Branched-chain amino acid metabolism and bone metabolism: Implications for osteoporosis pathogenesis and therapeutic strategies (Review)

QI XIAO[1,2*], HAIMIN ZENG[1,3*], RUHUI YANG[1,3*], YUXIN ZHAN[1,3], FANGZHEN LIN[1,3], BOFAN CHEN[1,3] and XIANG CHEN[1]

[1]Department of Rehabilitation Medicine, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330006, P.R. China; [2]The First Clinical Medical College, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330006, P.R. China; [3]The Second Clinical Medical College, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330006, P.R. China

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Abstract. Branched-chain amino acids (BCAAs) are biologically active amino acids with branched carbon chains, recognized for their diverse biological functions and therapeutic potential. BCAAs have demonstrated promising effects in the prevention and treatment of various conditions, including muscle growth disorders, cardiovascular diseases and cancer. Despite extensive research confirming their targeted therapeutic effects in multiple domains, the mechanisms of action and therapeutic range of BCAAs remain incompletely understood. Osteoporosis, a metabolic bone disease, is a global public health issue characterized by an imbalance between osteoblast-mediated bone formation and osteoclast-induced bone resorption, resulting in fragile bones and an elevated risk of fractures. Given the well-documented therapeutic roles of BCAAs, their potential link to osteoporosis has been explored, emphasizing the influence of BCAA metabolism on bone metabolism. The present review aims to summarize findings on the relationship between BCAA metabolism and osteoporosis, and to investigate the mechanisms by which BCAA metabolism may exert anti-osteoporotic effects. The review first outlines the fundamental processes and key factors influencing bone metabolism, BCAA metabolism and osteoporosis. It then examines the interactions between these processes and the effects of BCAA metabolism on bone health. Finally, it explores the potential of targeting BCAA metabolic pathways as a future therapeutic strategy for osteoporosis, highlighting BCAAs as a promising target for treating this condition.

Correspondence to: Dr Xiang Chen, Department of Rehabilitation Medicine, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, 1 Minde Road, Donghu, Nanchang, Jiangxi 330006, P.R. China
E-mail: chenxiangteam2025@163.com

*Contributed equally

Abbreviations: BCAA, branched-chain amino acid; RANKL, receptor activator of NF-κB ligand; RANK, receptor activator of NF-κB; TGF-β, transforming growth factor-β; IGF-1, insulin-like growth factor-1; ATP, adenosine triphosphate; PANX1, Pannexin 1; P2X7R, P2X7 receptor; OPG, osteoprotegerin; PTH, parathyroid hormone; Cx43, connexin 43; BCAT, BCAA transaminase; BCKDH, branched-chain α-ketoacid dehydrogenase; BCKAs, branched-chain α-ketoacids; mTOR, mechanistic target of rapamycin; mTORC, mTOR complex; BAIBA, β-aminoisobutyric acid; 3-HIB, 3-hydroxyisobutyric acid; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; T_M, memory T; T_{EM}, effector T_M; BMSCs, bone marrow mesenchymal stem cells; NAP1L2, nucleosome assembly protein 1 like 2; BMD, bone mineral density; MMnet, macrophage multinucleation network; DAMP, damage-associated molecular pattern; PRRs, pattern recognition receptors; P2Y2, purinergic receptor P2Y 2; P2Y1, purinergic receptor P2Y 1; PTHrP, PTH-related protein; GH, growth hormone; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; KIC, α-ketoisocaproate; KIV, α-ketoisovalerate; KMA, α-ketomethylvalerate; PTH1R, PTH1 receptor; TCA, tricarboxylic acid; α-KG, α-ketoglutarate; BMDCs, bone marrow dendritic cells; SASP, senescence-associated secretory phenotype; Th17, T helper 17

Key words: BCAAs, osteoporosis, bone metabolism, BCAA metabolism, therapeutic target

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1. Introduction

Osteoporosis, a prevalent metabolic bone disease with notable medical and socioeconomic implications, is characterized by low bone mass and microarchitectural deterioration,

leading to weakened bone strength and an increased risk of fragility fractures (1). According to the National Health and Nutrition Examination Survey in the United States, ~20% of postmenopausal women have been diagnosed with osteoporosis (2). As the global population ages, this prevalence is expected to increase in the coming years (3). For individuals with osteoporosis, the lifetime risk of fractures can reach up to 40%; from the perspective of patients, fractures, along with the subsequent loss of mobility and independence, often result in a substantial decline in quality of life. Moreover, osteoporotic fractures, particularly of the hip and spine, are associated with a 12-month excess mortality rate of up to 20%, primarily due to hospitalization, which increases the risk of complications such as pneumonia or thromboembolic events from prolonged immobility, further compounding the public health burden (4). The pathophysiology of osteoporosis is marked by an imbalance between bone resorption and formation, which is influenced by factors such as aging, hormonal changes, nutritional deficiencies and genetics (5,6). Notably, the interaction between osteoblasts and osteoclasts is crucial for maintaining bone homeostasis. Osteoblasts express and secrete receptor activator of NF-κB ligand (RANKL), which promotes the differentiation of osteoclast precursors into mature osteoclasts. Conversely, when bone resorption disrupts the bone structure, osteoclasts release insulin-like growth factors (IGFs), which stimulate osteogenic differentiation (7). However, dysregulated bone remodeling negatively affects bone mass. A reduction in osteoblast activity, responsible for producing the calcified organic extracellular matrix, leads to increased bone resorption. Simultaneously, osteoclasts degrade the extracellular matrix and the cumulative effect of these processes can result in bone loss (8). Understanding the underlying mechanisms of bone remodeling and the factors influencing bone mass is critical for developing effective strategies to prevent and treat osteoporosis.

Branched-chain amino acids (BCAAs), including leucine, isoleucine and valine, are essential amino acids primarily known for their role in muscle protein synthesis (9). In addition to their function in skeletal muscle, BCAAs have been linked to the regulation of metabolic disorders such as diabetes, cardiovascular diseases and cancer (10). They may also influence aging and longevity in animal models (11). Recent research has identified a range of molecules involved in maintaining bone homeostasis, with BCAAs emerging as potential modulators within this regulatory network (12).

The present review summarizes the interactions between bone metabolism and BCAA metabolism, focusing on the causes and consequences of metabolic abnormalities. It also explores the relationship between bone metabolism and osteoporosis, highlighting how dysregulated BCAA metabolism may contribute to osteoporosis. Finally, the potential of BCAAs as a treatment for osteoporosis is discussed, offering novel insights into their role in bone health. In conclusion, the current review may enhance understanding of the mechanisms by which BCAAs contribute to the pathogenesis of osteoporosis. It not only provides dietary recommendations but also emphasizes the potential for BCAA-based interventions in the management of osteoporosis, paving the way for novel therapeutic approaches to combat this disease.

2. Bone metabolism

Structure and function of bone. Bone is a dynamic, metabolically active tissue and an essential organ system in higher vertebrates, serving as the primary structural component of the skeleton. It is a specialized connective tissue composed of osteocytes, osteoblasts, bone-lining cells and osteoclasts. The bone matrix consists of ~60% inorganic mineral phase (primarily semi-crystalline, carbonated hydroxyapatite), 30% organic phase, which includes type I collagen fibrils and non-collagenous proteins, and 10% water (13). Additionally, small leucine-rich proteoglycans, a key component of non-collagenous proteins, are present in the bone matrix (14).

Bone performs four critical functions: i) Providing structural support and anchorage for muscles, ii) protecting vital organs such as the brain and bone marrow, iii) supporting hematopoiesis (15-17), and iv) serving as a metabolic reservoir for calcium and phosphate. These physiological functions rely on the tightly regulated processes of bone modeling and remodeling to maintain skeletal homeostasis (18).

Process of bone metabolism. Bone remodeling involves the resorption of old or damaged bone by osteoclasts, followed by the formation of new bone by osteoblasts (19). In contrast to bone modeling, remodeling is a coupled, spatially and temporally coordinated process that does not alter bone shape (20). It is a tightly regulated physiological process and dysfunction in any component of this system can disrupt bone metabolism, contributing to conditions such as osteoporosis (21).

Bone metabolism is a complex process precisely coordinated by osteoclasts, osteoblasts and osteocytes. Osteoclasts originate from mononuclear precursors of the monocyte/macrophage lineage, and their differentiation and activation depend on two critical signals: Macrophage colony-stimulating factor (22) and RANKL (23,24), as substantiated by Nakahama *et al* (25). The binding of RANKL to receptor activator of NF-κB (RANK) on osteoclast precursors initiates osteoclastogenesis (26). Mature, functional osteoclasts form a ruffled border mediated by Src kinase (27,28) and secrete cathepsin K to degrade the bone matrix, accomplishing bone resorption (29,30). Gelb *et al* (29) demonstrated that osteoclasts from human patients with cathepsin K gene mutations fail to efficiently degrade the bone organic matrix, providing direct clinical evidence linking cathepsin K to osteoclastic resorption.

Osteoblasts are derived from various sources, including bone marrow stromal cells and bone-lining cells (31). During bone resorption, factors released from the bone matrix, such as transforming growth factor-β (TGF-β) and IGF-1, recruit osteoblast precursors to the bone surface (32). Osteoblast differentiation is primarily regulated by the canonical Wnt/β-catenin signaling pathway. Upon activation of this pathway, β-catenin is stabilized and translocates into the nucleus, where it binds to LEF/TCF transcription factors. This interaction activates the expression of osteogenic genes such as Runx2, promoting the differentiation of osteoblasts from progenitor cells into mature cells (33). Mature osteoblasts then secrete type I collagen and other components, forming osteoid and facilitating its mineralization to build new bone. After completing their task, most osteoblasts undergo apoptosis, while some differentiate into osteocytes or revert to quiescent bone-lining cells (34,35).

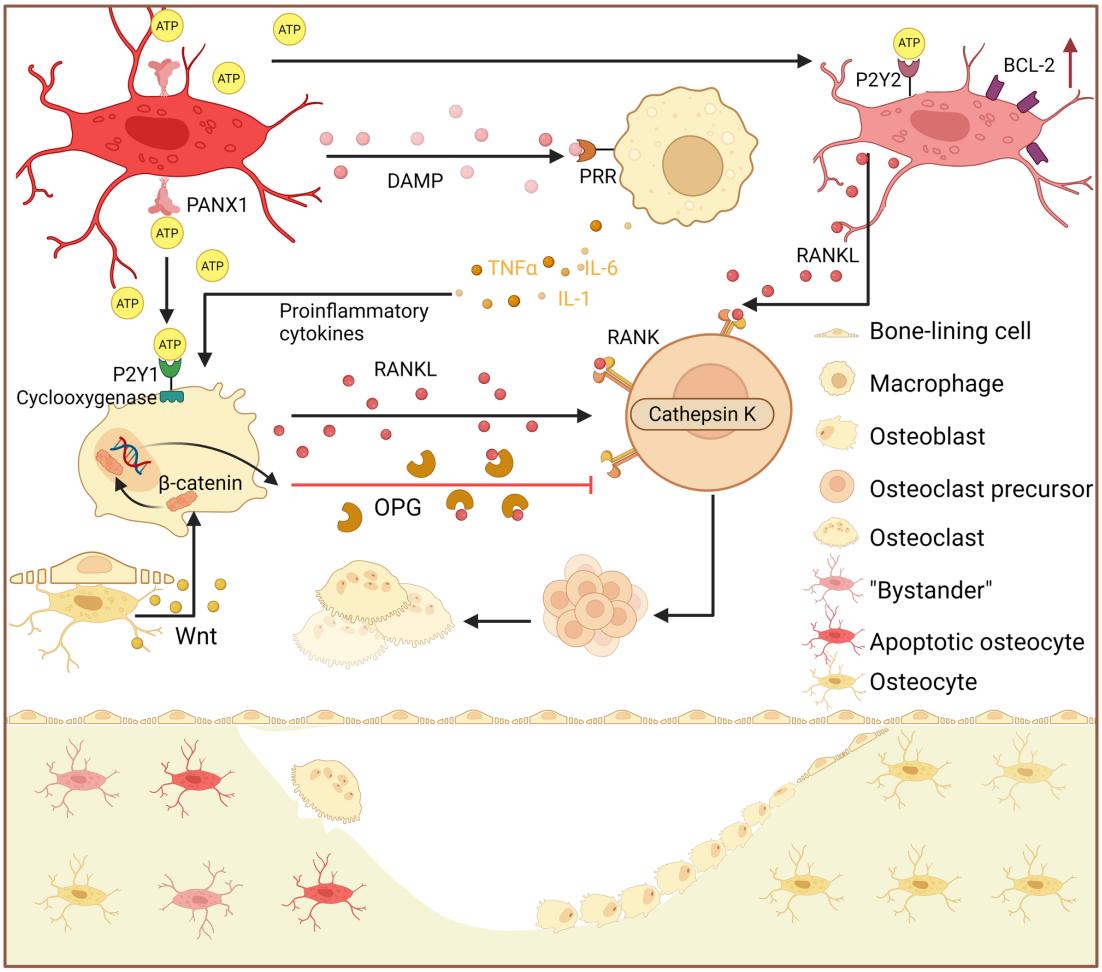

Figure 1. Bone metabolism process. Apoptotic osteocytes release ATP via PANX1 channels, activating P2Y1 receptors on neighboring osteocytes, which upregulate RANKL through cyclooxygenase-dependent pathways. Simultaneously, DAMPs from apoptotic cells engage macrophage PRRs, triggering the release of proinflammatory cytokines (such as TNFα and IL-6) that further enhance osteoblastic RANKL production. The RANKL-RANK interaction promotes osteoclast differentiation, with cathepsin K facilitating bone resorption. In parallel, osteocyte bone-lining syncytium activates Wnt/β-catenin signal: Wnt ligand binds to the receptor on the membrane to stabilize β-catenin, driving osteoblast differentiation and OPG production. This dual regulatory mechanism ensures a balance between bone resorption (RANKL-driven) and formation (Wnt-mediated) during remodeling. ATP, adenosine triphosphate; OPG, osteoprotegerin; P2Y, purinergic receptor P2Y; PANX1, Pannexin 1; PRR, pattern recognition receptor; RANK, RANKL, receptor activator of NF-κB; RANKL, RANK ligand; DAMP, damage-associated molecular pattern. Created in BioRender. zhan, a. (2025) https://BioRender.com/7e0mcn5.

Osteocytes, embedded within the mineralized matrix, serve as key regulators of bone homeostasis (36). By contrast, necrotic osteocytes release damage-associated molecular patterns (37), which bind to pattern recognition receptors (38), initiating the production of proinflammatory cytokines, such as TNFα, IL-1 and IL-6 (39). These cytokines indirectly amplify RANKL signaling (40) by increasing RANKL expression in osteoblasts (41). Osteocyte apoptosis is a critical trigger for bone remodeling (37), as these cells recruit osteoclasts to microcracks, initiating targeted bone resorption and maintaining dynamic bone tissue homeostasis (42). Kringelbach *et al* (41) demonstrated that apoptosis in the MLO-Y4 osteocyte cell line induces the release of adenosine triphosphate (ATP) via the activation of Pannexin 1 (PANX1) channels. A similar phenomenon has been observed in mice treated with a P2X7 receptor (P2X7R) inhibitor, highlighting the role of P2X7R as a coactivator of PANX1 (43). The released ATP subsequently stimulates RANKL expression through a signaling cascade involving the purinergic receptor P2Y (P2Y)1 receptor and cyclooxygenase activity (44-46). ATP released from apoptotic osteocytes likely binds to P2Y2 receptors on osteocytes in the penumbra regions, known as 'bystander' osteocytes (47); this binding may also trigger RANKL production and release (43).

The termination of bone remodeling involves multiple steps, including the secretion of osteoprotegerin (OPG) by mature osteoblasts and/or osteocytes, which may serve as a key inhibitory signal (48). Additionally, upregulation of the anti-apoptotic protein BCL-2 in 'bystander' osteocytes near the damage site helps protect viable osteocytes from osteoclastogenic stimuli originating from adjacent apoptotic cells (Fig. 1) (49,50).

Important factors in bone metabolism. Bone metabolism is regulated by both local intercellular signaling among bone cells and a range of systemic factors. Calcium and phosphate regulators maintain mineral homeostasis, which is crucial for bone mineralization. $1,25(OH)_2D_3$ enhances intestinal calcium and phosphate absorption directly (51), while also modulating osteoblast and osteoclast activity (52-54). Concurrently,

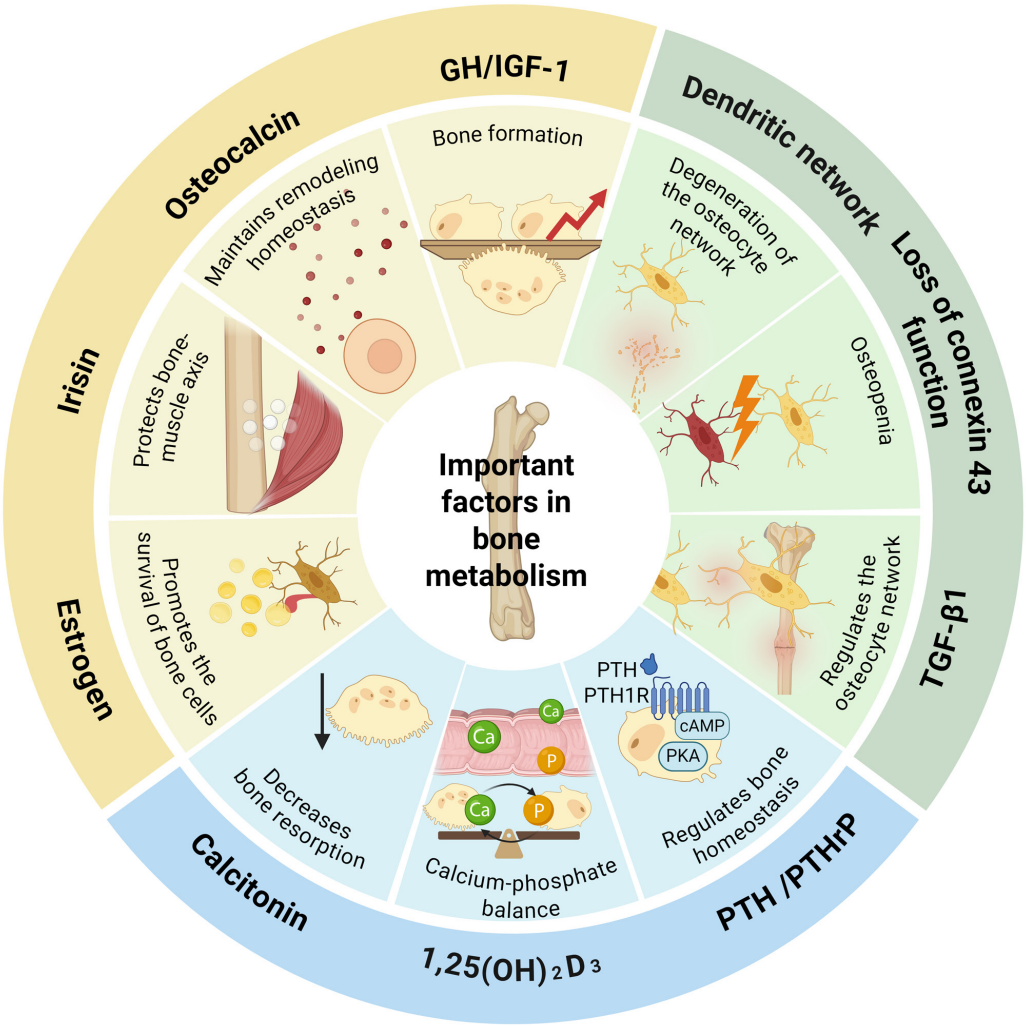

Figure 2. Key regulators of bone metabolism. Calcium-phosphate homeostasis factors (blue): PTH/PTHrP modulates calcium-phosphate metabolism through the PTH1R/cAMP/PKA pathway; 1,25 $(OH)_2D_3$ promotes intestinal calcium and phosphate absorption; calcitonin suppresses osteoclast activity. Osteocyte network factors (green): Connexin 43 mediates intercellular communication; degeneration of the dendritic network of bone cells leads to a decline in bone function; TGF-β1 regulates the integrity of the intrinsic regulatory network. Bone formation and balance factors (yellow): GH/IGF-1 drives bone remodeling; estrogen promotes bone cell survival; osteocalcin maintains bone metabolism homeostasis; irisin protects the bone-muscle axis. cAMP, cyclic adenosine monophosphate; GH, growth hormone; IGF-1, insulin-like growth factor-1; PKA, protein kinase A; PTH, parathyroid hormone; PTH1R, PTH1 receptor; PTHrP, PTH-related protein; TGF-β, transforming growth factor-β. Created in BioRender. zhan, a. (2025) https://BioRender.com/cgf8v8x.

parathyroid hormone (PTH) and PTH-related peptide regulate calcium-phosphate homeostasis in bone and the kidneys by activating the cyclic adenosine monophosphate-protein kinase A pathway through the PTH1 receptor (55,56). Elevated phosphate levels, in turn, stimulate the secretion of fibroblast growth factor 23, which suppresses 1,25$(OH)_2D_3$ synthesis and promotes renal phosphate excretion, creating a critical feedback loop (57,58). Calcitonin acts antagonistically by directly inhibiting bone resorption to lower blood calcium levels (59,60), thereby ensuring precise regulation of calcium homeostasis.

Osteocyte communication and the integrity of the network are central to the mechanosensing and signaling system of bone. Connexin 43 (Cx43) underpins intercellular communication among osteocytes, and its loss of function directly impairs bone mass acquisition and maintenance (61-63). Similarly, the integrity of the osteocyte dendritic network is essential, with age-related declines in network function directly associated with cortical bone deterioration (64). Additionally, TGF-β1 signaling is a key intrinsic regulator of this network, preserving bone mechanical integrity by modulating dendritic length and the expression of genes such as sclerostin and MMPs (65). These factors, particularly in aging and metabolic diseases (including diabetes and obesity), interact with the broader bone metabolism regulatory network (66).

The balance between bone formation and resorption directly determines the net outcome of bone remodeling. For example, growth hormone, by stimulating IGF-1 expression, increases bone turnover with a net anabolic effect, leading to modest bone mass gain (67,68). Estrogen promotes osteocyte survival via semaphorin 3A (69), fluid flow shear stress (70), Wnt/β-catenin signaling (71) and Cx43 expression (72), helping to counteract age-related bone loss. The myokine irisin also serves a protective role in the bone-muscle axis by reducing osteocyte apoptosis (73). Additionally, vitamin K-dependent osteocalcin, secreted by osteoblasts, connects bone metabolism to systemic energy metabolism, broadening the regulation of bone homeostasis (Fig. 2) (74).

Table I. Impact of multiple factors on bone metabolism imbalance.

Factor	Impact on bone metabolism imbalance	(Refs.)
Hormonal changes		
Decreased estrogen levels	Increase	(76)
PTH	Increase	(77)
Nutritional deficiencies		
Calcium	Increase	(79)
Vitamin D	Increase	(79)
High protein	Increase	(80)
Vitamin K	Increase	(74)
Genetic susceptibility		
Hypophosphatasia	Increase	(81)
Lysosomal storage disease	Increase	(81)
Abnormal purine metabolism	Increase	(82)
Environment and lifestyle		
Lack of physical activity	Increase	(83-85)
Smoking	Increase	(83-85)
Excessive alcohol consumption	Increase	(83-85)

PTH, parathyroid hormone.

Reasons for an imbalance in bone metabolism. Bone metabolic imbalance is a complex condition arising from a variety of physiological and pathological factors. A primary underlying mechanism is the disruption of the dynamic balance between osteoclastic bone resorption and osteoblastic bone formation. This dysregulation can lead to skeletal disorders such as osteoporosis, which is characterized by reduced bone mass and increased susceptibility to fractures. Contributing factors include hormonal imbalances, inadequate nutrition and genetic predispositions (75).

Hormonal changes, particularly those involving estrogen and PTH, serve a central role in bone metabolism. Estrogen deficiency, commonly observed in postmenopausal women, accelerates bone resorption, thereby promoting osteoporosis (76). Similarly, parathyroid gland disorders disrupt calcium and phosphate metabolism, further exacerbating bone loss (77). The skeleton also functions as an endocrine organ; hormones such as osteocalcin regulate both energy metabolism and bone homeostasis, highlighting the close link between skeletal and metabolic health (78).

Nutritional factors markedly influence bone health. Adequate calcium and vitamin D intake is essential for maintaining bone density, with deficiencies in these nutrients leading to impaired bone mineralization and an increased fracture risk (79). Additionally, while high protein intake exerts a bone-anabolic effect, this benefit can be counteracted by a high dietary acid load, ultimately promoting bone loss (80). The role of vitamin K, particularly in relation to osteocalcin, is also important; vitamin K is involved in the carboxylation of osteocalcin, a process essential for bone mineralization and metabolic regulation (74).

Genetic factors and metabolic disorders predispose individuals to bone metabolism disorders. Conditions such as hypophosphatasia and lysosomal storage disease result in skeletal abnormalities and heightened osteoporosis risk. These genetic disorders often cause imbalances in calcium and phosphate metabolism, which are critical for bone health (81). Additionally, abnormalities in purine metabolism have been identified as a notable factor in bone remodeling, contributing to osteoporosis in various high-risk populations (82).

Environmental and lifestyle factors, such as physical inactivity, smoking and excessive alcohol consumption, are well-established negative influences on bone health. These factors increase oxidative stress and inflammation, both of which are detrimental to bone remodeling (83-85). The accumulation of advanced oxidation protein products has been shown to contribute to bone-fat imbalance during skeletal aging, highlighting the impact of oxidative stress on bone metabolism (Table I) (86-88).

3. Function of BCAA metabolism in bone metabolism

Type and source of BCAA. BCAAs, comprising leucine, isoleucine and valine, are essential amino acids that must be sourced from the diet, as they cannot be synthesized endogenously in animals (89). Despite being classified together as BCAAs, leucine, isoleucine and valine exhibit distinct structural, metabolic and functional characteristics, which underlie their intricate regulation of bone metabolism (90). Leucine, with its highly hydrophobic isobutyl side chain, is the most hydrophobic of the three, a property essential for its function as a signaling molecule. This hydrophobicity facilitates the role of leucine in activating downstream targets, establishing its dominant role in signal transduction (91).

Role of BCAAs in bone metabolism. Beyond serving as fundamental components for protein synthesis, BCAAs are key regulators of cellular metabolism, energy production and signal transduction (92). After ingestion, BCAAs undergo

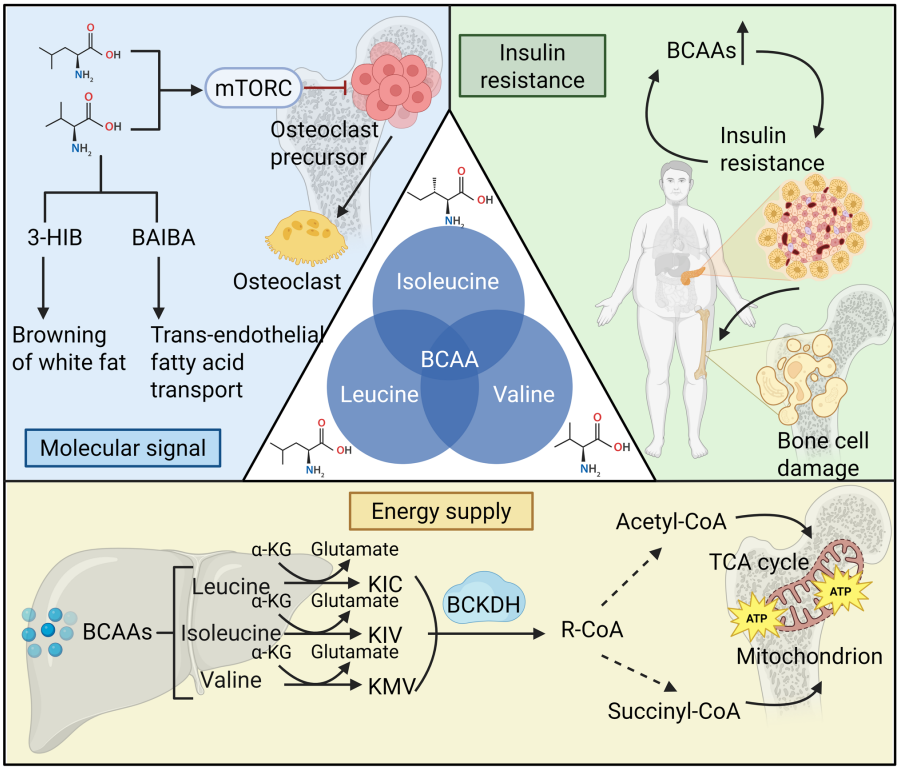

Figure 3. Role of BCAAs in bone metabolism. BCAAs (leucine, isoleucine and valine) undergo deamination to produce α-ketoacids (KIC, KIV and KMV), which are then oxidatively decarboxylated by BCKDH. The resulting metabolites are further processed through enzymatic reactions to generate acetyl-CoA (from leucine and isoleucine) and succinyl-CoA (from valine and isoleucine). Acetyl-CoA and succinyl-CoA enter the TCA cycle, influencing mitochondrial function and oxidative stress. BCAA metabolites, including 3-HIB and BAIBA, regulate trans-endothelial fatty acid transport, white adipose tissue browning and osteoclast precursor differentiation. mTORC1 signaling, activated by BCAAs, modulates osteoclastogenesis and bone resorption, while insulin resistance linked to BCAA dysregulation impairs osteoblast function and exacerbates bone cell damage. 3-HIB, 3-hydroxyisobutyric acid; α-KG, α-ketoglutarate; ATP, adenosine triphosphate; BAIBA, β-aminoisobutyric acid; BCAA, branched-chain amino acid; BCKDH, branched-chain α-ketoacid dehydrogenase; mTORC, mechanistic target of rapamycin complex; KIC, α-ketoisocaproate; KIV, α-ketoisovalerate; KMA, α-ketomethylvalerate; TCA, tricarboxylic acid; R-CoA, acyl-CoA. Created in BioRender. zhan, a. (2025) https://BioRender.com/9461i1f.

enzymatic transformation across various tissues, with the highest concentrations observed in skeletal muscle, brown adipose tissue, liver, kidney and heart (93). Enzymes such as BCAA transaminase (BCAT) and branched-chain α-ketoacid dehydrogenase (BCKDH) catalyze the production of important metabolites, including branched-chain α-ketoacids (BCKAs), acetyl-CoA and succinyl-CoA, which contribute to processes such as the tricarboxylic acid cycle and fatty acid metabolism (Fig. 3) (94). The distinct metabolic pathways of the three BCAAs suggest that they may exert differential effects on bone metabolism by regulating cellular energy status, metabolite pools and signal transduction pathways.

As critical nutrient signals, BCAAs modulate cellular metabolism and energy production. They activate anabolic pathways, particularly the mechanistic target of rapamycin (mTOR) signaling pathway, which promotes protein synthesis in skeletal muscle and enhances immune cell proliferation and function, including T cells and natural killer cells (95). Additionally, emerging evidence has highlighted a 'muscle-bone axis', where skeletal muscle and bone tissue interact bidirectionally (96). Immune cells, including osteoclast precursors and macrophages, also serve pivotal roles in bone resorption and remodeling (97). By influencing both the musculoskeletal and immune systems, BCAAs likely exert indirect yet notable effects on bone metabolism and homeostasis. Further research is needed to elucidate the direct regulatory roles of BCAAs in bone metabolism, particularly through pathways involving cellular metabolism and energy balance.

BCAAs and their metabolic derivatives function as molecular signals in bone metabolism. Both leucine (98) and valine (99) activate the mTOR complex 1 (mTORC1) pathway. The biochemical pathways of BCAA metabolism are well-characterized, and preclinical studies have indicated that inhibition of mTOR suppresses osteoclast differentiation and survival, potentially impairing bone resorption (100-103). These findings are further supported by the BOLERO-2 trial, where everolimus, a clinically used mTOR inhibitor, demonstrated beneficial effects on bone in patients with advanced breast cancer (104). Metabolic derivatives of valine, such as β-aminoisobutyric acid (BAIBA) and 3-hydroxyisobutyric acid (3-HIB), act as myo-osseous metabolic messengers, regulating bone homeostasis through distinct signaling pathways. BAIBA, regulated by peroxisome proliferator-activated receptor (PPAR)γ coactivator-1α (PGC-1α), activates the PPARα pathway, inducing white adipose tissue browning, improving insulin sensitivity and potentially enhancing osteogenesis while inhibiting osteoclastogenesis (105). Conversely, 3-HIB promotes trans-endothelial fatty acid transport via FATP3/4, leading to lipotoxicity and insulin resistance, which may disrupt bone homeostasis (106). Further research is needed to better define the direct roles of BCAAs in bone metabolism through these signal transduction pathways, supported by additional well-designed clinical studies.

Metabolomic analyses from large randomized controlled trials have established circulating BCAA levels as key indicators of metabolic health. These levels, beyond body mass index, predict the risk of insulin resistance, cardiovascular diseases and diabetes, and reveal ethnic differences in obesity-associated metabolic disturbances (107,108). A Mendelian randomization study further indicated that elevated BCAA levels are linked to an increased risk of type 2 diabetes (109). Collectively, these findings suggest that dysregulated BCAA metabolism contributes to the pathogenesis of insulin resistance, obesity and diabetes (110,111). Moreover, insulin resistance may promote BCAA accumulation (112,113), creating a self-perpetuating cycle. Insulin resistance, frequently accompanied by altered BCAA metabolism, adversely affects bone health by impairing osteoblast function and inhibiting bone formation (Fig. 3) (114).

Influence of abnormal BCAA metabolism on bone metabolism. Disorders in BCAA metabolism contribute to a complex pathological network that impacts bone metabolism. This network involves both direct regulation of bone cells (osteoblasts and osteoclasts) (115), and indirect effects mediated by systemic metabolic disturbances, ultimately disrupting bone homeostasis (114,116).

A key mechanism through which BCAA metabolism directly influences bone metabolism is its role in osteoclast maturation. Studies have shown that inhibition of BCAT1, a key enzyme in BCAA metabolism, effectively reduces osteoclast maturation (12,117). BCAT1 catalyzes the conversion of BCAAs to their metabolites (BCKAs), which fuel cellular energy production (90) and sustain the expression of essential osteoclastogenic factors (such as NFATc1 and ATP6v0d2) (118), as well as the regulation of fusion-related genes (including DCSTAMP and CD9) (119,120). These processes collectively underlie its critical role in the later stages of osteoclast differentiation. *In vivo* animal experiments have further confirmed that BCAT1 is central to the osteoclast multinucleation regulatory network. Its deletion markedly inhibits osteoclast activity, increases bone mass and improves bone strength. These results establish a strong link between abnormal BCAA metabolism and bone metabolic disorders mediated by osteoclasts (117).

In contrast to osteoclasts, the impact of BCAA metabolism on osteoblasts is more complex, highlighting the adverse effects of abnormal BCAA metabolism on bone health. Singha *et al* (121) demonstrated that rapamycin, an mTOR inhibitor, can effectively suppress osteoblast proliferation and differentiation by reducing RUNX2 protein expression, decreasing alkaline phosphatase activity and inhibiting matrix mineralization, supporting the pro-osteogenic role of mTORC1 in osteogenesis. However, dysregulated BCAA metabolism, such as chronic overaccumulation or insufficient breakdown products, may disrupt the mTORC1 pathway (122). Prolonged activation of mTORC1 can induce 'metabolic stress' in osteoblasts, characterized by G_1 phase cell cycle arrest and reduced proliferative capacity, ultimately impairing bone metabolism (123). These findings suggest that BCAAs regulate osteoblast differentiation to a certain extent via the mTOR signaling pathway; however, its translational applicability in humans remains to be confirmed through rigorously designed clinical investigations.

High glutamine levels further inhibit the mTORC2/Akt-S473/RUNX2 axis by activating mTORC1, which leads to the ubiquitin-mediated degradation of RUNX2, thereby suppressing osteogenic differentiation (124). These findings indicate that the regulatory role of mTORC1 signaling in osteoblast differentiation may be context-dependent, necessitating additional *in vitro* experiments or clinical studies to confirm these results.

As aforementioned, dysregulated BCAA metabolism is linked to various metabolic disorders, including obesity and type 2 diabetes, both of which are well-established risk factors for osteoporosis and other bone-related conditions (125). In patients with obesity and type 2 diabetes, elevated BCAA levels are strongly associated with insulin resistance. BCAAs activate the mTORC1 signaling pathway, which decouples insulin signal transduction, thereby exacerbating insulin resistance (114,126). Furthermore, intermediate products of BCAA metabolism, such as BCKAs, inhibit insulin signal transduction, further aggravating metabolic disorders (127). These metabolic disruptions not only affect systemic metabolism but also impair bone homeostasis by disrupting energy metabolism and signal transduction in osteocytes (115,128).

Additionally, BCAAs influence lipid metabolism, and disruptions in this pathway can lead to altered lipid profiles that may negatively affect bone density and strength. Impaired BCAA catabolism has been linked to lipid accumulation, which can adversely impact bone tissue (129,130). BCAA metabolic disorders may worsen the complex pathological network of bone metabolism by modulating oxidative stress and inflammatory responses. Elevated BCAA and fatty acid levels induce mitochondrial dysfunction, increase oxidative stress, and activate inflammatory signaling pathways, all of which can contribute to bone metabolic diseases, such as osteoporosis, by impairing osteocyte function and disrupting the bone microenvironment (131,132). Furthermore, BCAA metabolic disorders may indirectly influence bone metabolism by interfering with lipid metabolism (133).

Regarding the mTORC1 pathway, Lin *et al* (134) demonstrated that reduced angiopoietin-like-4 levels modulate BCAA metabolism, activating mTOR signaling and promoting accelerated proliferation in osteosarcoma cells. This suggests that disturbances in this pathway, resulting from abnormal BCAA metabolism, may influence bone formation and remodeling, ultimately contributing to bone metabolic disorders.

4. Association between osteoporosis and bone metabolism

Definition and clinical manifestations of osteoporosis. Osteoporosis is a prevalent metabolic bone disorder characterized by generalized bone mass loss and deterioration of bone microarchitecture, which increases bone fragility and the risk of fragility fractures (135). Notably, osteoporosis also elevates the likelihood of secondary complications, such as pneumonia or thromboembolic events, particularly due to immobilization following a fracture (4). Rather than a singular condition, osteoporosis encompasses a spectrum of distinct pathological states, typically classified as primary or secondary. Primary osteoporosis includes two main subtypes: Type I, or postmenopausal osteoporosis, which predominantly affects women after menopause due to estrogen deficiency, and type II, also known

as age-related or senile osteoporosis, which is associated with aging in both sexes. By contrast, secondary osteoporosis arises from various underlying medical conditions, reduced physical activity or the adverse effects of medical treatments (136).

Effect of bone metabolism on developing osteoporosis. The primary pathological features of osteoporosis include decreased bone mass, disrupted bone microarchitecture and an imbalance in bone remodeling, where bone resorption outpaces bone formation, leading to a net loss of bone tissue (135).

Type I osteoporosis primarily results from estrogen deficiency, which accelerates bone resorption by increasing the RANKL/OPG ratio and enhancing osteoclast activity (137). Several bone metabolism pathways are implicated in this process: i) Estrogen deficiency prolongs the lifespan of bone marrow dendritic cells and increases the secretion of IL-7 and IL-15, which promote the conversion of memory T (T_M) cells into effector T_M cells. The subsequent release of TNFα and IL-17A acts synergistically with RANKL to stimulate osteoclastogenesis and enhance osteoclast activity. ii) Estrogen deficiency also increases intestinal permeability and triggers inflammation in the intestinal mucosa, resulting in elevated production of T helper 17 (Th17) cells. IL-17A produced by Th17 cells further enhances osteoclast differentiation and bone resorption. Additionally, metabolites from gut microbiota, such as butyric acid, polyamines and other short-chain fatty acids, may indirectly promote osteoclast activity; however, the exact mechanisms remain to be fully elucidated (138).

Vitamin D deficiency impairs calcium absorption, a condition further exacerbated by inadequate dietary calcium intake. This disruption in calcium homeostasis leads to increased bone resorption and heightened bone remodeling. In a large European cohort study of 8,532 postmenopausal women with insufficient vitamin D levels, 97% were found to have osteoporosis (139). Another study revealed that 82% of individuals with osteoporosis had calcium intakes below the recommended daily amount of 1,000 mg (140). Moreover, phosphorus deficiency, a common marker of poor nutritional status in elderly patients, is associated with an elevated risk of fractures (141). Thus, deficiencies in vitamin D, calcium and phosphorus further increase fracture risk in elderly women with osteoporosis.

During the progression of osteoporosis in the elderly, both cellular senescence and epigenetic regulatory pathways serve key roles in modulating bone metabolism. As aging progresses, bone marrow mesenchymal stem cells (BMSCs) undergo senescence, accompanied by an upregulation of nucleosome assembly protein 1 like 2 (NAP1L2) expression. NAP1L2 contributes to bone loss through two primary mechanisms. First, it activates the NF-κB signaling pathway, leading to increased secretion of senescence-associated factors, such as IL-6 and IL-8. These factors exacerbate cellular senescence and impair the osteogenic differentiation of BMSCs, thus negatively impacting bone formation. Second, as a histone chaperone, NAP1L2 recruits sirtuin 1 to deacetylate H3K14ac at the promoters of key osteogenic genes, including Runx2, Sp7 and Bglap, causing their transcriptional repression. This epigenetic modification further inhibits osteogenic differentiation, reduces bone formation, and accelerates the development of osteoporosis (142).

Abnormal cellular functions also contribute to osteoporosis pathogenesis: i) Inhibition of osteoblast differentiation and function, which is associated with downregulation of the BMP/Smad (143) and Wnt/β-catenin (144) pathways, thus preventing MSCs from differentiating into osteoblasts; ii) overactivation of osteoclasts, bone matrix degradation is accelerated due to lysosomal acidification abnormalities, such as increased V-ATPase activity (145) and elevated cathepsin K activity (146); and iii) dysfunction in the osteocyte network, where osteocyte apoptosis and the accumulation of microdamage impair mechanosignal perception, inhibiting bone repair (147). Furthermore, senescence or mechanical stimulation reduces the upregulation of sclerostin, which antagonizes the Wnt pathway and inhibits bone formation (148).

Dysregulated molecular signaling pathways also contribute to osteoporosis, particularly those involved in the RANKL/RANK/OPG system, the Wnt/β-catenin pathway, the BMP-Smad pathway and the PI3K/Akt/mTOR pathway. Additionally, hormonal and cytokine networks, particularly those involving PTH and estrogen, are disrupted, with well-established roles in bone metabolism (Table II; Fig. 4).

Effects of abnormal BCAA metabolism on osteoporosis. BCAA catabolism primarily occurs in skeletal muscle, where they are broken down into their respective ketoacids and further metabolized. This process is essential for maintaining muscle function and overall metabolic balance. Impaired BCAA catabolism can lead to elevated circulating levels of BCAAs and their ketoacids, which are associated with metabolic disturbances that may contribute to the development of osteoporosis. For example, increased BCAA levels can disrupt insulin signaling pathways, potentially resulting in insulin resistance, a recognized risk factor for osteoporosis (149).

Moreover, the regulation of key enzymes in BCAA metabolism, such as BCAT and BCKDH, is crucial for maintaining metabolic homeostasis. Inhibition of BCAT1 has been shown to impair osteoclast differentiation, suggesting its potential as a therapeutic target to halt the progression of osteoporosis (12). Emerging evidence has indicated that the expression of these metabolic enzymes is influenced by factors such as physical activity and transcriptional coactivators, including PGC-1α. In skeletal muscle, PGC-1α enhances the expression of BCAA-metabolizing enzymes, facilitating BCAA degradation and potentially alleviating the detrimental effects of their accumulation (150).

5. Potential treatment options

Supplementation of exogenous BCAA. As the incidence of osteoporotic events continues to increase, the management of osteoporosis has increasingly focused on long-term strategies. Consequently, identifying safe, accessible and effective nutritional interventions to maintain skeletal health has become a key area of clinical research. BCAAs, due to their widespread presence in daily diets and ease of adherence, have attracted growing interest for their potential effects on bone metabolism, suggesting translational and clinical intervention value.

Cellular and animal studies have shown that exogenous BCAAs can modulate bone metabolism through the activation of signaling pathways, such as mTOR. This regulation

Table II. Molecular pathways involved in osteoporosis.

Pathway	Mechanism	Impact on osteoporosis	(Refs.)
RANKL/RANK/OPG signaling pathway	RANKL expression is upregulated and binds to RANK on osteoclasts, inducing osteoclast formation	Increase	(137)
	OPG expression is upregulated and binds to RANKL, preventing its interaction with RANK	Decrease	(48)
Wnt/β-catenin signaling pathway	Wnt protein promotes the accumulation and nuclear translocation of β-catenin after binding to its receptor. β-catenin induces the expression of osteogenic genes	Decrease	(33,144)
BMP-Smad signaling pathway	Promotes differentiation of MSCs into osteoblasts	Decrease	(143)
PI3K/Akt/mTOR signaling pathway	mTORC1 hinders osteoclast differentiation through calcineurin and NFATc1	Decrease	(169)
	Inhibition of mTOR signaling pathway reduces osteoclast differentiation and survival	Decrease	(100-103)

MSC, mesenchymal stem cell; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; OPG, osteoprotegerin; RANK, receptor activator of NF-κB; RANKL, RANK ligand.

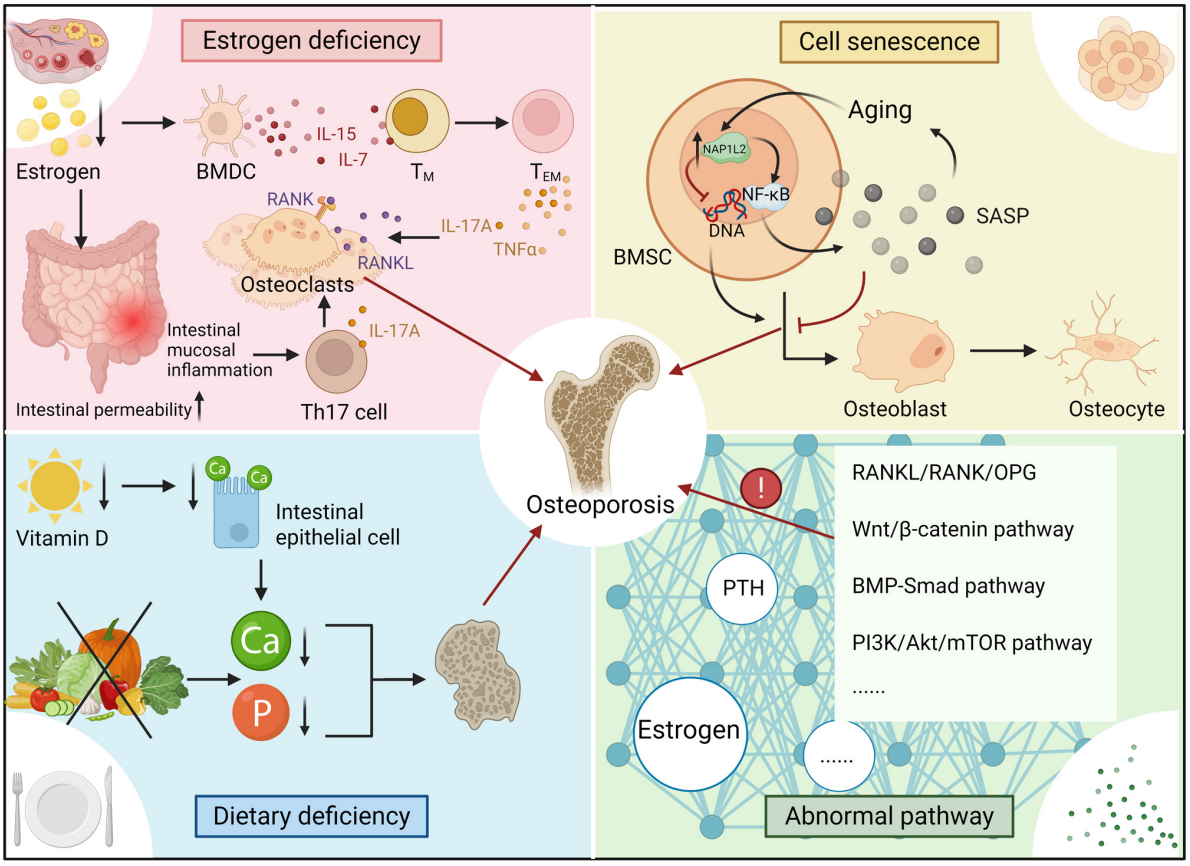

Figure 4. Mechanisms of bone metabolism dysregulation in osteoporosis pathogenesis. Estrogen deficiency triggers immune activation (IL-15 and IL-7) in BMDCs, promoting the differentiation of T_M cells into T_{EM} cells, which secrete TNFα and IL-17A to synergize with RANKL in osteoclastogenesis. Increased intestinal permeability and mucosal inflammation amplify Th17 cell-derived IL-17A, exacerbating osteoclast activity. Vitamin D deficiency and dietary calcium/phosphate insufficiency impair mineralization. Cellular senescence in BMSCs elevates SASP factors (IL-6 and IL-8), inhibiting osteoblast differentiation through epigenetic suppression. Dysregulated pathways (RANKL/RANK/OPG, Wnt/β-catenin, BMP-Smad and PI3K/Akt/mTOR) disrupt osteoblast-osteoclast coupling, while estrogen loss reduces osteocyte survival and mechanotransduction. PTH imbalance disrupts calcium-phosphate homeostasis, collectively driving bone resorption over formation. These factors ultimately exacerbate osteoporosis development. BMDC, bone marrow dendritic cell; BMSC, bone marrow mesenchymal stem cell; mTOR, mechanistic target of rapamycin; NAP1L2, nucleosome assembly protein 1 like 2; OPG, osteoprotegerin; PTH, parathyroid hormone; RANK, receptor activator of NF-κB; RANKL, RANK ligand; SASP, senescence-associated secretory phenotype; T_{EM}, effector T_M; Th17, T helper 17; T_M, memory T. Created in BioRender. zhan, a. (2025) https://BioRender.com/3k6hy0g.

occurs through two concurrent effects: Promoting osteogenic differentiation and inhibiting excessive osteoclast activation (151-154). Additionally, clinical observational studies have identified a positive association between higher BCAA levels and the preservation of bone mineral density (BMD) (151). These findings suggest that BCAA supplementation may offer therapeutic potential in delaying osteoporosis progression. Similarly, Carbone *et al* (155) and Urano *et al* (156) have indicated that higher BCAA levels are associated with better BMD. Together, these studies imply that elevated BCAA levels may be associated with improved bone health and a reduced risk of osteoporosis.

However, these findings do not establish a causal relationship. Residual confounding factors, such as total dietary protein intake, combination with other substances or physical activity, may influence both BCAA levels and bone health. Additionally, the relationship between BCAAs and bone health has been reported to vary across different disease stages or metabolic conditions (116). Therefore, well-designed clinical studies are critical, and further research involving additional human data is necessary.

Among the BCAAs, leucine is recognized as a critical amino acid for muscle function (157-159). BCAAs can effectively prevent and improve sarcopenia, as well as reduce fat infiltration in skeletal muscles, thus preserving muscle mass and function (160). A clinical intervention study conducted by Wang *et al* (161) demonstrated that leucine supplementation enhances muscle performance by improving cytoskeletal dynamics.

Skeletal muscle serves a pivotal role in bone growth and remodeling (162). Accumulating evidence has indicated that mechanical stimulation exerted by skeletal muscle promotes the proliferation and maturation of chondrocytes through factors such as osteocrin, which is secreted by periosteal osteoblasts, contributing to the elongation of long bones (163). Furthermore, mechanical signals regulate the dynamic balance between bone formation and resorption, enhancing bone strength through chemical messengers, including nitric oxide produced by osteocytes (164). Muscles also influence bones through the secretion of factors such as irisin, which promotes bone mass accumulation by inhibiting sclerostin expression, enhancing bone formation and reducing osteoclast numbers to suppress bone resorption (165). These mechanisms collectively impact the onset and progression of osteoporosis (166).

In elderly individuals and post-surgical rehabilitation populations, the combination of BCAA supplementation and exercise has proven effective in enhancing muscle strength, which is critical for restoring mobility and providing mechanical stimulation to the skeleton (167,168). Although the direct efficacy of BCAA supplementation in treating osteoporosis in humans requires further validation, it remains a promising approach and warrants targeted clinical research.

Regulation of BCAA metabolic processes. BCAT1 catalyzes the transfer of the amine group from BCAAs to α-ketoglutarate, generating glutamate and α-ketoacids, which are subsequently oxidized to provide cellular energy. Therefore, BCAT1 is crucial for preserving BCAA homeostasis and ensuring their continued availability for energy production. In a mouse model, Go *et al* (12) observed that a 400 μM BCAA solution effectively promoted osteoclast differentiation, whereas a higher concentration (800 μM) inhibited it, suggesting a negative feedback mechanism for BCAAs. Additionally, Huynh *et al* reported (169) that mTORC1, a key nutrient sensor known to be activated by BCAAs (98), inhibits osteoclast differentiation through calcineurin and NFATc1 signaling. BCAA levels are regulated not only by BCATs but also by their primary transporter, LAT1. Ozaki *et al* demonstrated that deleting the gene encoding LAT1 (Slc7a5) specifically in osteoclasts resulted in osteoclast activation and bone loss (170). Furthermore, Pereira *et al* (117) validated the functional role of the macrophage multinucleation network (MMnet), a trans-regulated gene co-expression network enriched for osteoclast-related genes, in regulating osteoclast multinucleation, resorption, bone mass and strength. These findings suggest that factors such as BCAT1, mTORC1, Slc7a5 and MMnet may serve as potential therapeutic targets to inhibit osteoclast formation, offering a strategy for osteoporosis treatment.

Other potential treatments. A recent study indicated that elevated BCAA levels are associated with insulin resistance and an increased risk of metabolic syndrome (171). In addition, a longitudinal study conducted between 2016 and 2022 with 3,090 Brazilian participants revealed a positive association between total BCAA intake (specifically >16 g) and the risk of obesity (172). These findings, along with the results from other experiments, are summarized in Table III. Additionally, in populations with BCAA metabolism disorders, such as patients with diabetes mellitus and liver cirrhosis, abnormal BCAA levels may impact bone metabolism (173). Therefore, the potential benefits of regulating BCAAs must be evaluated in conjunction with the metabolic health status of the individual.

Recently, You *et al* (174) developed alendronate-functionalized bone-targeting liposomes that encapsulate arginine and metformin. These liposomes enhance therapeutic efficacy against osteoporosis through dual mechanisms: Combined bone-targeted delivery and modulation of the hepatic-osseous axis. By integrating advanced nanomedicine technologies, the successful establishment of a multi-drug synergy strategy, featuring bone-targeted delivery and a collaborative mechanism, provides a novel approach to addressing potential adverse reactions in BCAA therapy. Additionally, personalized metabolic profiles derived from multi-omics analysis allow for the implementation of precise nutritional interventions. These interventions aim to identify the optimal BCAA intake level that supports bone health without inducing metabolic disorders, striking a key balance between therapeutic benefits and risks (175). However, further well-designed clinical studies are required to explore the relationship between BCAAs and bone metabolism/osteoporosis. Currently, notable scientific challenges, technical barriers and gaps in human data limit the clinical translation of BCAA therapy.

The accumulation of adipose tissue within the bone marrow space can induce an inflammatory state (176), which in turn promotes bone resorption and impairs the differentiation of MSCs and hematopoietic stem cells (177). Furthermore, plant-based foods, rich in dietary fiber and polyphenols, can enhance energy expenditure through thermogenesis and regulation of lipid metabolism, thereby helping reduce fat accumulation (178). Increasing the proportion of healthy plant-based foods in the diet, which may reduce bone marrow

Table III. Research summary on BCAA and bone metabolism.

First author, year	Study type	Population/model	BCAA intervention/association	Key findings	(Refs.)
Liang, 2021	*In vitro*	SAT explants	BCAA supplementation	Activates mTOR and insulin signaling in SAT	(153)
Lv, 2022	Clinical observation study	Elderly individuals	BCAA supplementation	Positive association with maintenance of BMD	(151)
Carbone, 2023	Clinical observation study	Middle-aged and elderly African-American and white men and women	Plasma leucine concentration	Positive association with BMD of total hip and femoral neck	(155)
Urano, 2024	Longitudinal study	Japanese women	Serum BCAA concentration	A decrease in BCAA concentration was shown to be an important risk factor for fractures	(156)
Kitajima, 2018	Longitudinal study	Japanese patients with liver cirrhosis	BCAA supplementation	Maintains muscle mass and function	(160)
Wang, 2025	Clinical intervention experiment	Basketball players	Leucine supplementation	Muscle performance can be improved by improving cytoskeleton dynamics	(161)
Zhang, 2022	Animal experiments	Finishing pig model	Serum BCAA ratio	Appropriate BCAA ratio increases skeletal muscle mass	(167)
Go, 2022	Animal experiments	Mouse model	BCAA concentration	400 μM BCAA solution promotes osteoclast differentiation, while higher concentrations tend to inhibit osteoclast differentiation	(12)
Rivera, 2023	*In vitro*	Myotube model	BCAA level	Elevated BCAA levels are associated with increased risk of insulin resistance and metabolic syndrome	(171)
da Silva, 2025	Longitudinal study	Brazilian adults	BCAA intake level	Intake of BCAA is positively associated with the risk of obesity	(172)

BCAA, branched-chain amino acid; BMD, bone mineral density; mTOR, mechanistic target of rapamycin; SAT, subcutaneous fat.

adipose tissue or modulate the function of bone marrow adipocytes, could serve as a potential target for improving bone quality and has important implications for the development of novel therapeutic strategies (179).

6. Conclusions and perspective

BCAA has attracted increasing attention due to its diverse biological activities and therapeutic potential. The present review focused on its effects in bone metabolism and osteoporosis. Notably, BCAA regulates the muscular and immune systems by activating the mTOR pathway, thereby influencing bone function. It also acts as a molecular signal to exert direct or indirect effects on bone metabolism and bone homeostasis. BCAA metabolic disorders contribute to a complex pathological network that involves not only the direct regulation of osteoblasts and osteoclasts, but also indirect effects mediated by systemic metabolic abnormalities. Collectively, these

factors disrupt bone homeostasis and may ultimately lead to osteoporosis.

Evidence from animal and human studies have suggested that BCAA intake may be associated with increased BMD, supporting its potential as a nutritional target for maintaining bone health and preventing osteoporosis; however, most current evidence is derived from *in vitro* and animal experiments, which are limited by interspecies metabolic differences and dose conversion issues, restricting clinical translation (180,181). Moreover, high-quality population-based studies and prospective intervention trials remain scarce. Existing studies often suffer from poor reproducibility due to small sample sizes and inconsistent intervention methods (182,183). The specific mechanisms of BCAA action within the bone microenvironment have not been fully elucidated, and the effects of individual metabolic differences and disease states on BCAA metabolism require further investigation. Future work should explore the molecular mechanisms of BCAA in greater depth. Multicenter, large-sample, long-term randomized controlled trials are needed to determine the long-term effects of different BCAA doses and ratios on BMD and bone turnover markers (155). Integration of advanced technologies, such as metabolomics, may promote the development of precise nutritional intervention strategies.

As research on the modulation of bone metabolism by BCAAs and their role in osteoporosis treatment continues to grow, these studies will further enhance the understanding and improve strategies targeting BCAA metabolic processes in disease therapy. The current review not only provides a reference for further development and investigation of the impact of BCAA metabolism on osteoporosis progression, but also serves as a guide for regulating BCAA metabolism to achieve precision treatment of osteoporosis. Furthermore, these targeted therapeutic strategies may offer innovative treatment options for bone metabolism-related diseases.

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Authors' contributions

QX, HZ and RY drafted and revised the manuscript. YZ and FL contributed to the literature search, evidence extraction, thematic organization, critical interpretation of the reviewed studies, and the preparation and refinement of the figures. BC contributed to the literature search, screening, evidence evaluation, and assisted in organizing and interpreting the included studies. XC conceived the review, supervised the overall academic direction and critically revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

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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