxidative stress, adipokine alterations, and accumulation of bone marrow fat tissue are thought to be potential mechanisms.[83] Recently, HFD has been a hot research topic in the academic community, in-depth molecular mechanisms and intervention methods of HFD through the modulation of gut microbiota and its metabolites need to be more identified and explored.

5.3 Dietary carbohydrates

Both digestible and non-digestible carbohydrates may affect the composition and abundance of the gut microbiota, both of which have been verified to enhance the amount of *Bifidobacterium*.[84] The digestible carbohydrates in various fruits (such as glucose, sucrose, and fructose) have been demonstrated to decrease the abundance of *Bacteroides* and *Clostridium*.[85] The non-digestible carbohydrates (such as resistant starches and sugars) reach the large intestine, where they can be fermented by the gut microbiota to provide energy or produce postbiotics.[86,87] Indigestible carbohydrates are also known as dietary fiber. Recently, with the rapid development of research on the gut-bone axis, SCFAs fermented from dietary fiber have become a crucial medium, focusing on the link between gut microbiota and osteoporosis.[88] Moreover, dietary fiber alters the gut microbiota by modulating the ratio of *Bacteroidetes* to *Firmicutes*, and alters multiple functional pathways (including the amino acid- and lipid-related metabolism), thus participating in the regulation of bone metabolism.[89] The researchers analyzed the consequences of insufficient dietary fiber intake in the humanized mice and observed that a low-fiber diet markedly reduced microbial diversity for up to three generations and that microbial diversity cannot be recovered after dietary fiber supplementation.[90] On this basis, scholars conducted a research cohort that randomly divided the included population into two groups, where one group was assigned to a high-fat/low-fiber diet for 10 days, while the other group was given a high-fiber/low-fat diet for 10 days.[91] Results showed that a HFD slowed down intestinal transit times by as much as 3 days, although specific taxa variations varied between individuals. More importantly, researchers summarized that ingesting more fiber-rich food (including coarse grains, fresh fruits and vegetables), combined with sufficient exercise, proper water intake, and regular bowel movements, might contribute to maintaining human intestinal and bone health, especially in middle-aged and elderly people, to prevent the osteoporosis.[92] Therefore, consuming dietary fiber from multiple foods is crucial for maintaining the intestinal health and preventing bone loss.

6. Influences of dietary patterns on osteoporosis by regulating gut microbiota and its metabolites

Due to the synergistic influences of multiple nutrients in food, there are certain drawbacks in analyzing the association between specific nutrient elements and bone health, and the association between different kinds of nutrients and osteoporosis is still unclear.[93] Dietary patterns refer to relative composition of types and quantities of various food consumed in diets,[94] The formation and induction of dietary patterns is a long-term process, affected by various factors, such as the population, agricultural production, food circulation, food processing, consumption level, ingesting habits, cultural traditions, and scientific knowledge of a country or region.[95] As a method to evaluate the total consumption of food, the analysis of dietary patterns focuses on analyzing the types of food ingested by research objects, rather than a single food or nutrient element, which has been widely recognized in studies of food nutrition and health.[96] Recently, the link between dietary patterns and osteoporosis has attracted increasing attention from researchers. Figure 4 shows the different dietary patterns of osteoporosis by modulating gut microbiota and its metabolites. The effects of different dietary patterns on gut microbiota, metabolites, and bone health are summarized in Table 1.

6.1 Western diet

Western diet usually refers to the dietary habits of most people in United States and Europe, with meat and meat products, refined carbohydrates, dairy products, and processed food accounting for a relatively high proportion, whereas fiber accounts for a relatively low proportion.[97] Western diet is considered an unhealthy diet with high-fat consumption, especially in low-income and middle-income countries, and the prevalence of hypertension, diabetes, coronary heart disease, and osteoporosis among people on the Western diet is on a significant rise.[98] The characteristics of Western diet include the intake of large amounts of refined sugars (mainly candies and desserts, as well as high-sugar soft drinks), animal fats (high intake of saturated and omega-6 fatty acids, low intake of omega-3 fatty acids), processed meat (especially red meat), refined grains, high-fat dairy products, conventionally raised animal products, salt, eggs, potatoes, corn, while fruits, vegetables, whole grains, herbivore products, fish, and nuts are low in intake.[119] Taken together, Western diet is low in fiber, vitamins, minerals, and other plant-derived molecules (such as antioxidants). Research evidence from China suggests that adopting a healthy or cautious dietary pattern could prevent hip fractures, while the long-term consumption of a Western diet represented by high-fat food may enhance the risk of hip fracture.[120]

Western diet promotes alterations in the gut microbiota, leading to the intestinal microecological disorders, intestinal barrier damage, enhanced intestinal permeability, and leakage of toxic bacterial metabolites into the circulatory system, all of which may result in the progression of systemic low-grade inflammation, and then contribute to the occurrence and development of osteoporosis.[99,121,122] Long-term consumption of a western diet could result in a decrease in the diversity of gut microbiota, promote the proliferation of *Firmicutes* and *Proteobacteria* among the individuals, induce the production of pro-inflammatory cytokines, and facilitate excessive storage of lipids in liver and adipose tissue.[100] Meanwhile, HFD can stimulate the proliferation of gram-negative bacteria, leading to endotoxemia, which increases the risk of osteoporosis.[123] In summary, the imbalance of gut microbiota driven by Western diet is closely related to intestinal barrier damage, indicating that the Western diet induces adverse changes in gut microbiota and further endangers bone health.

6.2 Mediterranean diet

Mediterranean diet is common in countries or regions bordering Mediterranean Sea, such as Greece, Spain, France, and southern Italy.[124] Regarding this kind of dietary pattern, there are more vegetables, fruits, fish, and beans in diets, while there is less red meat.[101] As a result, the

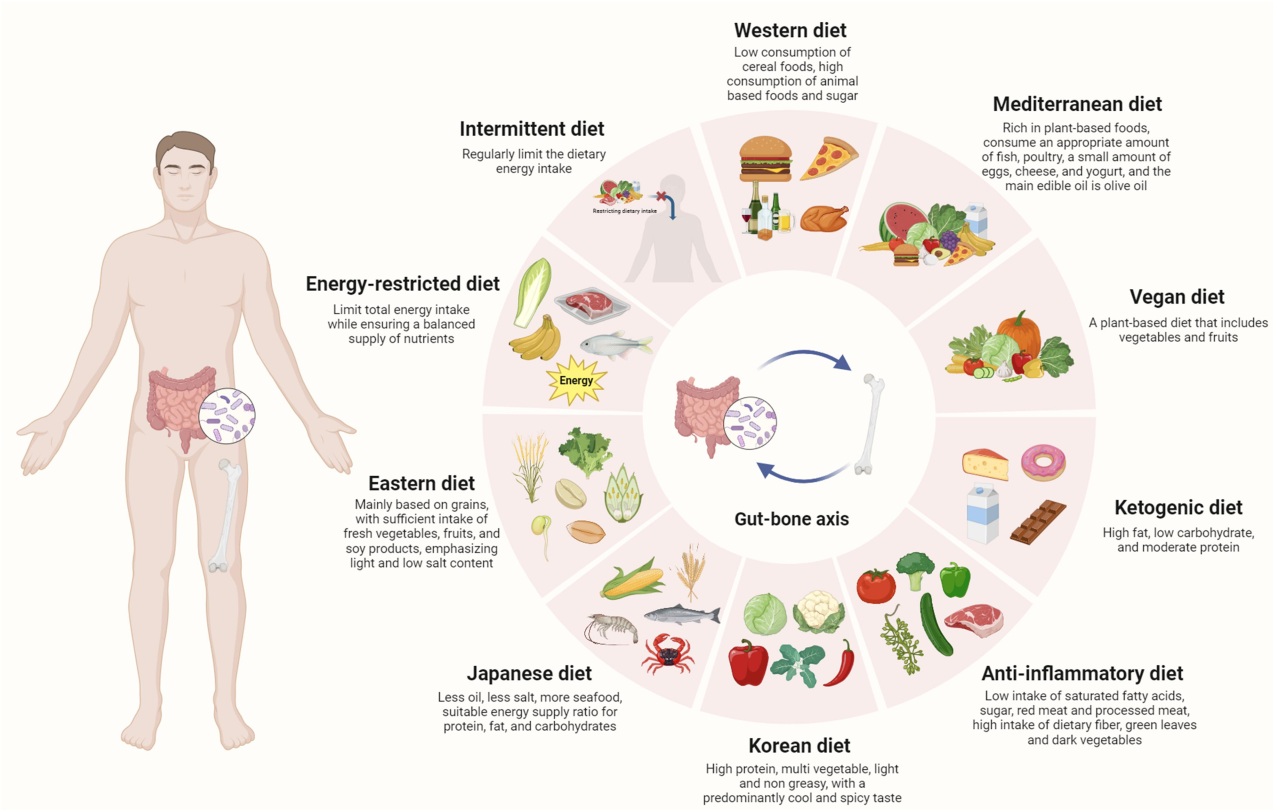

Figure 4. Different dietary patterns on osteoporosis by modulating the gut microbiota and its metabolites. Different dietary nutrients (such as protein, fat, carbohydrates, etc.) and different dietary patterns (such as Western diet, vegan diet, mediterranean diet, etc.) may affect gut microbiota and its metabolites, and the changes of gut microbiota and its metabolites may also influence the metabolic status of host, thereby adjusting the bone metabolism and modulating the occurrence and development of osteoporosis. The effects of different dietary patterns on gut microbiota and bone metabolism are exhibited in this figure.

Mediterranean diet has a relatively high intake of vegetables and fruits, rich in dietary fiber and other complex carbohydrates, and low levels of saturated fatty acids, which contribute to the prevention of diabetes, cardiovascular, and cerebrovascular diseases, and osteoporosis.[102] Based on several previous studies, the Mediterranean diet is conducive to the growth and existence of gut microbiota and is related to a lower incidence rate of common chronic diseases, and its regulatory effects on gut microbiota and its metabolites can effectively reduce the risk of chronic diseases.[125] Further studies have suggested that some individual components of Mediterranean diet are associated with specific classifications of gut microbiota. For example, grains are linked to *Bifidobacterium* and *Faecalibacterium*, olive oil is associated with *Tenericutes* and *Dorea*, and the red wine is associated with *Faecalibacterium*, and so on, the specific classifications of gut microbiota mentioned above have been proven to be related to inhibition of osteoclasts.[103,126,127] Meanwhile, scholars suggested that adherence to the Mediterranean diet may enhance the content of SCFAs in the host and increase the proportion of *Bacteroidetes* to *Firmicutes*, and thereby be conducive to maintaining the balance of osteoblasts and osteoclasts and promoting the bone health.[128] Collectively, Mediterranean diet plays a crucial role in improving the bone health and preventing osteoporosis owing to its unique dietary characteristics.

6.3 Vegan diet

A Vegan diet can promote the abundance and diversity of gut microbiota, while it is related to the duration of dietary pattern adherence, and the rapid alterations in dietary structure can also result in a decline in microbial diversity.[104] The long-term vegetarians may experience a decrease in

Table 1. The effects of different dietary patterns on gut microbiota, metabolites, and bone health.

Dietary patterns	Dietary characteristics	Affected microbiota and metabolites	Impacts on gut and bone	Involved mechanisms
Western diet[97–100]	High in calories, fat, and proteins Low in carbohydrates and dietary fiber	↑ *Firmicutes*, *Clostridium*, *Acetitomaculum*, *Faecalibacterium* ↓ *Bacteroides*	Increase the absorption of calories from food Promote fat synthesis and accumulation Alleviate insulin resistance and chronic inflammation Damage the intestinal mucosal barrier and enhance intestinal permeability Damage to bone tissue and endanger bone health	Modulate the composition, abundance, and diversity of gut microbiota Reduced SCFAs (specifically propionic acid and butyric acid) Elevated LPS in circulation
Mediterranean diet[101–103]	Appropriate calories, fats, and proteins High in whole grains and dietary fiber	↑ *Prevotella*, *Bacteroides*, *Enterococcus*, *Lactobacillus*, *Bifidobacterium* ↓ *Clostridium*	Inhibit the synthesis of cholesterol and fat Promote cholesterol excretion through feces Alleviate insulin resistance and chronic inflammation Maintain the intestinal integrity Optimize overall metabolic status and improve bone health	Enhanced SCFAs (specifically acetic acid, propionic acid, and butyric acid) Reduced LPS in circulation Increased contents of beneficial microbiota
Vegan diet[104–107]	No intake of animal derived foods Proper calories, fats, proteins, and carbohydrates High in dietary fiber	↑ *Prevotella*, *Xylanibacter* ↓ *Enterococcus*, *Bifidobacterium*	Reduce the absorption of calories in food Inhibit the synthesis of cholesterol and fat Promote cholesterol excretion through feces Alleviate insulin resistance and chronic inflammation Maintain the intestinal integrity The intake of vegan diet is positively correlated with an increase in BMD in population, while the absolute vegetarians have lower BMD and higher risk of fractures, and it is necessary to ensure sufficient intake of calcium, vit D, and protein	Modulate the composition, abundance, and diversity of gut microbiota Enhanced SCFAs (specifically acetic acid, propionic acid, and butyric acid) Reduced LPS in circulation
Anti-inflammatory diet[108–111]	Mainly based on plant-based foods, with abundant intake of dietary fiber High in whole grains, omega-3 fatty acids, and spices	↑ *Faecalibacterium prausnitzii*, *Lactobacillus*, *Bifidobacterium*, *Prevotella*, *Bacteroides* ↓ *Acidaminococcus*, *Clostridium*	Reduce the absorption of calories in food Alleviate insulin resistance and chronic inflammation Provide a variety of antioxidants Inhibit the synthesis of cholesterol and fat Reduce the negative impacts of inflammation on bone health	Enhanced SCFAs (specifically acetic acid, propionic acid, and butyric acid) Reduced LPS in circulation Increased contents of beneficial microbiota
Ketogenic diet[112–114]	High fat, low carbohydrate, and moderate proteins	↑ *Lactobacillus*, *Akkermania mucophilus*, *Actinomycetes*, *Parabacterium* ↓ *Bifidobacterium*, *Escherichia*, *Salmonella*, *Vibrio*, *Escherichia coli*, *Shigella*	Insufficient intake of dietary fiber, essential vitamins, and minerals Promote weight loss, improve blood sugar control, and enhance metabolic efficiency The impacts of ketogenic diet on bone health is still controversial	Modulate the composition, abundance, and diversity of gut microbiota Enhanced SCFAs (specifically butyric acid)

(*Continued*)

Table 1. (Continued).

Dietary patterns	Dietary characteristics	Affected microbiota and metabolites	Impacts on gut and bone	Involved mechanisms
Korean diet[115–117]	High protein, multi vegetable, light and non-greasy, with a predominantly cool and spicy taste	↑ *Firmicutes*, *Weissella*, *Coprococcus*, *Ruminococcus*, *Oscillospira*, *Gemmiger*, *Blautia*, *Coprococcus* ↓ *Bacteroidetes*	Reduce the pH value of intestine Inhibit the synthesis of cholesterol and fat Reduce the absorption of calories in food Excessive salt and saturated fat intake have negative impacts on bone health	Enhanced SCFAs (specifically acetic acid, propionic acid, and butyric acid) Increased contents of beneficial microbiota
Intermittent diet[118]	Control meal times to improve body composition and overall health, including restricted fasting, overnight fasting, and religious fasting	↑ *Akkermania mucophilus*, *Paralactobacillus* ↓ *Escherichia coli*, *Turicibacter*	Maintain the intestinal integrity Relieve LPS leakage and systemic inflammatory response Improve metabolic status and reduce risk of obesity and obesity-related diseases Improve bone health by enhancing the abundance and diversity of beneficial microbial communities, while there is still a lack of sufficient research evidence to support	Modulate the composition, abundance, and diversity of gut microbiota Enhanced SCFAs (specifically acetic acid, propionic acid, and butyric acid) Reduced LPS in circulation

SCFAs, short chain fatty acids; LPS, lipopolysaccharide; BMD, bone mineral density; vitamin D.

intestinal pH, accompanied by higher levels of SCFAs, lower amounts of *Bacteroides*, and higher amounts of *Prevotella*.[129] This intestinal environment is conducive to the absorption of calcium in the host, thereby promoting bone formation and inhibiting bone loss.[105,106] The scholars indicated in a case-control study that the intake of vegetables and fruits was positively correlated with an increase in BMD in the population, whereas it was negatively correlated with the risk of fractures.[130] Researchers also noticed in a population-based study that the serum levels of β-crypto-flavin and β-carotene in 699 postmenopausal women were positively correlated with BMD, indicating that a higher intake of vegetables and fruits may be beneficial to bone health.[107] Moreover, compared with the omnivorous population, the contents of fibrous degrading bacteria, such as *Spirillum*, are higher in vegetarians, and the increase in *Akkermania mucophilus* and decline in *Bacteroides fragilis* in body have beneficial effects on obesity, fat accumulation, insulin resistance, and bone metabolism disorders.[131] Scholars suggested that *Haemophilus*, *Neisseria*, *Aggregatibacter*, and *Veillonella* were more prevalent among individuals with a long-term Vegan diet, and these bacteria have been verified to be associated with the bone health in the population.[132] In addition, among the population adopting a Vegan diet, the lacto-ovo vegetarians have BMD close to that of omnivores, while the absolute vegetarians have lower BMD and higher risk of fractures, and it is necessary to ensure sufficient intake of calcium, vitamin D, and protein. Collectively, the vegetarians can meet the calcium needs by consuming calcium-rich food such as beans, soy products, nuts, vegetables, and whole grains, but people should seek professional nutritional guidance when choosing Vegan diet based on their own needs and circumstances.

6.4 Anti-inflammatory diet

Diet is crucial to systemic inflammation, and an improper diet (pro-inflammatory food) may facilitate the progression of systemic inflammation, whereas an appropriate diet (anti-inflammatory food) may minimize systemic inflammation, reduce the risk of multiple chronic diseases such as hypertension, diabetes, coronary heart disease, and osteoporosis, optimize the body mass index (BMI), and improve the quality of life.[108] The dietary inflammation index (DII) was designed and promoted by scholars to evaluate the overall inflammatory potential of personal diet.[133] Scholars revealed that higher DII was associated with an increased risk of osteoporosis in female, while no link was found in male, and a greater pro-inflammatory diet might be related to lower BMD in both female and male.[109] Researchers suggested that the consumption of a pro-inflammatory diet enhanced the risk of fracture in Chinese female aged less than 50 years, and high consumption of anti-inflammatory food and low consumption of pro-inflammatory food may be a vital strategy to prevent fractures in female.[110] In addition, DII is negatively correlated with the abundance of *Faecalibacterium prausnitzii* in body, and the decline in the abundance of *Faecalibacterium prausnitzii* caused by excessive DII might lead to a decrease in the production of SCFAs, thus affecting regulatory effects of gut microbiota-related metabolites on bone formation and inducing the bone loss.[111,134] A population-based study also suggested that high inflammatory food intake was associated with a high abundance of *Acidam inococcus*, and it was positively correlated with circulating plasminogen activator inhibitor-1 (PAI-1), which is an inflammatory marker associated with the risk of obesity, type 2 diabetes, cardiovascular diseases, and osteoporosis.[135] As a result, anti-inflammatory diet could provide necessary nutrients for body to maintain intestinal health, and a stable state of gut microbiota can reduce the level of inflammation in intestine, thus reducing the negative impacts of inflammation on bone health.

6.5 Ketogenic diet

The ketogenic diet is an extremely low-carbohydrate diet; although there have not been sufficient and robust experimental designs to definitively recognize the impact of a ketogenic diet on bone health, an increasing number of scholars are focusing on and exploring this direction.[136] The scholars noticed that long-term consumption of a ketogenic diet could induce higher levels of ketone and higher fat percentage in the body, resulting in lower body weight and damage to bone mass and mechanical properties.[112] Scholars demonstrated that metformin effectively attenuates cancellous bone loss induced by a ketogenic diet and maintains the biomechanical properties of long bones, providing evidence for metformin as a treatment approach for ketogenic diet-induced osteoporosis.[113] Moreover, the long-term consumption of a ketogenic diet may decrease the diversity of gut microbiota, reduce the abundance of pathogens such as *Escherichia*, *Salmonella*, and *Vibrio*, enhance the abundance of *Lactobacillus* and *Akkermania mucophilus*, promote the generation of SCFAs; and play a role in reducing weight and lowering blood sugar.[137] A ketogenic diet could also result in a continuous decrease in the abundance of *Bifidobacterium*, thereby reducing the level of Th17 cells and improving bone metabolism, and a ketogenic diet containing protein may have stronger effects on reducing the ratio of *Firmicutes* and enhancing the ratio of *Bacteroidetes*.[114] However, it should be noted that although Ketogenic diet has certain benefits in weight control and other health aspects, its impact on bone health is still controversial and should be treated with caution.

6.6 Korean diet

The characteristics of Korean diet is characterized by high vegetable and whole grain content, low animal-based and saturated fat content, and a high consumption of fermented food.[115] A previous study on the Korean population suggested that adding fruits and dairy products as part of the traditional Korean diet might reduce the risk of osteoporosis in postmenopausal Korean women, compared to consuming diets rich in meat, alcohol, and sugar.[116] Moreover, subjects with a higher intake of rice, kimchi, and seaweed have a higher risk of osteoporosis.[138] After the intervention of traditional Korean diet, abundance of *Bacteroidetes* in intestinal bacterial community decreased, whereas the abundance of *Firmicutes*, *Weissella*, and *Coprococcus* increased.[117,139] In addition, scholars showed in a population-based study that individuals with a long-term intake of Korean diet contained dominant bacteria, including *Ruminococcus*, *Oscillospira*, *Gemmiger*, *Blautia*, and *Coprococcus*.[140] However, it should be noticed that Korean diet includes partial high-salt food, such as the pickled vegetables and fried chicken. Excessive salt and saturated fat intake may have negative impacts on intestinal and bone health, and the intake of above food needs to be controlled while pursuing the Korean diet.

6.7 Other dietary patterns

Other relatively rare dietary patterns include Japanese diet, Eastern diet, Energy-restricted diet, and Intermittent diet. Therein, 1) Japanese diet is mainly dominated by vegetables, seafood, beans, whole grains, and seaweed. This dietary pattern is rich in nutrients such as fiber, plant protein, healthy fats, and various vitamins and minerals, which contributes to maintaining intestinal and bone health.[141]2) Eastern diet refers to the dietary patterns of Asian countries, such as China, Japan, South Korea, etc. This dietary pattern is mainly based on vegetables, fruits, beans, whole grains, seafood, etc., rich in fiber, plant protein, healthy fats, vitamins, and minerals. Eastern diet may have positive impacts on osteoporosis by regulating gut microbiota, providing dietary fiber, and probiotics, but more research evidence is needed to verify specific mechanisms.[142]3) Energy-restricted diet is a dietary pattern that reduces energy intake, typically used to lose weight, or improve metabolic status. Several studies have revealed that a moderate Energy-restricted diet may have positive influences on the bone health by reducing weight, improving metabolic status, and modulating gut microbiota.[143,144] Intuitively, reducing body weight may reduce the load on bone and reduce the risk of fractures, while excessive Energy-restricted diet may also lead to insufficient protein intake, which in turn can be harmful to bone health.[145]4) Intermittent diet refers to the periodic alternating eating and fasting. Existing research evidence suggests that Intermittent diet may have impacts on the composition and function of gut microbiota, enhancing the abundance and diversity of beneficial microbiota, and thus influencing bone health.[118] However, current researches on the relationship between Intermittent diet and osteoporosis is still relatively limited, and more research is needed to verify specific mechanisms.[146] Moreover, during the process of intermittent diet, individuals should also pay attention to maintaining abundant intake of nutrients, especially the protein and calcium, to ensure the bone health.

7. The reasonable dietary recommendations based on the regulatory influences of gut microbiota and its metabolites on osteoporosis

The gut microbiota plays a crucial role in the modulation of host health, and the composition of the gut microbiota varies significantly among different individuals, which is influenced by various factors such as diet and environment, among which diet is a vital factor that cannot be ignored.[147] Different dietary patterns have different effects on the structure, metabolism, and function of gut microbiota and are involved in various physiological activities, such as the food digestion, nutrient metabolic absorption, energy supply, immune modulation, and maintenance of gastrointestinal homeostasis, which are closely associated with the occurrence and development of osteoporosis.[148] In addition, diets can affect not only the structure and composition of the gut microbiota but also its genes and function.[149] Even bacteria of the same genus have significant differences in functional and core genes under the influence of different dietary patterns.[150] The vegan and Mediterranean diets could enhance the diversity of gut microbiota and promote the growth of beneficial bacteria, such as *Bifidobacterium*, *Lactobacillus*, and *Prevotella*, while the Western diet could reduce the diversity of gut microbiota and increase the ratio of *Firmicute*s to *Bacteroidetes*.[151] Different dietary components may shape the intestinal bacterial community in a time-dependent manner, and the effects of different dietary components on gut microbiota are significantly different[152]. Hence, a reasonable dietary composition, proper dietary habits and methods, and appropriate nutrient ratios are the foundation for ensuring human health, whereas unreasonable dietary patterns are the culprit of several chronic diseases, including hypertension, diabetes, and osteoporosis.[153] On this basis, it is also essential to propose reasonable dietary recommendations based on the regulatory impacts of gut microbiota and its metabolites on osteoporosis, and Figure 5 shows the different influences on the bone by modulating the gut microbiota and its metabolites under different dietary recommendations.

The reasonable dietary patterns integrate the characteristics of healthy dietary patterns such as a Mediterranean diet and an anti-inflammatory diet, mainly including diversified food, high fiber intake, low sugar intake, low fat intake, and high grains intake.[154] The reasonable dietary patterns are mainly based on the principles of food diversification, and it is recommended to consume more vegetables, fruits, beans and their products, fish, and seafood, while consuming less red meat and saturated fatty acids to ensure sufficient intake of plant-based food and a proper amount of animal-based food, thus obtaining a complete variety of dietary nutrients, sufficient quantities, and appropriate proportions, and meeting the physiological needs of middle-aged and older populations to maintain bone health and prevent osteoporosis.[155] Reasonable dietary patterns also lay a solid foundation for the shaping of intestinal homeostasis, multiplication of beneficial bacteria, elimination of harmful bacteria, and maintenance of the diversity of gut microbiota.[156] Hence, it is essential to encourage middle-aged and elderly individuals to choose the corresponding dietary patterns based on their bone and intestinal conditions and maintain reliable dietary habits.

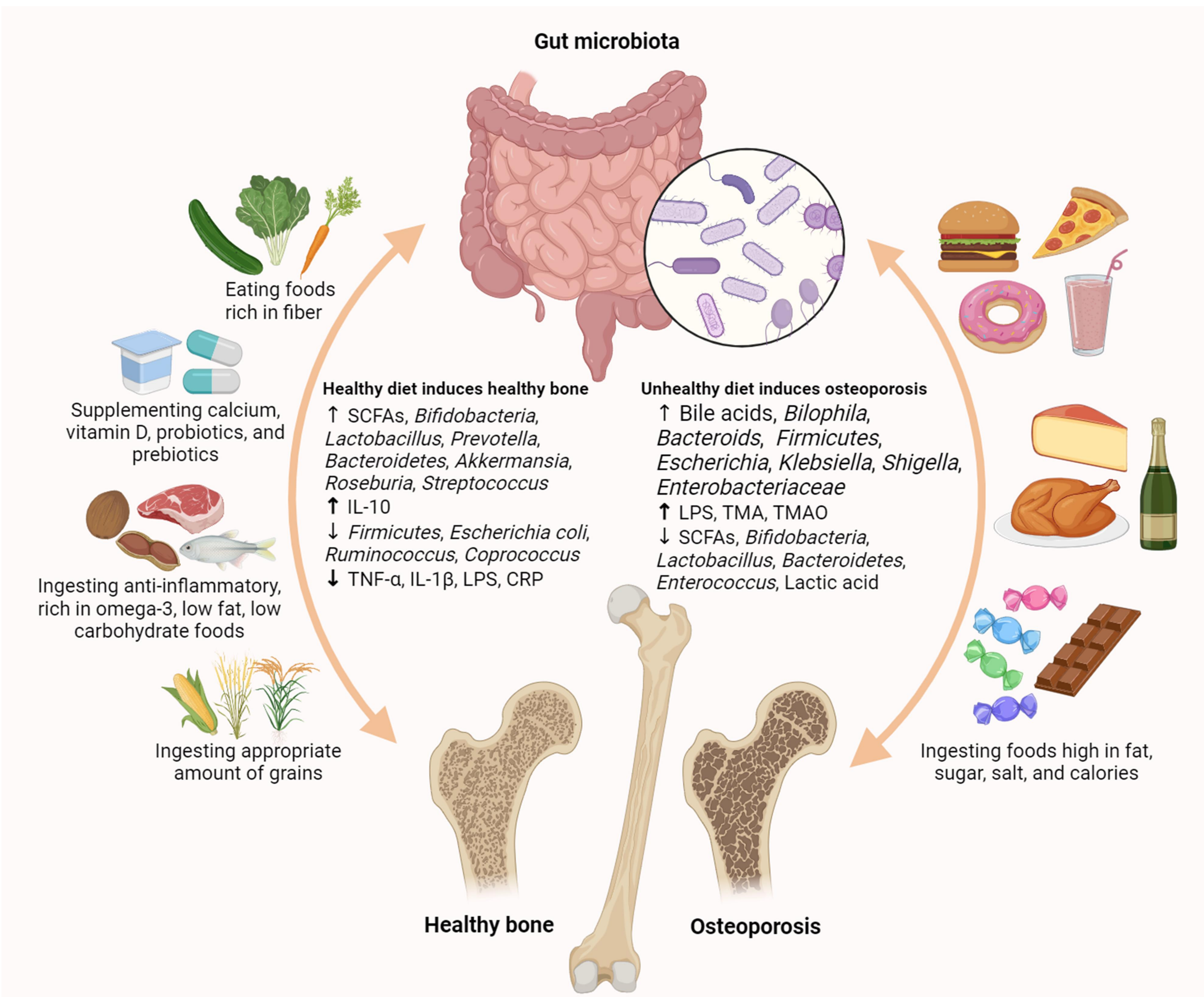

Figure 5. Different impacts on bone by modulating gut microbiota and its metabolites under different dietary recommendations. The reasonable dietary patterns integrate the characteristics of healthy dietary patterns, such as a Mediterranean diet and an anti-inflammatory diet, mainly including the diversified food, high fiber intake, low sugar intake, low fat intake, and high grains intake, thereby maintaining the bone health and preventing osteoporosis. On the contrary, unhealthy dietary pattern (such as Western diet), represented by high-fat, high sugar, high salt, and high calorie dietary intake, is not conducive to maintaining the intestinal and bone health. SCFAs, short chain fatty acids; TMAO, trimetlylamine oxide; TMA, trimethylamine; LPS, lipopolysaccharide; TNF-α, tumor necrosis factor-α; CRP, C-reactive protein; IL-10, interleukin-10; IL-1β, interleukin-1β.

8. Conclusions and perspectives

The impacts of gut microbiota on the osteoporosis have been widely studied and recognized. As one of the most important symbiotic partners of the human body, the gut microbiota is related to bone health, and there are various factors affecting the gut microbiota and its metabolites, including diet, age, genetics, antibiotics, medication, hormone levels, and emotional stress, which alter and re-shape unique gut microbiota of each person.[157] However, in the short term, dietary content and dietary patterns are regarded as the most significant driving factors for shaping gut microbiota and its metabolites. In the long term, diets are also a relatively effective and healthy choice for adjusting and intervening in gut microbiota, which has profound regulatory effects on bone metabolism.[158] Hence, based on gut-bone axis, the scientific popularization of dietary regulation on osteoporosis is of great significance, which can be regarded as the most common intervention approach in daily life to participate in the prevention of osteoporosis.

However, from the perspective of the gut-bone axis, it is still essential to identify and recognize the current shortcomings of the effects of diet on gut microbiota and its metabolites in modulating osteoporosis. First, the specific mechanisms by which diets affect the gut microbiota and its metabolites to modulate osteoporosis are not yet fully understood, and there is still a lack of unified conclusions on alterations in the dietary patterns and the characteristics of individuals with osteoporosis.[159] Further in-depth researches are needed to determine the effects of different dietary patterns on diversity and composition of the gut microbiota in hosts with osteoporosis. On this basis, large-scale population-based cohorts are still needed to comprehensively assess the effects of demographic characteristics, alterations in dietary patterns, physical activity, daily exercise, and other factors on gut microbiota and its metabolites in individuals with osteoporosis. Second, there is still a lack of a comprehensive layout of dietary patterns to analyze the characteristics of gut microbiota and its metabolites. Current studies tend to focus more on the abundance of characteristic food or nutrients in different dietary patterns to explain their impacts on the gut microbiota, and subsequently on the modulation of osteoporosis.[160] It should also be noted that dietary patterns are not static, and some of their components have also been altered over the past few decades.[161] Third, current researches have not been able to focus on the metabolic potential and development process of microbial communities. Although the short-term dietary interventions could affect the composition of gut microbiota, long-term interventions could produce relatively stable responses to alterations in the microbiota caused by alterations in diet, and current investigations cannot show alterations in the microbiota over time.[162] Nevertheless, with the advancement of sequencing technology, the cost of microbial sequencing may be lower, and the data analysis may be more convenient; thus, studies on microbiomes may become more vigorous. Ultimately, the impacts of different dietary patterns on gut microbiota and its metabolites, and their involvement in the modulation of bone metabolism, have been widely recognized.[163] However, further studies are still needed on the interactions between food or nutrients and the gut microbiota and its metabolites, upstream regulatory mechanisms, and downstream effects.[164] More scientific popularization of dietary regulation on osteoporosis based on gut-bone axis also needs to be mentioned and expanded. It could be expected that when the above issues are resolved, this approach of improving gut microbiota and its metabolites by adjusting dietary patterns, thus affecting the human gene expression, digestion, absorption, metabolism, and immune processes, and further generating the health effects, might be a more economical, effective, and simple means of reducing the side effects in the future.

Abbreviations

GF	germ-free
BMD	bone mineral density
TMAO	trimethylamine N-oxide
SCFAs	short chain fatty acids
IGF-1	insulin-like growth factor-1
GLP-1	glucagon-like peptide-1
LPS	lipopolysaccharide
SFB	segmental filamentous bacteria
IFN-γ	interferon-γ
IL-17	interleukin-17

OVX	ovariectomy
N-3 PUFA	*N*-3 polyunsaturated fatty acids
HFD	high-fat diets
FOS	*Fructooligosaccharides*
GOS	*Galactooligosaccharides*
BMI	body mass index
DII	dietary inflammation index
PAI-1	plasminogen activator inhibitor-1

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Data availability statement

There are no research data in this paper.

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