Obesity and lipid metabolism in the development of osteoporosis (Review)

XIAOCHUAN WANG[1*], CHI ZHANG[1*], GUANG ZHAO[2*], KEDA YANG[1] and LIN TAO[1]

[1]Department of Orthopedics, First Hospital of China Medical University, Shenyang, Liaoning 110001, P.R. China;
[2]Department of Orthopedics, Fourth Hospital of China Medical University, Shenyang, Liaoning 110165, P.R. China

Abstract. Osteoporosis is a common bone metabolic disease that causes a heavy social burden and seriously threatens life. Improving osteogenic capacity is necessary to correct bone mass loss in the treatment of osteoporosis. Osteoblasts are derived from the differentiation of bone marrow mesenchymal stem cells, a process that opposes adipogenic differentiation. The peroxisome proliferator-activated receptor γ and Wnt/β-catenin signaling pathways mediate the mutual regulation of osteogenesis and adipogenesis. Lipid substances play an important role in the occurrence and development of osteoporosis. The content and proportion of lipids modulate the activity of immunocytes, mainly macrophages, and the secretion of inflammatory factors, such as IL-1, IL-6 and TNF-α. These inflammatory effectors increase the activity and promote the differentiation of osteoclasts, which leads to bone imbalance and stronger bone resorption. Obesity also decreases the activity of antioxidases and leads to oxidative stress, thereby inhibiting osteogenesis. The present review starts by examining the bidirectional differentiation of BM-MSCs, describes in detail the mechanism by which lipids affect bone metabolism, and discusses the regulatory role of inflammation and oxidative stress in this process. The review concludes that a reasonable adjustment of the content and proportion of lipids, and the alleviation of inflammatory storms and oxidative damage induced by lipid imbalances, will improve bone mass and treat osteoporosis.

Correspondence to: Dr Keda Yang or Professor Lin Tao, Department of Orthopedics, First Hospital of China Medical University, 155 Nanjing North Street, Shenyang, Liaoning 110001, P.R. China
E-mail: terrykeda@163.com
E-mail: taolindr@163.com

*Contributed equally

Contents

1. Introduction

Osteoporosis is a common systemic bone disease (1). Bone quality decreases and bone mass loss in patients with osteoporosis are important risk factors for fractures (2). Osteoporosis can be divided into primary and secondary types. Primary osteoporosis includes postmenopausal osteoporosis and senile osteoporosis (3). Secondary osteoporosis is mainly represented by diabetic osteoporosis but includes a number of types, such as secondary kidney disease and gastrointestinal disease (4). Postmenopausal women, elderly men and diabetic patients are the main populations at high risk for osteoporosis. Due to the diversity of osteoporosis types, methods for directly promoting osteogenesis and inhibiting osteoclasts are used to treat osteoporosis in the clinic, but the effects are not satisfactory (5). Scientists have conducted sufficient research on the pathogenesis of various types of osteoporosis but have not reached a unified conclusion (6,7). Identifying common pathogenic factors of multiple osteoporosis types will be beneficial for clinical diagnosis and treatment.

Compared with the increase in osteoclast activity, decreased osteogenesis is the most important factor in the occurrence and development of osteoporosis. On the one hand, bone resorption by osteoclasts contributes to the metabolism of bone tissue (8), while on the other hand, inhibiting osteoclastogenesis relieves further loss of bone mass, but does not improve bone mass, and patients are still in an osteoporotic state (9). Therefore, the role of osteoblasts is key to exploring the regulation of multiple types of osteoporosis. Osteoblasts are differentiated from bone marrow mesenchymal stem cells (BM-MSCs) (10).

BM-MSCs are pluripotent stem cells with multidirectional differentiation ability (11). Adipogenic differentiation is another main differentiation direction that is balanced with osteogenesis (12). Increasing the adipogenesis of BM-MSCs is an important factor in the development of osteoporosis, as it decreases osteogenesis (13). Therefore, determining the role of fat formation will contribute to unifying the mechanisms of the pathogenesis of osteoporosis.

Postmenopausal women are at the highest risk of osteoporosis. A previous study indicated that more than one-half of postmenopausal women suffer from metabolic syndrome, and nearly 60% of them have dyslipidemia (14). Furthermore, estrogen deficiency can induce hyperlipidemia in animals (15,16). With aging, the activity of lipid metabolic enzymes undergoes obvious changes (17). Lipid peroxidation also accelerates the aging process (18). Additionally, lipid metabolism dysfunction and type 2 diabetes are inextricably linked (19). Obesity is not only an important risk factor for type 2 diabetes, but hyperinsulinemia in diabetic patients also affects the synthesis and degradation of lipids (20-22). Lipid metabolism disorders are common in patients with several typical types of osteoporosis. Therefore, the present review aims to systematically discuss the role of lipid metabolism in the occurrence and development of osteoporosis.

2. Obesity-induced osteoporosis

Obesity is a high risk factor for osteoporosis. The view that the accumulation of fat increases the protection of bones is doubted and challenged (23). Based on the balance of osteogenesis and adipogenesis, the expansion of bone marrow adipose tissue is common in populations at a high risk for osteoporosis, leading to decreased bone formation (24). Bone mineral density decreases significantly with increasing fat levels in bone marrow and blood, and obesity increases the risk of fracture by approximately six-fold (25,26). There is a significant negative correlation between visceral adipose tissue and bone mineral density (27). Additionally, a population-based study indicated that the weight-adjusted waist circumference index was positively correlated with hip and spine fractures (28). Redistribution of adipose tissue and the infiltration of muscle are important in the pathogenesis of fractures (29). The extra weight in obese individuals leads to the occurrence of osteoporosis due to the considerable load on the joints and bones. Calcium deficiency and poor calcium deposition are the main pathogeneses of obesity-induced osteoporosis. Obese individuals have difficulty absorbing vitamin B12 and vitamin D, which is not conducive to bone tissue remodeling (30). In a previous study, 86.2% of obese women were reported to be deficient in vitamin D and had difficulty absorbing calcium (31). Vitamin D deficiency can alter adipogenesis, lipogenesis and lipolysis, and exacerbate obesity (32). The vicious cycle of obesity and vitamin D accelerates bone loss. Hypovitaminosis D also occurs during the weight loss process (33). Aging also reduces the absorption of vitamin D, which increases the risk of bone loss and osteoporosis (34). Therefore, an appropriate intake of vitamin D and calcium contributes to improving the adverse effects of obesity and weight loss on bone remodeling.

3. Balance of osteogenesis and adipogenesis

BM-MSCs are pluripotent stem cells with self-renewal and multidirectional differentiation abilities that are the precursor cells of osteoblasts and adipocytes (35). There is a mutual balance and modulation between these two differentiation trends (36). Scientists have discovered that peroxisome proliferator-activated receptor γ (PPARγ) and Wnt signaling are factors that mediate the balance between osteogenesis and adipogenesis (37). Activation of Wnt/β-catenin signaling promotes the expression of bone morphogenetic proteins (38,39). PPARγ inhibits the osteogenic effect of the Wnt/β-catenin signaling pathway by activating the Wnt inhibitor Dickkopf and directly acting on the β-catenin nuclear transcription factor complex (40). DNA methylation plays an important role in BM-MSC differentiation. Methylation of histone H3 lysine 9 dimethylation (H3K9me2) at the runt-related transcription factor 2 (Runx2) promoter modulates the osteogenic differentiation and mineralization of BM-MSCs (41). In one study, a DNA methylation profile revealed that zinc-finger E homeobox-binding transcription factors participated in the osteogenic and adipogenic differentiation of BM-MSCs, and were correlated with body mass index and PPARγ expression (42). The non-canonical Wnt pathway participates in the inhibition of PPARγ by activating histone-lysine N-methyltransferase SETDB1 to induce histone H3K9 methylation of target genes (43,44) (Fig. 1).

4. Hyperlipemia-induced pathological changes and osteoporosis

Inflammation and oxidative stress are the main pathological changes in the development of osteoporosis (Fig. 2). Inflammatory status is a common element for pathological change in obese individuals. The accumulation of adipose tissue can induce chronic inflammation and lead to an imbalance in the release of hormones and adipokines (45). Adipocytes can directly release inflammatory factors, including TNF-α, IL-6, C-reactive protein and adiponectin (46). The metabolic activity of adipocytes is increased in obese individuals, who require a large amount of protein synthesis. Endoplasmic reticulum stress occurs when the endoplasmic reticulum cannot meet protein synthesis needs, thus activating the inflammatory response (47). Macrophages and lymphocytes are also activated to release inflammatory factors in adipose tissue (48). Additionally, the abundance of fatty acid-producing bacteria increases in the intestines of obese individuals, leading to intestinal mucosa injury and an inflammatory response to promote systemic chronic inflammation (49). Inflammation is regarded as an important mediator of obesity-induced osteoporosis. In mice fed a high-fat diet (HFD), serum lipid levels increase, bone mineral density decreases, and serum inflammatory factors, including IL-1 and TNF-α, increase (50,51). IL-1 activates the NF-κB and MAPK pathways by stimulating TNF receptor-associated factor 6 (TRAF6) to promote osteoclastogenesis with the assistance of receptor activator of nuclear factor κB ligand (RANKL) (52). TNF-α slows the differentiation of osteoblasts and enhances the activity of osteoclasts by recruiting TRAF and activating the NF-κB/c-Fos/nuclear factor of activated T-cells cytoplasmic 1 (NFATc1) pathway,
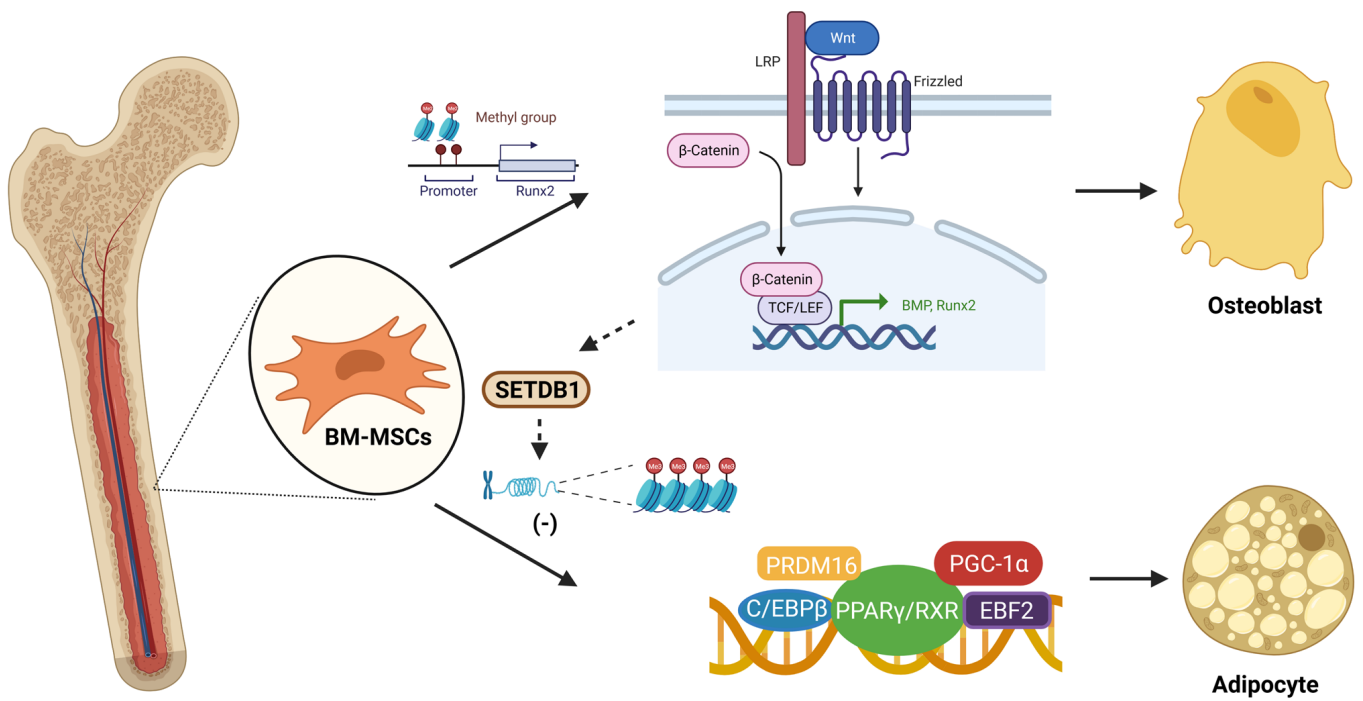
Figure 1. Balance of osteogenesis and adipogenesis in BM-MSCs. Wnt/β-catenin signaling mediates the osteogenic differentiation of BM-MSCs. Activation of PPARγ signaling promotes adipogenesis. There are mutual inhibitory effects between Wnt/β-catenin and PPARγ signaling mediated by histone methylation. BM-MSCs, bone marrow-mesenchymal stem cells; Runx2, runt-related transcription factor 2; LRP, lipoprotein receptor related protein; TCF, T-cell factor; LEF, lymphoid enhancing factor; SETDB1, histone-lysine N-methyltransferase SETDB1; Me2/3, demethylation/trimethylation; PRDM16, PR domain containing 16; C/EBPβ, CCAAT/enhancer-binding protein β; PPARγ, peroxisome proliferator-activated receptor γ; RXR, retinoid X receptor; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; EBF2, early B-cell factor 2.
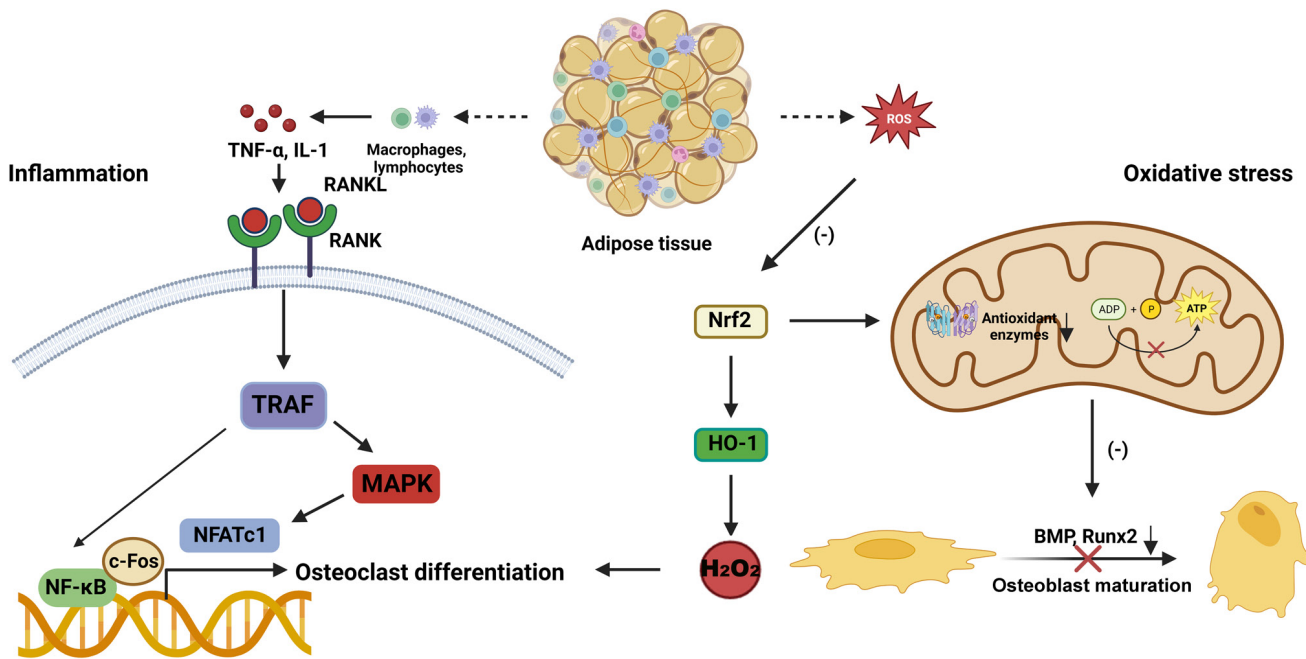

Figure 2. Induced pathological changes and osteoporosis. Inflammation and oxidative stress are the main pathological changes in the development of osteoporosis. Accumulation of adipose tissue induces the release of inflammatory factors to activate RANKL-mediated osteoclast differentiation. A high-fat state inhibits Nrf2/HO-1 signaling and destroys mitochondrial function to induce intracellular oxidative stress. Excessive generation of ROS inhibits osteogenesis and promotes osteoblast differentiation. RANKL, receptor activator of nuclear factor κB ligand; TRAF, TNF receptor-associated factor; NFATc1, nuclear factor of activated T-cells cytoplasmic 1; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; ROS, reactive oxygen species; Runx2, runt-related transcription factor 2.

which is independent of the RANKL/RANK system (53,54). Additionally, a HFD induces many CD11c^{+} macrophages to aggregate and express IL-18 and IL-1β (55). Macrophages participate in the pathogenesis of osteonecrosis, which is the

main mechanism by which immune cells affect bone metabolism (56). Macrophages are also progenitors of osteoclasts that contribute to bone absorption (57). In conclusion, limiting the activity of macrophages and the release of inflammatory factors helps alleviate the damage to bone balance caused by hyperlipidemia.

Oxidative stress is another important pathological state induced by obesity that accelerates bone metabolism disorders (58). In one study, the levels of serum markers of oxidative stress, including hydrogen peroxide and malondialdehyde, in obese individuals almost doubled compared with those in individuals of normal weight (mean age, 71.0±5.7) (59). Oxidized low-density lipoprotein is an oxidative stress biomarker that is involved in the negative effects of obesity (60). Mitochondrial dysfunction is the main cause of obesity-induced oxidative stress (61). Hyperlipidemia destroys the structure of the mitochondria, changes the membrane potential and affects ATP synthesis (62). Obese individuals have difficulties clearing reactive oxygen species (ROS) based on decreased antioxidant enzyme activity, leading to ROS accumulation and the aggravation of oxidative stress (63). In HFD-fed mice, serum total antioxidant capacity and levels of superoxide dismutase, which is associated with bone biomechanical strength and microarchitecture, are decreased (64). Hyperlipidemia also decreases the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and antioxidant enzymes in bone tissue (50). HFD consumption induces the overexpression of ROS to inhibit the Wnt/β-catenin pathway (65). Oxidative injury decreases the expression of BMP2 and Runx2 in osteoblasts (66). Oxidized lipids contribute to PPARγ-induced adipogenesis and inhibit β-catenin-induced osteogenesis in osteoporosis (67,68). HFD consumption reduces the glutathione/oxidized glutathione ratio to not only inhibit bone formation, but also to increase the expression of bone resorption markers such as cross-linked N-telopeptides of bone type I collagen (69). HFD intake promotes osteoclast activity and differentiation by inhibiting the Nrf2/heme oxygenase-1/catalase signaling pathway (70).

5. Lipids and osteoporosis

Triglycerides are an important form of fat; they are the main energy source in the body, and have the greatest storage and production capacity. Triglyceride levels were positively associated with an increased risk of osteoporosis in a study of serum fat markers in 481 individuals (71). The levels of triglycerides were obviously different among the normal, osteopenia and osteoporosis groups (71), which indicated that variations in triglycerides were strongly related to the occurrence and development of osteoporosis (72). Some drugs for the treatment of osteoporosis, such as bisphosphonates and calcium, have also been found to cause abnormal triglyceride metabolism in adipose tissue while promoting bone growth, showing that interfering with fat metabolism is beneficial for improving bone mass (73,74). At the cellular level, the adipogenic differentiation of BM-MSCs leads to the accumulation of triglycerides, which are a risk factor for osteogenesis (75). Triglycerides decrease the expression of the bone growth factor FGF2 and increase the expression of the inflammatory mediator TNF-α, which inhibits the proliferation of osteoblasts (76). Notably,

appropriate modification of triglycerides and adjustment of their concentration can improve bone mineral density by promoting the transdifferentiation of chondrocytes to osteoblasts in postmenopausal mice (77).

Cholesterol is a substance involved in the structural arrangement of the body and the regulation of cell function. As an important synthetic substance consisting of estrogen and vitamin D, cholesterol is involved in the regulation of bone metabolism (78). Previous studies have indicated that serum total cholesterol (TC) levels are negatively correlated with bone mineral density (71,79). A high-cholesterol diet inhibits the differentiation and proliferation of osteoblasts, and reduces bone formation (66,80). Osteoclast synthesis also requires exogenous cholesterol (81). Cholesterol is classified as high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). A number of studies have demonstrated the fact that HDL-C is positively associated with bone mineral density (82-84). Dysfunctional HDL-C increases the expression of PPARγ and decreases the expression of osteogenic markers (85). When HDL-C inhibits the activity of inflammatory factors, these factors suppress osteogenic formation via the Wnt/β-catenin axis (86). In contrast to HDL-C, LDL-C is a negative regulator of bone homeostasis. On the one hand, LDL-C inhibits alkaline phosphatase activity and cell mineralization to interfere with osteogenesis (87), while on the other hand, LDL-C activates RANKL and promotes cell fusion during osteoclastogenesis (88,89). Based on this evidence, decreasing TC levels and increasing the proportion of HDL-C are beneficial for attenuating the development of osteoporosis.

Phospholipids are the main components of biological membrane structures. Phospholipids interfere with bone homeostasis mainly in their oxidized form (90). The accumulation of oxidized phospholipids leads to a systemic inflammatory state by influencing immunocytes, which causes inflammatory bone loss (91). Various phospholipids exhibit toxicity to osteoblasts after oxidation (92). Oxidized phospholipids reduce the expression of osteogenic markers and attenuate parathyroid hormone signaling (93). Bioactive oxidized phospholipids also decrease the response of BM-MSCs to osteogenic factors to inhibit osteogenesis by binding to receptors on the cell surface (94). Additionally, a previous study indicated that oxidized phospholipids could enhance the production of RANKL by T lymphocytes to promote osteoclastogenesis (95). These phospholipids also induce osteoblasts to secrete cell cytokines such as IL-6 and TNF-α, both of which contribute to osteoclast differentiation (96). Neutralization of oxidized phospholipids is beneficial for improving bone mass (97,98). The oxidation-specific epitopes of oxidized phospholipids are potential targets for osteoporosis treatment (99).

Glycolipids are a class of lipid compounds involved in the biological structure of cell membranes and are closely related to the development of osteoporosis (100). Glycolipid-induced toxicity is an important factor in diabetic patients with osteoporosis (101). Menopause-related hormone therapy for osteoporosis is also relevant to glycolipid metabolism (102). Leucine-rich repeat-containing G-protein coupled receptor 4, which is related to glycolipids, has been shown to have an osteogenic effect by upregulating the expression of components

of the Wnt/β-catenin signaling pathway (103). Some studies have indicated that glycolipids conjugated to receptors on natural killer (NK) T cells protect against osteolytic pathogenesis (104,105). However, invariant NK T cells increase the expression of RANKL to promote osteoclastogenesis (106). The effect of glycolipids on NK cells might be a key factor in osteoimmunology.

Bile acid is the main route of cholesterol conversion, and it is also the main component of bile and is involved in fat metabolism. Serum metabolomic analysis of ovariectomized mice revealed that serum bile acid levels were closely related to the development of postmenopausal osteoporosis (107). Serum bile acid level is positively correlated with bone mineral density (108). However, different types of bile acids have different effects on bone metabolism. Osteoporosis is a common complication of biliary cholangitis (109). The use of ursodeoxycholic acid to treat cholestatic liver disease plays a positive role in the treatment of osteoporosis (110). Ursodeoxycholic acid also promotes the differentiation of osteoblasts by increasing the expression of Runx2 and inhibiting osteoblast apoptosis induced by bilirubin (109,111). Targeted stimulation of bile acid receptors contributes to preventing osteoporosis in postmenopausal mice (112,113). In contrast to ursodeoxycholic acid, lithocholic acid plays a negative role in bone balance. In human osteoblasts, lithocholic acid decreased the expression of osteogenic proteins, dampened the effect of vitamin D and increased the expression of apoptosis markers in osteoblasts (114,115). Additionally, lithocholic acid enhances osteoclast activity by upregulating RANKL expression (109). Overall, increasing the level of deoxycholic acid might prevent the occurrence of osteoporosis.

Triglyceride metabolism results in the production of glycerol and large amounts of fatty acids, both of which affect bone homeostasis. Glycerol is widely used in drug modification and the design of bone scaffolds via tissue engineering technology due to its satisfactory permeability and membrane fusion properties (116-118). Fatty acids are classified as saturated and unsaturated fatty acids. Unsaturated fatty acids are generally considered beneficial to the human body (119). However, the positive effect depends on the ratio of n-3 fatty acids to n-6 fatty acids. With an increase in the ratio of n-3/n-6 fatty acids, the bone mineral density increases and the fracture ratio decreases (120). n-3 fatty acids can reverse the effects of aging and promote the proliferation and differentiation of osteoblasts (121). Fatty acids are catabolized in the liver to produce ketone bodies, which are involved in bone metabolism. Acetoacetate can promote osteoblast differentiation and generate far fewer free radicals than the equivalent amount of glucose under the same conditions, thereby reducing oxidative damage to osteoblast precursor cells (122,123). However, β-hydroxybutyrate plays a negative role in osteogenic differentiation (122). As aforementioned, high triglyceride levels are detrimental to bones, and the effects of their ketogenic metabolites are multifaceted. Decreasing triglyceride levels and adjusting the ratio of their ketogenic metabolites will increase bone mass in patients with osteoporosis. Genes associated with fatty acid biosynthesis and degradation participate in the regulation of bone metabolism. Acyl-CoA synthetase

long-chain family members (ACSLs) play a key role in fatty acid metabolism by converting free long-chain fatty acids into fatty acyl-CoA esters. ACSL1 is a potential biomarker of osteoporosis, as it modulates the activity of microRNAs during adipogenesis (124). ACSL1 is also involved in the inflammatory response in osteoporosis (125). Previous studies found that ACSL3 is significantly correlated with total hip bone mineral density (126), while ACSL5 is associated with sarcopenia during hip fractures (127). Differential gene analysis via the Gene Expression Omnibus database revealed that ACSL5 is a potential target for osteoporosis treatment (128). Malonyl-CoA-acyl carrier protein transacylase (MCAT) is a component of the fatty acid synthase complex in mitochondria and is the specific substrate of the zinc finger DHHC-type palmitoyltransferase 13 (ZDHHC13) enzyme. ZDHHC13 deficiency leads to the accumulation of MCAT proteins and induces mitochondrial damage, causing osteoporosis (129) (Table I).

6. Obesity in postmenopausal osteoporosis

The incidence of obesity in postmenopausal women is increasing. With increasing age, the metabolism of body fat slows. According to past dietary habits, obesity will inevitably occur. Estrogen is an important endogenous hormone that regulates lipid metabolism. On the one hand, estrogen affects the distribution of fat in the body. As estrogen levels decrease, fat is redistributed and accumulates from the limbs and trunk to the abdomen and viscera (130). The levels of fatty acid metabolites are increased in visceral adipose tissue (131). On the other hand, estrogen regulates lipid synthesis and decomposition. Estrogen regulates hypothalamic neurons and transmits signals to control adipose tissue catabolism and thermogenesis (132). Estrogen receptor α mediates the activation of thermogenic uncoupling protein-1 to promote fat consumption (133). Estrogen receptor α also promotes histone modification and regulates the DNA methylation of genes associated with lipid metabolism to inhibit adipogenesis (134). In an estrogen-deficient state, β-oxidation of free fatty acids to provide energy does not occur, leading to fat accumulation (135). Postmenopausal obesity is a high risk factor for the development of osteoporosis. Obesity accelerates bone loss and increases bone fragility in postmenopausal women (136). Obesity is positively correlated with the occurrence of all-cause fractures but protects against pelvic fractures in postmenopausal women (137). A meta-analysis indicated that serum adipokines were potential predictors of bone mineral density and fracture risk in postmenopausal women (138). Selective inhibition of adipogenesis could prevent the development of osteoporosis in ovariectomized (OVX) mice (139). High levels of β-crosslap and low levels of procollagen type 1 N-terminal propeptide indicate an imbalance in bone formation and resorption in postmenopausal obese women (140). The decrease in plasma calcium and phosphorus levels also indicated weak osteogenesis in obese OVX mice. The levels of obesity-associated proteins, which colocalize with tartrate-resistant acid phosphatase (TRAP) and upregulate NFATc1 and c-FOS expression to promote RANKL-mediated osteoclast differentiation, are increased in postmenopausal obese mice (141). Increasing calcium intake could help reduce

Table I. Effect of lipids in bone metabolism.

Lipids and metabolites	Mechanism	Effect in bone metabolism	(Refs.)
Triglyceride	Decreasing FGF2 expression and promoting TNF-α secretion	Decreased osteoblasts and increased osteoclasts	(75)
HDL-C	Activating Wnt/β-catenin	Increased osteoblasts	(85)
	Inhibiting PPARγ	Decreased adipocytes	(84)
LDL-C	Inhibiting ALP activity and bone mineralization	Decreased osteoblasts	(86)
	Activating RANKL	Increased osteoclasts	(87,88)
Phospholipid	Inhibiting osteogenic differentiation and PTH signaling	Decreased osteoblasts	(92)
	Promoting IL-6 and TNF-α secretion; activating RANKL	Increased osteoclasts	(94,95)
Ursodeoxycholic acid	Increasing Runx2 expression	Increased osteoblasts	(108,110)
Lithocholic acid	Reducing vitamin D	Decreased osteoblasts	(113,114)
	Upregulating RANKL	Increased osteoclasts	(108)
n-3 fatty acid and differentiation	Reversing aging, promoting proliferation	Increased osteoblasts	(120)
Acetoacetate	Promoting differentiation	Increased osteoblasts	(121,122)
β-hydroxybutyrate	Inhibiting differentiation	Decreased osteoblasts	(121)

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PPARγ, peroxisome proliferator-activated receptor γ; ALP, alkaline phosphatase; RANKL, receptor activator of nuclear factor κB ligand; PTH, parathyroid hormone; Runx2, runt-related transcription factor 2.

postmenopausal weight and increase serum leptin levels, which helps alleviate bone loss (142).

7. Lipid metabolism disorders in osteoporotic patients with diabetes

Obesity is related to and impacts diabetes. Patients with diabetes are prone to abnormal blood lipid levels, as fat synthesis is reduced, degradation is accelerated and disorders of lipid metabolism cause an increase in blood lipids (143). In diabetes, large amounts of fatty acids and glycerol enter the liver due to accelerated fat degradation with a decrease in the insulin/glucagon ratio. Excessive fatty acids are re-esterified into triglycerides and released into the bloodstream in the form of very-low-density lipoproteins (VLDLs) (144). Additionally, the activity of lipoprotein lipase decreases, making it difficult for VLDLs and chylomicrons to be cleared from the plasma (145). Abnormal hormone secretion in diabetes promotes the activity of β-hydroxy β-methylglutaryl-CoA reductase to increase cholesterol synthesis (146). The synthesis of triglycerides also increases in diabetic patients (147). In addition, adipose tissue secretes a variety of inflammatory factors, such as leptin and adiponectin, which reduce insulin sensitivity and aggravate diabetes (148). Abnormal lipid metabolism is a driving factor of the development of osteoporosis in diabetic patients (149). TC, triglyceride and LDL-C levels are negatively correlated with bone mineral density in diabetic patients. Hyperglycemia inhibits osteogenesis and promotes adipogenic differentiation (150). High glucose-induced lipid peroxidation leads to ferroptosis in

osteoblasts (151,152). In a previous study, diabetic mice with excess fat showed obviously elevated TRAP levels, which indicated enhanced bone resorption (153).

8. Discussion

The incidence of osteoporosis, a latent disease, has increased in recent years (154). According to statistics, the prevalence of osteoporosis in women aged ≥50 years can reach 33%, while the prevalence in men can reach 20%. Since the onset of osteoporosis has no obvious symptoms, it is generally diagnosed after a fracture or spinal deformity (155). However, once these symptoms appear, the patient has already lost considerable bone mass and the osteoporosis is difficult to cure. Therefore, routine physical examination and medication intervention in high-risk groups are key to preventing osteoporosis complications. Due to the diversity of osteoporosis types and unclear pathogenesis, the effects of current drugs are not satisfactory. Osteoporosis occurs mainly secondary to different endocrine diseases or physiological state changes, and understanding the direct effects on bones is beneficial for unifying the theories of the pathogenesis of osteoporosis (156,157). Designing drugs based on common pathogenesis will contribute to improving the effectiveness and universality of osteoporosis drug treatments.

Osteoblasts are differentiated from mesenchymal stem cells in the bone marrow. BM-MSCs have multiple differentiation abilities, and an improvement in one differentiation ability will affect the abilities other types of differentiation. Among these differentiation trends, osteogenesis and adipogenesis

are considered relevant groups with a clear negative correlation (158). The present review discusses the osteogenic and adipogenic differentiation of BM-MSCs and the mutual regulatory effects mediated by the PPARγ and Wnt/β-catenin signaling pathways. The review also examines the role of other lipid substances in the occurrence and development of osteoporosis. The results indicate that most of these substances play a dual role in bone metabolism. Excessive accumulation of lipids inhibits osteogenesis, while proper stimulation increases bone mass. The total body fat content is clearly negatively correlated with bone mineral density (159). Moreover, lipid metabolism disorders induce specific pathologies, including inflammation and oxidative stress, to alter the bone microenvironment. Numerous secreted inflammatory factors, but mainly IL-1 and TNF-α, promote the differentiation of osteoclasts. Oxidative damage also inhibits osteogenesis and reduces bone strength. Additionally, lipid metabolism disorders are common in populations that are at high risk for osteoporosis, including postmenopausal women, diabetic patients and obese individuals. Lipidomic profiling contributes to the diagnosis, prevention and treatment of osteoporosis (160).

The present review highlights the mutual regulation of the osteogenic and adipogenic differentiation of BM-MSCs, and the role of various lipids in the development of osteoporosis, and discusses the mechanism by which lipids affect the skeletal system. The bidirectional effect of lipids on bone metabolism suggests that a reasonable adjustment of the content and proportion of lipids will increase bone mass. In addition, relieving inflammatory storms and oxidative damage induced by lipid imbalances is key to preventing bone loss. This review contributes to unifying theories on the pathogenesis of osteoporosis and optimizing treatments for osteoporosis.

Acknowledgements

Funding

Availability of data and materials

Not applicable.

Authors' contributions

XW was responsible for data curation and writing the original draft. CZ performed data curation and helped in writing of the original draft. GZ performed data curation and writing of the original draft. KY was responsible for funding acquisition,, and reviewing and editing the manuscript. LT was responsible for funding acquisition, project administration, resources, and reviewing and editing the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ebeling PR, Nguyen HH, Aleksova J, Vincent AJ, Wong P and Milat F: Secondary osteoporosis. Endocr Rev 43: 240-313, 2022.
2. Flores LE, Nelson S, Waltman N, Kupzyk K, Lappe J, Mack L and Bilek LD: Examining effects of habitual physical activity and body composition on bone structure in early post-menopausal women: A pQCT analysis. Osteoporos Int 33: 425-433, 2022.
3. Compston J, Cooper A, Cooper C, Francis R, Kanis JA, Marsh D, McCloskey EV, Reid DM, Selby P and Wilkins M; National Osteoporosis Guideline Group (NOGG): Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. Maturitas 62: 105-108, 2009.
4. Mirza F and Canalis E: Management of endocrine disease: Secondary osteoporosis: Pathophysiology and management. Eur J Endocrinol 173: R131-R151, 2015.
5. Liu GF, Wang ZQ, Liu L, Zhang BT, Miao YY and Yu SN: A network meta-analysis on the short-term efficacy and adverse events of different anti-osteoporosis drugs for the treatment of postmenopausal osteoporosis. J Cell Biochem 119: 4469-4481, 2018.
6. Ying S, Sifan W, Yujiao W, Rongyi C, Qingrong H, Lili M, Huiyong C and Lindi J: The roles of miRNA, lncRNA and circRNA in the development of osteoporosis. Biol Res 53: 40, 2020.
7. Feng K, Yu M, Lou X, Wang D, Wang L and Ren W: Multi-omics analysis of bone marrow mesenchymal stem cell differentiation differences in osteoporosis. Genomics 115: 110668, 2023.
8. Gritsaenko T, Pierrefite-Carle V, Creff G, Simoneau B, Hagège A, Farlay D, Pagnotta S, Orange F, Jaurand X, Auwer CD, et al: Low doses of uranium and osteoclastic bone resorption: Key reciprocal effects evidenced using new in vitro biomimetic models of bone matrix. Arch Toxicol 95: 1023-1037, 2021.
9. Chung HJ, Cho L, Shin JS, Lee J, Ha IH, Park HJ and Lee SK: Effects of JSOG-6 on protection against bone loss in ovariectomized mice through regulation of osteoblast differentiation and osteoclast formation. BMC Complement Altern Med 14: 184, 2014.
10. Dey D, Jingar P, Agrawal S, Shrivastava V, Bhattacharya A, Manhas J, Garg B, Ansari MT, Mridha AR, Sreenivas V, et al: Symphytum officinale augments osteogenesis in human bone marrow-derived mesenchymal stem cells in vitro as they differentiate into osteoblasts. J Ethnopharmacol 248: 112329, 2020.
11. Zhang L, Yuan Y, Wu W, Sun Z, Lei L, Fan J, Gao B and Zou J: Medium-intensity treadmill exercise exerts beneficial effects on bone modeling through bone marrow mesenchymal stromal cells. Front Cell Dev Biol 8: 600639, 2020.
12. Zuo R, Liu M, Wang Y, Li J, Wang W, Wu J, Sun C, Li B, Wang Z, Lan W, et al: BM-MSC-derived exosomes alleviate radiation-induced bone loss by restoring the function of recipient BM-MSCs and activating Wnt/β-catenin signaling. Stem Cell Res Ther 10: 30, 2019.
13. Cheng H, Qiu L, Ma J, Zhang H, Cheng M, Li W, Zhao X and Liu K: Replicative senescence of human bone marrow and umbilical cord derived mesenchymal stem cells and their differentiation to adipocytes and osteoblasts. Mol Biol Rep 38: 5161-5168, 2011.
14. Chedraui P, Miguel GS, Vintimilla-Sigüenza I, Villacreses D, Romero-Huete L, Domínguez A, Jaramillo W, Escobar GS, Pérez-López FR, Genazzani AR, et al: The metabolic syndrome and its components in postmenopausal women. Gynecol Endocrinol 29: 563-568: 2013.

15. Hur HJ, Jeong YH, Lee SH and Sung MJ: Quercitrin ameliorates hyperlipidemia and hepatic steatosis in ovariectomized mice. Life (Basel) 10: 243, 2020.
16. Chen L, Liu Y, Tang Z, Shi X, Song Z, Cao F, Wei P, Li M, Li X, Jiang D, *et al*: Improvements in estrogen deficiency-induced hypercholesterolemia by Hypericum perforatum L. extract are associated with gut microbiota and related metabolites in ovariectomized (OVX) rats. Biomed Pharmacother 135: 111131, 2021.
17. Mutlu AS, Duffy J and Wang MC: Lipid metabolism and lipid signals in aging and longevity. Dev Cell 56: 1394-1407, 2021.
18. Miró O, Casademont J, Casals E, Perea M, Urbano-Márquez A, Rustin P and Cardellach F: Aging is associated with increased lipid peroxidation in human hearts, but not with mitochondrial respiratory chain enzyme defects. Cardiovasc Res 47: 624-631, 2000.
19. van de Wiel A: Diabetes mellitus and alcohol. Diabetes Metab Res Rev 20: 263-267, 2004.
20. Maggio CA and Pi-Sunyer FX: Obesity and type 2 diabetes. Endocrinol Metab Clin North Am 32: 805-822, 2003.
21. Comuzzie AG, Tejero ME, Funahashi T, Martin LJ, Kissebah A, Takahashi M, Kihara S, Tanaka S, Rainwater DL, Matsuzawa Y, *et al*: The genes influencing adiponectin levels also influence risk factors for metabolic syndrome and type 2 diabetes. Hum Biol 79: 191-200, 2007.
22. Xu Z, Huo J, Ding X, Yang M, Li L, Dai J, Hosoe K, Kubo H, Mori M, Higuchi K and Sawashita J: Coenzyme Q10 improves lipid metabolism and ameliorates obesity by regulating CaMKII-Mediated PDE4 inhibition. Sci Rep 7: 8253, 2017.
23. Fassio A, Idolazzi L, Rossini M, Gatti D, Adami G, Giollo A and Viapiana O: The obesity paradox and osteoporosis. Eat Weight Disord 23: 293-302, 2018.
24. Ali D, Tencerova M, Figeac F, Kassem M and Jafari A: The pathophysiology of osteoporosis in obesity and type 2 diabetes in aging women and men: The mechanisms and roles of increased bone marrow adiposity. Front Endocrinol (Lausanne) 13: 981487, 2022.
25. Lopes KG. Rodrigues EL, da Silva Lopes MR, do Nascimento VA, Pott A, Guimarães RCA, Pegolo GE and Freitas KC: Adiposity metabolic consequences for adolescent bone health. Nutrients 14: 3260, 2022.
26. Salzmann SN, Ortiz Miller C, Carrino JA, Yang J, Shue J, Sama AA, Cammisa FP, Girardi FP and Hughes AP: BMI and gender increase risk of sacral fractures after multilevel instrumented spinal fusion compared with bone mineral density and pelvic parameters. Spine J 19: 238-245, 2019.
27. Perna S, Gasparri C, Allehdan S, Riva A, Petrangolini G, Ferraris C, Guido D, Alalwan TA and Rondanelli M: Discovering the Physio-pathological mechanisms of interaction between bone mineral density, muscle mass, and visceral adipose tissue in female older adults through structural equation modeling. J Clin Med 12: 2269, 2023.
28. Tao J, Zhang Y, Tan C and Tan W: Associations between weight-adjusted waist index and fractures: A population-based study. J Orthop Surg Res 18: 290, 2023.
29. Piñar-Gutierrez A, García-Fontana C, García-Fontana B and Muñoz-Torres M: Obesity and bone health: A complex relationship. Int J Mol Sci 23: 8303, 2022.
30. Aaseth JO and Alexander J: Postoperative osteoporosis in subjects with morbid obesity undergoing bariatric surgery with gastric bypass or sleeve gastrectomy. Nutrients 15: 1302, 2023.
31. Albaik M, Khan JA, Sindi I, Akesson KE and McGuigan FEA: Bone mass in Saudi women aged 20-40 years: The association with obesity and vitamin D deficiency. Arch Osteoporos 17: 123, 2022.
32. Di Filippo L, De Lorenzo R, Giustina A, Rovere-Querini P and Conte C: Vitamin d in osteosarcopenic obesity. Nutrients 14: 1816, 2022.
33. Bassatne A, Chakhtoura M, Saad R and Fuleihan GE: Vitamin D supplementation in obesity and during weight loss: A review of randomized controlled trials. Metabolism 92: 193-205, 2019.
34. Bosetti M, Sabbatini M, Calarco A, Borrone A, Peluso G and Cannas M: Effect of retinoic acid and vitamin D3 on osteoblast differentiation and activity in aging. J Bone Miner Metab 34: 65-78, 2016.
35. Wang C, Tian W, Hu SY, Di CX, He CY, Cao QL, Hao RH, Dong SS, Liu CC, Rong Y, *et al*: Lineage-selective super enhancers mediate core regulatory circuitry during adipogenic and osteogenic differentiation of human mesenchymal stem cells. Cell Death Dis 13: 866, 2022.

36. Hao RH, Guo Y, Wang C, Chen F, Di CX, Dong SS, Cao QL, Guo J, Rong Y, Yao S, *et al*: Lineage-specific rearrangement of chromatin loops and epigenomic features during adipocytes and osteoblasts commitment. Cell Death Differ 29: 2503-2518, 2022.
37. Yuan Z, Li Q, Luo S, Liu Z, Luo D, Zhang B, Zhang D, Rao P and Xiao J: PPARγ and wnt signaling in adipogenic and osteogenic differentiation of mesenchymal stem cells. Curr Stem Cell Res Ther 11: 216-225, 2016.
38. Yao XT, Li PP, Liu J, Yang YY, Luo ZL, Jiang HT, He WG, Luo HH, Deng YX and He BC: Wnt/β-Catenin promotes the osteoblastic potential of BMP9 through Down-Regulating Cyp26b1 in mesenchymal stem cells. Tissue Eng Regen Med 20: 705-723, 2023.
39. Zhang Y, Zhao Y, Xie Z, Li M, Liu Y and Tu X: Activating Wnt/β-Catenin signaling in osteocytes promotes osteogenic differentiation of BMSCs through BMP-7. Int J Mol Sci 23: 16045, 2022.
40. Vallée A and Lecarpentier Y: Crosstalk between peroxisome Proliferator-Activated receptor gamma and the canonical WNT/β-Catenin pathway in chronic inflammation and oxidative stress during carcinogenesis. Front Immunol 9: 745, 2018.
41. Kang P, Wu Z, Huang Y, Luo Z, Huo S and Chen Q: Histone H3K9 demethylase JMJD2B/KDM4B promotes osteogenic differentiation of bone marrow-derived mesenchymal stem cells by regulating H3K9me2 on RUNX2. PeerJ 10: e13862, 2022.
42. Gómez R, Barter MJ, Alonso-Pérez A, Skelton AJ, Proctor C, Herrero-Beaumont G and Young DA: DNA methylation analysis identifies key transcription factors involved in mesenchymal stem cell osteogenic differentiation. Biol Res 56: 9, 2023.
43. Takada I, Kouzmenko AP and Kato S: Wnt and PPARgamma signaling in osteoblastogenesis and adipogenesis. Nat Rev Rheumatol 5: 442-447, 2009.
44. Takada I, Suzawa M, Matsumoto K and Kato S: Suppression of PPAR transactivation switches cell fate of bone marrow stem cells from adipocytes into osteoblasts. Ann N Y Acad Sci 1116: 182-195, 2007.
45. Barakat B and Almeida MEF: Biochemical and immunological changes in obesity. Arch Biochem Biophys 708: 108951, 2021.
46. Ellulu MS, Khaza'ai H, Abed Y, Rahmat A, Ismail P and Ranneh Y: Role of fish oil in human health and possible mechanism to reduce the inflammation. Inflammopharmacology 23: 79-89, 2015.
47. Ajoolabady A, Lebeaupin C, Wu NN, Kaufman RJ and Ren J: ER stress and inflammation crosstalk in obesity. Med Res Rev 43: 5-30, 2023.
48. Sardi C, Martini E, Mello T, Camelliti S, Sfondrini L, Marcucci F, Kallikourdis M, Sommariva M and Rumio C: Effect of acetyl-salicylic acid on inflamed adipose tissue. Insulin resistance and hepatic steatosis in a mouse model of diet-induced obesity. Life Sci 264: 118618, 2021.
49. Zhou X, Pak S, Li D, Dong L, Chen F, Hu X and Ma L: Bamboo shoots modulate gut microbiota, eliminate obesity in high-fat-diet-fed mice and improve lipid metabolism. Foods 12: 1380, 2023.
50. He H, Zhang Y, Sun Y, Zhang Y, Xu J, Yang Y and Chen J: Folic acid attenuates high-fat diet-induced osteoporosis through the AMPK signaling pathway. Front Cell Dev Biol 9: 791880, 2021.
51. Kang YS, Kim JC, Kim JS and Kim SH: Effects of swimming exercise on serum irisin and bone FNDC5 in rat models of High-Fat Diet-Induced osteoporosis. J Sports Sci Med 18: 596-603, 2019.
52. Walsh MC, Kim GK, Maurizio PL, Molnar EE and Choi Y: TRAF6 autoubiquitination-independent activation of the NFkappaB and MAPK pathways in response to IL-1 and RANKL. PLoS One 3: e4064, 2008.
53. Wu WJ, Xia CL, Ou SJ, Yang Y, Ma YF, Hou YL, Yang QP, Zhang J, Li JW, Qi Y and Xu CP: Novel elongator protein 2 inhibitors mitigating tumor necrosis Factor-α induced osteogenic differentiation inhibition. Biomed Res Int 2021: 3664564, 2021.
54. Yao Z, Getting SJ and Locke IC: Regulation of TNF-induced osteoclast differentiation. Cells 11: 132, 2021.
55. Zhang Y, Li Q, Rao E, Sun Y, Grossmann ME, Morris RJ, Cleary MP and Li B: Epidermal Fatty Acid binding protein promotes skin inflammation induced by high-fat diet. Immunity 42: 953-964, 2015.
56. Gkouveris I, Soundia A, Gouveris P, Zouki D, Hadaya D and Tetradis S: Macrophage involvement in Medication-related osteonecrosis of the jaw (MRONJ): A comprehensive, short review. Cancers (Basel) 14: 330, 2022.

57. Russo R, Zito F and Lampiasi N: MiRNAs expression profiling in Raw264.7 macrophages after Nfatc1-Knockdown elucidates potential pathways involved in osteoclasts differentiation. Biology (Basel) 10: 1080, 2021.

58. Korkmaz HA and Özkan B: Impact of obesity on bone metabolism in Children. J Pediatr Endocrinol Metab 35: 557-565, 2022.

59. Leanza G, Conte C, Cannata F, Isgrò C, Piccoli A, Strollo R, Quattrocchi CC, Papalia R, Denaro V, Maccarrone M, et al: Oxidative stress in postmenopausal women with or without obesity. Cells 12: 1137, 2023.

60. Gutiérrez-Solis AL, Garrido-Dzib AG, Rochel-Pérez A, Magallón-Zertuche V, Chávez-Loría G, Medina-Vera I and Avila-Nava A: Oxidative stress biomarkers in mexican subjects with overweight and obesity: A systematic review. Metab Syndr Relat Disord 21: 188-196, 2023.

61. Cojocaru K, Cojocaru KA, Luchian I, Ursu RG, Butnaru O and Foia L: Mitochondrial dysfunction, oxidative stress, and therapeutic strategies in diabetes, obesity, and cardiovascular disease. Antioxidants (Basel) 12: 658, 2023.

62. Jing J, Peng Y, Fan W, Han S, Peng Q, Xue C, Qin X, Liu Y and Ding Z: Obesity-induced oxidative stress and mitochondrial dysfunction negatively affect sperm quality. FEBS Open Bio 13: 763-778, 2023.

63. Lubkowska A, Dudzińska W and Pluta W: Antioxidant enzyme activity and serum HSP70 concentrations in relation to insulin resistance and lipid profile in lean and overweight young men. Antioxidants (Basel) 12: 655: 2023.

64. Xia B, Zhu R, Zhang H, Chen B, Liu Y, Dai X, Ye Z, Zhao D, Mo F, Gao S, et al: Lycopene improves bone quality and regulates AGE/RAGE/NF-κB signaling pathway in high-fat diet-induced obese mice. Oxid Med Cell Longev 2022: 3697067, 2022.

65. Wang YN, Jia TT, Feng Y, Liu SY, Zhang WJ, Zhang DJ and Xu X: Hyperlipidemia impairs osseointegration via the ROS/Wnt/β-Catenin pathway. J Dent Res 100: 658-665, 2021.

66. You L, Sheng ZY, Tang CL, Chen L, Pan L and Chen JY: High cholesterol diet increases osteoporosis risk via inhibiting bone formation in rats. Acta Pharmacol Sin 32: 1498-1504, 2011.

67. Almeida M, Ambrogini E, Han L, Manolagas SC and Jilka RL: Increased lipid oxidation causes oxidative stress, increased peroxisome proliferator-activated receptor-gamma expression, and diminished pro-osteogenic Wnt signaling in the skeleton. J Biol Chem 284: 27438-27448, 2009.

68. Ronis MJ, Mercer K and Chen JR: Effects of nutrition and alcohol consumption on bone loss. Curr Osteoporos Rep 9: 53-59, 2011.

69. Xiao Y, Cui J, Li YX, Shi YH, Wang B, Le GW and Wang ZP: Dyslipidemic high-fat diet affects adversely bone metabolism in mice associated with impaired antioxidant capacity. Nutrition 27: 214-220, 2011.

70. Li G, Park JN, Park HJ, Suh H and Choi HS: High Cholesterol-Induced bone loss is attenuated by arctiin via an action in osteoclasts. Nutrients 14: 4483, 2022.

71. Kan B, Zhao Q, Wang L, Xue S, Cai H and Yang S: Association between lipid biomarkers and osteoporosis: A cross-sectional study. BMC Musculoskelet Disord 22: 759, 2021.

72. Lu CW, Wang CH, Hsu BG and Tsai JP: Serum osteoprotegerin level is negatively associated with bone mineral density in patients undergoing maintenance hemodialysis. Medicina (Kaunas) 57: 762, 2021.

73. Martini C, Sosa FN, Malvicini R, Pacienza N, Yannarelli G, Del C and Vila M: Alendronate inhibits triglyceride accumulation and oxidative stress in adipocytes and the inflammatory response of macrophages which are associated with adipose tissue dysfunction. J Physiol Biochem 77: 601-611, 2021.

74. Mao H, Wang W, Shi L, Chen C, Han C, Zhao J, Zhuo Q, Shen S, Li Y and Huo J: Metabolomics and physiological analysis of the effect of calcium supplements on reducing bone loss in ovariectomized rats by increasing estradiol levels. Nutr Metab (Lond) 18: 76, 2021.

75. Sutjarit N, Thongon N, Weerachayaphorn J, Piyachaturawat P, Suksamrarn A, Suksen K, Papachristou DJ and Blair HC: Inhibition of adipogenic differentiation of human bone Marrow-Derived mesenchymal stem cells by a phytoestrogen diarylheptanoid from curcuma comosa. J Agric Food Chem 68: 9993-10002, 2020.

76. Huang H, Luo L, Liu Z, Li Y, Tong Z and Liu Z: Role of TNF-α and FGF-2 in the fracture healing disorder of type 2 diabetes model induced by high fat diet followed by streptozotocin. Diabetes Metab Syndr Obes 13: 2279-2288, 2020.

77. Zhang T, Tian Y, Wang Q, Fu M, Xue C and Wang J: Comparative study of DHA with different molecular forms for ameliorating osteoporosis by promoting Chondrocyte-to-Osteoblast transdifferentiation in the growth plate of ovariectomized mice. J Agric Food Chem 69: 10562-10571, 2021.

78. Antonenko A, Leahy A, Babenko M and Lyons D: Low dose hydrophilic statins are the preferred agents for females at risk of osteoporosis. Bone Rep 16: 101152, 2022.

79. Liu, J, Deng X, Liang X and Li L: The phytoestrogen glabrene prevents osteoporosis in ovariectomized rats through upregulation of the canonical Wnt/β-catenin signaling pathway. J Biochem Mol Toxicol 35: e22653, 2021.

80. Zhou Y, Deng T, Zhang H, Guan Q, Zhao H, Yu C, Shao S, Zhao M and Xu J: Hypercholesterolaemia increases the risk of high-turnover osteoporosis in men. Mol Med Rep 19: 4603-4612, 2019.

81. Luegmayr E, Glantschnig H, Wesolowski GA, Gentile MA, Fisher JE, Rodan GA and Reszka AA: Osteoclast formation, survival and morphology are highly dependent on exogenous cholesterol/lipoproteins. Cell Death Differ 11 (Suppl 1): S108-S118, 2004.

82. Dumitru N, Carsote M, Cocolos A, Petrova E, Olaru M, Dumitrache C and Ghemigian A: The link between bone osteocalcin and energy metabolism in a group of postmenopausal women. Curr Health Sci J 45: 47-51, 2019.

83. Papachristou NI, Blair HC, Kypreos KE and Papachristou DJ: High-density lipoprotein (HDL) metabolism and bone mass. J Endocrinol 233: R95-R107, 2017.

84. Tang Y, Wang S, Yi Q, Xia Y and Geng B: High-density lipoprotein cholesterol is negatively correlated with bone mineral density and has potential predictive value for bone loss. Lipids Health Dis 20: 75, 2021.

85. Barsh GS and Schwartz MW: Genetic approaches to studying energy balance: Perception and integration. Nat Rev Genet 3: 589-600, 2002.

86. Clevers H: Wnt/beta-catenin signaling in development and disease. Cell 127: 469-480, 2006.

87. Dawodu D, Patecki M, Dumler I, Haller H and Kiyan Y: oxLDL inhibits differentiation of mesenchymal stem cells into osteoblasts via the CD36 mediated suppression of Wnt signaling pathway. Mol Biol Rep 46: 3487-3496, 2019.

88. Okayasu M, Nakayachi M, Hayashida C, Ito J, Kaneda T, Masuhara M, Suda N, Sato T and Hakeda Y: Low-density lipoprotein receptor deficiency causes impaired osteoclastogenesis and increased bone mass in mice because of defect in osteoclastic cell-cell fusion. J Biol Chem 287: 19229-19241, 2012.

89. Hada N, Okayasu M, Ito J, Nakayachi M, Hayashida C, Kaneda T, Uchida N, Muramatsu T, Koike C, Masuhara M, et al: Receptor activator of NF-κB ligand-dependent expression of caveolin-1 in osteoclast precursors, and high dependency of osteoclastogenesis on exogenous lipoprotein. Bone 50: 226-236, 2012.

90. Lee KG, Lee GB, Yang JS and Moon MH: Perturbations of lipids and oxidized phospholipids in lipoproteins of patients with postmenopausal osteoporosis evaluated by asymmetrical flow field-flow fractionation and nanoflow UHPLC-ESI-MS/MS. Antioxidants (Basel) 9: 46, 2020.

91. Leitinger N: The role of phospholipid oxidation products in inflammatory and autoimmune diseases: Evidence from animal models and in humans. Subcell Biochem 49: 325-350, 2008.

92. Fallah A, Pierre R, Abed E and Moreau R: Lysophosphatidylcholine-induced cytotoxicity in osteoblast-like MG-63 cells: Involvement of transient receptor potential vanilloid 2 (TRPV2) channels. Mol Membr Biol 30: 315-326, 2013.

93. Huang MS, Morony S, Lu J, Zhang Z, Bezouglaia O, Tseng W, Tetradis S, Demer LL and Tintut Y: Atherogenic phospholipids attenuate osteogenic signaling by BMP-2 and parathyroid hormone in osteoblasts. J Biol Chem 282: 21237-21243, 2007.

94. Wang L, Chai Y, Li C, Liu H, Su W, Liu X, Yu B, Lei W, Yu B, Crane JL, et al: Oxidized phospholipids are ligands for LRP6. Bone Res 6: 22, 2018.

95. Graham LS, Parhami F, Tintut Y, Kitchen CM, Demer LL and Effros RB: Oxidized lipids enhance RANKL production by T lymphocytes: Implications for lipid-induced bone loss. Clin Immunol 133: 265-275, 2009.

96. Tseng W, Lu J, Bishop GA, Watson AD, Sage AP, Demer L and Tintut Y: Regulation of interleukin-6 expression in osteoblasts by oxidized phospholipids. J Lipid Res 51: 1010-1016, 2010.

97. Palmieri M, Almeida M, Nookaew I, Gomez-Acevedo H, Joseph TE, Que X, Tsimikas S, Sun X, Manolagas SC, Witztum JL and Ambrogini E: Neutralization of oxidized phospholipids attenuates age-associated bone loss in mice. Aging Cell 20: e13442, 2021.

98. Palmieri M, Kim HN, Gomez-Acevedo H, Que X, Tsimikas S, Jilka RL, Manolagas SC, Witztum JL and Ambrogini E: A neutralizing antibody targeting oxidized phospholipids promotes bone anabolism in chow-fed young adult mice. J Bone Miner Res 36: 170-185, 2021.

99. Ambrogini E, Que X, Wang S, Yamaguchi F, Weinstein RS, Tsimikas S, Manolagas SC, Witztum JL and Jilka RL: Oxidation-specific epitopes restrain bone formation. Nat Commun 9: 2193, 2018.

100. Inagaki M: Structure and biological activity of glycosphingo-lipids from starfish and feather stars. Yakugaku Zasshi 128: 1187-1194, 2008 (In Japanese).

101. Liang B, Shen X, Lan C, Lin Y, Li C, Zhong S and Yan S: Glycolipid toxicity induces osteogenic dysfunction via the TLR4/S100B pathway. Int Immunopharmacol 97: 107792, 2021.

102. Ran SY, Yu Q, ChenY and Lin SQ: Prevention of postmeno-pausal osteoporosis in Chinese women: A 5-year, double-blind, randomized, parallel placebo-controlled study. Climacteric 20: 391-396, 2017.

103. Yu WJ, Zhang Z, Fu WZ, He JW, Wang C and Zhang ZL: Association between LGR4 polymorphisms and peak bone mineral density and body composition. J Bone Miner Metab 38: 658-669, 2020.

104. Melgar-Rodríguez S, Cafferata EA, Díaz NI, Peña MA, González-Osuna L, Rojas C, Sierra-Cristancho A, Cárdenas AM, Díaz-Zúñiga J and Vernal R: Natural Killer T (NKT) cells and periodontitis: Potential regulatory role of NKT10 cells. Mediators Inflamm 2021: 5573937, 2021.

105. Naruo M, Negishi Y, Okuda T, Katsuyama M, Okazaki K and Morita R: Alcohol consumption induces murine osteoporosis by downregulation of natural killer T-like cell activity. Immun Inflamm Dis 9: 1370-1382, 2021.

106. Tilkeridis K, Kiziridis G, Ververidis A, Papoutselis M, Kotsianidis I, Kitsikidou G, Tousiaki NE, Drosos G, Kapetanou A, Rechova KV, *et al*: Immunoporosis: A new role for invariant natural Killer T (NKT) cells through overexpres-sion of nuclear Factor-κB ligand (RANKL). Med Sci Monit 25: 2151-2158, 2019.

107. Wen K, Tao L, Tao Z, Meng Y, Zhou S, Chen J, Yang K, Da W and Zhu Y: Fecal and serum metabolomic signatures and micro-bial community profiling of postmenopausal osteoporosis mice model. Front Cell Infect Microbiol 10: 535310, 2020.

108. Zhao YX, Song YW, Zhang L, Zheng FJ, Wang XM, Zhuang XH, Wu F and Liu J: Association between bile acid metabolism and bone mineral density in postmenopausal women. Clinics (Sao Paulo) 75: e1486, 2020.

109. Ruiz-Gaspà S, Guañabens N, Jurado S, Combalia A, Peris P, Monegal A and Parés A: Bilirubin and bile acids in osteocytes and bone tissue. Potential role in the cholestatic-induced osteo-porosis. Liver Int 40: 2767-2775, 2020.

110. Ahn TK, Kim KT, Joshi HP, Park KH, Kyung JW, Choi UY, Sohn S, Sheen SH, Shin DE, Lee SH and Han IB: Therapeutic potential of tauroursodeoxycholic acid for the treatment of osteoporosis. Int J Mol Sci 21: 4274, 2020.

111. Ruiz-Gaspà S, Dubreuil M, Guañabens N, Combalia A, Peris P, Monegal A and Parés A: Ursodeoxycholic acid decreases bilirubin-induced osteoblast apoptosis. Eur J Clin Invest 44: 1206-1214, 2014.

112. Li Z, Huang J, Wang F, Li W, Wu X, Zhao C, Zhao J, Wei H, Wu Z, Qian M, *et al*: Dual targeting of bile acid Receptor-1 (TGR5) and Farnesoid X Receptor (FXR) prevents estrogen-dependent bone loss in mice. J Bone Miner Res 34: 765-776, 2019.

113. Wang Q, Wang G, Wang B and Yang H: Activation of TGR5 promotes osteoblastic cell differentiation and mineralization. Biomed Pharmacother 108: 1797-1803, 2018.

114. Ruiz-Gaspà S, Guañabens N, Jurado S, Dubreuil M, Combalia A, Peris P, Monegal A and Parés A: Bile acids and bilirubin effects on osteoblastic gene profile. Implications in the pathogenesis of osteoporosis in liver diseases. Gene 725: 144167, 2020.

115. Ruiz-Gaspà S, Guañabens N, Enjuanes A, Peris P, Martinez-Ferrer A, de Osaba MJ, Gonzalez B, Alvarez L, Monegal A, Combalia A and Parés A: Lithocholic acid down-regulates vitamin D effects in human osteoblasts. Eur J Clin Invest 40: 25-34, 2010.

116. Medrano-David D, Lopera AM, Londoño ME and Araque-Marín P: Formulation and characterization of a new injectable bone substitute composed PVA/Borax/CaCO₃ and demineralized bone matrix. J Funct Biomater 12: 46, 2021.

117. Deng D, Pan C, Wu Z, Sun Y, Liu C, Xiang H, Yin P and Shang D: An integrated metabolomic study of osteoporosis: Discovery and quantification of hyocholic acids as candidate markers. Front Pharmacol 12: 725341, 2021.

118. Naito C, Katsumi H, Yoneto K, Omura M, Nishidono M, Kamei S, Mizoguchi A, Tamba A, Tanaka A, Morishita M and Yamamoto A: Development of a phosphoric Acid-Mediated hyaluronic acid gel sheet for efficient transdermal delivery of alendronate for Anti-osteoporotic therapy. Pharmaceutics 11: 642, 2019.

119. Asefy Z, Tanomand A, Hoseinnejhad S, Ceferov Z, Oshaghi EA and Rashidi M: Unsaturated fatty acids as a co-therapeutic agents in cancer treatment. Mol Biol Rep 48: 2909-2916, 2021.

120. Xiao WJ, Ke YH, He JW, Zhang H, Yu JB, Hu WW, Gu JM, Gao G, Yue H, Wang C, *et al*: Polymorphisms in the human ALOX12 and ALOX15 genes are associated with peak bone mineral density in Chinese nuclear families. Osteoporos Int 23: 1889-1897, 2012.

121. Wu Y, Zhang M, Chen X, Zhou Y and Chen Z. Metabolomic analysis to elucidate the change of the n-3 polyunsaturated fatty acids in senescent osteoblasts. Biosci Biotechnol Biochem 85: 611-620, 2021.

122. Saito A, Yoshimura K, Miyamoto Y, Kaneko K, Chikazu D, Yamamoto M and Kamijo R: Enhanced and suppressed miner-alization by acetoacetate and β-hydroxybutyrate in osteoblast cultures. Biochem Biophys Res Commun 473: 537-544, 2016.

123. Board M, Lopez C, van den Bos C, Callaghan R, Clarke K and Carr C: Acetoacetate is a more efficient energy-yielding substrate for human mesenchymal stem cells than glucose and generates fewer reactive oxygen species. Int J Biochem Cell Biol 88: 75-83, 2017.

124. Yi X, Liu J, Wu P, Gong Y, Xu X and Li W: The key microRNA on lipid droplet formation during adipogenesis from human mesenchymal stem cells. J Cell Physiol 235: 328-338, 2020.

125. Li L, Wang XQ, Liu XT, Guo R and Zhang RD: Integrative analysis reveals key mRNAs and lncRNAs in monocytes of osteoporotic patients. Math Biosci Eng 16: 5947-5971, 2019.

126. Reppe S, Refvem H, Gautvik VT, Olstad OK, Høvring PI, Reinholt FP, Holden M, Frigessi A, Jemtland R and Gautvik KM: Eight genes are highly associated with BMD variation in post-menopausal Caucasian women. Bone 46: 604-612, 2010.

127. Kang YJ, Yoo JI and Baek KW. Differential gene expression profile by RNA sequencing study of elderly osteoporotic hip fracture patients with sarcopenia. J Orthop Translat 29: 10-18, 2021.

128. Zhang X, Chen K, Chen X, Kourkoumelis N, Li G, Wang B and Zhu C: Integrative analysis of genomics and transcriptome data to identify regulation networks in female osteoporosis. Front Genet 11: 600097, 2020.

129. Shen LF, Chen YJ, Liu KM, Haddad ANS, Song IW, Roan HY, Chen LY, Yen JJY, Chen YJ, Wu JY and Chen YT: Role of S-Palmitoylation by ZDHHC13 in mitochondrial function and metabolism in liver. Sci Rep 7: 2182, 2017.

130. Andersson T, Söderström I, Simonyté K and Olsson T: Estrogen reduces 11beta-hydroxysteroid dehydrogenase type 1 in liver and visceral, but not subcutaneous, adipose tissue in rats. Obesity (Silver Spring) 18: 470-475, 2010.

131. Yamatani H, Takahashi K, Yoshida T, Soga T and Kurachi H: Differences in the fatty acid metabolism of visceral adipose tissue in postmenopausal women. Menopause 21: 170-176, 2014.

132. Mahboobifard F, Pourgholami MH, Jorjani M, Dargahi L, Amiri M, Sadeghi S and Tehrani FR: Estrogen as a key regu-lator of energy homeostasis and metabolic health. Biomed Pharmacother 156: 113808, 2022.

133. Yepuru M, Eswaraka J, Kearbey JD, Barrett CM, Raghow S, Veverka KA, Miller DD, Dalton JT and Narayanan R: Estrogen receptor-{beta}-selective ligands alleviate high-fat diet- and ovariectomy-induced obesity in mice. J Biol Chem 285: 31292-31303, 2010.

134. Bjune JI, Strømland PP, Jersin R, Mellgren G and Dankel SN: Metabolic and epigenetic regulation by estrogen in adipocytes. Front Endocrinol (Lausanne) 13: 828780, 2022.

135. Ko SH and Jung Y: Energy metabolism changes and dysregu-lated lipid metabolism in postmenopausal women. Nutrients 13: 4556, 2021.

136. Ali D, Figeac F, Caci A, Ditzel N, Schmal C, Kerckhofs G, Havelund J, Faergeman N, Rauch A, Tencerova M and Kassem M: High-fat diet-induced obesity augments the deleterious effects of estrogen deficiency on bone: Evidence from ovariectomized mice. Aging Cell 21: e13726, 2022.

137. Liu HF, Meng DF, Yu P, De JC and Li HY: Obesity and risk of fracture in postmenopausal women: A meta-analysis of cohort studies. Ann Med 55: 2203515, 2023.

138. Lee S, Kim JH, Jeon YK, Lee JS, Kim K, Hwang SK, Kim JH, Goh TS and Kim YH: Effect of adipokine and ghrelin levels on BMD and fracture risk: An updated systematic review and meta-analysis. Front Endocrinol (Lausanne) 14: 1044039, 2023.

139. Sardar A, Gautam S, Sinha S, Rai D, Tripathi AK, Dhaniya G, Mishra PR and Trivedi R: Nanoparticles of naturally occurring PPAR-γ inhibitor betulinic acid ameliorates bone marrow adiposity and pathological bone loss in ovariectomized rats via Wnt/β-catenin pathway. Life Sci 309: 121020, 2022.

140. López-Gómez JJ, Pérez-Castrillón JL, García de Santos I, Pérez-Alonso M, Izaola-Jauregui O, Primo-Martín D and De Luis-Román DA: Influence of obesity on bone turnover markers and fracture risk in postmenopausal women. Nutrients 14: 1617, 2022.

141. Zhuang J, Ning H, Wang M, Zhao W, Jing Y, Liu X, Zu J, Kong P, Wang X, Sun C and Yan J: Downregulated fat mass and obesity-associated protein inhibits bone resorption and osteoclastogenesis by nuclear factor-kappa B inactivation. Cell Signal 87: 110137, 2021.

142. Wawrzyniak N, Suliburska J, Kulczyński B, Kołodziejski P, Kurzawa P and Gramza-Michałowska A: Calcium-Enriched pumpkin affects serum leptin levels and fat content in a rat model of postmenopausal osteoporosis. Nutrients 13: 2334, 2021.

143. Fu Q, Zhang Z, Hu W and Yang Y: The correlation of triglyceride/high-density lipoprotein cholesterol ratio with muscle mass in type 2 diabetes patients. BMC Endocr Disord 23: 93, 2023.

144. Kalhan SC, Bugianesi E, McCullough AJ, Hanson RW and Kelley DE: Estimates of hepatic glyceroneogenesis in type 2 diabetes mellitus in humans. Metabolism 57: 305-312, 2008

145. Niu YG and Evans RD: Myocardial metabolism of triacylglycerol-rich lipoproteins in type 2 diabetes. J Physiol 587: 3301-3315, 2009.

146. Ishikawa M, Iwasaki Y, Yatoh S, Kato T, Kumadaki S, Inoue N, Yamamoto T, Matsuzaka T, Nakagawa Y, Yahagi N, et al: Cholesterol accumulation and diabetes in pancreatic beta-cell-specific SREBP-2 transgenic mice: A new model for lipotoxicity. J Lipid Res 49: 2524-2534, 2008.

147. Yang Q, Xu H, Zhang H, Li Y, Chen S, He D, Yang G, Ban B, Zhang M and Liu F: Serum triglyceride glucose index is a valuable predictor for visceral obesity in patients with type 2 diabetes: A cross-sectional study. Cardiovasc Diabetol 22: 98, 2023.

148. Gavin KM, Sullivan TM, Maltzahn JK, Jackman MR, Libby AE, MacLean PS, Kohrt WM, Majka SM and Klemm DJ: Hematopoietic stem Cell-Derived adipocytes modulate adipose tissue cellularity, leptin production and insulin responsiveness in female mice. Front Endocrinol (Lausanne) 13: 844877, 2022.

149. Chen Z, Zhao GH, Zhang YK, Shen GS, Xu YJ and Xu NW: Research on the correlation of diabetes mellitus complicated with osteoporosis with lipid metabolism, adipokines and inflammatory factors and its regression analysis. Eur Rev Med Pharmacol Sci 21: 3900-3905, 2017.

150. Figeac F, Tencerova M, Ali D, Andersen TL, Appadoo DRC, Kerckhofs G, Ditzel N, Kowal JM, Rauch A and Kassem M: Impaired bone fracture healing in type 2 diabetes is caused by defective functions of skeletal progenitor cells. Stem Cells 40: 149-164, 2022.

151. Jin C, Tan K, Yao Z, Lin BH, Zhang DP, Chen WK, Mao SM, Zhang W, Chen L, Lin Z, et al: A novel Anti-Osteoporosis mechanism of VK2: Interfering with ferroptosis via AMPK/SIRT1 pathway in type 2 diabetic osteoporosis. J Agric Food Chem 71: 2745-2761, 2023.

152. Yang Y, Lin Y, Wang M, Yuan K, Wang Q, Mu P, Du J, Yu Z, Yang S, Huang K, et al: Targeting ferroptosis suppresses osteocyte glucolipotoxicity and alleviates diabetic osteoporosis. Bone Res 10: 26, 2022.

153. Kanda J, Furukawa M, Izumo N, Shimakura T, Yamamoto N, Takahashi HE and Wakabayashi H: Effects of the linagliptin, dipeptidyl peptidase-4 inhibitor, on bone fragility induced by type 2 diabetes mellitus in obese mice. Drug Discov Ther 14: 218-225, 2020.

154. Peyman H, Elizabeth E, Dominik O and Robert B: Bone evaluation study-2: Update on the epidemiology of osteoporosis in Germany. Arch Osteoporos 19: 26, 2024.

155. Matsunaga T, Miyagi M, Nakazawa T, Murata K, Kawakubo A, Fujimaki H, Koyama T, Kuroda A, Yokozeki Y, Mimura Y, et al: Prevalence and characteristics of spinal sagittal malalignment in patients with osteoporosis. J Clin Med 10: 2827, 2021.

156. Louwers YV and Visser JA: Shared genetics between age at menopause, early menopause, POI and other traits. Front Genet 12: 676546, 2021.

157. Farooqui KJ, Mithal A, Kerwen AK and Chandran M: Type 2 diabetes and bone fragility-An under-recognized association. Diabetes Metab Syndr 15: 927-935, 2021.

158. Russell AL, Lefavor R, Durand N, Glover L and Zubair AC: Modifiers of mesenchymal stem cell quantity and quality. Transfusion 58: 1434-1440, 2018.

159. Giudici KV, de França NAG, Peters BSE, Fisberg RM and Martini LA: Associations between markers of glucose metabolism and bone measures among diabetic and non-diabetic adults. J Diabetes Metab Disord 20: 1247-1255, 2021.

160. Aleidi SM, Al-Ansari MM, Alnehmi EA, Malkawi AK, Alodaib A, Alshaker M, Benabdelkamel H and Abdel Rahman AM: Lipidomics profiling of patients with low bone mineral density (LBMD). Int J Mol Sci 23: 12017, 2022.