Role of vitamins in the development and treatment of osteoporosis (Review)

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Abstract. Osteoporosis has escalated into a pressing public health challenge amidst global demographic aging. Conventional diagnostic approaches and therapeutic interventions demonstrate growing limitations in both risk stratification and epidemiological control. In this context, serological monitoring and targeted nutrient supplementation emerge as promising preventive strategies. Vitamins, fundamental regulators of cellular homeostasis, demonstrate particular significance in bone remodeling processes. The present comprehensive review elucidates the pathophysiological mechanisms through which specific vitamins differentially modulate osteoblastic activity and osteoclastic regulation, summarizing contemporary evidence from the molecular to clinical research levels. While vitamin A exhibits dual effects, other vitamins predominantly show positive impacts on bone homeostasis. Oxidative stress and inflammation are key pathological changes associated with osteoporosis. Vitamins play a protective role by enhancing the expression of antioxidant enzymes, activating antioxidant pathways and inhibiting the secretion of inflammatory cytokines, thereby mitigating these conditions. Serum vitamin concentrations exhibit significant correlations with bone mineral density alterations and osteoporosis progression, providing predictive biomarkers for fracture risk assessment. However, serum vitamin profiles exhibit marked heterogeneity across osteoporosis risk strata, necessitating population-specific therapeutic protocols. Precision-adjusted supplementation strategies effectively attenuate pathological bone resorption while preserving physiological remodeling homeostasis. The present review systematically delineates the therapeutic potential of vitamins in osteoporotic management, underscoring the necessity for evidence-based precision nutrient protocols tailored to at-risk populations to prevent disease progression.

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Abbreviations: BMD, bone mineral density; VDR, vitamin D receptor; 25(OH)D, 25-hydroxyvitamin D; OVX, ovariectomized; HFD, high-fat diet; GSH, glutathione; MSC, mesenchymal stem cell; CRP, C reactive protein; ALP, alkaline phosphatase

Key words: vitamin, osteoporosis, oxidative stress, inflammation

Contents

1. Introduction

Osteoporosis is a progressive metabolic bone disorder defined by diminished bone mineral density (BMD) and microarchitectural deterioration of osseous tissue (1). A previous report indicated that the prevalence of osteoporosis among middle-aged and elderly individuals in China is ~33.49%, broken down as 20.73% in men and 38.05% in women (2). Osteoporosis primarily manifests as pain and skeletal deformities, with fractures constituting the most severe complication that imposes substantial burdens on patients and significantly compromises their quality of life (3). Osteoporotic fractures predominantly comprise vertebral compression fractures and hip fragility fractures. Notably, hip fractures represent >40% of these cases, while the refracture rate following vertebroplasty for vertebral compression fractures approaches 20% (4,5). Skeletal homeostasis is dynamically regulated through coupled bone remodeling processes, mediated by osteoblastic bone formation and osteoclastic bone resorption within specialized bone multicellular units (6). The balanced interplay between osteoblastic and osteoclastic activities maintains physiological bone turnover while preventing pathological alterations in bone mass. However, age-related endocrine changes, particularly estrogen deficiency in postmenopausal women, coupled with metabolic dysregulation such as chronic hyperglycemia and adiposity, disrupt this equilibrium. This imbalance leads

to predominant osteoclastic resorption over osteoblastic formation, resulting in progressive bone mass depletion and eventual osteoporotic deterioration (7). Owing to the exclusion of BMD assessments from routine physical examinations and insufficient awareness of bone health maintenance, patients frequently present with clinically detectable reductions in BMD only upon the manifestation of severe complications. Consequently, implementing proactive diagnostic measures and preventative strategies becomes imperative for populations with elevated osteopathic risks.

Vitamins represent a category of essential micronutrients that must be acquired through dietary sources to support fundamental physiological processes. These micronutrients serve critical functions in human growth, metabolic regulation and developmental processes (8,9). Although vitamins neither constitute structural components of bodily tissues nor serve as energy substrates, they mediate the regulation of biochemical metabolism through enzymatic cofactor activities (10). Vitamins play crucial roles in maintaining skeletal integrity and facilitating bone repair mechanisms (11). Clinical evidence demonstrates that vitamin deficiencies constitute significant risk factors for osteoporosis development (12). Vitamin D plays a pivotal role in skeletal mineralization through the regulation of calcium homeostasis; it facilitates intestinal calcium absorption by inducing the expression of calcium-binding proteins and enhancing the bioavailability of calcium salts within the gastrointestinal tract (13). Clinical evidence also supports the therapeutic efficacy of vitamin B supplementation in enhancing BMD (14). Additionally, vitamins C and E demonstrate therapeutic potential in ameliorating oxidative stress-mediated skeletal deterioration, effectively mitigating osteoporotic bone loss in clinical populations (15). Furthermore, Vitamin K has been established as a critical biochemical indicator for assessing osteoporotic vertebral fracture risk (16). This evidence collectively establishes that vitamins play integral roles in the diagnostic evaluation, preventive strategies and therapeutic management of osteoporosis. The present review systematically examines the regulatory functions of vitamins in bone metabolism while elucidating the pathophysiological mechanisms underlying osteoporosis associated with vitamin homeostasis dysregulation.

2. Vitamins and osteoporosis

Vitamin A plays a critical role in regulating cellular differentiation and metabolic homeostasis, and is predominantly stored in hepatic tissues of animal-derived food sources (17). Vitamin A and its provitamin precursors exhibit osteoprotective effects by stimulating osteoblastic activity while suppressing osteoclastic differentiation through retinoic acid receptor-mediated transcriptional regulation (18). Vitamin A exerts a dose-dependent influence on bone metabolism, where moderate short-term intake enhances bone formation, while chronic excessive accumulation demonstrates catabolic effects on skeletal integrity (19). Recent investigation has revealed stage-dependent effects of vitamin A during osteogenesis, promoting osteoblast differentiation while impairing matrix mineralization (18). Retinoid receptors participate in the modulatory effects of vitamin A in bone metabolism (16). Vitamin A deficiency induces significant developmental abnormalities characterized by impaired skeletal morphogenesis and aberrant cortical bone remodeling (20). Lind *et al* (21) demonstrated that supraphysiological vitamin A intake induces aberrant vascular endothelial growth factor overexpression, thereby compromising bone marrow microvascular integrity and predisposing to spontaneous fracture development (21). Emerging evidence suggests that vitamin A demonstrates therapeutic potential in ameliorating mechanical loading-induced skeletal dysregulation (22). Retinol and retinoic acid represent the principal bioactive forms of vitamin A. A significant U-shaped relationship exists between plasma retinol concentrations and BMD (23). Moderate enhancement of retinol signaling promotes osteogenesis while inhibiting osteoclast genesis (24). Crosstalk exists between the Wnt/β-catenin signaling pathway and retinoic acid signaling pathways (25). In postmenopausal women, elevated serum retinol levels exhibit significant associations with accelerated bone loss and heightened risk of osteoporotic fractures (26). Excessive vitamin A leads to accumulation of its metabolite retinoic acid, which accelerates receptor activator of nuclear factor κB ligand (RANKL)-dependent osteoclast differentiation and subsequent bone mass reduction (27,28) (Table I). In animal experiments, retinoic acid was found to markedly decrease bone calcium and phosphorus by promoting bone resorption and collagen metabolism (29,30). All-trans retinoic acid further inhibits osteogenic activity through suppression of the canonical Wnt/β-catenin signaling pathways (31). Carotenes demonstrate beneficial effects on bone formation. Epidemiological studies have established that increased β-carotene intake enhances BMD and reduces the risk of fractures (32,33). The B vitamin complex exerts essential regulatory functions in skeletal metabolic homeostasis (34). Osteoporosis and hip fracture incidence have both been associated with inadequate dietary intake of B vitamins (35). Current research on the role of vitamin B1 in osteoporosis pathogenesis remains limited. Functioning as a coenzyme, vitamin B1 facilitates glycolytic metabolism in bone cells. Osteoblasts primarily rely on aerobic glycolysis for energy production, whereas osteoclasts predominantly utilize oxidative phosphorylation as their main energy-generating pathway (36). Vitamin B1 modulates osteoblastic glucose metabolism to regulate osteogenic processes. Preliminary evidence suggests its potential to inhibit RANKL-induced osteoclast differentiation, thereby mitigating osteoporosis progression (37). Vitamin B2 exerts beneficial effects on bone homeostasis. A clinical investigation has demonstrated that dietary vitamin B2 supplementation correlates with reduced osteoporosis incidence (38). Vitamin B2 promotes osteogenic differentiation and vascular angiogenesis, thereby enhancing bone mass accrual (39). Vitamin B2 treatment significantly upregulates the expression levels of Runt-related transcription factor 2 (Runx2) and β-catenin (40). Elevated vitamin B6 intake is associated with increased BMD at the hip and spine (41), while diminished serum vitamin B6 concentrations demonstrate a significant association with an elevated risk (42). Bioactivated vitamin B6 enhances *in vivo* osteointegration processes (43), while vitamin B6 deficiency impedes fracture repair by impairing callus maturation (44). Vitamin B9 supplementation demonstrates beneficial effects on BMD (14). Vitamin B9 enhances osteogenic differentiation by inducing the expression of Runx2 and alkaline phosphatase

Table I. Role of vitamins in bone metabolism.

Vitamins	Mechanism	Effect in bone metabolism	(Refs.)
Vitamin A	Moderate: Promoting osteogenesis and inhibiting osteoclastogenesis via the Wnt/β-catenin pathway	Osteoblast (+) Osteoclast (-)	(25,26,28, 29)
	Excessive: Inhibiting Wnt signaling and promoting RANKL-mediated osteoclast differentiation	Osteoblast (-) Osteoclast (+)	
Vitamin B1	Inhibiting RANKL-induced osteoclast differentiation	Osteoclast (-)	(38)
Vitamin B2	Increasing the expression of Runx2 and β-catenin	Osteoblast (+)	(41)
Vitamin B6	Contributing to osteointegration and promoting callus maturation	Osteoblast (+)	(44,45)
Vitamin B9	Inducing the expression of Runx2 and ALP Activating the Wnt/β-catenin signaling pathway	Osteoblast (+)	(46,48)
Vitamin C	Increasing the expression of BMP2, Runx2, osteocalcin and Collagen I Participating in the formation of calcified nodules	Osteoblast (+)	(61,62,65)
	Decreasing the concentration of CTX-1 and RANKL Inhibiting the expression of TRAP and CTSK	Osteoclast (-)	
Vitamin D	Assisting Ca^{2+} in passing through the osteoblast membrane Increasing the expression of SMAD1-3 and 5, and β-catenin Increasing the expression of Runx2 and Collagen I Increase ALP activity and osteocalcin expression	Osteoblast (+)	(69-71,73)
Vitamin E	Increasing the expression of cyclin D1 and c-myc, and activating the Wnt/β-catenin signaling pathway in osteoblasts Increasing the expression of BMP2, osterix, collagen I and osteocalcin	Osteoblast (+)	(83-85,89,90)
	Reducing the production of serum C-terminal telopeptide of type I collagen Deactivating RANKL-mediated osteoclast differentiation	Osteoclast (-)	
Vitamin K1	Participating in the biosynthesis of osteocalcin and bone matrix Gla protein	Osteoblast (+)	(96)
Vitamin K2	Increasing the expression of Runx2 and osteocalcin via the Bcl-6/STAT axis and the IL-6/JAK/STAT signaling pathway	Osteoblast (+)	(100)

(+), positive effects; (-), negative effects; RANKL, receptor activator of nuclear factor κB ligand; Runx2, runt-related transcription factor 2; ALP, alkaline phosphatase; CTX-1, C-terminal peptide of type I collagen; TRAP, tartrate-resistant acid phosphatase; CTSK, cathepsin K.

(ALP) (45). Vitamin B9 activates the canonical Wnt/β-catenin signaling pathway during osteogenic differentiation (46) (Table I). Adults with suboptimal vitamin B12 status exhibit compromised skeletal integrity and diminished bone health outcomes (47). Vitamin B12 deficiency is associated with diminished total skeletal mass and elevated fracture susceptibility (48,49). Additionally, deficiency of the vitamin B family leads to high homocysteine concentrations, which could promote bone resorption and increase the fracture risk (50). Hyperhomocysteinemia potentiates osteoclastogenesis through enhanced catalytic activity of tartrate-resistant acid phosphatase (TRAP) and cathepsin K (CTSK) (51). Homocysteine exerts inhibitory effects on osteoblastic proliferation and mineralization, thereby compromising bone formation processes (52).

Vitamin C, scientifically termed ascorbic acid, critically catalyzes collagen biosynthesis within osseous matrices (53). Vitamin C in combination with β-glycerophosphate and dexamethasone constitutes a standard osteogenic differentiation induction protocol (54). Clinical investigations have established a positive correlation between serum vitamin C concentrations and BMD, with enhanced dietary vitamin C intake demonstrating favorable associations with improved bone mass parameters (55). Increased vitamin C intake is associated with elevated BMD at the hip and lumbar spine (56), and a diet high in vitamin C demonstrates a significant reduction in hip fracture risk (57). Vitamin C actively contributes to the regenerative processes following osseous defect formation (58). Vitamin C and its derivatives demonstrate significant osteogenic enhancement (59). Vitamin C administration upregulates the expression of BMP2, Runx2, Osteocalcin and Collagen I during osteogenic differentiation processes (60). Vitamin C also facilitates proline hydroxylase activity to catalyze collagen biosynthesis and post-translational maturation, thereby supporting osteocalcin production and coordinating bone tissue remodeling processes (61). Vitamin C metabolism is mechanistically linked to the biosynthesis of procollagen type I N-terminal propeptide (PINP) (62). Additionally, vitamin C

facilitates calcified nodule formation during biomineralization and activates extracellular matrix deposition processes (63). Vitamin C downregulates the expression of TRAP and CTSK, effectively inhibiting osteoclast differentiation (60) (Table I).

Vitamin D serves as a critical biomarker for bone formation, and its deficiency directly contributes to osteoporosis development (64). Vitamin D is closely related to bone metabolism and its main function is to regulate the absorption of calcium and phosphorus, which are involved in neo-osteogenesis (65). Vitamin D primarily enhances bone tissue calcification by regulating plasma calcium and phosphorus levels, and promoting their deposition as bone salts (66); it facilitates Ca^{2+} transport across osteoblast membranes into osseous tissue (67). Vitamin D further stimulates osteogenic signaling pathways through upregulation of SMAD1-3 and 5 and β-catenin expression (68). Vitamin D stimulation significantly upregulates the expression of osteogenic biomarkers, including Runx2 and collagen type I (69). The vitamin D receptor (VDR) critically regulates skeletal metabolic homeostasis (70). VDR activation enhances ALP enzymatic activity and stimulates osteocalcin biosynthesis in osteoblasts (71) (Table I). Vitamin D further induces VDR activation within osteoblasts, demonstrating the capacity to suppress osteoclastic activity (72). VDR-targeted genetic interventions demonstrate therapeutic efficacy in bone metabolic regulation, establishing innovative pharmacological strategies for osteoporosis management (73). Additionally, Vitamin D exerts dual therapeutic effects by restoring trabecular microarchitecture and augmenting musculoskeletal function, thereby enhancing skeletal integrity and physical performance in osteoporotic populations (74). Vitamin D, as a fundamental supplement for skeletal health, is extensively employed in osteoporosis clinical management alongside calcium. A longitudinal investigation involving over 20,000 participants demonstrated that sustained bolus vitamin D administration maintained fracture risk neutrality, affirming its safety in both preventive and therapeutic osteoporosis applications (75). Moreover, vitamin D deficiency serves as a principal etiological determinant in the pathogenesis of pediatric rickets (76). Vitamin D deficiency precipitates dysregulated calcium-phosphorus homeostasis and impairs both metaphyseal mineralization and skeletal matrix maturation. Enhanced vitamin D supplementation during pregnancy and the neonatal period effectively prevents the development of rickets (77).

Vitamin E and its derivatives demonstrate beneficial effects on bone metabolism (78). Vitamin E participates in the maintenance of bone homeostasis by modulating osteocyte-derived bone-related peptides (79) Diminished serum concentrations predispose to the development of hip fractures (80). Vitamin E stimulates osteoblast proliferation through upregulation of cyclin D1 and c-myc expression, while concurrently enhancing osteogenic differentiation via activation of the canonical Wnt/β-catenin signaling pathway (81). Osteogenic markers, including BMP-2, Osterix, Collagen type I and Osteocalcin, are upregulated to induce osteogenesis (82,83). Vitamin E preserves plasma membrane integrity in osteocytes subjected to mechanical loading by mitigating membrane disruptions (84). Vitamin E exhibits protective effects on mineralized surfaces, effectively preventing bone erosion (85). Meanwhile, it also significantly suppresses osteoclast-specific biomarker expression and attenuates osteoclastic resorptive activity (86). Vitamin E reduces serum levels of type I collagen C-terminal telopeptide, thereby suppressing bone resorption activity (87). Vitamin E deficiency activates RANKL-mediated osteoclast genesis in multinucleated precursor cells (88) (Table I).

Vitamin K constitutes a critically underrecognized modulator of skeletal homeostasis (89). Genetic polymorphisms in vitamin K regulatory enzymes constitute significant genetic determinants for osteoporosis risk stratification (90). Vitamin K deficiency significantly accelerates bone loss progression (91). Increased vitamin K intake reduces osteoporosis risk and prevents fractures (92). Both osteocalcin and matrix Gla protein (MGP) are vitamin K-dependent proteins (93). Vitamin K1 is essential for the biosynthesis of osteocalcin and MGP (94). Periostin, Protein S and growth arrest-specific 6 protein constitute vitamin K1-dependent proteins essential for skeletal homeostasis (95). Vitamin K2 demonstrates beneficial regulatory effects on skeletal homeostasis through dual mechanisms of stimulating osteoblastic activity and suppressing osteoclastic differentiation (96). Vitamin K2 has been applied as a supplement for the prevention and treatment of osteoporosis (97). Transcriptomic profiling demonstrated vitamin K2-mediated upregulation of Runx2 and osteocalcin through coordinated activation of the Bcl-6/STAT transcriptional axis and the IL-6/JAK/STAT signaling cascade (98) (Table I). The intestinal microbiota and metabolites regulate bone metabolism (99). Integrative analysis of 16S rRNA sequencing data with serum bone metabolic parameters revealed *Bacteroides*-mediated modulation of vitamin K2 homeostasis and skeletal remodeling processes (100). Vitamin K2 enhances osteogenic differentiation and matrix mineralization through autophagy pathway activation in osteoblasts (101). Vitamin K in combination with vitamin D and calcium may constitute a more efficacious supplement regimen for osteoporosis prophylaxis and therapeutic management (102,103). However, notably, vitamin K antagonist oral antibiotics demonstrate diminished BMD and elevated fracture susceptibility through coherent pharmacological mechanisms (104).

3. Vitamins in high-risk populations for osteoporosis

Postmenopausal women. Vitamins, as essential micronutrients, demonstrate significant associations with osteopenia in postmenopausal women (105). Reduced vitamin intake exacerbates postmenopausal osteoporotic deterioration (106). Vitamin A serves as a critical supplement for postmenopausal women, effectively enhancing health-related quality of life (107). Serum carotenoid concentrations demonstrate significant associations with estrogen receptor-positive malignancy risk (108). However, elevated circulating vitamin A concentrations constitute a significant risk factor for osteoporosis (26). Chronic supplementation significantly elevates fracture incidence (109). Vitamin B9 and vitamin B12 are the primary B vitamins associated with bone metabolism in postmenopausal women. Epidemiological evidence indicates that vitamin B9 and B12 deficiencies are associated with an increased incidence of asymptomatic osteoporotic vertebral fractures (110). Vitamin B9 demonstrates beneficial regulatory effects through upregulation of osteocalcin biosynthesis and β-cross-linked C-telopeptide expression (111). Vitamin B12

serves as a protective factor against osteoporosis in postmenopausal women (112). Vitamin C stimulates gonadal secretory activity and enhances circulating estrogen levels (113); it primarily mediates the enhancement of endothelial function in postmenopausal physiological states (114,115). Serum vitamin C concentrations demonstrated an inverse association with the pathogenesis of postmenopausal osteoporosis (116). Plasma vitamin C deficiency serves as a significant predictive biomarker for hip BMD (117). Vitamin C-enriched dietary regimens ameliorate the dysfunctional crosstalk among skeletal, muscular and adipose tissues secondary to estrogen deficiency through multi-tissue regulatory mechanisms (118). Vitamin D is essential for female reproductive physiology, with its receptor (VDR) mediating therapeutic benefits within the genitourinary system (119). Vitamin D deficiency is associated with premature menopause onset and diminished reproductive lifespan in women (120). Serum 25-hydroxyvitamin D [25(OH)D] levels are associated with the healthy index (lower levels of glycohemoglobin, glucose and higher levels of HDL) of postmenopausal women (121). Serum 25(OH D concentrations demonstrated significant correlations with health status indices in postmenopausal populations (122). Vitamin D is critical for maintaining BMD and reducing fracture risk in postmenopausal women (123), serving as a pivotal bone turnover marker that enhances bone quality and mechanical strength (124). Postmenopausal women with combined vitamin D insufficiency and elevated circulating retinol concentrations demonstrate significantly heightened susceptibility to osteoporotic progression (125). Serum vitamin D metabolites serve as critical diagnostic biomarkers for predicting the onset of postmenopausal osteoporosis (126). Therapeutically, vitamin D supplementation is employed to prevent estrogen deficiency-induced bone loss (127). Vitamin D combined with calcium supplementation is more effective for improving the process of bone remodeling (128). Vitamin D upregulates irisin expression to synergistically augment musculoskeletal function and BMD (129). Vitamin E, scientifically termed tocopherol, demonstrates the capacity to stimulate estrogen biosynthesis and secretory processes (130). Vitamin E has been incorporated into hormone replacement regimens, serving as an adjuvant to mitigate climacteric symptomatology (131). Oral gavage of vitamin E significantly enhances bone mineral content and restores trabecular microarchitecture in ovariectomized (OVX) rat models (132). The principal therapeutic mechanism involves sclerostin downregulation, which enhances osteogenic activity through modulation of the RANKL/osteoprotegerin equilibrium (133). Meanwhile, vitamin E suppresses estrogen deficiency-driven monocyte/lymphocyte proliferation, thereby attenuating inflammation-mediated osteoclast differentiation (134). The antioxidative capacity of vitamin E attenuates oxidative stress-mediated bone resorption, thereby ameliorating osteopenic progression in postmenopausal women (135). Vitamin K demonstrates beneficial effects on bone ultrastructure enhancement (136); it plays a pivotal role in promoting osteogenic differentiation and facilitating matrix mineralization during postmenopausal bone remodeling. Oral vitamin K administration upregulates the expression of Runx2 and BMP2 while downregulating nuclear factor of activated T-cells cytoplasmic 1 (NFATC1) expression (137). Vitamin K derivatives also inhibited the expression of NFATc1 and CTSK to reverse bone resorption in a study with OVX mice (92). Vitamin K derivatives inhibited NFATc1 and CTSK expression, effectively reversing bone resorption in OVX mice (138). Vitamin K1 serves as a critical diagnostic and therapeutic biomarker for postmenopausal osteoporosis management (139). Elevated circulating vitamin K1 concentrations positively correlate with enhanced BMD in postmenopausal populations (140). Vitamin K2 supplementation may contribute to the maintenance and improvement of lumbar BMD by enhancing osteocalcin biosynthesis (141,142) (Table II). In summary, vitamins primarily counteract bone loss through direct interaction with estrogen receptors to modulate estrogen secretion or ameliorate pathological alterations induced by estrogen deficiency. Early assessment of serum vitamin levels facilitates the prevention of BMD reduction in postmenopausal women. Targeted vitamin supplementation further refines intervention strategies and enhances therapeutic outcomes for postmenopausal osteoporosis.

Diabetic patients. Vitamins serve as critical factors in the synergistic regulation of blood glucose homeostasis. B-group vitamins function as coenzymes in glucose metabolism pathways, with vitamin B1 deficiency specifically impairing glucose oxidation, thereby inducing pyruvate accumulation and compromising cellular energy supply (143). Notably, vitamin B1 insufficiency is highly prevalent in diabetic populations (144). Serum vitamin B1 concentrations demonstrate a significant positive correlation with diabetes mellitus progression (145). Vitamin B1 supplementation demonstrates therapeutic efficacy in ameliorating osteoporosis associated with diabetes mellitus (146). Vitamin B12 deficiency is prevalent among diabetic patients, particularly following metformin administration (147). Vitamin B12 supplementation may mitigate the risk of hyperglycemia-associated fragility fractures (148). Vitamin C exerts indirect regulatory effects on blood glucose homeostasis. Notably, vitamin C has been shown to inhibit the formation of advanced glycation end products (149). Conversely, vitamin C has been demonstrated to promote insulin secretion, enhance the degree to which insulin promotes glucose breakdown and attenuate insulin resistance (150). Low serum vitamin C levels have been established as a significant contributing factor to reduced BMD in diabetic patients (55). Vitamin D plays a pivotal role in blood glucose homeostasis and the modulation of glycemic indicators (151). Serum 25(OH)D3 concentrations exhibit a progressive decline associated with diabetes mellitus progression (152). Vitamin D deficiency has been mechanistically linked to insulin resistance, potentiating the risk of diabetic osteoporosis through impaired bone metabolic efficiency (153). VDR activation has been shown to mitigate Wnt signaling pathway suppression and stimulate the upregulation of osteogenic marker proteins, thereby counteracting diabetes-associated bone resorption (154). Vitamin D-induced osteogenic effects on osteoblasts are mediated through forkhead box protein O1 (FoxO1) signaling inhibition (155,156). Vitamin E demonstrates therapeutic potential in modulating glycemic regulation (78). Vitamin E supplementation enhances glucose homeostasis through improved glucose-insulin regulatory mechanisms, while ameliorating hyperglycemia-associated

Table II. Vitamins in the development of postmenopausal osteoporosis.

Vitamins	Role in women's health	Effects on bone tissue	Mechanism
Vitamin A	Associated with the risk of estrogen receptor-tumors	Increasing the occurrence offractures	-
Vitamin B9	-	Decreasing asymptomatic osteoporotic vertebral fractures	Increasing osteocalcin and β-CrossLaps levels
Vitamin B12	-	Preventing osteoporosis in postmenopausal women	-
Vitamin C	Promoting the secretion of gonads and increasing the concentration of estrogen	Associated with hip BMD	Improving the abnormal state between bones, muscles and adipose tissue
Vitamin D	Delaying menopause and extending reproductive lifespan, associated with the healthy index of postmenopausal women	Elevating bone quality and strength	An important bone turnover marker, improving irisin levels to enhance skeletal muscle strength and increase bone mass
Vitamin E	Promoting the secretion of estrogen and improving menopausal complications	Improving bone mineral content and reconstructing bone microstructure	Inhibiting the expression of sclerostin and decreasing the RANKL/OPG ratio
Vitamin K	-	Promoting osteogenic differentiation and matrix mineralization	Increasing the expression of Runx2 and BMP2, but decreasing NFATC1 and CTSK expression

BMD, bone mineral density; RANKL, receptor activator of nuclear factor κB ligand; OPG, osteoprotegerin; Runx2, Runx2, runt-related transcription factor 2; NFATC1, nuclear factor of activated T-cells cytoplasmic 1; CTSK, cathepsin K.

bone resorption by upregulating PINP synthesis to stimulate osteogenic activity (157) (Fig. 1). Vitamin K2 upregulates SIRT1 expression to inhibit hyperglycemia-induced mesenchymal stem cell (MSC) ferroptosis (158). The synergistic administration of vitamins K2 and D3 represents a promising therapeutic strategy for the management of diabetic osteoporosis (159). In conclusion, vitamins primarily ameliorate bone loss in diabetic populations through their involvement in glucose metabolism and modulation of insulin secretory dynamics and bioactivity. Optimal-dose vitamin supplementation demonstrates dual efficacy in maintaining glycemic stability and attenuating hyperglycemia-driven osteoclastic resorption.

Obese groups. In obese populations, vitamin A deficiency exhibits a stronger association with pathological bone deterioration and microarchitectural degradation (18). Obesity demonstrates a significant inverse association with serum retinol concentrations (160). Vitamin A enhances lipid oxidative metabolism and promotes adipose tissue catabolism (161). Retinol-binding protein 4 serves as a critical adipokine mediating the regulatory effects of vitamin A on lipid metabolism, while exhibiting an inverse correlation with serum osteocalcin concentrations (162,163). The vitamin B group plays integral roles in lipid metabolic processes. Specifically, vitamin B2 orchestrates adipose tissue biosynthesis, catabolism and secretory regulation. Vitamin B2-enriched dietary regimens effectively reduce adipose accumulation while preventing BMD loss (157). Vitamin B9 activates the AMPK signaling pathway to attenuate high fat diet (HFD)-induced osteoporosis by increasing the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and antioxidant enzymes (164). Meanwhile, serum vitamin B12 concentrations exhibited a significant inverse association with adiposity indices (165). Vitamin C demonstrates inhibitory effects on triglyceride deposition and adipose tissue hypertrophy (166), and modulates MSC differentiation trajectories, preferentially steering lineage commitment toward osteogenesis while suppressing adipogenic propensity (167). Clinical investigations have established that dietary vitamin C sufficiency exerts preventive effects against the development of obesity-related osteoporosis (118). Comparative analysis stratified by body mass index revealed that obese individuals demonstrated a significant reduction in serum 25-hydroxyvitamin D concentrations relative to non-obese controls (168). Obese individuals exhibit impaired vitamin D metabolism that adversely impacts bone formation (169). In the osteoporotic population, serum 25(OH D3 levels (the predominant circulating form of vitamin D) demonstrate a significant inverse association with triglyceride concentrations, while exhibiting positive correlations with apolipoprotein A1, lipoprotein (a) and high-density lipoprotein cholesterol levels (170). Vitamin E inhibits the synthesis of cholesterol to treat hyperlipidemia (171). Vitamin E exerts inhibitory effects on hepatic cholesterol biosynthesis, thereby ameliorating hyperlipidemic conditions through modulation of key lipid metabolic pathways (172).

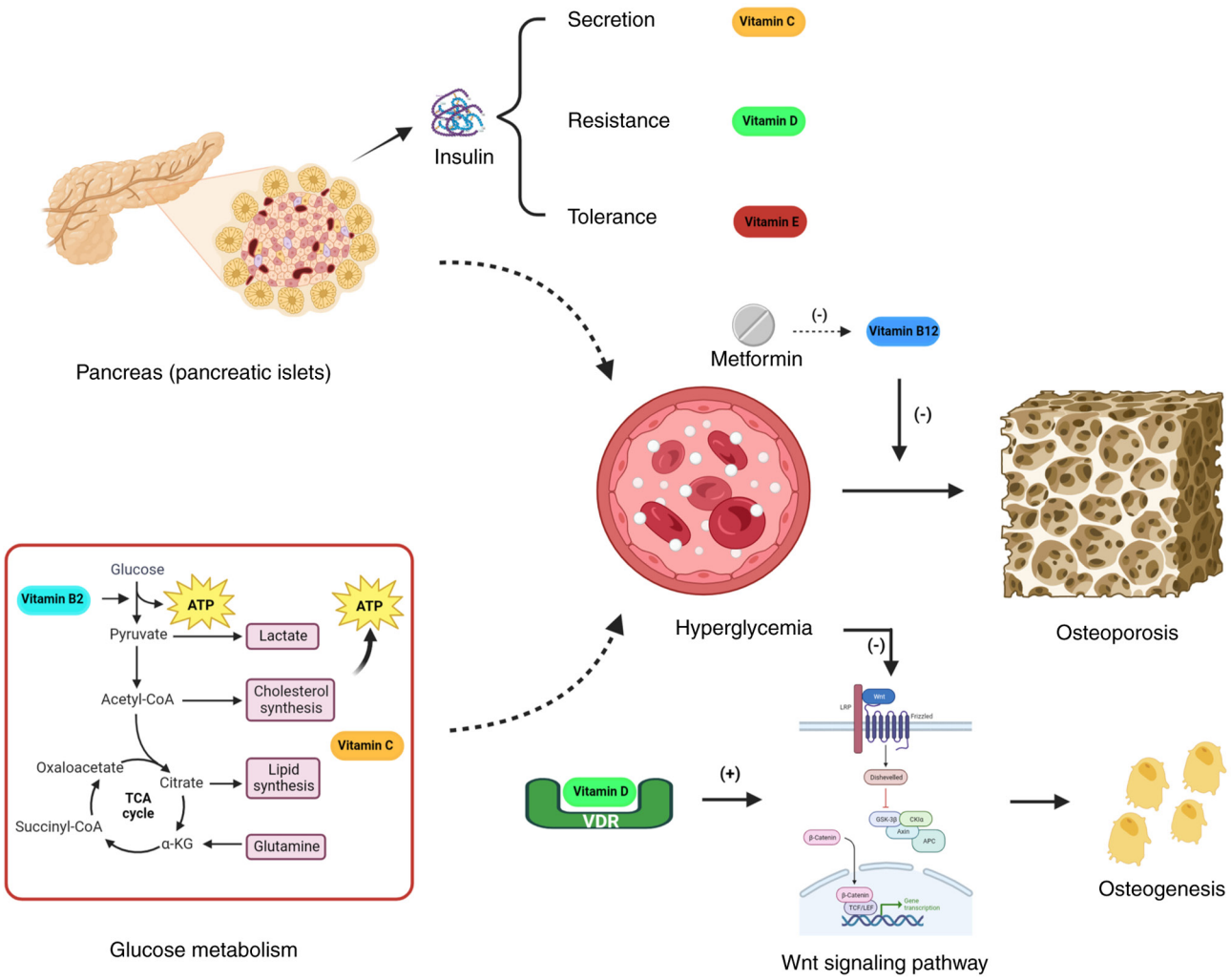

Figure 1. Positive effects of vitamins in diabetic osteoporosis. TCA, tricarboxylic acid cycle; VDR, vitamin D receptor; LRP, LDL receptor-related protein; GSK-3β, glycogen synthase kinase 3β; CKIα, casein kinase Iα; APC, adenomatous polyposis coli; TCF/LEF, T cell factor/lymphoid enhancer binding factor.

Vitamin K demonstrates regulatory effects on adipose tissue metabolism (173). The supplementation of vitamin K in HFD rats was shown to prevent bone loss through dual mechanisms, namely, enhancing osteocalcin-mediated bone formation and suppressing RANKL-induced osteoclastic resorption (174). The combined administration of vitamin K2 and D3 synergistically enhanced the expression of osteogenic transcription factors, specifically osteocalcin, osterix and Runx2, in diet-induced obese murine models (159) (Table III). Overall, vitamins serve as key regulatory factors in lipid metabolism homeostasis. Adequate vitamin intake prevents adipocyte hypertrophy by optimizing lipid turnover rates and attenuating hyperlipidemia-associated comorbidities. Implementation of a vitamin-enriched dietary regimen synergized with structured physical activity constitutes an evidence-based intervention for improving metabolic parameters and preserving BMD in obese populations.

4. Modulatory mechanism of vitamins in osteoporosis

Antioxidant effect. Oxidative stress has been identified as a pathophysiological hallmark in clinically vulnerable cohorts predisposed to osteoporosis, functioning as a critical underlying mechanism driving accelerated BMD decline (7). Vitamins A, C and E are primary regulators of the redox balance. Vitamin A elevates thioredoxin reductase expression to counteract nitric oxide-induced oxidative damage and augments glutathione peroxidase activity to reduce free radical accumulation (175). Meanwhile, vitamin A effectively attenuates lipid peroxidation chain reactions and suppresses malondialdehyde production in lipid metabolic processes (176). Vitamin A intake enhances systemic antioxidant capacity through dual pathways: Attenuating plasma sulfhydryl (SH) group depletion while mitigating oxidative protein modifications (177). Vitamin C exerts antioxidant effects through two primary mechanisms: Protecting SH groups from oxidation, and serving as an electron donor to regenerate reduced glutathione (GSH) from its oxidized form (GSSG) (178). Vitamin E suppresses lipid peroxidation chain reactions, thereby attenuating oxidative stress-induced cellular damage. Concurrently, it facilitates the transfer of membrane-bound lipid peroxides to vitamin C for subsequent enzymatic reduction into non-toxic fatty acids and glycerol derivatives (15,179). Vitamin E significantly enhances systemic antioxidant defense by elevating total antioxidant capacity in serum through potentiation of radical-scavenging enzymatic systems (180).

Table III. Vitamins in the development of obesity-associated osteoporosis.

Viatmins	Role in obesity	Effects on bone tissue	Mechanism
Vitamin A	Increasing the efficiency of fat burning	Inhibiting bone loss and destruction	Related to osteocalcin concentration
Vitamin B2	Regulating the synthesis, decomposition and secretion of fat, lowering body fat levels	Preventing bone loss	-
Vitamin B9	-	Attenuating HFD-induced osteoporosis	Increasing the expression of Nrf2 and antioxidant enzymes, activating the AMPK signaling pathway
Vitamin B12	Negatively correlated with body fat	-	-
Vitamin C	-	Preventing the occurrence of obesity-associated osteoporosis	Propelling the differentiation direction of MSCs toward osteogenesis rather than adipogenesis
Vitamin D	Negatively correlated with blood triglyceride concentration but positively correlated with apolipoprotein A, lipoprotein A and high-density lipoprotein cholesterol	-	-
Vitamin E	Inhibiting the synthesis of cholesterol to treat hyperlipidemia	Enhancing bone quality	-
Vitamin K	-	Preventing HFD-induced bone loss	Promoting osteocalcin-mediated bone formation and inhibiting RANKL-induced bone resorption

HFD, high-fat diet; MSC, mesenchymal stem cell; RANKL, receptor activator of nuclear factor κB ligand; Nrf2, nuclear factor erythroid 2-related factor 2; MSC, mesenchymal stem cell.

Antioxidant vitamins demonstrate significant therapeutic potential in enhancing BMD through attenuation of oxidative stress-mediated bone resorption and promotion of osteoblastic activity (181). Epidemiological evidence substantiates that dietary vitamins A, C and E confer significant risk reduction for osteoporosis through synergistic mitigation of oxidative stress, while serving as essential modulators of bone remodeling homeostasis (182). The composite dietary antioxidant index, encompassing vitamins A, C and E, demonstrates a significant inverse correlation with BMD during osteoporotic progression (106). Oral antioxidant vitamins demonstrate therapeutic benefits in attenuating age-related physiological decline and ameliorating oxidative stress-associated bone deterioration through comprehensive modulation of redox homeostasis (183). Meanwhile, these antioxidant vitamins, especially vitamin E, can notably decrease fracture occurrence at any site (184). Vitamins C and E enhance collagen synthesis, osteogenic differentiation and matrix mineralization through their antioxidant properties (185). Vitamin C demonstrates therapeutic efficacy in counteracting oxidative skeletal damage resulting from diverse pathological stressors (186,187). Vitamin C treatment effectively reduces stress-induced osteoblast death and inhibits RANKL/macrophage colony-stimulating factor-mediated osteoclast differentiation under oxidative conditions (188). Sodium-dependent vitamin C co-transporters orchestrate the homeostatic regulation of redox balance in osseous tissue through dual mechanisms: Modulating transcriptional activation of antioxidant enzyme systems, while coordinating osteogenic differentiation processes (189,190). Vitamin E exerts bone-protective effects during osseous metabolism through its antioxidant properties, which mitigate oxidative damage to bone tissue components and maintain redox homeostasis (191). Vitamin E modulates the redox balance to suppress adipogenic differentiation in bone marrow MSCs, thereby preserving their osteogenic potential under oxidative conditions (192). Vitamin E protects osteoblasts from reactive oxygen species (ROS)-induced oxidative stress by elevating the GSH redox ratio (GSSH/GSSG), thereby enhancing cellular antioxidant defenses in bone-forming cells (193). Moreover, vitamin E restores mitochondrial function to suppress ROS-mediated osteoclastogenesis (86). Multiple vitamins modulate redox processes to regulate bone metabolic equilibrium. Activated vitamin D enhances mitochondrial ultrastructure and functional restoration,

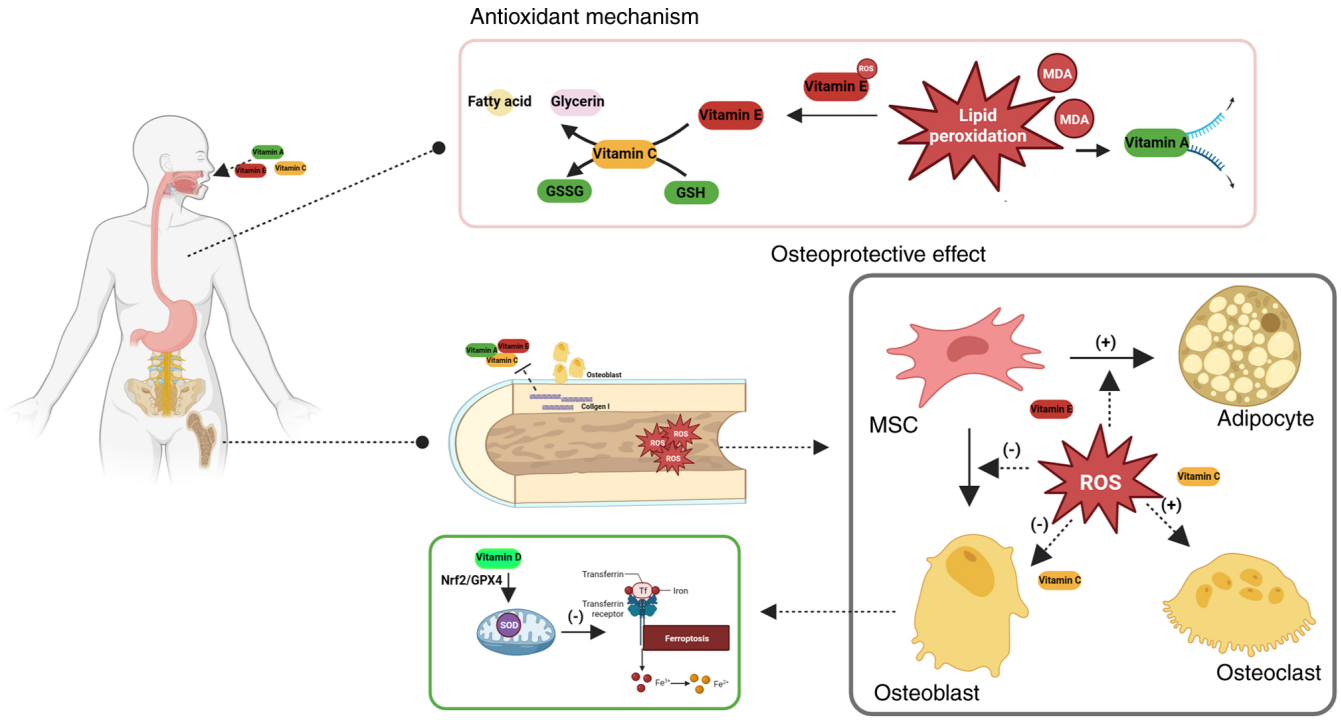

Figure 2. Antioxidant effects of vitamins in the prevention and treatment of osteoporosis. GSH, glutathione; GSSG, oxidized glutathione; MDA, malondialdehyde; MSC, mesenchymal stem cell; ROS, reactive oxygen species; Nrf2, nuclear factor erythroid 2-related factor 2; GPX4, glutathione peroxidase 4; Tf, transferrin; SOD, superoxide dismutase.

thereby optimizing redox homeostasis in osseous tissue (194). Vitamin D upregulates antioxidant enzyme expression to alleviate oxidative stress, thereby preventing osteoblast apoptosis through enhanced cellular redox homeostasis (195). VDR activation suppresses oxidative damage-induced osteoblast ferroptosis through Nrf2/glutathione peroxidase 4 pathway stimulation (196) (Fig. 2). Pantothenic acid orchestrates dual cytoprotective mechanisms through FoxO1/2 and Nrf2 signaling pathway activation, attenuating osteoclastogenesis via suppression of intracellular ROS overproduction (197). Vitamin K2 functions as an antioxidant in bone tissue engineering, effectively reducing ROS-induced damage to enhance bone repair processes (198). Vitamin K2 derivatives demonstrate inhibitory effects on oxidative stress-mediated osteoblast apoptosis (199).

Anti-inflammatory effect. Inflammation is an important pathogenic factor in the development of osteoporosis (200). Vitamin C demonstrates anti-inflammatory efficacy in OVX rats by attenuating TNF-α-mediated inflammatory infiltration in osseous tissues (201). Vitamin D deficiency induces systemic metabolic derangements and endocrine axis imbalance, culminating in elevated secretion of pro-inflammatory cytokines IL-6 and TNF-α (122). Vitamin D deficiency is also associated with an elevated erythrocyte sedimentation rate, C reactive protein (CRP) level and IL-6 level, which has a negative effect on BMD by decreasing osteocalcin (202). Vitamin D deficiency is associated with elevated levels of inflammatory markers (erythrocyte sedimentation rate (ESR), CRP and IL-6), which collectively contribute to reduced BMD via inhibition of osteocalcin production (203,204). Vitamin E supplementation attenuates inflammatory responses through downregulation of IL-1, IL-6 and CRP, effectively inhibiting osteoporotic progression (205). Vitamin K2 suppresses the secretion of pro-inflammatory cytokines, specifically IL-1α, IL-1β and TNF-α (206). Vitamin K2 suppresses both the activation and proliferation of circulating T cells, thereby enhancing bone mass through immunoregulatory mechanisms (207). Vitamin A exerts detrimental effects on bone metabolism through pro-inflammatory pathways. Specifically, retinoic acid suppresses the osteogenic differentiation of MSCs by stimulating the NF-κB/NLRP3 inflammasome axis and triggering IL-1β release (208). Downregulation of IL-6 secretion correlates with reduced expression of ALP and osteocalcin, critical biomarkers of osteogenic differentiation (209).

5. Discussion

Amidst the global demographic aging trend and the proliferation of sedentary lifestyle patterns, contemporary healthcare systems face escalating demands for enhanced quality-of-life metrics and optimized management of chronic degenerative diseases. Osteoporosis, a prevalent bone metabolic disorder, is pathologically manifested as progressive deterioration of bone microarchitecture with concomitant declines in mineral density (210). Current diagnostic paradigms rely on dual-energy X-ray absorptiometry (DXA) as the clinical gold standard, while suffering from inherent limitations, including cost-prohibitive screening protocols and suboptimal diagnostic accuracy in heterogeneous populations due to physiological confounding factors (211). Meanwhile, current osteoporosis treatment primarily employs drugs that directly stimulate osteogenesis and suppress osteoclastogenesis, yet these therapeutic approaches demonstrate constrained clinical

efficacy and notable adverse effects (212). This context necessitates the development of novel diagnostic methodologies and therapeutic regimens to address contemporary clinical requirements in osteoporosis management.

Vitamins constitute indispensable micronutrients critical for human physiological homeostasis. These compounds orchestrate fundamental biological processes encompassing substrate metabolism, bioenergetic flux and homeostatic governance (213). Emerging evidence has elucidated their regulatory roles in bone metabolism through pleiotropic mechanisms (214,215). The present review systematically delineates vitamin-mediated physiological networks and elucidates their differential modulatory effects across heterogeneous bone tissue compartments. In the diagnostic paradigm, serum vitamin D quantification combined with bone turnover marker profiling augments the clinical utility of DXA through comprehensive evaluation of osteoporotic status (216). Research has also demonstrated the potential of other vitamins in the prediction of the risk of osteoporosis. Vitamin K and its derivatives have been confirmed to decrease in serum concentration earlier than vitamin D during the development of osteoporosis, suggesting that their measurement might detect the trend of bone loss earlier (126). Vitamin E demonstrates predictive value for BMD, although its clinical utility is confounded by demographic variables, including age, sex and ethnicity (217). Quantitative analysis of multiple vitamins in the blood is a potential method for predicting bone mass and evaluating bone mass based on different conditions. Vitamins are also effective substances for preventing and treating osteoporosis. In addition to the dual effects of vitamin A, other related vitamins showed positive effects on bone homeostasis. Vitamin D-calcium co-supplementation is recognized as the foundational therapeutic adjuvant in osteoporosis management (218). Moreover, the present review demonstrates that vitamins could increase the expression of osteogenic biomarkers and promote the mineralization of the bone matrix. Inhibition of bone resorption could also be enhanced after vitamin intake. Deeply exploring the role of vitamins in the development of osteoporosis contributes to optimizing diagnosis and treatment plans.

Vitamin disturbance is common in high-risk populations for osteoporosis. In postmenopausal women, vitamins participate in the regulation of reproductive function. Vitamins influence the secretion of estrogen, and estrogen performs biological functions through vitamin receptors. Vitamins are also important mediators involved in the action of estrogen in bone metabolism, and are associated with the development of osteoporosis. Vitamins A and D could also predict the risk of osteoporotic fractures in postmenopausal women. In diabetic patients, vitamin supplementation is beneficial for improving blood glucose and preventing complications. Vitamins not only regulate glucose metabolism processes, but also increase sensitivity and reduce resistance to insulin. Conventional treatments for diabetes, such as oral metformin, could lead to deficiencies in certain vitamins. Therefore, vitamins are essential in the maintenance and treatment of diabetes mellitus. In obesity groups, vitamins mainly affect blood lipid concentration by regulating the synthesis and decomposition of adipose tissue. On the one hand, vitamins induced osteogenic differentiation of MSCs rather than adipogenesis. On the other hand, reasonable lipid composition and content maintain the balance of bone formation and resorption. Additionally, the pathological changes can be improved with vitamin treatment in osteoporosis. Vitamins increase the expression of antioxidant enzymes and activate the antioxidant pathways to relieve the oxidative stress induced by the primary changes in osteoporosis. Decreasing the production of ROS and repairing the function of mitochondria contribute to attenuating osteoblast injury and inhibiting osteoclast activity. The redox balance is also positive for the maintenance of bone homeostasis. Improving the inflammatory response is another mechanism of vitamins in the treatment of osteoporosis. Vitamins inhibit the secretion of inflammatory cytokines and deactivate inflammasomes, which relieves the inhibition of osteogenesis. Circular RNA enrichment analysis has also indicated that vitamin digestion and absorption are associated with the development of osteoporosis (219,220). Based on large sample sizes of clinical trial data, it can be concluded that targeted delivery of vitamin molecules, such as loading nanoparticles, contributes to improving the diagnosis and treatment efficiency of osteoporosis in high-risk populations (221-223).

The present review systematically delineates the pleiotropic regulatory roles of vitamins in bone metabolism through their functional interplay with osseous homeostasis and skeletal remodeling dynamics. Blood vitamin content is significantly associated with the development of osteoporosis. The combination of multiple vitamins helps predict the risk of osteoporosis and bone loss under different primary etiologies. The positive effect of vitamins on bone formation determines the potential for osteoporosis treatment. The improvement of oxidative stress and inflammation in high-risk populations for osteoporosis also indicates the systemic modulation of vitamins. Specific vitamin supplements will effectively prevent and improve bone loss. Developing vitamin guidelines for people with osteoporosis is a research topic of considerable interest.

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Authors' contributions

MJ was responsible for data curation, literature search methodology, use of the software for literature analysis and classification, and writing the original draft. GL was responsible for literature search methodology, validation of the literature and writing the original draft. KY was responsible for literature organization, use of the software for literature

analysis, validation of the literature, and reviewing and editing the manuscript. LT was responsible for funding acquisition, project administration, and reviewing and editing the manuscript. All authors have read and approved the 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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