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

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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.

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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,

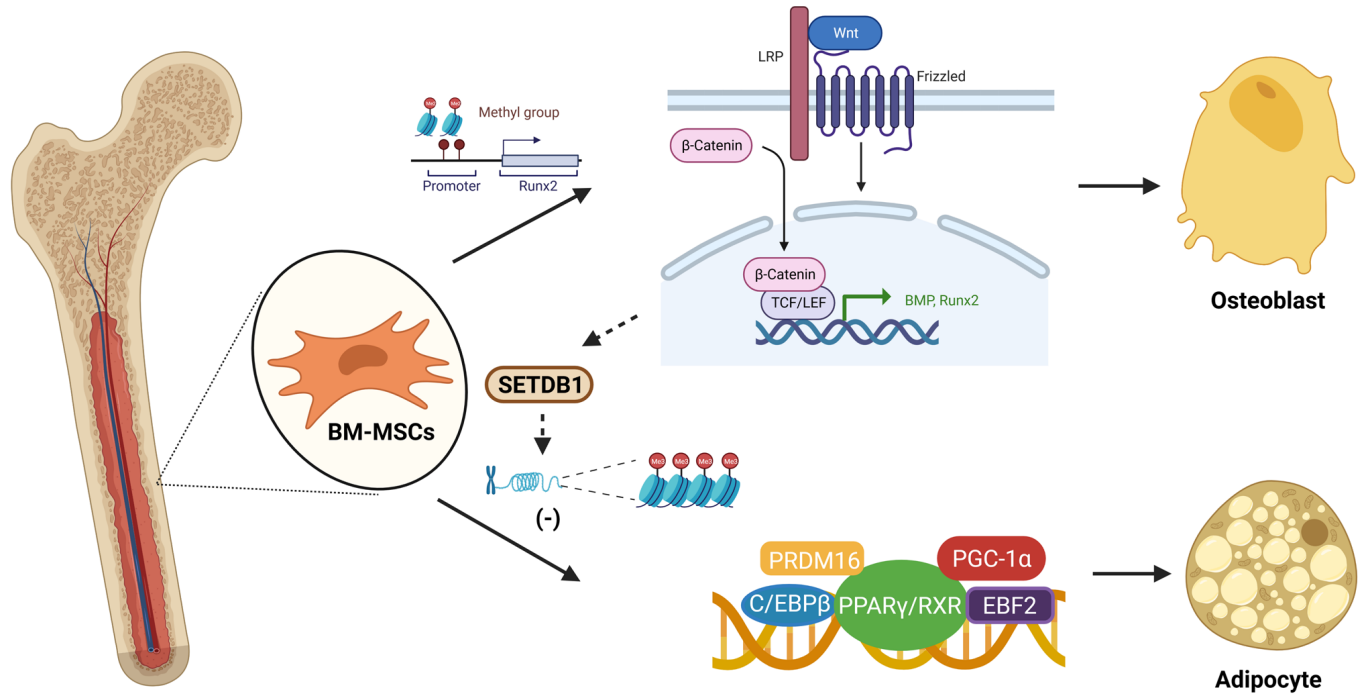

Figure 1. Balance of osteogenesis and adipogenesis in BM-MSCs. Wnt/β-catenin signaling mediates the osteogenic differentiation of BM-MSCs. Activation of PPARγ signaling promotes adipogenesis. There are mutual inhibitory effects between Wnt/β-catenin and PPARγ signaling mediated by histone methylation. 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.

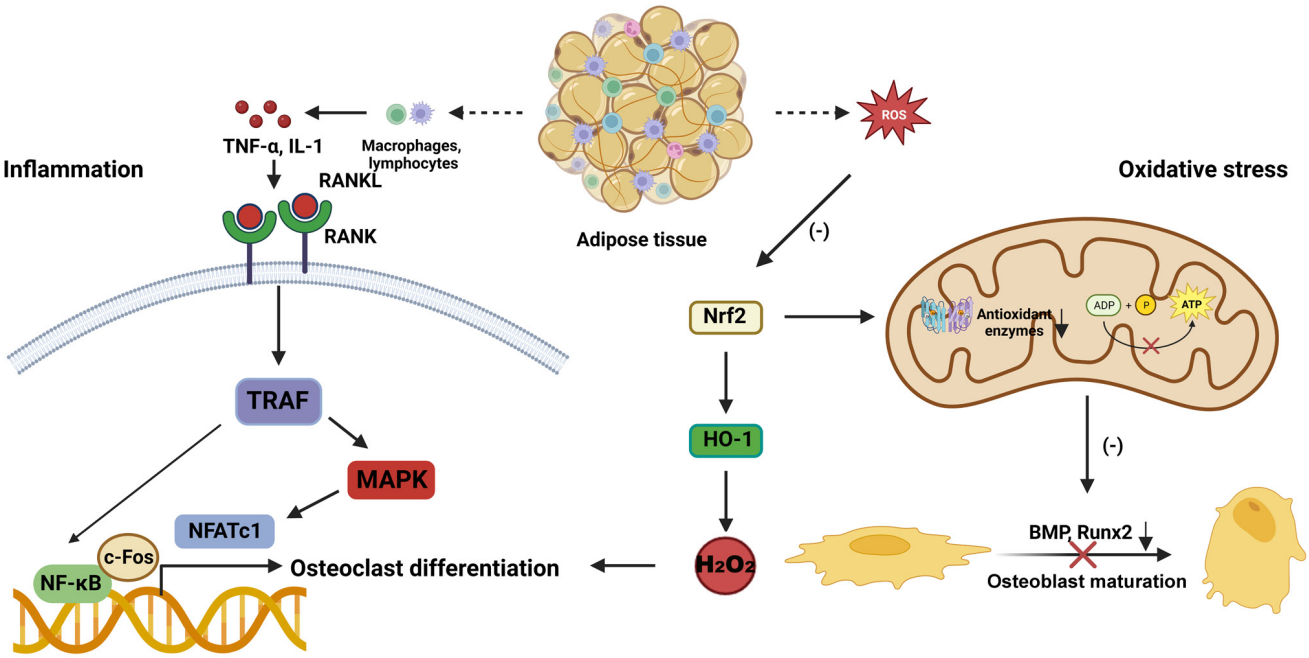

Figure 2. Induced pathological changes and osteoporosis. Inflammation and oxidative stress are the main pathological changes in the development of osteoporosis. Accumulation of adipose tissue induces the release of inflammatory factors to activate RANKL-mediated osteoclast differentiation. A high-fat 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.

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Availability of data and materials

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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.

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