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How aging affects bone health via the intestinal micro-environment

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Abstract: Increasing life expectancy and an aging population lead to age-related bone diseases like osteoporosis and low bone mass more prevalent. These conditions represent a common, costly and chronic burden, not only for elderly but also to society at large. Consequently, elucidating the pathophysiology and developing effective therapies for these diseases is of paramount importance. Recent advances in research have identified the gut as a novel and promising target for addressing bone disorders, giving rise to the concept of the "gut-bone axis". An in-depth review of the latest insights into the effects of age-related physiological changes in the gastrointestinal tract on bone health is presented in this article. It examines how the "gut-bone" axis interacts with bone aging across various domains, including metabolism, nutrition, intestinal permeability, immunity, and oxidative stress.

Introduction

The human intestinal tract harbors trillions of microorganisms that constitute a selective permeability barrier, essential for safeguarding against the ingress of deleterious entities such as exogenous antigens, pathogens, and toxins. Simultaneously, this barrier facilitates the absorption of vital nutrients, electrolytes, and immune sensing. The maintenance of intestinal barrier integrity is vital for overall health, with its compromise leading to the opportunistic penetration of pathogenic bacteria and their metabolites, potentially inflicting damage on distant organs and overall well-being. The intestinal microenvironment is linked to a variety of diseases and is shaped by an array of factors, including age, genetics, environmental exposure, lifestyle, stress, and diet [1].

Aging is a complex process characterized by the progressive decline of physiological systems and the deterioration of organ structures and functions. It is often accompanied by disruptions to the integrity of the intestinal barrier, changes in the composition of gut microbiota (GM), and an increased susceptibility to various aging-related diseases, including neurodegenerative disorders, cardiovascular conditions, metabolic disorders, musculoskeletal ailments, immune system dysregulation, and cancers [2]. Among these diseases, there have been reports highlighting skeletal issues associated with aging, such as bone loss, degenerating articular cartilage, and narrowing of intervertebral discs, which are precursors to conditions like osteoporosis, arthritis, and fractures [3,4]. Bone health is intricately regulated by the dynamic balance between bone formation and resorption, which is mediated by osteoblasts and osteoclasts, respectively. However, during aging, the cell lineages of skeletal system underwent rigorous changes, senescence accumulation in osteoprogenitors like bone marrow mesenchymal stem cells (BMSCs) lead to impaired osteogenesis and cause imbalance [5]. Additionally, in senescence-related cancer, BMSCs also contribute to the formation of a cancer-promoting microenvironment [6,7].

However, the precise causal relationships or correlations between these phenomena and age-related changes in the intestinal microenvironment remain poorly understood. This knowledge gap represents a great challenge, particularly in terms of understanding the implications for bone health and the potential underlying regulatory mechanisms.

Accordingly, this review endeavors to enhance the current comprehension of the interplay between the age-related intestinal microenvironment and bone health. It also aims to pinpoint the research lacunae that warrant further investigation.

Aging and Bone Health: The Role of the Intestinal Barrier

Regulation of skeletal system is influenced by a myriad of signals, including inflammatory factors and endocrine

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hormones. Notably, the intestinal barrier is integral to this regulatory network. These interactions are critical for managing systemic chronic low-grade inflammation and metabolism, which have significant implications for bone health.

Endocrine interactions

The endocrine hormones that regulate bone health in elderly individuals primarily include estrogen, parathyroid hormone, insulin-like grown factor-1, and serotonin (5-HT). The gastrointestinal tract, as the largest endocrine organ, secretes hormones such as glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 and 2 (GLP-1, GLP-2), which have profound effects on bone metabolism and are considered essential components of the gut-bone axis [8,9]. For instance, GIP has been found to reduce the levels of biochemical marker carboxy-terminal collagen crosslinks (CTX), which is indicative of bone absorption. Supplementing with exogenous GIP has been shown to effectively mitigate bone absorption in postmenopausal women [10,11]. Conversely, GLP-1 receptor agonists promote osteoblastogenesis and suppress bone resorption through the advanced glycation endproducts (AGEs)-receptor of AGE (RAGE)-reactive oxygen species (ROS, AGEs-RAGE-ROS) pathway and GLP-1 receptor interaction [12]. Maintaining high GIP levels, particularly in aging individuals, especially pre-/post-menopausal women, can thus play a protective role against bone strength deterioration.

Approximately 95% of 5-HT is produced in the intestines, where it inhibits osteoblast proliferation and bone growth by binding to receptors on pre-osteoblasts. Targeted knockout of tryptophan hydroxylase 1 gene (*Tph*1), the rate-limiting enzyme for intestinal 5-HT synthesis, in enterocytes has been found to increase osteoblast numbers and bone formation, resulting in high bone mass [13]. Conversely, brain-derived 5-HT has been shown to promote bone formation by inhibiting peripheral autonomic nerves [14]. Thus, intestinal-derived 5-HT may hold promise as a potential therapeutic approach for increasing bone mass.

Depression in the elderly is associated with osteoporosis [15]. Although selective serotonin reuptake inhibitors (SSRIs) are effective as antidepressants, they have been implicated in reduced bone mineral density (BMD) and increased fracture risk. This possibly due to desensitization of the 5-HT receptor 2C (HTR2C), which mediates brain-derived 5-HT's effects on bone [16]. A novel drug, (R)-ketamine, has shown efficacy in effectively improving BMD in ovariectomized mice with depression. This improvement is attributed to its anti-inflammatory actions, which involve the regulation of dysregulated intestinal microbiota and its metabolites. Specifically, at the phylum level of intestinal flora, there was a decrease in the abundance of Tenericutes and an increase in Kiloniella. Additionally, there were decreased levels of metabolites such as succinic acid and dihydrouracil [17].

Intestinal barrier homeostasis

The maintenance of intestinal barrier homeostasis is crucial for bone health. Disruptions to the gut flora, such as those induced by prednisolone, can lead to intestinal barrier dysfunction, increased serum endotoxin levels, inhibition of Wnt10b signaling, and apoptosis of osteoblasts and osteocytes, culminating in glucocorticoid-induced osteoporosis (GIO). Conversely, mucus supplements can bolster barrier function and counteract trabecular bone loss caused by glucocorticoids [18].

Although direct evidence is scarce, age-related intestinal changes are strongly correlated with bone loss. The intestinal barrier, composed of the mucus layer, epithelial cell layer, and lamina propria, is critical for preventing the entry of harmful substances and maintaining homeostasis. However, its integrity is compromised by aging [19] (Fig. 1).

The integrity of the intestinal epithelial cell (IEC) layer relies heavily on the health of tight junction proteins and intestinal epithelial stem cells (IESCs). In the process of aging, there is a decrease in the expression of tight junction proteins such as zonula occludens (ZOs), occludins, claudins, and junctional adhesion molecules (JAMs, Fig. 1), resulting in increased colon permeability [19]. Furthermore, aging disrupts the balance between JUN kinase/protein phosphatase I and results in increased intestine-specific actin (ACT-5) phosphorylation, compromising intestinal intercellular interaction and barrier integrity. The number and proliferative capacity of IESCs also decline with age, impeding the timely self-renewal and repair of the intestinal mucosa [20]. This decline may be linked to the downregulation of Wnt and bone morphogenetic protein (BMP) signaling pathways [21,22]. Clinical and experimental evidence suggests that age-related disruption of the intestinal epithelial barrier is linked to immune activation, elevated inflammation, and reduced bone density [23].

The disruption of the intestinal mucus layer is characterized by a decrease in mucus secretion and thickness, as well as increased degradation and permeability. Such changes expose the IECs to bacteria, precipitating infections and inflammatory conditions like ulcerative colitis (UC) and Crohn's disease (CD) [24,25] (Fig. 1). Mccin2 (MUC2), the major mucus component, imparts gel-like properties through its abundant and variable O-linked oligosaccharides (O-glycans) [26]. In elderly hosts, upregulation of miR-124-3p correlates with diminished mucus thickness and frequent bacterial translocation, attributable to suppressed O-glycan expression. Moreover, the age-related thinning of the mucus layer may stem from downregulated mucus biosynthesis genes, a proliferation of pathogenic microbes, and a reduction in beneficial bacterial populations [27].

The host and intestinal resident bacteria form a complex, symbiotic micro-ecosystem that acts as a biological defense against external pathogens. Aging, however, can disrupt this delicate equilibrium, leading to a decrease in beneficial gut bacteria and a proliferation of pathogenic strains [28]. The gut microbiome undergoes maladaptive changes with aging (Fig. 1), including a reduction in bacteria that produce short-chain fatty acids (SCFAs) and an elevated Firmicutes/Bacteroidetes (F/B) ratio [29,30]. In peri-/post-menopausal women with low BMD, there is often a higher abundance of *Bacteroides vulgatus* and a lower level of serum valeric acid [31]. Interestingly, studies have shown that colonizing mice with the GM of healthy children can

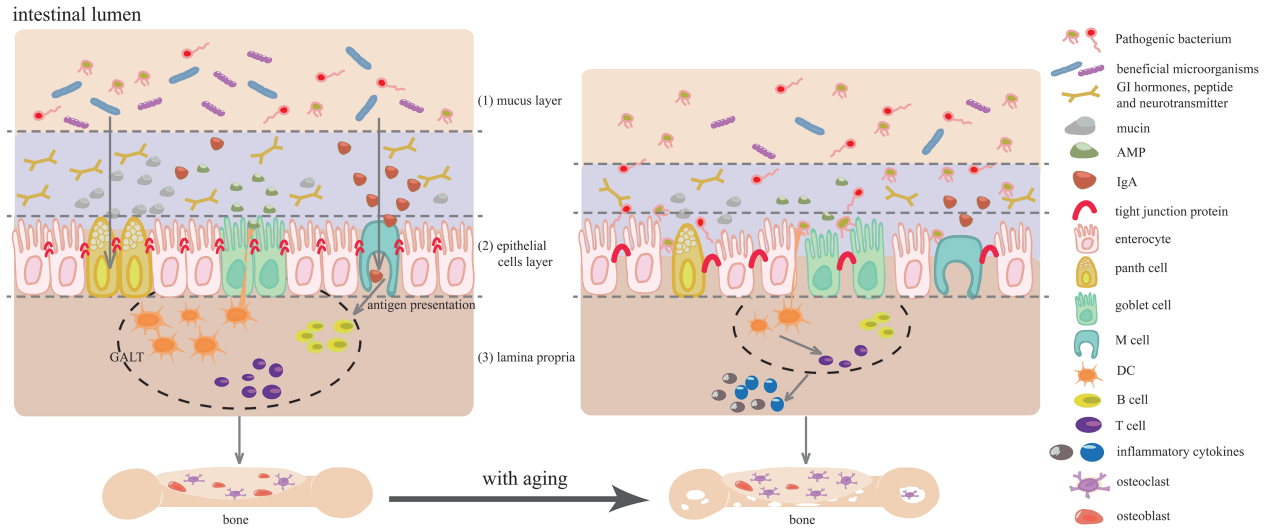

FIGURE 1. The impact of aging on intestinal barrier regulation and its negative effect on bone health. (1) the maladaptive remodeling of the gut microbiota (GM), characterized by declined diversity and stability, decreased beneficial microorganisms, and increased facultative anaerobic and pathogenic bacteria. Additionally, aging leads to a reduction in mucus thickness, dysregulation of antimicrobial peptide (AMP) expression, and bacteria translocation; (2) the downregulation of tight junction proteins, resulting in compromised intercellular interaction and barrier integrity; (3) the activation of intestinal immune cells due to aging-related altered microbiota and epithelial barrier dysfunction, coupled with a decline in gut mucosal immune system, resulting in local and systemic inflammation. These aging-associated changes in gut microecology, including remodeled gut flora, increased gut permeability, and imbalanced gut immune homeostasis, contribute to the development of age-related bone diseases. Abbreviation list: GALT: gut-associated lymphoid tissues, GI: gastrointestinal, M cell: microfold cell, DC: dendritic cell.

reverse the reduction of *Akkermansia muciniphila* caused by ovariectomy and prevent estrogen deficiency-induced osteoporosis [32]. Similarly, transplantation of the GM from wild-type mouse or *A. muciniphila* into prematurely aging mice has been found to restore secondary bile acid metabolism, normalize age-accelerated gut dysbiosis, and improve overall health and longevity [33]. This reshaping of the GM with age heightens the risk of systemic inflammation and age-related bone diseases [34–36].

Intestinal mucosal immunity

The gut mucosal immune system is primarily comprised of gut-associated lymphoid tissue (GALT), which includes a variety of lymphoid tissues like Peyer's patches (PPs) in the small intestine, cecal patches and appendix, as well as isolated lymphoid follicles (ILFs). As individuals age, there is a notable decline in the functional maturation of Microfold (M) cells within the follicle-associated epithelia that overlay PPs, which are specialized for transepithelial transport. This decline hampers antigen presentation capabilities [37]. Concurrently, plasmacytoid dendritic cells (pDCs), pivotal in detecting pathogens or infection signals, show age-related impairments in migration, a reduction in both absolute numbers and proportions, culminating a marked decrease in mucosal immune efficiency [38]. In the mucosal tissue of aged host, isolated DCs display a compromised immune priming function, diminishing their capacity to initiate antigen-specific T-cell responses [39]. Furthermore, aging is associated with a significant downregulation of genes involved in innate and adaptive immunity, including a decreased expression of T cell-specific transcripts and alterations in T cell signaling pathways [40].

CD4 T cells, which represent a majority of T cells in the intestinal lamina propria, demonstrate a diminished expression of inhibitory receptors, increased rated of spontaneous apoptosis, decreased frequencies of specific Th cell subsets, and altered functional responses due to aging [41]. These changes hinder the T cell responses to the GM, leading to both local and systemic inflammation in the elderly. Moreover, heightened inflammation within the bone marrow microenvironment is implicated in bone loss [42,43]. Conversely, studies have shown that dietary intervention with prebiotics in accelerated aging (SAMP6) mice can enhance the GM, mitigate systemic inflammation, and reduce bone resorption, underscoring the importance of the gut microenvironment in the aging process and its influence on bone health [44].

Regulatory Pathways of the Gut-Bone Axis on Age-Related Bone Diseases

The age-related changes in intestinal barrier function are believed to negatively impact bone health in older individuals. It is therefore reasonable to speculate that enhancing intestinal barrier function could improve bone health in the elderly. Various strategies, such as dietary and lifestyle modifications, pharmacological interventions, probiotic supplementation, exercise, and modulation of the intestinal microenvironment have been identified as potential approaches to regulate bone health. These strategies act through pathways involving immune regulation, nutrient absorption, neuronal signals, hormonal pathways, metabolism, microRNA, intestinal barrier function, and oxidative stress (Fig. 2).

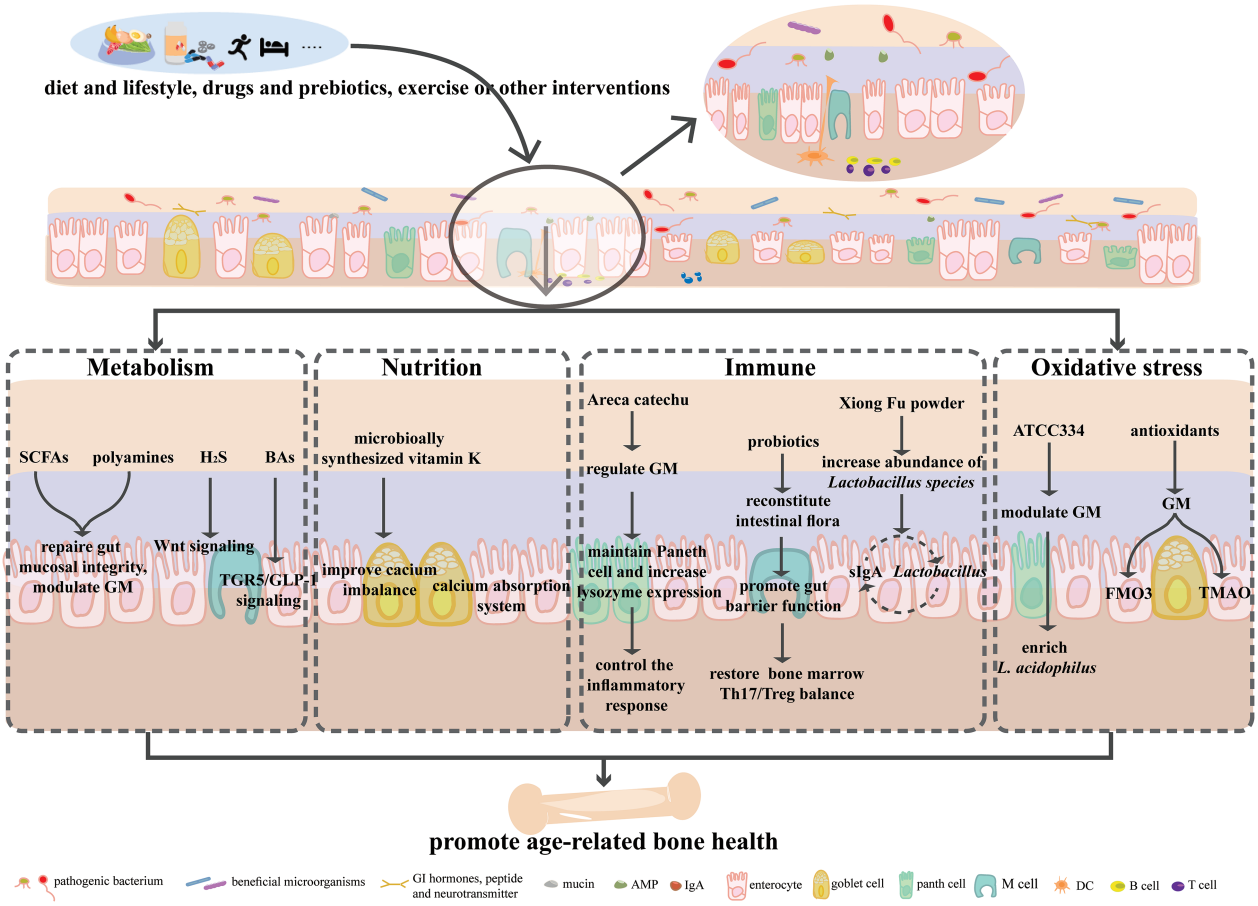

FIGURE 2. Regulatory pathways of the gut-bone axis on bone diseases. The shifts in diet, lifestyle, intakes of drugs and probiotics, exercise, or other interventions can pose various effects on the intestinal micro-environments, and regulate age-related bone health via metabolism, nutrition, immunity, and oxidative stress. Abbreviation list: SCFAs: short-chain fatty acids, H_2S: hydrogen sulfide, BAs: bile acids, TGR5: G-protein-coupled bile acid receptor, GLP-1: glucagon-like peptide-1, Treg: upregulating regulatory T cells, sIgA: secretory immunoglobulin A, FMO3: flavin containing dimethylaniline monoxygenase 3, TMAO: trimethylamine-N-oxide, ATCC334: *Lactobacillus acidophilus* stain.

Metabolism

The GM can produce a diverse array of bioactive compounds in response to dietary nutrients. These metabolites act as signaling molecules, facilitating communication with the endocrine system, immune system, and host metabolism. This network, known as host-microbe metabolic axis, involves various microbial species and host cell pathways and is crucial in regulating metabolic homeostasis.

SCFAs, such as formic acid, acetic acid, propionic acid, and butyric acid, are produced by microbial fermentation of indigestible carbohydrates in the gut [45]. They play a vital role in maintaining intestinal barrier integrity by regulating gut pH, stimulating mucus production, providing fuel for IECs, and modulating mucosal immune response [46,47]. SCFAs also act as critical regulators and mediators of gut-bone homeostasis. Studies have shown that direct supplementation of SCFAs or a high-fiber diet can inhibit osteoclast differentiation by directly suppressing the expression of genes involves in osteoclastogenesis, such as *TRAF6* (tumor necrosis factor (TNF) receptor associated factor 6) and *NFATc*1 (nuclear factor-activated T cell 1), while upregulating regulatory T cells (Tregs) populations, thereby improving bone mass and reducing postmenopausal bone loss [48]. Similarly, oral administration of supplements such as fructooligosaccharides and inulin can inhibit osteoclastogenesis and bone resorption by increasing SCFA levels and maintaining GM homeostasis, intestinal permeability, and intestinal immune function, thereby preventing bone loss induced by estrogen deficiency [49]. Additionally, the probiotic strain *Lactobacillus plantarum* TWK10 has also been found to mitigate age-related bone loss by modulating gut dysbiosis and increasing total SCFA levels [50].

Polyamines are fatty amines that act as physiological regulators of intestinal development and barrier integrity [51]. However, with age, both the levels of polyamines and their biosynthetic capacity decline [52]. Adequate supplementation of polyamines has been found effective in treating cardiovascular diseases, metabolic bone diseases, and in delaying cellular aging [53,54]. Heat exposure can increase the abundance of polyamine-producing bacteria and enhance bacterial polyamine synthesis capacity, thus alleviating the age-related decline in total polyamine levels and improving bone loss caused by ovariectomy [55]. Direct supplementation of natural polyamine agents can also prevent bone loss by interfering with osteoclast differentiation and maturation [56]. Enhancing polyamine biosynthesis in gut bacteria may inhibit abnormal osteoclast

activation and holds promise as a preventive and therapeutic approach for age-related metabolic bone diseases.

Hydrogen sulfide (H_2S) is a signaling molecule in the form of gas that is generated by cysteine in the intestine, produced by epithelial cells and GM. It serves as an energy source for gastrointestinal epithelial cells and is crucial in maintaining mucosal integrity. It has been discovered that H_2S has the ability to inhibit lymphocyte infiltration and suppress T cell proliferation to prevent inflammation [57]. Additionally, H_2S is involved in bone metabolism and can slow down the aging process by inhibiting free radical reactions, activating Sirtuin 1 (SIRT1), and interacting with age-related gene *Klotho* [58–60]. While Glucocorticoids may impair endogenous H_2S synthesis, supplementation of exogenous H_2S can activate the Wnt signaling pathway to enhance bone formation and prevent osteoporosis [61]. The decline of H_2S levels and its biosynthetic pathway are considered contributing factors to bone loss in estrogen-deficient mice [60].

Bile acids (BAs) are produced in the liver and further modified by GM, regulating lipid and bone metabolism [62]. Serum BA levels were positively correlated with bone density and negatively correlated with bone turnover markers, reflecting bone resorption. It is significantly lower in postmenopausal osteoporosis patients compared with healthy controls [63]. The G protein-coupled BA receptor 5 (TGR5) is involved in bone mass reduction and osteoblast differentiation [64]. BA-induced activation of TGR5 on small intestinal cells promotes the secretion of GLP-1 by enteroendocrine cells, which in turn promotes bone formation and inhibits bone resorption [65,66]. S-propargyl-cysteine (SPRC), an endogenous H_2S donor, provides substrates for H_2S synthesis, exhibits anti-inflammatory effects, and attenuates bone damage in rheumatoid arthritis. This effect is related to changes in GM composition, particularly the enrichment of bile salt hydrolase-producing bacteria, and BA metabolism [67].

Nutrition

Minerals, such as calcium, are vital for healthy aging. Calcium absorption in the small intestine is predominantly an ATP-dependent active process, accounting for approximately 90% of total calcium uptake. Postmenopausal women often experience a decline in calcium absorption, which possibly due to reduced active calcium transport or diffusion components of the calcium absorption system [68]. Supplements such as Astragalus polysaccharide, which are designed to repair the intestinal barrier, can restore intestinal function and alleviate osteoporosis by promoting osteoclast differentiation and reactivating the calcium signaling pathway [69].

Vitamin K, a fat-soluble nutrient, is present in two natural forms: phylloquinone (vitamin K_1, PK), primarily obtained from vegetables, and menaquinones (vitamin K_2, MKn), primarily synthesized by intestinal bacteria. This vitamin serves as a modulator of the GM composition and can be converted into various MKn forms by GM remodeling. Clinical evidence suggests that high vitamin K level can mitigate inflammation and inhibit abnormal calcification and mineralization linked to aging-related diseases. In contrast, vitamin K deficiency is linked to an increased risk of skeletal disorders in the elderly, such as osteoarthritis and osteoporosis [70]. In studies conducted on ovariectomized rats, MKn has been shown to enhance bone matrix quality and intestinal calcium absorption, thus preventing age-related bone loss [71]. Additionally, in obese mice, the bone-protective effects of tea polyphenol supplements were accompanied by changes in the composition and function of GM, specifically an increase in *A. muciniphila* abundance and enhancement of MKn biosynthesis pathways [72].

Vitamin D, despite its name, functions as a steroid hormone with two main forms: vitamin D2 (ergocalciferol), derived from plants, and vitamin D3 (cholecalciferol), synthesized from cholesterol [73]. It regulates calcium and phosphate homeostasis by facilitating calcium absorption in the intestine and influencing osteoblast and osteoclast activity [74]. As a member of the nuclear receptor superfamily, vitamin D receptor (VDR) mediates the effects of 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), which is the active metabolite of vitamin D [75]. Due to the widespread expression of VDR in various cell types, particularly in the small intestine, the vitamin D/VDR signaling pathway not only regulates intestinal barrier and immune function but also modulates nutrient transport [76]. Studies have shown that mice lacking VDR specifically in the small intestine exhibit suppressed expression of Paneth cell-specific α-defensins, the converting enzyme matrix metalloproteinase 7 (MMP7), tight junction proteins, and MUC2. This leads to mucosal collapse, increased intestinal permeability, dysbiosis, and systemic inflammation [77]. Conversely, a high dietary vitamin D has been associated with lower intestinal permeability and stronger trabecular bone structure [78]. This suggests that vitamin D contributes to bone health in the elderly by improving intestinal barrier function.

Immune

Osteoimmunology examines the interaction between the immune and skeletal system, which is regulated by a suite of shared molecules including receptors, chemokines, cytokines, and transcription factors [79]. Transforming growth factor-β (TGF-β) and inflammatory stimulate the differentiation of immature T cells into Th17 cells–a subset of T lymphocytes implicated in osteoclastogenesis [80,81]. Th17 cells facilitate the upregulation of Receptor activator of nuclear factor-κB (RANK) ligand (RANKL), which interacts with RANK on osteoclast precursors, fostering their maturation and enhancing bone resorption [82]. Additionally, interleukin 17 (IL-17) released by Th17 cells directly increases osteoclastogenesis [83].

In murine model, Th17 cells are mainly produced in the lamina propria of the intestine, with their development being contingent upon segmented filamentous bacteria (SFB) [84,85]. SFB presence boosts IL-17α expression in the ileum and upregulates LCN2 in the liver and serum, both of which favor osteoclastogenesis while inhibiting osteoblastogenesis [86].

Aging-related factors and estrogen deficiency can downregulate epithelial binding proteins and increase

intestinal permeability, facilitating microbial translocation from the lumen to the subepithelial space. This incites the production of pro-inflammatory cytokines by immune cell, precipitating the emergence of age-related pathologies [87,88]. A multiethnic longitudinal cohort study corroborates the association of increased intestinal permeability during menopause with heightened inflammation and reduced bone density [23]. For example, estrogen deficiency exacerbates intestinal permeability, enabling microbial components to activate T cells and boost TNF and IL-17 production in the lamina propria. Subsequently, TNF+T cells and Th17 cells egress from the intestine through an S1P receptor 1 (S1PR1)-dependent pathway, with TNF+T cells migrating to the bone marrow through the C-X-C motif chemokine receptor 3 (CXCR3) and Th17 cells use the C-C chemokine receptor 6 (CCR6)/chemokine (C-C motif) ligand 20 (CCL20, CCR6/CCL20) axis, leading to trabecular bone loss [89].

Reducing the GM dysbiosis and intestinal permeability may protect bone by inhibiting intestinal and bone marrow inflammation [90,91]. For example, polyphenols from betel nut seeds can increase lysozyme expression, maintain Paneth cell numbers, regulate the GM, modulate inflammatory responses, and ameliorate osteoporosis [92]. Probiotics can also restore the GM, promote intestinal barrier function, and equilibrate the balance between Th17 and Treg cells in the bone marrow, thereby guarding against bone loss under estrogen-deficient conditions [93]. Traditional herbal formulas like Xiong Fu powder can modulate the GM, enrich *Lactobacillus* abundance, and alleviate bone destruction. One potential mechanism involves the interaction between secretory Immunoglobulin A (IgA), regulated by intestinal mucosal Treg and Th17 cells and *Lactobacillus* adhesion [94].

Oxidative stress

Oxidative stress arises from an imbalance between antioxidants and reactive oxygen species (ROS), due to either excessive ROS production or insufficient antioxidants. Recognized as a hallmark of aging, oxidative stress is associated with age-related bone disorders. ROS changes, alongside shifts in antioxidant systems, contribute to bone loss and compromised bone quality by simultaneously modulating osteoclasts and osteoblasts. Excessive ROS typically activate signaling pathways such as mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), nuclear factor-κB (NF-κB), and Ca^{2+}/Nuclear factor erythroid 2-related factor 2 (Ca^{2+}/Nrf2), culminating in the activation of osteoclast-related genes like *CTSK* (Cathepsin K), *MMP*9 (matrix metalloproteinase 9), and *NFATc*1 [95]. Concurrently, oxidative stress disrupts bone formation by upregulating MAPK, releasing cytochrome C, and downregulating pathways such as Wnt/β-catenin, bone morphogenetic protein 2/Smad (BMP2/Smad), and focal adhesion kinase (FAK) phosphorylation, thereby inducing osteoblasts apoptosis [96]. The loss of sex hormones, such as estrogen or androgen, in aged individuals accelerates skeletal aging by diminishing oxidative stress defense and interfering with Wnt signaling [97,98].

Oxidative imbalances in the gut not only impede its own function but also affect overall health. While it can typically handle oxidative stress, its defensive capacity is overwhelmed by aging or heightened ROS levels. Oxidative stress-induced pathophysiological changes may impair calcium absorption by altering the expression and/or function of proteins integral to intracellular and/or intercellular Ca^{2+} transport [99,100].

Antioxidants have demonstrated potential in improving bone health by modulating the gut microenvironment [101,102]. For instance, *Lactobacillus acidophilus* (ATCC334) supplementation can enrich *L. acidophilus* abundance, stabilize redox balance, downregulate pro-inflammatory cytokine expression, and alleviate arthritis symptoms [103].

Conclusion

The current body of research on age-related bone diseases has largely concentrated on mechanisms related to telomere attrition, cellular apoptosis, immunosenescence, low-grade systemic inflammation, and Wnt signaling pathways [104–107]. Advances in research methodologies and omics technologies has deepened our comprehension of the gut microenvironment. The gut's ability to rapidly respond to external stimuli is crucial for maintaining homeostasis, which is integral to overall health. Dysfunctions in intestinal barrier, which may lead to increased permeability and dysbiosis, could contribute to age-related osteoporosis by disrupting bone immune homeostasis. The gut environment's influence on age-related bone diseases encompasses pathways related to metabolism, nutrient absorption, intestinal permeability, immunology, and oxidative stress. The potential for manipulating the gut microenvironment to prevent bone loss is a subject of ongoing research.

However, due to the high costs and technical limitations of sequencing and analytical methods, most studies on the intestinal microbiota and human health have relied on 16S rRNA amplicon sequencing. This approach provides only partial microbial species information, lacking gene-level and transcriptional insights, which hinders establishing a definitive causal link between the microbiota and health outcomes. Therefore, it is too early to conclude that assessments of the gut microenvironment can reliably reflect bone health. Furthermore, as the majority of current studies are preclinical and based on animal models, translating these findings to human clinical practice requires further rigorous and comprehensive efforts.

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