Clinical Interventions in Aging

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Bone Marrow Adipose Tissue as a Critical Regulator of Postmenopausal Osteoporosis - A Concise Review

Huifang Niu[1,2,*], Minfeng Zhou[1,*], Xiaoyun Xu[2], Xiaojuan Xu[1]

[1]Union Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China; [2]Key Laboratory of Environment Correlative Dietology (Ministry of Education), Hubei Key Laboratory of Fruit Vegetable Processing Quality Control (Huazhong Agricultural University), School of Food Science and Technology, Huazhong Agricultural University, Wuhan, Hubei, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiaoyun Xu; Xiaojuan Xu, Email xuxiaoyun@mail.hzau.edu.cn; xu_xiaojuan2009@163.com

Abstract: Postmenopausal osteoporosis (PMOP) is a major health problem affecting millions of women worldwide. PMOP patients are often accompanied by abnormal accumulation of bone marrow adipose tissue (BMAT). BMAT is a critical regulator of bone homeostasis, and an increasing BMAT volume is negatively associated with bone mass reduction or fracture. BMAT regulates bone metabolism via adipokines, cytokines and the immune system, but the specific mechanisms are largely unknown. This review emphasizes the impact of estrogen deficiency on bone homeostasis and BMAT expansion, and the mechanism by which BMAT regulates PMOP, providing a promising strategy for targeting BMAT in preventing and treating PMOP.

Keywords: postmenopausal osteoporosis, bone marrow adipose tissue, bone metabolism, immune system, cytokines

Introduction

Osteoporosis pathologically manifests as a decrease in bone mineral density (BMD), destruction of the microstructure of bone tissue and easy fractures, often occurring in the elderly. Postmenopausal women are an important disease group. In menopause, estrogen deficiency accelerates osteoclastic bone resorption and inhibits bone formation, resulting in bone loss and increased fracture risk. Postmenopausal osteoporosis (PMOP) has become a global public health problem. According to reports, about 50% of postmenopausal women globally suffer from osteoporosis, and up to 40% suffer from fractures.[1,2] Therefore, it is urgent to comprehensively understand the deep pathological mechanism of PMOP and to develop effective therapeutic strategies. Bone marrow adipose tissue (BMAT) is a critical regulator of bone homeostasis, and accumulating evidence shows that bone loss in postmenopausal women or ovariectomized animals is often accompanied by abnormal accumulation of BMAT.[3–5] Treatment with anti-osteoporosis drugs, such as bisphosphonates, raloxifene, and teriparatide, was accompanied by a decrease in bone marrow fat content.[4–6] This correlation suggested that BMAT may have a key role in the pathological process of PMOP. Therefore, this article systematically discussed the effects of estrogen decline on bone homeostasis and BMAT expansion, and the relevant molecular mechanisms by which BMAT regulates PMOP based on adipokines, cytokines, and the immune system, providing a theoretical basis for targeting BMAT as a therapeutic target for treating PMOP.

The Pathological Mechanism of PMOP

Osteoporosis is the result of an unbalanced bone homeostasis. Decreased osteoblast number and increased osteoclast number result in a large loss of minerals, decreased bone density, and increased bone fragility, eventually fractures. Common sites for fractures are the spine, forearm, and hip bones. Age-related bone loss, on the other hand, is a natural physiological process where everyone's bone density gradually decreases with age. This decline in bone density typically begins around the age of 30 and accelerates after menopause. While both conditions result in a reduction in bone density, they have different underlying physiological mechanisms. However, age-related bone loss can become a risk factor for

Received: 28 February 2024
Accepted: 27 June 2024
Published: 11 July 2024

osteoporosis, especially in individuals with other osteoporosis-related factors. PMOP, a type of primary osteoporosis, is characterized by its close association with the decline in estrogen levels after menopause in females. While it shares similar pathological features and mechanisms with other types of primary osteoporosis, the reduction of estrogen plays a pivotal role in its pathogenesis. Estrogen plays an irreplaceable role in promoting bone formation, inhibiting bone resorption and maintaining the balance of bone metabolism. After menopause, decreased estrogen levels in women led to bone loss and increased fractures risk.

Bone Remodeling

Bone remodeling is an important physiological pathway for maintaining bone homeostasis. It mainly includes bone formation and resorption (Figure 1). Osteoblasts play a crucial role in bone formation. Osteoblasts are mononuclear cells, accounting for 4–6% of the total bone cells, originating from bone mesenchymal stem cells (BMSCs).[7] Osteoblast precursor cells differentiated from BMSCs activate the Wnt signaling pathway to further proliferate and differentiate into osteoblasts.[8] Differentiated osteoblasts synthesize and secrete bone matrix proteins, such as collagen, osteocalcin and osteopontin, which mineralize to form bone.[9] Sclerostin is a cysteine-knot glycoprotein product of the SOST gene, predominately expressed by osteocytes.[10] Sclerostin binds to the Wnt receptor of bone-forming cells, preventing the

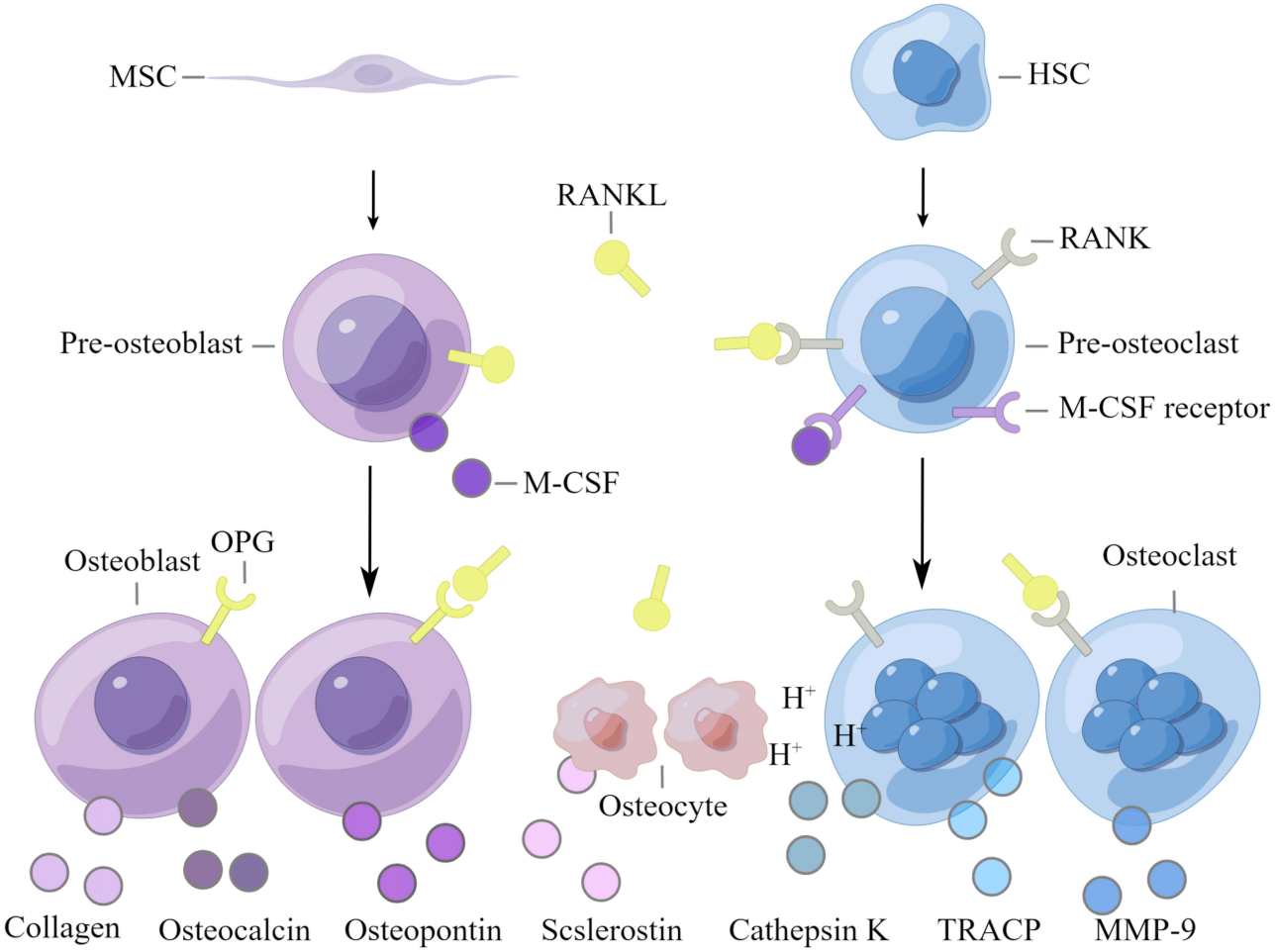

Figure 1 Bone remodeling. Osteoblasts originate from bone mesenchymal stem cells (BMSCs). Osteoclasts originate from the macrophage and monocyte lineages of hematopoietic stem cells (HSCs). Osteoblasts synthesize and secrete bone matrix proteins, such as collagen, osteocalcin, and osteopontin, which mineralize to form bone cells, thereby playing a role in bone formation. Osteoclasts expose the organic matter in the bone by forming a local acidic microenvironment, and the organic matter is degraded by enzymes such as cathepsin K, tartrate-resistant acid phosphatase (TRACP) and matrix metalloproteinase-9 (MMP-9). Osteoblast precursor cells promote the proliferation and differentiation of osteoclast precursor cells or osteoclasts by secreting RANKL and macrophage colony-stimulating factor (M-CSF). Osteoblasts produce osteoprotegerin (OPG), which competes for RANKL binding. Mature osteocytes can inhibit bone formation by secreting sclerostin, thereby regulating bone metabolism. The figure was created using Figdraw 1.0 (www.figdraw.com). The export authorization code for Figure 1 is ID: RWUOA454db.

normal activation of the Wnt signaling pathway and inhibiting bone formation,[10] thereby regulating bone metabolism. Osteoclasts are formed by the fusion of multiple monocytes originating from the macrophage and monocyte lineages of hematopoietic stem cells (HSCs). It accounts for 1–4% of the total bone cell population.[11] These cells, upon stimulation by RANKL, differentiate into osteoclast precursor cells, and with further stimulation from macrophage colony-stimulating factor (M-CSF), they differentiate into mature osteoclasts. During bone resorption, osteoclasts form a local acidic microenvironment under the action of integrins, lysosomal enzymes and acidic substances. The acidic environment dissolves the minerals in the bone and exposes the organic matter. The exposed organic fraction is eventually degraded by enzymes such as cathepsin K, tartrate-resistant acid phosphatase (TRACP), and matrix metalloproteinase-9 (MMP-9).[12] Furthermore, the osteoprotegerin (OPG) / receptor activator of nuclear factor-κB ligand (RANKL) / receptor activator of the nuclear factor-κB (RANK) system is the most important signal transduction pathway in bone metabolism. RANKL is an essential molecule for osteoclastogenesis derived from various cells, including osteoblast spectrum cells, activated T lymphocytes and B lymphocytes.[13] RANKL binds to the receptor RANK on the surface of osteoclast precursors and mature osteoclasts to promote osteoclast differentiation, activation and survival.[14] OPG derived from bone marrow stromal cells, B lymphocytes and osteoblasts inhibit osteoclastogenesis by competitively binding to RANKL. All three together regulate the bone remodeling process.

Mechanism of Estrogen Deficiency-Induced Osteoporosis

With the aging of the global population, the incidence of osteoporosis has increased dramatically. Therefore, as one of the common types of osteoporosis, PMOP has attracted attention. Estrogen deficiency is the main cause of PMOP (Figure 2). As one of the crucial influencing factors in bone metabolism regulation, estrogen functions to promote an increase in bone cell count. After menopause, with the sharp drop in estrogen levels in women, the rate of bone formation is much lower than the

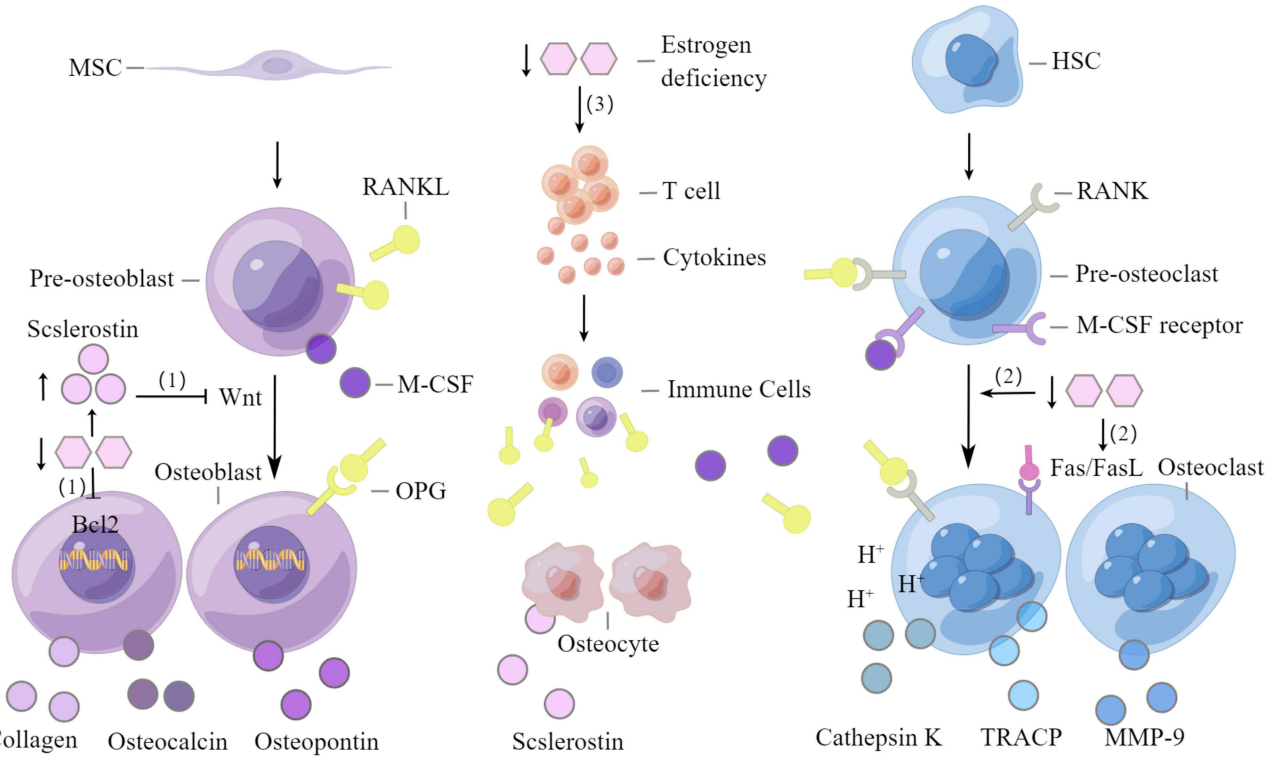

Figure 2 Effects of estrogen deficiency on bone metabolism. (1) Estrogen deficiency can lead to an increased sclerostin level. Sclerostin inhibits the differentiation of osteogenic precursor cells into osteoblasts via the Wnt signaling pathway. Estrogen deficiency down-regulates the expression of the anti-apoptotic gene Bcl2 in osteoblasts and promotes the apoptosis of osteoblasts. (2) Estrogen can bind to the surface receptors of precursor osteoclasts and inhibit their further proliferation and differentiation. Estrogen inhibits osteoclast apoptosis by inhibiting the Fas/FasL system. (3) Estrogen deficiency promotes the formation of RANKL and M-CSF by stimulating the immune system and promoting osteoclasts' proliferation and differentiation. The figure was created using Figdraw 1.0 (www.figdraw.com). The export authorization code for Figure 1 is ID: IURII81aa8.

rate of bone resorption, resulting in decreased bone density, enhanced bone fragility, and eventually osteoporosis. The impact of estrogen deficiency on bone metabolism is primarily through the following pathways: (1) estrogen deficiency increases the level of sclerostin,[15] and high levels of sclerostin bind to the Wnt receptor of bone-forming cells, preventing the normal activation of the Wnt signaling pathway and inhibiting osteoblasts formation. In addition, estrogen deficiency down-regulates the expression of osteoblast anti-apoptotic gene Bcl2 and promotes osteoblast apoptosis.[16] (2) Estrogen exerts its influence on bone formation in post-menopausal women through several mechanisms, including prolonging the osteogenic differentiation and maturation of BMSCs and inducing apoptosis in osteoclasts.[17] For instance, estrogen promotes the production of insulin-like growth factor (IGF)-1 and IGF-β as well as pre-collagen synthesis in osteoblasts.[18] Studies on ERα (Estrogen receptor, ER) -deficient mice have shown reduced proliferation and differentiation of osteoblasts in mesenchymal progenitor cells.[19] However, in patients with PMOP, these functional activities decrease as estrogen levels decline, ultimately leading to a reduction in osteoblasts, an increase in osteoclast proliferation, and enhanced bone resorption. (3) Estrogen binds to receptors on the surface of osteoclast precursor cells, inhibiting their further proliferation and differentiation. Estrogen also inhibits osteoclast apoptosis by inhibiting the Fas/FasL system.[20] However, in PMOP patients, with the decline of estrogen levels, its functional activities also decrease, eventually leading to the proliferation of osteoclasts and enhanced bone resorption. (4) Estrogen deficiency results in enhanced activity of T lymphocytes and increased levels of inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-17, and tumor necrosis factor α (TNF-α).[21,22] These inflammatory factors stimulate T cells, B cells, stromal cells and osteoblasts to produce RANKL and M-CSF. RANKL and M-CSF bind to corresponding receptors on the surface of osteoclast precursor cells to promote osteoclast proliferation and differentiation. Under normal physiological conditions, B cells can produce approximately 40–60% of the total bone marrow-derived osteoprotegerin (OPG), competitively binding to RANKL and inhibiting osteoclast differentiation. However, previous studies have indicated that the number of B lymphocytes, specifically B lymphocytes ($CD19^+$), memory B lymphocytes ($CD19^+$/$CD27^+$), memory B lymphocytes expressing CD38 ($CD19^+$/$CD27^+$/$CD5^-$/$CD38^+$), and $RANK^+$ memory B ($CD19^+$/$CD27^+$/$RANK^+$) lymphocytes, is reduced in osteoporotic women.[23] In summary, estrogen deficiency can inhibit osteoblast formation and promote osteoclast proliferation and differentiation.

Besides estrogen, testosterone, cortisol, parathyroid hormone (PTH), and thyroid hormones also influence the metabolism of osteoblasts and osteoclasts. Testosterone, the primary androgen produced mainly by the testes, plays a role in bone tissue by promoting osteoblasts to synthesize and deposit new bone. This contributes to increased bone density and mass, maintaining skeletal strength and stability. Testosterone also inhibits osteoclast activity in bone tissue, thereby reducing bone resorption (Normal bone physiology, remodeling and its hormonal regulation). Cortisol, a glucocorticoid steroid hormone produced by the adrenal cortex, induces apoptosis and dysfunction in osteoblasts and bone cells by inhibiting RUNX2, bone morphogenetic protein, and Wnt signaling pathways. In post-menopausal women, cortisol levels tend to increase.[24] Additionally, thyroid hormones play a crucial regulatory role in skeletal development and bone remodeling. The thyroid releases triiodothyronine (T3), which binds to thyroid hormone receptor α to further mediate increased expression of osteoblast-related genes in bone tissue while suppressing the expression of osteoclast-related genes, thereby inhibiting osteoclast formation and activity.[25] After menopause, thyroid function declines, resulting in reduced thyroid hormone secretion.[26] Thyroid-stimulating hormone (TSH), a glycoprotein hormone produced by the anterior pituitary thyrotrophs, plays a significant role in regulating thyroid development and function. In vitro, TSH inhibits osteoclast differentiation, leading to reduced numbers of tartrate-resistant acid phosphatase-positive cells and decreased expression of tartrate-resistant acid phosphatase, matrix metalloproteinase 9, and protease K in RAW264.7 cells.[27] The results confirm that TSH, at least partially, increases bone volume, improves bone microstructure, and enhances bone strength by inhibiting osteoclast formation. However, some studies have also shown that TSH inhibits osteoblast differentiation and the expression of type I collagen independently of Runx2 and osterix by reducing the activity of Wnt and VEGF signaling pathways. The findings from these studies have produced conflicting results, indicating that TSH may enhance, inhibit, or have no effect on osteoblast differentiation and function.[28] Hormonal regulation of bone homeostasis is crucial, but in the context of PMOP, the lack of estrogen remains the primary and most significant contributing factor.

Physiological Characteristics and Expansion Mechanism of BMAT in PMOP

The expansion of BMAT in PMOP is closely associated with aging and estrogen deficiency. With increasing age, there is an imbalance in the differentiation of BMSCs, characterized by reduced osteogenesis and increased adipogenic differentiation. The number and proliferative potential of BMSCs also decline, contributing to age-related defects in osteoblast quantity and function.[29] During the aging process, the self-renewal capacity of BMSCs is impaired, as evidenced by downregulation of stemness-related genes such as OCT4, SOX2, and NANOG, and upregulation of aging-related genes like Cdkn1a (also known as p21, Cip1, and Waf1), Cdkn2a (encoding mouse p16 Ink4a and p19 Arf, and human p14 Arf), and Cdkn2b (encoding p14 Ink4b and p15 Ink4b).[30–32] BMSC aging, including the dysregulation of lineage commitment in the aging bone marrow microenvironment, is critically involved in the pathogenesis of osteoporosis.[33,34] Estrogen inhibits the adipogenic differentiation of BMSCs, but in patients with PMOP, this functional activity decreases with the decline of estrogen levels.[35] With advances in single-cell transcriptome analysis, marrow adipogenic lineage precursors expressing specific markers for adipocytes have been identified as a major cellular component of BMAT.[36] In addition to its role in fat storage, BMAT is intricately associated with skeletal growth, metabolism, and regulation of the bone marrow microenvironment. As one of the most influential factors in BMAT generation, estrogen has received considerable attention (Table 1), particularly in PMOP. In order to better simulate PMOP, the researchers established an animal model by removing the ovaries of rats. The results showed that the abnormal accumulation of BMAT was negatively correlated with osteoblastogenesis and positively correlated with osteoclastogenesis.[20] Beekman KM et al randomly divided 20 14-week-old female C3H/HeJ mice into two groups, which underwent sham surgery or ovariectomy (OVX), respectively, and continued feeding for four weeks before being euthanized. The BMAT volume fraction (BMAT volume/bone marrow volume) was detected by polyoxometalate-based contrast-enhanced nano-computed tomography, and the BMAT volume fraction in the OVX group was found to be larger than the sham surgery group.[37] Another study also had consistent findings.[38] A study was conducted on 58 postmenopausal females (age 49.2–77.4 years), including 24 patients with normal bone density, 19 with osteopenia, and 15 with osteoporosis. The researchers used a modified Dixon technique to measure vertebral marrow fat fraction and demonstrated that the bone marrow fat content was higher in subjects with osteopenia and osteoporosis compared to those with normal bone density.[39] Whether in animal models or clinical trials, the negative correlation between BMAT and bone mass suggests its crucial role in

Table 1 Effect of Estrogen on BMAT Formation

Research Subjects	Estrogen Level	Study Group	BMAT Variation	Ref.
Human	Deficiency	N=145, Females; N=114, males; age range, 62–90 years)	↑: Vertebral marrow fat content between 55 and 65 years of age	[40]
Mice	Deficiency	N=4-8, sham group; N=4-8, OVX group	Compared to sham group, OVX group: ↑: BMAT of tibia bone	[41]
Mice	Deficiency	Ovary-intact group; OVX group	Compared to Ovary-intact group, OVX group: ↑: BMAT	[42]
Human	Replacement	Postmenopausal osteoporotic women (mean age, 64 years) N=27, placebo group; N=29, transdermal estradiol group (0.1 mg/d, n = 29) for 1 year	Compared to transdermal estradiol group, placebo group: ↓: Accumulation of BMAT in iliac crest; ↓: Bone marrow adipocytes (BMAs) size ↑: BMAs number	[43]
Mice	Replacement	N=6, gonadally intact group; N=6, OVX group; N=6, OVX+ estratien-3,17-β-diol	Compared to gonadally intact group, OVX group: ↓: BMAT	[44]
Human	Replacement	N=6, postmenopausal women (50–60 years) + 17-β estradiol	By comparing the physiological indicators before and after oral administration of 17-β estradiol: ↓: Vertebral bone marrow after oral	[45]

Notes: "↑"indicates increase or addition; "↓"indicates decrease or reduction.

PMOP. Before determining the role of BMAT in the pathology of PMOP, it is necessary to understand the molecular mechanism of the abnormal expansion of BMAT following estrogen withdrawal.

Origin, Classification, and Development

BMAT is homologous to osteoblasts and originates from BMSCs. BMSCs are identified by lineage tracing and flow cytometry as a $Prx1^{+}Osx1^{+}$ leptin receptor $(LepR)^{+}$ $Nestin^{+}$ $CD45^{-}$ $CD31^{-}$ $Sca1^{+}$ cell population. It differentiates sequentially into early mesenchymal progenitors, late mesenchymal progenitors and lineage-committed progenitors. Adipogenic progenitor cells expressing $CD31^{-}$ $CD45^{-}$ $Sca1^{+}$ $CD24^{-}$ are differentiated from this pathway. Under the regulation of transcription factors Zfp521, Zfp423, peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT-enhancer-binding protein α (C/EBPα)/C/EBPβ, adipogenic progenitor cells finally differentiate into adipocytes.[46] BMATs are classified into regulatory and constitutive types based on their morphology. Regulatory BMAs are smaller in size, enriched in the proximal and central parts of the bone, and usually form a generally perivascular niche with endothelial cells, perivascular progenitor cells, osteoblasts, and granulocyte/macrophage lineage cells. Constitutive BMAs are larger, distributed in the distal bone, and have histologically dense adipocyte clusters.[47] Both types of BMAT are absent at birth. The bone marrow in infancy is mainly composed of HSCs. As the infant ages, the fat cells in the bone marrow increase dramatically, and by age 25, BMAT accounts for 50–70% of the total bone marrow volume.[48] After that, BMAT has continued to increase at a slow rate.[49] Notably, the fat content of the spinal marrow in women over 65 years old is about 10% higher than that of men of the same age due to estrogen deficiency. In addition, expansion of the BMAT generally occurs from the distal bones of the extremities and then progresses to the proximal bones,[50] gradually replacing the red marrow in the bone cavity with the yellow marrow.[40]

Estrogen Deficiency-Induced BMAT Expansion

Recently, many clinical and animal experiments have observed that decreased estrogen levels are related to the abnormal accumulation of BMAT (Table 1). With the deepening of research, its internal mechanism was gradually revealed. Studies have shown that estradiol inhibits adipogenesis in bone marrow stromal cell line ST 2, and its mechanism is realized by inducing the expression of connective tissue growth factor-mediated by TGF-β.[51] Estrogen receptors can also be directly involved in the differentiation of BMSCs into osteoblasts or adipocytes,[52] and silencing estrogen receptors can induce the proliferation of BMAs.[53] Thus, estrogen can inhibit the adipogenic differentiation of BMSCs. In the case of menopausal estrogen deficiency, the effect of inhibiting the adipogenic differentiation of BMSCs decreases, resulting in abnormal accumulation of BMAT. Additionally, estrogen inhibits the production of osteosclerostin by bone cells. Osteosclerostin levels are elevated in PMOP patients.[15] High levels of osteosclerostin inhibit the formation of osteoblasts via inhibiting the Wnt signaling pathway, promoting the adipogenic differentiation of BMSCs and the BMAT formation. Moreover, estrogen deficiency stimulates the immune system to produce the inflammatory factor TNF-α. TNF-α inhibits osteogenesis and enhances adipogenesis by upregulating the expression of P2 Y2 receptors in BMSCs.[54] Meanwhile, TNF-α activating NF-κB signaling inhibits the transcription of Runx2 mRNA in BMSCs, leading to BMAT amplification.[55] Therefore, menopausal estrogen deficiency has a driving effect on abnormal accumulation of BMAT.

The formation and expansion of BMAT are influenced not only by estrogen deficiency and aging but also by environmental, genetic, and nutritional factors. Studies had shown that regulatory BMAT in the tibia disappeared after 21 days of cold exposure, whereas constitutive BMAT remained unaffected.[56] Mice with type 4 congenital generalized lipodystrophy lost regulatory BMAT, while mice with type 3 congenital generalized lipodystrophy retained both regulatory and constitutive BMAT.[56] Furthermore, high-fat diet-induced obese mice exhibited greater BMAT deposition in the proximal femur compared to lean mice, primarily due to an increase in the number and size of BMAs.[57–59] In both type 1 and type 2 diabetes patients, an expansion of regulatory BMAT was observed.[60–62] Conversely, caloric restriction and exercise significantly reduced BMAT content.[57,63]

Regulation of Bone Metabolism by BMAT in PMOP

The pathological characteristics of PMOP include a decrease in bone density, bone quality and bone mass. It is positive correlation with BMAT volume. This positive regulatory relationship implies that BMAT could be a pivotal target for

preventing and treating PMOP. In vitro studies demonstrated that osteoblast proliferation and differentiation are inhibited when osteoblasts are co-cultured with BMSC-derived BMAs.[64] BMAs drive osteoblasts towards an adipocyte phenotype when extracellular vesicles containing adipogenic transcription factors are added as variables to the culture medium.[65] The adverse effect of BMAT on osteoblasts has piqued the interest of numerous researchers. Jessica A. Keune demonstrated the beneficial effects of BMAT deficiency on bone formation using BMAT-deficient $Kit^{W/W-v}$ mice.[66] We learned that BMA induces PPARγ activation in BMSCs, preosteoblasts and osteoblasts through free fatty acids production. PPARγ is a key factor in the differentiation of BMSCs into adipocytes. Activated PPARγ inhibits the activity of Runx2 mRNA and stimulates the further transformation of osteoblasts into adipocytes.[67,68] PPARγ plays a crucial role in the adipogenic differentiation of BMSCs, and inhibiting its activity is beneficial in reducing abnormal BMAT accumulation and improving bone mass and quality in PMOP. Previous studies have demonstrated that bisphenol a diglycidyl ether (BADGE) significantly reduces bone marrow adiposity and enhances osteogenic capacity and bone mass in male C57 BL/6 mice. However, there are also research results that contradict the above conclusion. BADGE did not show significant improvement in trabecular microarchitecture, biomechanical strength, and dynamic histomorphometric parameters in OVX rats.[69] Beekman KM et al, using fourteen-week-old female C3H/HeJ mice as study subjects and establishing an animal model through ovariectomy, sought to validate if PPARγ inhibition can prevent OVX -induced increase in BMAT and bone loss. The results showed that the PPARγ antagonist GW9662 had no effect on BMAT or bone volume.[70] This suggests that BMAT accumulation might be independent of PPARγ, and inhibiting PPARγ may not prevent bone loss.[71] The role of PPARγ in BMAT formation requires further exploration and confirmation. In addition, palmitic acid produced by BMA, the most prevalent fatty acid secreted by adipocytes in vitro, is taken up in the femur, tibia, and calvaria[72] and has a deleterious effect on osteoblast differentiation, bone nodule formation and mineralization.[73] In recent years, research has revealed that BMAs can directly produce RANKL. Upon binding to the RANK receptors on the surface of osteoclasts, this leads to the promotion of osteoclast proliferation and exacerbation of bone loss.[74,75] The above in vitro results illustrated the negative regulatory effect of BMAT on bone remodeling, but this effect needs to be further verified in vivo. An increasing number of animal experiments and clinical data have demonstrated that BMAT can regulate bone metabolism through the secretion of adipokines, cytokines, and the immune system.

Adipokines

BMAT can secrete a series of Adipokines, including leptin and adiponectin.[76] Leptin promotes the proliferation and differentiation of osteoblasts and increases the expression of OPG in osteoblasts,[4,49,77] further reducing the level of RANKL and inhibiting the activation of osteoblast-dependent osteoclasts. Serotonin is a neurotransmitter, and elevated levels of serotonin lead to decreased bone density, while leptin inhibits serotonin synthesis.[77] Furthermore, central leptin administration in ob/ob mice found that leptin can restore bone mass to control levels, proving that leptin's regulation on bone metabolism is positive. However, there are research findings that contradict the preceding conclusions. The corresponding receptors on hypothalamic VMH neurons activated the sympathetic nervous system (SNS) in response to leptin. Activated SNS inhibits cyclic AMP responsed element-binding protein -mediated osteoblast proliferation through signal transduction,[78] enhanced RANKL expression, and promoted osteopenia. Leptin reduced osteogenesis by activating the Jak2/Stat3 signaling pathway in bone marrow stromal cells.[79] Compared to premenopausal women, postmenopausal women showed an elevation in leptin levels,[80] especially in obese women.[81] Adiponectin is a hormone mainly secreted by adipocytes, which plays an important role in regulating energy metabolism and insulin sensitivity. Recently, many studies reported the regulatory effect of adiponectin on bone metabolism. Adiponectin can stimulate osteoblast formation and inhibit BMSC adipogenic differentiation, inhibiting SNS activity and promoting bone formation.[82–84] However, a study demonstrated that adiponectin reduces OPG production, increases RANKL levels, and promotes bone resorption by regulating the AdipoR 1/p38/MAPK pathway.[85] Compared to premenopausal women, contradictory reports exist regarding adiponectin levels in postmenopausal women: some studies have reported a decrease in serum adiponectin levels,[86] while others have found no change[87] or even detected an increase in serum adiponectin concentration.[88] However, in postmenopausal obese women, serum adiponectin levels were significantly lower than in non-obese women.[89] At present, the positive or negative regulatory effects of leptin and adiponectin on bone metabolism are controversial, and further extensive animal or clinical experiments are needed to investigate.

Cytokines and the Immune System

BMAT regulates PMOP by secreting cytokines (Figure 3). In vivo, BMAT secretes a series of cytokines, including IL-1β, IL-6 and TNF-α.[90,91] In postmenopausal women, estrogen deficiency similarly stimulates $CD4^+$ T cell dysregulation and induces elevated levels of inflammatory cytokines in the circulatory system, especially TNF-α.[54] IL-1β, TNF-α and IL-6 promote the proliferation and differentiation of osteoclasts. Additionally, IL-1β-induced osteoclasts have a very high level of resorption activity.[92] IL-1β binds to the corresponding receptors on the surface of osteoclasts and recruits MyD88, IL-1 receptor-associated kinase (IRAK), and TNF receptor-associated factor 6 (TRAF-6), which activates the downstream NF-κB and MAPK pathways promoting the proliferation and differentiation of osteoclasts.[93] TNF-α is one of the most potent osteoclast factors. TNF-α binds to the osteoclast surface receptor TNFR2 and induces the recruitment of TRAF 6, activating downstream NF-κB and MAPK pathways. Both pathways drive NFATc 1 activation, stimulating osteoclastogenesis.[94] IL-6 is different from the above two proinflammatory factors, because it stimulates osteoclast formation indirectly. IL-6 activates gp 130 and IL-6 receptor γ on the surface of osteoblasts, stimulating the production of downstream effector RANKL. The resulting effectors can directly activate osteoclast activity in a paracrine manner.[95] Additionally, BMAT can directly secrete M-CSF and RANKL. M-CSF activates monocytes in the bone marrow, promoting their differentiation into osteoclast precursor cells. RANKL binds to the RANK receptor on the surface of osteoclast precursor cells, triggering signal transduction pathways that promote their differentiation into mature osteoclasts.

BMAT directly or indirectly mediates the immune system to regulate PMOP by secreting cytokines (Figure 4). IL-1β, IL-6 and TNF-α activate immune cells, mainly including T lymphocytes, B lymphocytes, macrophages and neutrophils, and mediate the immune system to further regulate PMOP. Firstly, TNF-α promotes the differentiation of $CD4^+$ T helper (Th) cells 17[96] so that the content of Th 17 cells in the bone marrow of OVX mice gradually increases.[97] IL-17 secreted

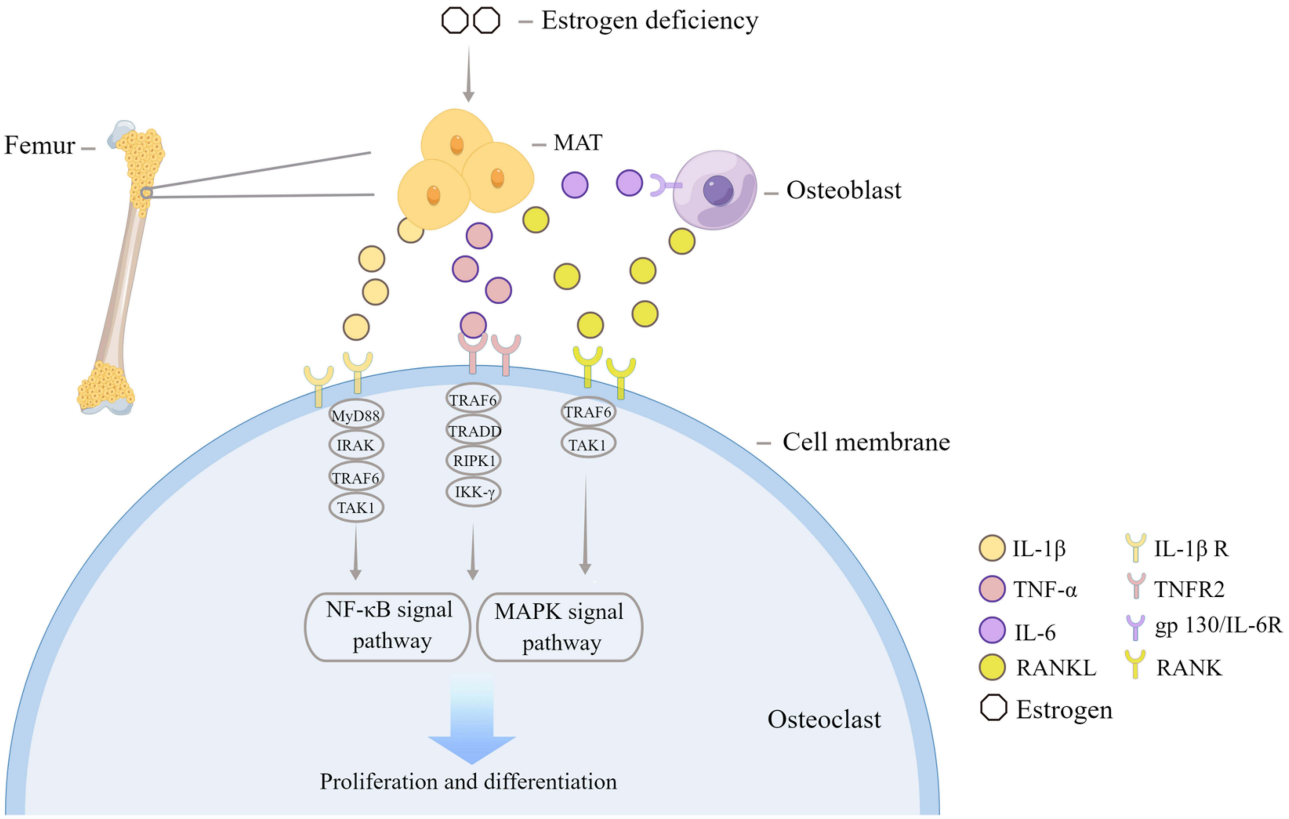

Figure 3 Bone marrow adipose tissue (BMAT) regulates osteoclast formation by secreting cytokines. BMAT can secrete interleukin (IL)-1β, IL-6, tumor necrosis factor-alpha (TNF-α) and RANKL. IL-1β and TNF-α bind to corresponding receptors on the surface of osteoclasts and activate downstream NF-κB and MAPK signaling pathways, regulating their proliferation and differentiation. IL-6 further stimulates the production of RANKL by activating gp 130 and IL-6 receptor γ on the surface of osteoblasts and indirectly promotes osteoclastogenesis. RANKL binds to its corresponding receptor RANK on the surface of osteoclasts, further promoting osteoclast proliferation and differentiation. The figure was created using Figdraw 1.0 (www.figdraw.com). The export authorization code for Figure 1 is ID: SIUUAbae3b.

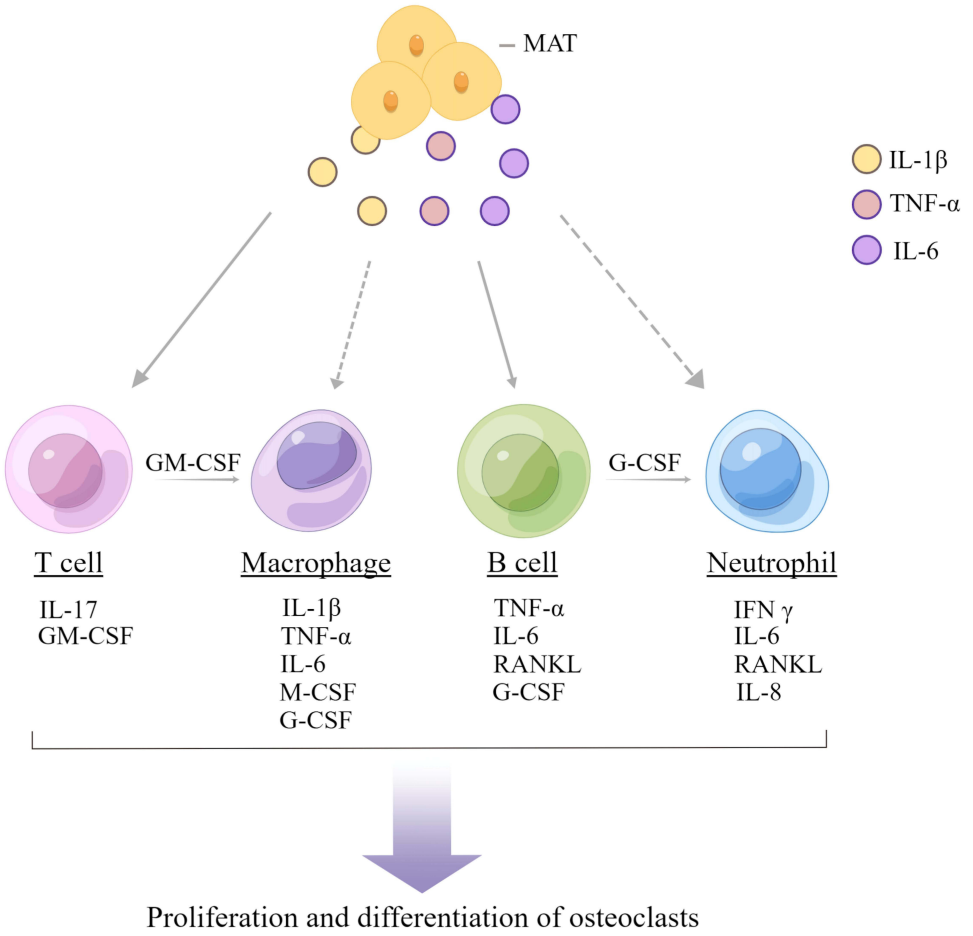

Figure 4 Bone marrow adipose tissue (BMAT) mediates immune system regulation of osteoclast formation. BMAT directly or indirectly activates T cells, B cells, macrophages, and neutrophils by secreting interleukin (IL)-1β, IL-6, and tumor necrosis factor α (TNF-α). Cytokines secreted by immune cells further act on the proliferation and differentiation of osteoclasts. The figure was created using Figdraw 1.0 (www.figdraw.com). The export authorization code for Figure 1 is ID: UIAUS15135.

by Th17 cells upregulates RANK on osteoclast progenitors, increasing their sensitivity to RANKL stimulation.[98] Furthermore, blocking IL-17 signaling prevented OVX-induced bone loss,[99] suggesting that cytokines secreted by T cells play an important role in the pathological process of PMOP. Secondly, TNF-α, as a B lymphocyte growth factor, promotes their proliferation and differentiation. IL-6 also has this effect.[100] Activated B cells secrete a series of cytokines: IL-6, TNF-α and granulocyte colony-stimulating factor (G-CSF). G-CSF promotes the proliferation of osteoclast progenitor cells.[101] B lymphocytes secrete RANKL under inflammatory conditions, indirectly stimulating osteoclast formation. In addition, as a vital part of the immune system, macrophages can be activated by granulocyte macrophage colony-stimulating factor (GM-CSF) produced by T cells, releasing cytokines: IL-1β, IL-6, TNF-α, M-CSF and G-CSF. These cytokines promote the production and differentiation of osteoclasts in different ways, further aggravating PMOP. Finally, G-CSF induces neutrophil expansion. The expanded neutrophils produce IFNγ, IL-6, RANKL, and IL-8, inducing osteoclast formation and promoting bone resorption.[102] BMAT indirectly regulates the effect of PMOP through the immune system, revealing that BMAT is likely to become a new target for treating PMOP.

Potential Strategies for the Prevention or Treatment of PMOP Through BMAT

As a critical regulatory factor in PMOP, targeting BMAT has become a potential approach for its prevention or treatment. PPARγ, as a key factor in the differentiation of MSCs into adipocytes, its positive or negative regulation of BMAT generation is not yet clear based on current research results, requiring further exploration and verification. As a bone formation negative

regulator, SOST has been shown to significantly reduce the elevated BMAT content in the OVX model through its knockout or by using antibodies to inhibit SOST.[103,104] Among them, the monoclonal SOST antibody romosozumab has been approved by the Food and Drug Administration for the treatment of PMOP.[105] Modified and functionalized nanoparticles with biotargeting capabilities, such as gold nanoparticles, have been shown to promote BMSCs' osteogenic differentiation and inhibit adipogenic differentiation by activating the p38/MAPK or ERK/MAPK signaling pathways to exert their effects.[106–110] In addition, treatment with senolytics such as dasatinib (Generic drug: a tyrosine kinase inhibitor) and quercetin (Flavonol: possessing antioxidant and chelating abilities) for 24 hours increased the proliferation rate of aged mouse BMSCs from 30% to 40%, without affecting the proliferation rate of young mouse BMSCs. Dasatinib and quercetin treatment can enhance the osteogenic capacity of aged BMSCs.[111,112] The bone marrow niche also provides cues that regulate BMSCs lineage commitment. Local elevation of prostaglandin E2 triggered EP4 receptors in sensory nerves and suppressed adipogenesis.[113] Mechanical forces facilitated osteogenic differentiation of BMSCs and suppressed BMAs production.[114] During mechanical loading, actin modulation induced BMSCs differentiation via the ERK and AKT pathways.[115] Endocrine molecules also impact BMSCs differentiation, including estrogen, parathyroid hormone, and leptin.

Furthermore, commonly used anti-osteoporosis drugs such as teriparatide, zoledronic acid, can also reduce bone marrow adiposity. Teriparatide, one of the pharmacological agents used to treat PMOP, has been shown to inhibit adipogenesis. In a 12-month study involving PMOP patients (n = 135; mean age 64.1 ± 8.9 years) treated with 20μg/d teriparatide or placebo, it was found that patients receiving teriparatide experienced a significant reduction in BMAT content at 6 and 12 months.[6] This clinical trial indicates that despite teriparatide's typical targeting of osteoblastogenesis, it also affects BMAT levels, suggesting a novel therapeutic avenue. Similarly, zoledronic acid is noted for its ability to reduce BMAT volume.[38] In a randomized clinical trial involving 100 postmenopausal women with osteoporosis, participants were randomly assigned to receive either zoledronic acid (5 mg) or placebo. The results revealed that after 12 months of treatment, women receiving zoledronic acid exhibited a notable decrease in BMAT volume.[5]

Conclusion and Outlook

Estrogen deficiency, the most prominent physiological characteristic of postmenopausal women, is a key factor leading to abnormal bone metabolism. This metabolic disorder typically manifests as reduced bone formation and increased bone resorption. The resulting disrupted bone homeostasis causes significant loss of bone minerals, decreased bone density, and increased bone fragility, ultimately leading to PMOP The development and progression of PMOP are often accompanied by an abnormal accumulation of BMAT. BMAT can regulate the secretion of IL-1β, IL-6, and TNF-α or mediate the immune system, directly or indirectly promoting the proliferation and differentiation of osteoclasts, thereby exacerbating PMOP. Given the negative correlation between BMAT content and PMOP severity, BMAT represents a potential novel target for PMOP treatment. Finding effective ways to reduce BMAT content or inhibit BMAT formation in postmenopausal women is a key area of future research, necessitating extensive animal experiments and human studies for further exploration.

Funding

This work was financially supported by "The mechanism study of qing-E Pill mediated BMP-Smads signaling pathway in regulating postmenopausal metabolic bone loss" National Natural Science Foundation of China Youth Science Fund Project 82004098.

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Ducy P, Amling M, Takeda S, et al. Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. *Cell*. 2000;100(2):197–207. doi:10.1016/s0092-8674(00)81558-5
2. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. *Lancet*. 2011;377(9773):1276–1287. doi:10.1016/S0140-6736(10)62349-5

3. Li S, Jiang H, Wang B, et al. Effect of Leptin on Marrow Adiposity in Ovariectomized Rabbits Assessed by Proton Magnetic Resonance Spectroscopy. *J Comput Assist Tomogr*. 2018;42(4):588–593. doi:10.1097/RCT.0000000000000725
4. Beekman KM, Veldhuis-Vlug AG, den Heijer M, et al. The effect of raloxifene on bone marrow adipose tissue and bone turnover in postmenopausal women with osteoporosis. *Bone*. 2019;118:62–68. doi:10.1016/j.bone.2017.10.011
5. Yang Y, Luo X, Yan F, et al. Effect of zoledronic acid on vertebral marrow adiposity in postmenopausal osteoporosis assessed by MR spectroscopy. *Skeletal Radiol*. 2015;44(10):1499–1505. doi:10.1007/s00256-015-2200-y
6. Yang Y, Luo X, Xie X, et al. Influences of teriparatide administration on marrow fat content in postmenopausal osteopenic women using MR spectroscopy. *Climacteric: the Journal of the International Menopause Society*. 2016;19(3):285–291. doi:10.3109/13697137.2015.1126576
7. Capulli M, Paone R, Nj R. Osteoblast and osteocyte: games without frontiers. *Archives of Biochemistry and Biophysics*. 2014;561:3–12. doi:10.1016/j.abb.2014.05.003
8. Yang F, Yang D, Tu J, Zheng Q, Cai L, Wang L. Strontium enhances osteogenic differentiation of mesenchymal stem cells and in vivo bone formation by activating Wnt/catenin signaling. *Stem Cells*. 2011;29(6):981–991. doi:10.1002/stem.646
9. Boskey AL. Bone composition: relationship to bone fragility and antiosteoporotic drug effects. *Bonekey Rep*. 2013;2:447. doi:10.1038/bonekey.2013.181
10. Sharifi M, Ereifej L, EMJRiE L, Disorders M. Sclerostin and skeletal health. *Reviews in Endocrine & Metabolic Disorders*. 2015;16(2):149–156. doi:10.1007/s11154-015-9311-6
11. Bonewald LF. The amazing osteocyte. *J Bone Miner Res*. 2011;26(2):229–238. doi:10.1002/jbmr.320
12. Teitelbaum SL. Bone Resorption by Osteoclasts. *Science*. 2000;289(5484):1504–1508. doi:10.1126/science.289.5484.1504
13. Edwards JR, Mundy GR. Advances in osteoclast biology: old findings and new insights from mouse models. *Nat Rev Rheumatol*. 2011;7(4):235–243. doi:10.1038/nrrheum.2011.23
14. Zha L, He L, Liang Y, et al. TNF-alpha contributes to postmenopausal osteoporosis by synergistically promoting RANKL-induced osteoclast formation. *Biomed Pharmacother*. 2018;102:369–374. doi:10.1016/j.biopha.2018.03.080
15. Bhattacharyya S, Pal S, Chattopadhyay N. Targeted inhibition of sclerostin for post-menopausal osteoporosis therapy: a critical assessment of the mechanism of action. *Eur J Pharmacol*. 2018;826:39–47. doi:10.1016/j.ejphar.2018.02.028
16. Khalid AB, Krum SA. Estrogen receptors alpha and beta in bone. *Bone*. 2016;87:130–135. doi:10.1016/j.bone.2016.03.016
17. Thapa S, Nandy A, Rendina-Ruedy EJFi P. Endocrinal metabolic regulation on the skeletal system in post-menopausal women. *Frontiers in Physiology*. 2022;13:1052429. doi:10.3389/fphys.2022.1052429
18. Locatelli V, VEJIjoe B. Effect of GH/IGF-1 on bone metabolism and osteoporosis. *International Journal of Endocrinology*. 2014;2014. doi:10.1155/2014/235060
19. Melville KM, Kelly NH, Khan SA, et al. Female mice lacking estrogen receptor-alpha in osteoblasts have compromised bone mass and strength. *Journal of Bone and Mineral Research: the Official Journal of the American Society for Bone and Mineral Research*. 2014;29(2):370–379. doi:10.1002/jbmr.2082
20. Nakamura T, Imai Y, Matsumoto T, et al. Estrogen prevents bone loss via estrogen receptor alpha and induction of Fas ligand in osteoclasts. *Cell*. 2007;130(5):811–823. doi:10.1016/j.cell.2007.07.025
21. Zhao R, Wang X, Feng F. Upregulated Cellular Expression of IL-17 by CD4+ T-Cells in Osteoporotic Postmenopausal Women. *Ann Nutr Metab*. 2016;68(2):113–118. doi:10.1159/000443531
22. Cenci S, Weitzmann MN, Roggia C, et al. Estrogen deficiency induces bone loss by enhancing T-cell production of TNF-alpha. *J Clin Invest*. 2000;106(10):1229–1237. doi:10.1172/JCI11066
23. Breuil V, Ticchioni M, Testa J, et al. Immune changes in post-menopausal osteoporosis: the Immunos study. *Osteoporosis International: a Journal Established as Result of Cooperation Between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2010;21(5):805–814. doi:10.1007/s00198-009-1018-7
24. Al-Rawaf HA, Alghadir AH, Sajdm G. Circulating MicroRNA expression, vitamin D, and hypercortisolism as predictors of osteoporosis in elderly postmenopausal women. *Cell*. 2021;2021.
25. Lademann F, Tsourdi E, Hofbauer LC, Rauner MJE, Endocrinology C. Diabetes. Thyroid hormone actions and bone remodeling–the role of the wnt signaling pathway. *Experimental and Clinical Endocrinology & Diabetes: Official Journal, German Society of Endocrinology [And] German Diabetes Association*. 2020;128(06/07):450–454. doi:10.1055/a-1088-1215
26. Bremner AP, Feddema P, Leedman PJ, et al. Age-related changes in thyroid function: a longitudinal study of a community-based cohort. *The Journal of Clinical Endocrinology and Metabolism*. 2012;97(5):1554–1562. doi:10.1210/jc.2011-3020
27. Zhang W, Zhang Y, Liu Y, et al. Thyroid-stimulating hormone maintains bone mass and strength by suppressing osteoclast differentiation. *Journal of Biomechanics*. 2014;47(6):1307–1314. doi:10.1016/j.jbiomech.2014.02.015
28. Gogakos AI, Bassett JD. Williams GRJAob, biophysics. *Thyroid and Bone*. 2010;503(1):129–136.
29. Bergman R, Gazit D, Kahn A, et al. Age-related changes in osteogenic stem cells in mice. *Journal of Bone and Mineral Research: the Official Journal of the American Society for Bone and Mineral Research*. 1996;11(5):568–577. doi:10.1002/jbmr.5650110504
30. Fafián-Labora J, Morente-López M, Sánchez-Dopico MJ, et al. Influence of mesenchymal stem cell-derived extracellular vesicles in vitro and their role in ageing. *Stem Cell Res*. 2020;11(1):1–12.
31. Li C, Chai Y, Wang L, et al. Programmed cell senescence in skeleton during late puberty. *Nature Commun*. 2017;8(1):1312.
32. Yang R, Chen J, Zhang J, et al. 1, 25-Dihydroxyvitamin D protects against age-related osteoporosis by a novel VDR-Ezh2-p16 signal axis. *Aging Cell*. 2020;19(2).
33. Li Y, Lu L, Xie Y, Chen X, Tian L, Liang Y. Interleukin-6 Knockout Inhibits Senescence of Bone Mesenchymal Stem Cells in High-Fat Diet-Induced Bone Loss. *Front Endocrinol (Lausanne)*. 2021;11.
34. Tencerova M, Frost M, Figeac F, et al. Obesity-associated hypermetabolism and accelerated senescence of bone marrow stromal stem cells suggest a potential mechanism for bone fragility. *Cell Rep*. 2019;27(7):2050–2062.e2056. doi:10.1016/j.celrep.2019.04.066
35. Rodríguez JP, Astudillo P, Rios S, Pino AM. Involvement of adipogenic potential of human bone marrow mesenchymal stem cells (MSCs) in osteoporosis. *Current Stem Cell Research & Therapy*. 2008;3(3):208–218. doi:10.2174/157488808785740325
36. Zhong L, Yao L, Seale P, Ljbp Q, Endocrinology RC. Marrow adipogenic lineage precursor: a new cellular component of marrow adipose tissue. *Best Practice & Research. Clinical Endocrinology & Metabolism*. 2021;35(4):101518. doi:10.1016/j.beem.2021.101518

37. Beekman KM, Zwaagstra M, Veldhuis-Vlug AG, et al. Ovariectomy increases RANKL protein expression in bone marrow adipocytes of C3H/HeJ mice. *American Journal of Physiology. Endocrinology and Metabolism*. 2019;317(6):E1050–E1054. doi:10.1152/ajpendo.00142.2019
38. Li GW, Xu Z, Chang SX, et al. Influence of early zoledronic acid administration on bone marrow fat in ovariectomized rats. *Endocrinology*. 2014;155(12):4731–4738. doi:10.1210/en.2014-1359
39. Li GW, Xu Z, Chen QW, et al. Quantitative evaluation of vertebral marrow adipose tissue in postmenopausal female using MRI chemical shift-based water-fat separation. *Clin Radiol*. 2014;69(3):254–262. doi:10.1016/j.crad.2013.10.005
40. Griffith JF, Yeung DK, Ma HT, Leung JC, Kwok TC, Leung PC. Bone marrow fat content in the elderly: a reversal of sex difference seen in younger subjects. *J Magn Reson Imaging*. 2012;36(1):225–230. doi:10.1002/jmri.23619
41. Lecka-Czernik B, Stechschulte LA, Czernik PJ, Sherman SB, Huang S, Krings A. Marrow Adipose Tissue: skeletal Location, Sexual Dimorphism, and Response to Sex Steroid Deficiency. *Front Endocrinol (Lausanne)*. 2017;8:188. doi:10.3389/fendo.2017.00188
42. Iwaniec UT, Turner RT. Failure to generate bone marrow adipocytes does not protect mice from ovariectomy-induced osteopenia. *Bone*. 2013;53(1):145–153. doi:10.1016/j.bone.2012.11.034
43. Syed FA, Oursler MJ, Hefferanm TE, Peterson JM, Riggs BL, Khosla S. Effects of estrogen therapy on bone marrow adipocytes in postmenopausal osteoporotic women. *Osteoporos Int*. 2008;19(9):1323–1330. doi:10.1007/s00198-008-0574-6
44. Elbaz A, Rivas D, Duque G. Effect of estrogens on bone marrow adipogenesis and Sirt1 in aging C57BL/6J mice. *Biogerontology*. 2009;10(6):747–755. doi:10.1007/s10522-009-9221-7
45. Limonard EJ, Veldhuis-Vlug AG, van Dussen L, et al. Short-Term Effect of Estrogen on Human Bone Marrow Fat. *J Bone Miner Res*. 2015;30(11):2058–2066. doi:10.1002/jbmr.2557
46. Ambrosi TH, Schulz TJ. The emerging role of bone marrow adipose tissue in bone health and dysfunction. *J Mol Med (Berl)*. 2017;95(12):1291–1301. doi:10.1007/s00109-017-1604-7
47. Craft CS, Li Z, MacDougald OA, Scheller EL. Molecular Differences Between Subtypes of Bone Marrow Adipocytes. *Current Molecular Biology Reports*. 2018;4(1):16–23. doi:10.1007/s40610-018-0087-9
48. Fazeli PK, Horowitz MC, MacDougald OA, et al. Marrow Fat and Bone—New Perspectives. *J Clin Endocrinol Metab*. 2013;98(3):935–945. doi:10.1210/jc.2012-3634
49. Justesen J, Stenderup K, Ebbesen E, Mosekilde L, Steiniche T, Kassem MJB. Adipocyte tissue volume in bone marrow is increased with aging and in patients with osteoporosis. *Biogerontology*. 2001;2(3):165–171. doi:10.1023/a:1011513223894
50. Blebea JS, Houseni M, Torigian DA, et al. Structural and functional imaging of normal bone marrow and evaluation of its age-related changes. *Semin Nucl Med*. 2007;37(3):185–194. doi:10.1053/j.semnuclmed.2007.01.002
51. Kumar A, Ruan M, Clifton K, Syed F, Khosla S, Oursler MJ. TGF-beta mediates suppression of adipogenesis by estradiol through connective tissue growth factor induction. *Endocrinology*. 2012;153(1):254–263. doi:10.1210/en.2011-1169
52. Wend K, Wend P, Drew BG, Hevener AL, Miranda-Carboni GA, Krum SA. ERalpha regulates lipid metabolism in bone through ATGL and perilipin. *J Cell Biochem*. 2013;114(6):1306–1314. doi:10.1002/jcb.24470
53. Rooney AM, van der Meulen MCH. Mouse models to evaluate the role of estrogen receptor alpha in skeletal maintenance and adaptation. *Ann N Y Acad Sci*. 2017;1410(1):85–92. doi:10.1111/nyas.13523
54. Du D, Zhou Z, Zhu L, et al. TNF-alpha suppresses osteogenic differentiation of MSCs by accelerating P2Y(2) receptor in estrogen-deficiency induced osteoporosis. *Bone*. 2018;117:161–170. doi:10.1016/j.bone.2018.09.012
55. Kaneki H, Guo R, Chen D, et al. Tumor Necrosis Factor Promotes Runx2 Degradation through Up-regulation of Smurf1 and Smurf2 in Osteoblasts. *J Biol Chem*. 2006;281(7):4326–4333. doi:10.1074/jbc.M509430200
56. Scheller EL, Doucette CR, Learman BS, et al. Region-specific variation in the properties of skeletal adipocytes reveals regulated and constitutive marrow adipose tissues. *Nature Communications*. 2015;6(1):7808. doi:10.1038/ncomms8808
57. Styner M, Pagnotti GM, McGrath C, et al. Exercise decreases marrow adipose tissue through ß-oxidation in obese running mice. *Journal of Bone and Mineral Research: the Official Journal of the American Society for Bone and Mineral Research*. 2017;32(8):1692–1702. doi:10.1002/jbmr.3159
58. Scheller EL, Khoury B, Moller KL, et al. Changes in skeletal integrity and marrow adiposity during high-fat diet and after weight loss. *Frontiers in Endocrinology*. 2016;7:102. doi:10.3389/fendo.2016.00102
59. Gevers EF, Loveridge N, Icje R. Bone marrow adipocytes: a neglected target tissue for growth hormone. *Endocrinology*. 2002;143(10):4065–4073. doi:10.1210/en.2002-220428
60. Botolin S, Lrje M. Bone loss and increased bone adiposity in spontaneous and pharmacologically induced diabetic mice. *Endocrinology*. 2007;148(1):198–205. doi:10.1210/en.2006-1006
61. Sulston RJ, Learman BS, Zhang B, et al. Increased circulating adiponectin in response to thiazolidinediones: investigating the role of bone marrow adipose tissue. *Frontiers in Endocrinology*. 2016;7:128. doi:10.3389/fendo.2016.00128
62. G-W L, Xu Z, Chen Q-W, Chang S-X, Tian Y-N, J-ZJSr F. The temporal characterization of marrow lipids and adipocytes in a rabbit model of glucocorticoid-induced osteoporosis. *Skeletal Radiology*. 2013;42(9):1235–1244. doi:10.1007/s00256-013-1659-7
63. Cawthorn WP, Scheller EL, Learman BS, et al. Bone marrow adipose tissue is an endocrine organ that contributes to increased circulating adiponectin during caloric restriction. *Cell Metabolism*. 2014;20(2):368–375. doi:10.1016/j.cmet.2014.06.003
64. Dong X, Bi L, He S, et al. FFAs-ROS-ERK/P38 pathway plays a key role in adipocyte lipotoxicity on osteoblasts in co-culture. *Biochimie*. 2014;101:123–131. doi:10.1016/j.biochi.2014.01.002
65. Martin PJ, Haren N, Ghali O, et al. Adipogenic RNAs are transferred in osteoblasts via bone marrow adipocytes-derived extracellular vesicles (EVs). *BMC Cell Biol*. 2015;16(1). doi:10.1186/s12860-015-0057-5.
66. Keune JA, Wong CP, Branscum AJ, Iwaniec UT, RTJSr T. Bone marrow adipose tissue deficiency increases disuse-induced bone loss in male mice. *Scientific Reports*. 2017;7(1):46325. doi:10.1038/srep46325
67. Li J, Liu X, Zuo B, Zhang L. The Role of Bone Marrow Microenvironment in Governing the Balance between Osteoblastogenesis and Adipogenesis. *Aging Dis*. 2016;7(4):514–525. doi:10.14336/AD.2015.1206
68. Elbaz A, Wu X, Rivas D, Gimble JM, Duque G. Inhibition of fatty acid biosynthesis prevents adipocyte lipotoxicity on human osteoblasts in vitro. *J Cell Mol Med*. 2010;14(4):982–991. doi:10.1111/j.1582-4934.2009.00751.x

69. Li G, Xu Z, Hou L, et al. Differential effects of bisphenol A diglicydyl ether on bone quality and marrow adiposity in ovary-intact and ovariectomized rats. *Aging Cell*. 2016;311(6):567.
70. Beekman KM, Veldhuis-Vlug AG, van der Veen A, et al. The effect of PPARγ inhibition on bone marrow adipose tissue and bone in C3H/HeJ mice. *American Journal of Physiology. Endocrinology and Metabolism*. 2019;316(1):E96–E105. doi:10.1152/ajpendo.00265.2018
71. Botolin S, LRJJocp M. Inhibition of PPARγ prevents type I diabetic bone marrow adiposity but not bone loss. *Journal of Cellular Physiology*. 2006;209(3):967–976. doi:10.1002/jcp.20804
72. Kushwaha P, Wolfgang MJ, Riddle RC. Fatty acid metabolism by the osteoblast. *Bone*. 2018;115:8–14. doi:10.1016/j.bone.2017.08.024
73. Gunaratnam K, Vidal C, Gimble JM, Duque G. Mechanisms of palmitate-induced lipotoxicity in human osteoblasts. *Endocrinology*. 2014;155(1):108–116. doi:10.1210/en.2013-1712
74. Hu Y, Li X, Zhi X, et al. RANKL from bone marrow adipose lineage cells promotes osteoclast formation and bone loss. *EMBO Rep*. 2021;22(7).
75. Yang J, Chen S, Zong Z, et al. The increase in bone resorption in early-stage type I diabetic mice is induced by RANKL secreted by increased bone marrow adipocytes. *Biochemical and Biophysical Research Communications*. 2020;525(2):433–439. doi:10.1016/j.bbrc.2020.02.079
76. Laharrague P, Larrouy D, Fontanilles AM, et al. High expression of leptin by human bone marrow adipocytes in primary culture. *FASEB J*. 1998;12(9):747–752. doi:10.1096/fasebj.12.9.747
77. Yadav VK, Oury F, Suda N, et al. A serotonin-dependent mechanism explains the leptin regulation of bone mass, appetite, and energy expenditure. *Cell*. 2009;138(5):976–989. doi:10.1016/j.cell.2009.06.051
78. Chen XX, Yang T. Roles of leptin in bone metabolism and bone diseases. *J Bone Miner Metab*. 2015;33(5):474–485. doi:10.1007/s00774-014-0569-7
79. Yue R, Zhou BO, Shimada IS, Zhao Z, SJJCsc M. Leptin receptor promotes adipogenesis and reduces osteogenesis by regulating mesenchymal stromal cells in adult bone marrow. *Cell Stem Cell*. 2016;18(6):782–796. doi:10.1016/j.stem.2016.02.015
80. Lecke SB, Morsch DM, PMJBJoM S, Research B. Leptin and adiponectin in the female life course. *Brazilian Journal of Medical and Biological Research = Revista Brasileira de Pesquisas Medicas e Biologicas*. 2011;44(5):381–387.
81. Khokhar KK, Sidhu S, GJEjoe K. Correlation between leptin level and hypertension in normal and obese pre-and postmenopausal women. *European Journal of Endocrinology*. 2010;163(6):873–878. doi:10.1530/EJE-10-0714
82. Lee HW, Kim SY, Kim AY, Lee EJ, Choi JY, Kim JB. Adiponectin stimulates osteoblast differentiation through induction of COX2 in mesenchymal progenitor cells. *Stem Cells*. 2009;27(9):2254–2262. doi:10.1002/stem.144
83. Williams GA, Wang Y, Callon KE, et al. In vitro and in vivo effects of adiponectin on bone. *Endocrinology*. 2009;150(8):3603–3610. doi:10.1210/en.2008-1639
84. Kajimura D, Lee HW, Riley KJ, et al. Adiponectin regulates bone mass via opposite central and peripheral mechanisms through FoxO1. *Cell Metab*. 2013;17(6):901–915. doi:10.1016/j.cmet.2013.04.009
85. Luo XH, Guo LJ, Xie H, et al. Adiponectin stimulates RANKL and inhibits OPG expression in human osteoblasts through the MAPK signaling pathway. *J Bone Miner Res*. 2006;21(10):1648–1656. doi:10.1359/jbmr.060707
86. Chu MC, Cosper P, Orio F, Carmina E, Lobo RA. Insulin resistance in postmenopausal women with metabolic syndrome and the measurements of adiponectin, leptin, resistin, and ghrelin. *American Journal of Obstetrics and Gynecology*. 2006;194(1):100–104. doi:10.1016/j.ajog.2005.06.073
87. Hong SC, Yoo SW, Cho GJ, et al. Correlation between estrogens and serum adipocytokines in premenopausal and postmenopausal women. *Menopause (New York, N.Y.)*. 2007;14(5):835–840. doi:10.1097/GME.0b013e31802cddca
88. Lee JM, Kim SR, Yoo SJ, Hong O, Son H, Imr CS. The relationship between adipokines, metabolic parameters and insulin resistance in patients with metabolic syndrome and type 2 diabetes. *The Journal of International Medical Research*. 2009;37(6):1803–1812. doi:10.1177/147323000903700616
89. Milewicz A, Jędrzejuk D, Dunajska K, Lwow FJM. Waist circumference and serum adiponectin levels in obese and non-obese postmenopausal women. *Cell*. 2010;65(3):272–275. doi:10.1016/j.maturitas.2009.11.008
90. Zupan J, Komadina R, JJJobs M. The relationship between osteoclastogenic and anti-osteoclastogenic pro-inflammatory cytokines differs in human osteoporotic and osteoarthritic bone tissues. *J Biomed Sci*. 2012;19:1–10.
91. Abildgaard J, Tingstedt J, Zhao Y, et al. Increased systemic inflammation and altered distribution of T-cell subsets in postmenopausal women. *PLoS One*. 2020;15(6):e0235174. doi:10.1371/journal.pone.0235174
92. Shiratori T, Kyumoto-Nakamura Y, Kukita A, et al. IL-1beta Induces Pathologically Activated Osteoclasts Bearing Extremely High Levels of Resorbing Activity: a Possible Pathological Subpopulation of Osteoclasts, Accompanied by Suppressed Expression of Kindlin-3 and Talin-1. *J Immunol*. 2018;200(1):218–228. doi:10.4049/jimmunol.1602035
93. Baud V, Liu Z-G, Bennett B, et al. Signaling by proinflammatory cytokines: oligomerization of TRAF2 and TRAF6 is sufficient for JNK and IKK activation and target gene induction via an amino-terminal effector domain. *Genes & Development*. 1999;13(10):1297–1308. doi:10.1101/gad.13.10.1297
94. Ono T, Nakashima T. Recent advances in osteoclast biology. *Histochem Cell Biol*. 2018;149(4):325–341. doi:10.1007/s00418-018-1636-2
95. Kwan Tat S, Padrines M, Theoleyre S, Heymann D, Fortun Y. IL-6, RANKL, TNF-alpha/IL-1: interrelations in bone resorption pathophysiology. *Cytokine Growth Factor Rev*. 2004;15(1):49–60. doi:10.1016/j.cytogfr.2003.10.005
96. Zheng Y, Sun L, Jiang T, Zhang D, He D, Nie H. TNFalpha promotes Th17 cell differentiation through IL-6 and IL-1beta produced by monocytes in rheumatoid arthritis. *J Immunol Res*. 2014;2014:385352. doi:10.1155/2014/385352
97. Yu M, Pal S, Paterson CW, et al. Ovariectomy induces bone loss via microbial-dependent trafficking of intestinal TNF+ T cells and Th17 cells. *J Clin Invest*. 2021;131(4). doi:10.1172/JCI143137.
98. Adamopoulos IE, C-c C, Geissler R, et al. Interleukin-17A upregulates receptor activator of NF-κB on osteoclast precursors. *J Biomed Sci*. 2010;12:1–11.
99. Tyagi AM, Mansoori MN, Srivastava K, et al. Enhanced immunoprotective effects by anti-IL-17 antibody translates to improved skeletal parameters under estrogen deficiency compared with anti-RANKL and anti-TNF-alpha antibodies. *J Bone Miner Res*. 2014;29(9):1981–1992. doi:10.1002/jbmr.2228
100. Aringer M, Smolen JS. SLE - Complex cytokine effects in a complex autoimmune disease: tumor necrosis factor in systemic lupus erythematosus. *Arthritis Res Ther*. 2003;5(4):172–177. doi:10.1186/ar770

101. Zhang Z, Yuan W, Deng J, et al. Granulocyte colony stimulating factor (G-CSF) regulates neutrophils infiltration and periodontal tissue destruction in an experimental periodontitis. *Mol Immunol*. 2020;117:110–121. doi:10.1016/j.molimm.2019.11.003
102. Fischer V, Haffner-Luntzer M. Interaction between bone and immune cells: implications for postmenopausal osteoporosis. *Semin Cell Dev Biol*. 2022;123:14–21. doi:10.1016/j.semcdb.2021.05.014
103. Li S, Huang B, Jiang B, Gu M, Yang X, Yin YJFi E. Sclerostin antibody mitigates estrogen deficiency-inducted marrow lipid accumulation assessed by proton MR spectroscopy. *Frontiers in Endocrinology*. 2019;10:159. doi:10.3389/fendo.2019.00159
104. Li X, Ominsky MS, Villasenor KS, et al. Sclerostin antibody reverses bone loss by increasing bone formation and decreasing bone resorption in a rat model of male osteoporosis. *Endocrinology*. 2018;159(1):260–271. doi:10.1210/en.2017-00794
105. Cheng C, Wentworth K, Shoback DMJARo M. New frontiers in osteoporosis therapy. *Annual Review of Medicine*. 2020;71:277–288. doi:10.1146/annurev-med-052218-020620
106. Gandhimathi C, Quek YJ, Ezhilarasu H, Ramakrishna S, Bay B-H, Srinivasan DKJIJo MS. Osteogenic differentiation of mesenchymal stem cells with silica-coated gold nanoparticles for bone tissue engineering. *International Journal of Molecular Sciences*. 2019;20(20):5135. doi:10.3390/ijms20205135
107. Mahmoud NS, Ahmed HH, Mohamed MR, et al. Role of nanoparticles in osteogenic differentiation of bone marrow mesenchymal stem cells. *Cytotechnology*. 2020;72(1):1–22. doi:10.1007/s10616-019-00353-y
108. Suh KS, Lee YS, Seo SH, Kim YS, EMJBter C. Gold nanoparticles attenuates antimycin A-induced mitochondrial dysfunction in MC3T3-E1 osteoblastic cells. *Biological Trace Element Research*. 2013;153(1–3):428–436. doi:10.1007/s12011-013-9679-7
109. Yi C, Liu D, Fong -C-C, Zhang J, MJAn Y. Gold nanoparticles promote osteogenic differentiation of mesenchymal stem cells through p38 MAPK pathway. *ACS nano*. 2010;4(11):6439–6448. doi:10.1021/nn101373r
110. Zhang D, Liu D, Zhang J, Fong C, Mjms Y, E C. Gold nanoparticles stimulate differentiation and mineralization of primary osteoblasts through the ERK/MAPK signaling pathway. *Materials Science & Engineering. C, Materials for Biological Applications*. 2014;42:70–77. doi:10.1016/j.msec.2014.04.042
111. Zhou Y, Xin X, Wang L, et al. Senolytics improve bone forming potential of bone marrow mesenchymal stem cells from aged mice. *NPJ Regenerative Med*. 2021;6(1):34.
112. Heim KE, Tagliaferro AR. Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships. *The Journal of Nutritional Biochemistry*. 2002;13(10):572–584. doi:10.1016/s0955-2863(02)00208-5
113. Hu B, Lv X, Chen H, et al. Sensory nerves regulate mesenchymal stromal cell lineage commitment by tuning sympathetic tones. *The Journal of Clinical Investigation*. 2020;130(7):3483–3498. doi:10.1172/JCI131554
114. Ozcivici E, Luu YK, Adler B, et al. Mechanical signals as anabolic agents in bone. *Nature Reviews. Rheumatology*. 2010;6(1):50–59. doi:10.1038/nrrheum.2009.239
115. Li R, Liang L, Dou Y, et al. Mechanical strain regulates osteogenic and adipogenic differentiation of bone marrow mesenchymal stem cells. *BioMed Res Int*. 2015;2015.