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Role of Myeloid Cells in Regulating New Mechanisms of Bone Aging and Drug Therapy

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Abstract

With the aging of the global population, bone degenerative diseases (such as osteoporosis) have become a major threat to the health of the elderly. The immune system plays a key role in the regulation of bone homeostasis and bone aging. This review describes the role of the immune microenvironment, and myeloid cells in bone aging, and explores their mechanisms in the regulation of osteoblast and osteoclast function. Meanwhile, this study explored drug interventions targeting myeloid cells in order to provide a new perspective for clinical treatment. Through a comprehensive analysis of the interaction of immune cells and bone metabolism, studies show the central role of the immune system in bone aging-related diseases and show promise for novel immunomodulatory therapies.

Keywords

Osteoporosis, Bone Homeostasis, Immune Cells, Bone Senescence

1. Introduction

Healthy aging is the key to cope with the aging of the population. Maintaining healthy activities is the premise and foundation for each elderly person to live independently and participate in the society. With the aging of the population and the change of lifestyle in China, the prevalence of bone aging-related diseases is rising rapidly and showing a trend of younger. The number of osteoporosis is about 90 million, and the prevalence of people aged 50 to 65 has risen from 19.2% to 32.0%. Age-induced bone injury caused by unbalanced bone homeostasis and decline in regenerative capacity has become a major medical challenge in public health care. At present, there is a large basic database of bone aging in China, and systematic early diagnosis and prevention and treatment strategies have not been

formed. In this paper, we review the pathophysiological mechanisms of the immune microenvironment and bone aging, the role of myeloid cells and related cytokines, and the treatment methods and clinical drugs to improve inflammatory bone loss, and provide new ideas for finding the targets of bone aging related diseases based on bone immunology.

2. Pathophysiological Mechanism of Bone Aging

Bone histomorphology plays a crucial role in studying the microstructure, morphology, lesion characteristics, and pathological processes of bone. The typical skeleton consists of collagen, matrix proteins, calcium-hydroxyapatite crystals, and cellular components. The different cellular components of bone include osteoblasts (Osteoblasts, OBs), osteoclasts (Osteoclasts, OCs), osteocytes (Osteocyte), chondrocytes (Chondrocyte), stromal cells, mesenchymal stem cells (Mesenchymal stem cells, MSCs), hematopoietic stem cells (Hematopoietic stem cell, HSCs), etc. Osteocytes are transformed from osteoblasts, accounting for skeletal cells 90% - 95%. Osteocyte is the main cell in adult bone tissue, located in the void of the mineralized bone matrix and sending its dendritic processes to interconnect with other osteocytes or surface osteoblasts. Osteocytes have mechanical stress transduction effects, which can regulate the balance of bone formation and bone resorption to maintain bone homeostasis, and complete the function of maintaining bone homeostasis through the conversion of mechanical signals and biochemical signals. However, osteoblasts and osteoclasts play a major role in skeletal remodeling, originating from mesenchymal stem cells with bone anabolic activity. They produce type I collagen, and matrix proteins (such as osteonectin and osteocalcin) that aid in calcium deposition in the form of calcium hydroxyapatite crystals. Mononuclear macrophages differentiated from myeloid progenitors in the bone marrow fuse and are induced by nuclear factor-κB (RANK)-receptor activator ligand, releasing proteolytic enzymes and acid substances to demineralize bone, thus controlling the anabolic activity of osteoblasts. The antagonistic activity of osteoblasts and osteoclasts leads to persistent formation and resorption of bone, a process known as bone remodeling [1], Is necessary to maintain the calcium levels in the blood. Bone remodeling occurs in several specific spaces in the bone, known as the bone remodeling chamber (BRC). In healthy bone, the interaction of RANK, the RANK receptor activation factor ligand RANKL and, and the Osteoprotecgerin OPG [2]. OPG is the decoy receptor for RANKL. RANKL secreted by osteoblasts binds to osteoclast surface surface RANK receptors and activates osteoclast surface signal transduction. However, to control bone resorption, the expression of RANKL secreted by osteoblasts is regulated by various factors, such as OPG, Wnt, and UPR signaling. Body imbalance is highly likely to lead to osteopenia, osteoporosis, bone hyperplasia and other bone abnormalities. Among them, osteoarthritis, as a common chronic disease of bone aging, its incidence will increase with age. Its main characteristics are cartilage degeneration and disappearance, as well as the attachment of the ligament at the joint edge and subchondral

bone reaction to form osteophytes, which causes joint pain [3]; In osteoporosis, aging changes the balance between osteoclasts and osteoblasts, manifested by a significant reduction in the amount of bone tissue, increased osteoclast formation, expansion of the osteoblast precursor pool and impaired differentiation [4]. Many different health status is closely related to osteoporosis, such as endocrine disorders (such as hyperparathyroidism, diabetes, premature menopause and men and women low testosterone and estrogen levels, etc.), autoimmune diseases (*e.g.*, rheumatoid joints, systemic lupus erythematosus and multiple sclerosis, etc.), prostate cancer, thalassemia, liver dysfunction, organ transplantation, and is also associated with osteoporosis [5]. During aging, physiological epigenetic metabolic changes drive chronic inflammation in the body, leading to osteoporosis. Therefore, many factors seem to be the pathogenic factors of osteoporosis. Hormonal imbalance was initially thought to be the main cause of osteoporosis, but in the 1970s, researchers first observed that the culture supernatant of human peripheral blood mononuclear PBMCs cells increased the activity of osteoclasts in fetal mouse bone cultures, indicating that immune cells play an important role in bone remodeling [6]. Age-driven changes in immune cell status explain the existence of chronic inflammation leading to osteoporosis, generating a new field of "bone immunology" based on the complex interactions between the immune system and the skeletal system [7].

3. Regulation of the Immune Microenvironment on Bone Senescence

The primary function of the bone marrow microenvironment is to provide signals that support and regulate the functions of various skeletal cell types (including hematopoietic stem cells and mesenchymal stem cells) to maintain homeostasis. Proper bone homeostasis depends on a coordinated cellular activity within the bone marrow, including osteoblastic bone formation, osteoclast bone resorption, and bone marrow fat accumulation. During aging, however, bone homeostasis is usually disrupted, characterized by reduced bone formation, increased bone marrow fat as well as stem cell failure, ultimately leading to osteoporosis and fragility-related bone damage [8]. In addition, senescent cells accumulate in the bone marrow with aging and secreted factors (called the aging-related secretion phenotype SASP). A growing number of studies have reported identifying the cell types and key SASP factors causing skeletal aging as potential therapeutic targets for the prevention of age-related bone degenerative diseases and multiple other age-related complications such as cardiovascular dysfunction and insulin resistance [9].

Innate immune cells are the main producers of proinflammatory mediators, and some of the immune cells share them in the bone marrow cavity microenvironment, sharing some of the same cytokines, hormones, receptors and transcription factors. The inflammatory response generated by innate immune cells to the body is one of the main factors triggering various skeletal diseases. Studies have shown that inflammatory cell death leads to osteogenic cell pyroptosis and is the

key to the development of osteoporosis. Various signals that induce inflammation in the body include exogenous signals such as PAMPs (pathogen-related molecular patterns) or endogenous signals DAMPs (death/damage-related molecular patterns) that can activate the immune system and lead to acute inflammatory diseases [10]. In addition, metabolic changes, tissue dysfunction, or long-term infections can often lead to chronic inflammatory diseases. These inflammatory mediators play a key role in the association of osteoporosis. In addition to the production of proinflammatory cytokines, macrophages, monocytes and dendritic cells can also act as precursors of osteoclasts, and other proinflammatory innate immune cells from bone marrow including neutrophils, eosinophils and mast cells, which also cause osteoporosis [11].

Macrophages are heterogeneously differentiated immune cells, which are activated and polarized into M1-like (pro-inflammatory phenotype) or M2-like (anti-inflammatory phenotype) states under different environmental signals, participating in a variety of physiopathological processes. Studies have shown that macrophages secrete cytokines that regulate bone homeostasis and regeneration. F4/80 macrophages close to the periosteum and intimal surface, known as "osteoma cells", function to regulate osteoblast mineralization in vitro and maintain mature osteoblast function in vivo. In addition, the tumor suppressor M (OSM) and IL-10 produced by macrophages stimulate osteoblast differentiation and mineralization [12]. TNF-α and IL-6, produced by activated M1-like macrophages, inhibit osteoblast function. However, the number and phenotype of macrophages change with age, and in juvenile life, macrophages usually secrete restorative factors, including Lrp 1, to promote fracture healing [13], While macrophage transplantation in aged mice delayed fracture healing. Exercise also promotes the secretion of a novel mechanosensitive lipid soluble factor, Reticulocalbin 2, by bone marrow macrophages bound to a functional receptor complex composed of Neuronilin-2 and Integrin β1, activating cAMP-PKA signaling pathway to initiate bone marrow adipolysis and promote the differentiation and function of mesenchymal and hematopoietic stem cells [14]. Neutrophils are polymorphonuclear phagocytes that account for 40 of leukocytes in human blood%-60%, Continuously monitor microbial infections and killing pathogens by various mechanisms such as phagocytosis, production of ROS, and granzyme B and perforin. Neutrophils also produce cytokines and chemokines such as CCL 2 and CCL 20, as well as recruitment of Th 17 to promote osteoporosis [15]. We found that neutrophils in the blood of healthy individuals expressed membrane-associated RANKL (mRANKL), and RANK expression depended on the stimulation of IL-4 and TNF-α, and in the synovial fluid of rheumatoid arthritis patients, it was found to express both mRANKL and RANK and secrete OPG [16]. The observation that inflammatory neutrophils significantly express RANK while healthy blood neutrophils only after stimulated individuals suggests the involvement of neutrophils in bone remodeling, including inflammation-mediated bone loss. Some studies have revealed that pro-inflammatory and pro-aging immune cells, mainly

composed of macrophages and neutrophils, accumulate and secrete granular calreticulin (GCA) in the bone marrow, thus inducing the imbalance of osteogenesis and lipogenesis of bone marrow stromal cells (BMSCs) [17]. Monocytes constitute the total number of human leukocytes 10%, The precursors of monocytes originate from hematopoietic stem cells in the bone marrow. Different subsets of monocytes exhibit distinct functions during homeostasis and during inflammation. Inflammatory monocytes showed high levels of chemokine receptor 2 (CCR 2) and low levels of CXC 3 chemokine receptor 1 (CX3CR1), while patrolling monocytes showed opposite expression [18]. In addition to acting as osteoclast precursors, monocytes can produce cytokines to participate in bone remodeling. Senescent monocytes that upregulate the inflammatory response and cellular senescence triggers can lead to osteoporosis and atherosclerosis. DCs are mainly antigen-presenting cells with the ability to activate adaptive immune responses. They express high levels of class MHC II and the costimulatory molecules required for antigen presentation, such as CD80 and CD86. The profound impact of DCs on bone metabolism has recently been widely recognized. DCs contribute to inflammation-mediated osteoclastogenesis and are involved in inflammatory bone disease. Using an in vivo model to report the osteolytic potential of DCs and observed recruitment of DCs to the site of osteitis and involvement in bone resorption, Maitra *et al*. [19]. Furthermore, DC can activate T cells by acting as an APC, and the activated T cells produce cytokines and soluble factors, which can drive bone remodeling. It was also observed that DCs directly interact with T cells to form aggregates that play a role in bone pathologies such as synovitis and periodontitis (**Table 1**).

Table 1. Interactions of immune cells and bone metabolism.

Immune cell types	EF	Effect on the osteoblasts	Effect on the osteoclasts
M1 type macrophages	TNF-α, IL-6, IL-1β, IFN-γ	Inhibit the proliferation and differentiation of osteoblasts and reduce bone matrix production; inhibit bone formation by reducing Wnt signaling	Activating the RANKL-RANK signaling pathway, promote precursor differentiation of osteocllasts and activates osteoclast activity
M2-type macrophages	IL-10, TGF-β, IL-4	Promote osteoblast differentiation and osteogenesis to bone morphogenic protein (BMP)	Inhibit osteoclast differentiation and reduce osteoclastic activity by inhibiting RANKL expression or increasing OPG (osteoprotegerin)
Th1 cells	IFN-γ, TNF-α	IFN-γ was able to inhibit osteoblast activity and reduce osteogenic differentiation	Promote bone resorption by enhancing osteoclast differentiation and maturation
Th2 cells	IL-4, IL-5, IL-13	Promote osteoblast proliferation and differentiation and enhance bone formation	Inhibit osteoclast differentiation and reduced bone resorption

Continued

Th17 cells	IL-17, IL-22, RANKL	IL-17 reduces osteogenesis by inhibiting the differentiation and function of osteoblasts	The secretion of RANKL and the enhancement of RANKL-RANK signaling significantly promotes osteoclast formation and activation
Treg cell	IL-10, TGF-β	Treg cells promote osteoblast proliferation and differentiation through the secretion of IL-10 and TGF-β	Inhibition of osteoclast activity, reduced osteocast formation and reduced bone resorption
Neutrophile Granulocyte	And MMP-9, elastase, and TNF-α	Secreted MMP-9 and elastase can inhibit osteoblast function and disrupt the extracellular matrix	By releasing TNF-α, it indirectly activates osteoclastic activity and promotes bone resorption
DC	IL-12, IL-23	And directly inhibiting osteoblast function by inducing IFN-γ secretion by Th 1 cells	Indirectly enhanced osteoclast formation and activity by activation of Th 17 cells
B cell	RANKL, TNF-α, IL-6	Inhibit osteoblast activity and reduce bone formation	Promote osteoclast formation and differentiation through RANKL and enhancing bone resorption
NK cell (natural killer)	IFN-γ, TNF-α	IFN-γ inhibits osteoblast differentiation and reduces bone formation	IFN-γ and TNF-α promote osteoclast formation and activity by enhancing the expression of RANKL

4. Immune Intervention Means and Drug Treatment for Bone Aging

Parathyroid hormone (PTH) is an important regulator of calcium homeostasis, and PTH is one of the first hormones considered for the treatment of senile osteoporosis. PTH 1-34 (teriparatide; Forteo) is a biosynthetic drug consisting of the first 34 amino acids of human parathyroid hormone, one of the first anabolic drugs approved by the European Union and the United States FDA for osteoporosis. Teriparatide mainly by activating the Wnt pathway to promote DNA repair to fight aging trigger, it has been shown to improve osteoblast function, increase osteoblast formation and reduce osteoblast apoptosis, but the exact mechanism of progenitor transformation in osteoblasts, the role of blood vessels and cell movement of bone formation is still in research, teriparatide because of high incidence of osteosarcoma side effects and limited in the treatment of osteoporosis [20].

Anti-sclerostin antibodies are an emerging therapy that is now under FDA approval. Sclerostin is a glycoprotein encoded by the SOST gene, which is secreted by bone cells and has an inhibitory effect on osteoblast function by negatively regulating Wnt and bone morphogenetic protein (BMP) signaling. Sclerostin has been shown to negatively regulate several cellular processes in the skeleton, and sclerostin levels at both serum and mRNA levels are commonly used as predictors of bone health. The limitations of sclerostin within bone make it a good candidate for osteoporosis with less systemic impact. The anabolic function of sclerostin is a possible treatment for osteoporosis and has a better anabolic effect than

teriparatide. Unlike teriparatide, R omosozumab has no oncogenicity problems in animals or humans. The effect of R omosozumab was reversible after drug withdrawal [21].

Bisphosphonates (B isphosphonates, BPs) are a new class of drugs used in all kinds of bone diseases and calcium metabolic diseases. It can specifically bind to hydroxyphosphonatite in bone and inhibit osteoclast activity, thus inhibiting bone resorption. Zoledronate has become one of the most widely accepted antiresorbers and as a treatment for osteoporosis, zoledronate improves DNA repair in mesenchymal stem cells, suggesting that it may act as a modulator of cellular aging and therefore is used as a treatment for bone aging [22]. Denoumab is a monoclonal antibody against RANKL that blocks the binding of RANKL to its receptor RANK on osteocast progenitors, inhibiting osteoclast function and thus acting as an antiresorptive agent to protect bone loss. Although denosumab may contribute to alleviate senile osteoporosis, there is no evidence that it may play a role in regulating aging as a mechanism.

Senolytics and SASP modulators are based on compounds that selectively kill senescent cells without affecting proliferating cells, or drugs that inhibit cellular senescence or SASP, called spermatology. Since senescent osteoblasts and osteocytes are identified in bone tissue, it is hypothesized that the senescent properties of these cells work with SASP to regulate bone remodeling. Thus removal of senescent cells and inhibition of SASP have become advantageous treatments for physiological and pathological skeletal aging. Induced elimination of p16 INK4A has been shown to improve age-related health and longevity as well as age-related osteoporosis [23]. The combination of dasatinib and mistletoe is also effective in the removal of senescent cells, which can effectively restore the physiological aging bone structure and the skeletal pathological aging in radiation-related osteoporosis. Although anabolic agents can promote bone formation and anti-resorptive agents can inhibit osteoclast function, anti-senescent cells responsible for stimulating osteoclast activity and inhibiting bone formation, making anti-senescent drugs promising strategies for the treatment of age-related osteoporosis.

Drugs that do not kill senescent cells but inhibit the production of pro-inflammatory proteins are called SASP modulators or S enomorphics. Among them, JAKi and R uxolitinib were shown to effectively alleviate age-related osteoporosis, and the mechanism may be the inhibition of the generation of specific inflammatory factors such as IL-6, IL-8 and PAI 1. TNF-α inhibitor can reduce active inflammatory disease and reduce systemic bone loss, increase bone density, so it can be applied to the treatment of RA, IBD, AS, adolescent idiopathic arthritis, monoclonal antibodies such as adamumab specifically binding TNF, and etanercept competitive inhibit the cell surface TNFR to eliminate its biological function [24]. For other pro-inflammatory cytokines, IL-1, IL-6, and IFN-γ. Although TNF-α blockers have been widely used in the clinic, the complete inhibition of TNF-α still brings the inevitable side effects. Studies targeting the TNF receptors TNFR 1 and TNFR 2 found that selective inhibition of TNFR 1 or activation of TNF/TNFR

2 was more safe and effective than TNF-α blockers, avoiding significant side effects [25]. The neutralizing monoclonal antibody of IL-6 receptor, serilimumab and tocilizumab, can block soluble or membrane-bound IL-6 receptor-mediated signaling and effectively control systemic inflammation, and can be used in the treatment of autoimmune diseases such as AS, RA, adult still disease and Crohns disease. Studies show that the overall efficacy and safety of serilimumab and tociluzumab are similar to those of TNF-α inhibitors, but tociluzumab has the advantage to be used as a monotherapy. Moreover, infection is the most common adverse effect of anti-IL-6R drugs, and the absence of significant CRP elevation tends to mask infection symptoms. As a chimeric monoclonal antibody stuximab targeting IL-6, it directly reduces IL-6 levels and could be used as a supplement to IL-6R inhibitors. Moreover, more anti-IL-6 drugs (such as olokizumab) are in the clinical research stage, and they are expected to be combined with methotrexate to treat inflammatory diseases such as RA [26]. IL-1 inhibitors block IL-1, thereby reducing cartilage and bone destruction. Anabarysin is a recombinant IL-1 receptor (IL-1R) antagonist that blocks the activity of IL-1 α and IL-1 β. It can be used clinically, alone or in combination with other drugs, to treat RA and neonatal multi-system inflammatory diseases and improve systemic bone loss, but is relatively low compared with biological agents associated with other inflammatory factors. Neutralization of IL-1 using the anti-IL-1 β mmab kananunumab may also exert anti-inflammatory and anti-bone loss effects [27]. IL-17A monoclonal antibody uchumumab and ecizumab and IL-17 receptor A monoclonal antibody Broliumumab is widely used to treat psoriasis, psoriatic arthritis and AS, such drugs are promising to improve systemic bone loss caused to inflammation, can be used when TNF-α treatment is ineffective, the most common side effect is mild to moderate infection [28]. Activated B cells and T cells can promote osteoclastogenesis through various pathways such as secretion of inflammatory factors, inhibit the activation and proliferation of these cells in chronic inflammation, and can have beneficial effects on the improvement of bone loss. The selective immunosuppressants abatacept and rituximab can inhibit or increase the production of T or B cells and may inhibit the progression of joint injury in RA patients.

Promoting bone regeneration through immunomodulation is a relatively new research field in bone tissue engineering, and biomaterials with immunomodulatory effects can suppress the local overactivated immune response while having the effect of enhancing bone regeneration. Controlling the morphology of biomaterials, wettability, surface charge, the release of cytokines, ions and other bioactive molecules can affect the immune response [29] and interference with bone metabolism. For example, the morphology of biomaterials can affect the polarization of macrophages, the persistence of M1 macrophages and the lack of M2 macrophages will lead to severe foreign body reaction and chronic inflammation, delayed tissue healing and failure of biomaterials integration; M2 macrophages can inhibit inflammation and promote bone tissue reconstruction by releasing TGF-β and IL-10. Alternatively, exosomes derived from mesenchymal stem cells also

function in immunomodulation and promoting osteogenic differentiation, acting as a novel bone inducer on biomaterials and producing few adverse effects. Studies have shown that exosomes from human MSCs can also significantly reduce the expression of proinflammatory genes and inducible nitric oxide in macrophages and promote the expression of early osteogenic markers in human MSCs (Table 2).

Table 2. Methods, mechanisms, specific applications, and related challenges for bone aging treatment.

Intervention means	Class	Specific methods	Machine-processed	Detailed role and application	Clinical challenge
Immune intervention	Immunomodulator	Anti-tumor necrosis factor therapy	By inhibiting TNF-*α*, reducing inflammation, inhibiting osteoclast activity, and slowing bone resorption.	It is often used in osteoporosis caused by chronic inflammatory diseases such as rheumatoid arthritis and osteoarthritis.	It may trigger immunosuppression and increase the risk of infection, so the long-term use should be cautious.
		And Interleukin-6 inhibitor	Blocking IL-6 signaling, reducing osteoclastogenesis, and inhibiting bone resorption.	It is suitable for the treatment of chronic inflammatory osteoporosis, and it is still in the clinical research stage.	It may affect other immune processes in the body, and there is a risk of systemic side effects.
	Bone metabolism-related cellular regulation	Regulation of T cell and B cell functions	Regulate immune cells, affect the interaction between osteoclasts and osteoblasts, and balance bone metabolism.	Against bone diseases caused by dysregulation of the immune system, such as bone damage caused by systemic lupus erythematosus.	Immune cell regulation with unknown long-term effects requires personalized treatment options.
	Stem cell therapy	Fine mesenchyme dry graft	MSC differentiate into osteoblasts that promote bone repair and regulate immunity by secreted cytokines.	It can be used in fracture healing and bone defect repair, and it is expected to be used in the treatment of osteoporosis.	Transplantation techniques are complex and there are risks such as graft rejection and an immune response.
		Cytokine therapy (*e.g.*, IL-10)	IL-10 acts as an anti-inflammatory cytokine to regulates immune response and reducing bone absorption.	It may be used in patients with osteoporosis to reduce the bone loss caused by inflammation, and has great potential for future clinical application.	Cytokine system is complex, and excessive inhibition may trigger other health problems.
Medication	Bone resorption inhibitor	Bisphosphonates (*e.g.* alendronate, zoledronic acid)	By binding to osteoclasts, they induce their apoptosis and significantly reduce bone resorption.	It is often used in postmenopausal osteoporosis and other high fracture risk patients.	Long-term use may cause osteonecrosis of the jaw and atypical femur fractures, which require duration monitoring.

Continued

Medication		Anti-RANKL antibody (desosumab)	Blocking the RANKL-RANK signaling pathway and inhibiting osteoclastogenesis and its function.	Suitable for high-risk osteoporosis patients, the fracture prevention effect is remarkable.	It may lead to hypocalcemia, rapid bone loss after withdrawal, and long-term monitoring of bone mineral density.
	Osteogenic promoters	Selective oestrogen receptor modulators (SERMs, such as raloxifene)	It mimics estrogen action, stimulates osteoblast proliferation, suppresses osteoclast activity and increases bone density.	Suitable for osteoporosis in postmenopausal women to reduce the risk of spinal fracture.	May increase thrombosis risk, especially in patients with a history of cardiovascular disease.
		Recombinant human PTH (teriparatide)	By directly stimulating osteoblasts, it promotes bone formation, suppresses bone resorption, and increases bone mineral density.	The effect is significant in patients with severe osteoporosis and is especially suitable for patients with high risk of multiple fractures.	Limited use time, long-term use may lead to the risk of osteosarcoma, requiring strict control of the course of treatment.
	Other drugs	Vitamin D supplements (*e. g.*, vitamin D3)	Promote calcium absorption, enhance bone mineralization, and maintain bone health.	It is particularly important for the elderly and people in areas with insufficient sunshine, and the basic treatment to prevent osteoporosis.	Overdose can cause hypercalcemia, leading to problems like kidney stones.
		Calcium supplement	Provide the calcium required for osteogenesis, prevent osteoporosis, and maintain bone mineral density.	It is often used in combination with vitamin D, especially for the elderly, pregnant women and other people prone to calcium deficiency.	Excessive intake may lead to side effects such as kidney stones and vascular calcification.
		Nonsteroidal anti-inflammatory drugs (NSAIDs)	Inhibiting cyclooxygenase (COX) to reduce inflammation and relieve bone and joint pain.	It is widely used in osteoarthritis and inflammatory diseases accompanying bone aging to improve patient quality of life.	Long-term use may lead to gastrointestinal discomfort, kidney injury, and cardiovascular problems.

5. Conclusions

Bone degenerative diseases, especially osteoporosis, have become one of the major public health challenges in a global aging society. Studies show that the role of the immune system in bone health is critical, especially the dual role of myeloid cells in regulating bone homeostasis and bone aging. However, there are still some deficiencies in the existing studies, mainly reflected in the incomplete understanding of the specific mechanism of action of myeloid cells, especially their dynamic

changes under different pathological conditions. First, although the role of myeloid cells in bone loss has been identified, the specific differentiation mechanisms of their different subtypes (*e.g.*, M1 and M2 macrophages) and their precise role in bone aging still need further investigation. In particular, how M1 type macrophages inhibit osteoblast function through the inflammatory response, and how M2 type macrophages promote this process remains to be further explored. Second, the current study has focused more on cytokine-and immunomodulator-based therapies for osteoporosis, but the mechanism of interaction between immune cells and bone cells is not fully defined. Future studies could further explore the role of myeloid cells at different stages, especially in aging and inflammation-induced bone loss, to identify specific drug targets.

The prospect of bone aging treatment, mainly for osteoporosis, can be considered from these aspects. First, the implementation of personalized treatment, and future treatment methods can combine gene editing technology and immune regulation strategies to develop personalized immune cell regulation programs. By detecting the activity of myeloid cells in patients, customized, targeted therapy is expected to reduce bone loss and promote bone regeneration; second, the development of new drugs should focus on the inhibition of anti-inflammatory and osteogenic functions, especially the targeted drugs for specific subtypes of immune cells; the third is to combine immune regulation with bone tissue engineering to promote bone tissue regeneration and repair by utilizing immunogenic biomaterials or stem cell exosomes. In conclusion, the role of myeloid cells in bone aging and related diseases is widely recognized, but there are still many mechanisms to be elucidated. By deeply exploring the immunomodulatory function of these cells, more effective treatment options can be developed to improve the quality of life of osteoporosis patients in the future.

Data Availability

All data included or relevant to the study are available upon request by contact with the corresponding author.

Authors' Contributions

Xianqi Qin, Wujia Yang, Luo Dong, Luchang Chen, and Jihua Wei finished the drawing and manuscript revision work.

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Conflicts of Interest

All authors declare that there has not been any commercial or associative interest

that represents competing interests in connection with the work submitted.

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