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Review

Comprehensive Review of Therapeutic Efficacy and Underlying Mechanisms of Various Exercise Modalities in Treating Osteoporosis

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ABSTRACT: Osteoporosis (OP) is a major public health challenge affecting over 200 million individuals worldwide. While pharmacological interventions represent mainstream treatment, concerns regarding long-term side effects and patient compliance have driven the exploration of alternative therapies. Exercise interventions have emerged as promising complementary approaches due to their excellent safety profiles, cost-effectiveness, and high adherence rates. Diverse exercise modalities, including aerobic, resistance, and balance exercises, effectively modulate bone homeostasis by promoting osteogenesis, inhibiting osteoclastogenesis, enhancing muscle-bone crosstalk, regulating the vascular/lymphatic systems, and modulating inflammation. This review synthesizes current knowledge on exercise-based therapies for musculoskeletal disorders, with a particular emphasis on their anti-OP mechanisms, which target osteoblast- and osteoclast-mediated bone homeostasis, endocrine regulation, immune function, and muscle performance. Furthermore, we explore the potential of combining exercise with other therapies and systematically compare the clinical efficacy of various exercise types. This review provides deeper mechanistic insights into exercise-mediated bone protection and offers evidence-based perspectives for developing innovative therapeutic strategies in OP management.

Keywords: osteoporosis, exercise intervention, anti-osteoporotic mechanism, osteogenesis, osteoclastogenesis

Introduction

Osteoporosis (OP) is one of the most prevalent metabolic bone disorders globally, affecting over 200 million individuals and imposing a substantial burden on healthcare systems [1]. This systemic skeletal condition is characterized by reduced bone mass and deteriorated bone microstructure, resulting in heightened bone fragility and elevated fracture risk [2,3]. Epidemiological studies have identified multiple risk factors contributing to the onset and progression of OP, including smoking, excessive alcohol consumption, and aging [4]. The prevalence of OP shows a marked demographic pattern: postmenopausal women are particularly vulnerable, with rising incidence rates in women aged > 55 years and men aged > 65 years [5]. Beyond its direct impact on bone health, OP significantly compromises patient quality of life and creates considerable socioeconomic challenges, with

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annual treatment costs exceeding billions of dollars globally [6]. Current therapeutic strategies for OP predominantly rely on pharmacological treatments, particularly bisphosphonates and other antiresorptive agents. However, these conventional treatments face several limitations, including high costs, potential adverse effects (such as atypical femoral fractures and osteonecrosis of the jaw), and suboptimal long-term compliance [7, 8]. These challenges have spurred an intensive search for alternative therapeutic strategies that offer better safety profiles and cost-effectiveness while maintaining high patient compliance.

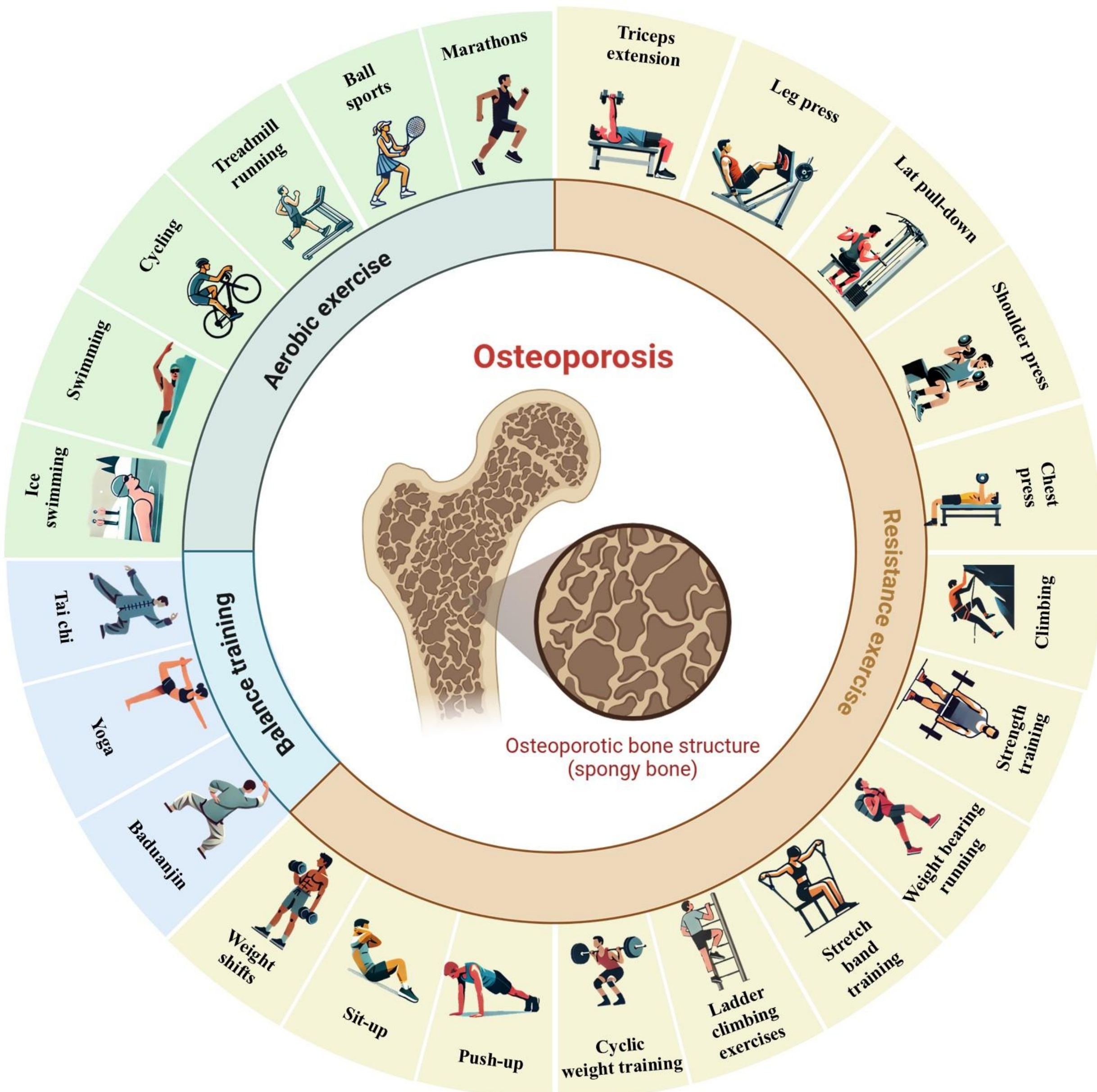

Figure 1. Classification and therapeutic applications of exercise modalities in OP management. The figure illustrates the three main categories of exercise interventions widely employed in OP management: [1] Aerobic exercise, which includes activities such as treadmill running, swimming, cycling, and ball sports, primarily enhances cardiovascular function and stimulates bone formation through mechanical loading. [2] Resistance training, encompassing activities like resistance weight training, climbing exercises, and stretch band training, focuses on improving muscle strength and bone density through mechanical stress. [3] Balance training, including traditional practices such as Tai Chi, Yoga, and Pilates, aims to enhance postural stability and reduce fall risk while promoting bone health through controlled movements. Each exercise modality targets specific aspects of bone metabolism and overall physical function, offering complementary therapeutic benefits in OP management. The integration of these exercise types, either individually or in combination, provides a comprehensive approach to preventing bone loss and improving quality of life in OP patients.

Exercise-based interventions have emerged as promising complementary approaches for the management of musculoskeletal disorders, including OP [9-11]. For instance, a landmark randomized controlled trial in New Zealand involving 206 patients with hip or knee osteoarthritis demonstrated significant improvements in symptoms and physical function following structured exercise therapy [12]. Current exercise modalities for OP management can be categorized into three main types [13-15]: aerobic exercise (such as treadmill running, swimming, cycling, and ball sports) [16-18], resistance training (such as weight-bearing exercises, sit-ups, and stretch band training) [19], and balance training (such as Tai Chi, Yoga, and Pilates) [20,21] (Fig. 1). Each modality offers unique benefits while targeting different aspects of bone health and overall physical function.

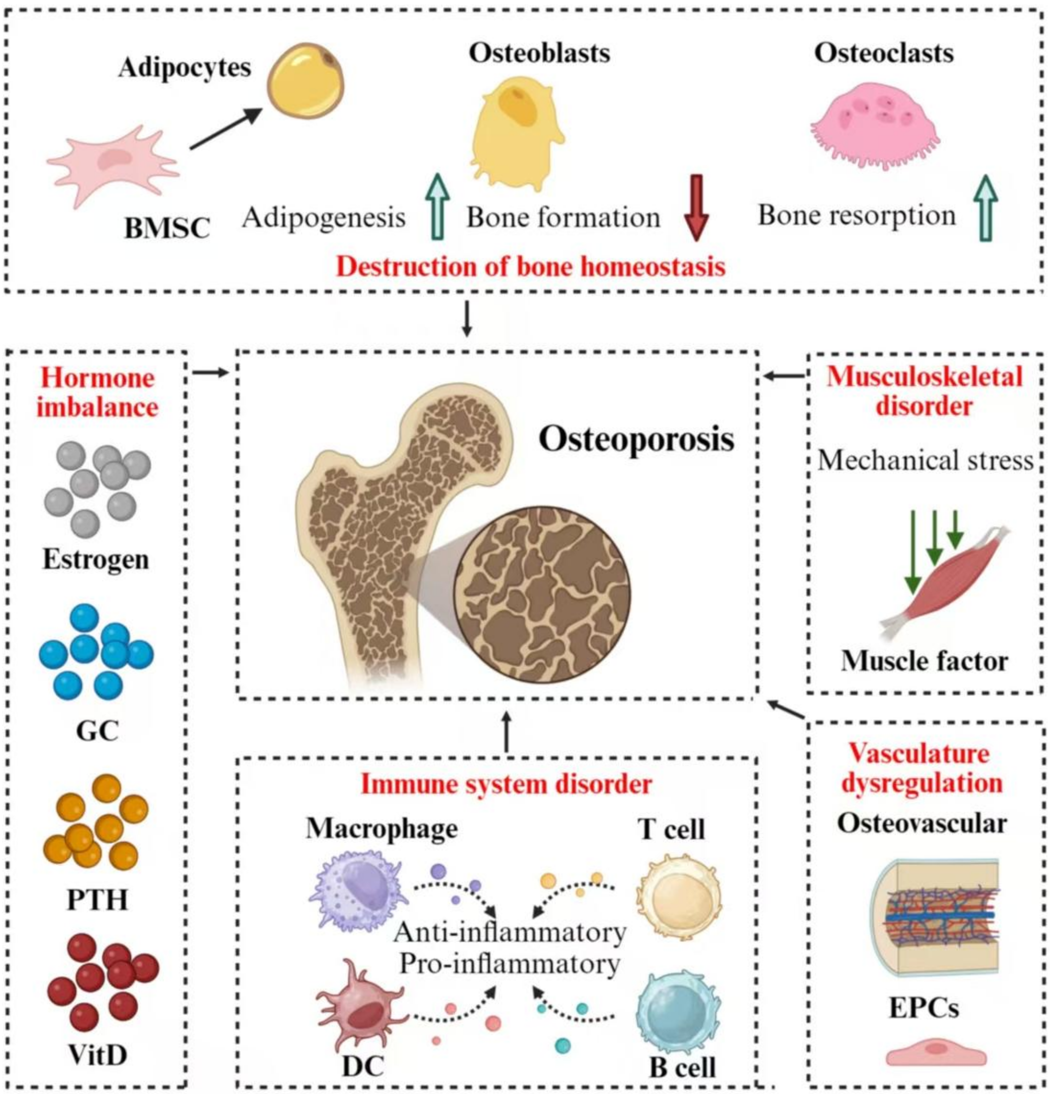

Figure 2. The Mechanism of OP pathogenesis. The advancement of OP is influenced by a multitude of factors, including compromised bone formation facilitated by OB, enhanced bone resorption catalyzed by OC, heightened adipogenic differentiation of BMSCs, along with hormonal imbalances, immune dysfunction, and various other elements such as vascular system dysregulation and the interconnected dynamics between bone and muscle.

Recent advances in molecular biology and clinical research have significantly deepened our understanding of how exercise benefits skeletal health. Swimming showed remarkable efficacy in improving bone mineral density (BMD) in the postmenopausal spine and femoral neck, particularly among long-term practitioners [22]. Similarly, Chen et al. demonstrated that daily treadmill running for 1 hour effectively corrects epigenetic alterations, restores Nrf2 levels, and improves femoral bone mass [23]. The impact of exercise intensity has also been explored; even short bursts of intense activity (such as 10 minutes on a bicycle ergometer) increase plasma parathyroid hormone (PTH) levels and mobilize calcium stores, resulting in a positive skeletal balance [24].

In the realm of resistance training, ladder climbing exercises have proven effective in counteracting weight gain in ovariectomized (OVX) osteoporotic rats while simultaneously enhancing BMD and trabecular bone microarchitecture [25]. Clinical studies, such as Banitalebi's trial involving 63 women with osteosarcopenic obesity, demonstrated that 12 weeks of elastic band resistance training significantly improved OP markers, including BMD, vitamin D, and alkaline phosphatase (ALP) levels [26]. Similarly, Mosti's report highlighted that strength training improved skeletal properties in postmenopausal women with osteopenia or OP [27]. Balance exercises have also shown promise, with Tai Chi demonstrating particular efficacy in attenuating BMD loss in the lumbar spine and proximal femoral neck across diverse populations, including older adults, perimenopausal and postmenopausal women, individuals with osteoarthritis, and cancer survivors [28]. Pilates and Yoga have also been shown to improve bone density in adult women [29].

Despite these encouraging findings, the mechanisms by which these exercise modalities contribute to OP management are not fully understood. To address this knowledge gap, this review provides a comprehensive analysis of both clinical and preclinical research findings. We outline the latest advances in understanding OP pathological mechanisms, followed by a detailed exploration of the impacts and underlying mechanisms of various exercise modalities on bone homeostasis, the vascular and immune systems, muscle function, and cytokine production. Additionally, we offer new perspectives on combined exercise therapies.

Mechanisms of op pathogenesis

The pathogenesis of OP involves multiple interconnected mechanisms, including disrupted bone homeostasis, immune dysfunction, hormonal imbalance, and vascular abnormalities [30, 31] (Fig. 2).

Bone homeostasis

Bone homeostasis represents a dynamic equilibrium between bone formation and resorption, orchestrated through the coordinated activities of osteoblasts (OBs), osteoclasts (OCs), and bone marrow mesenchymal stem cells (BMSCs) [32, 33].

OBs, the primary bone-forming cells, are regulated by key transcription factors including RUNX2 and Osterix (Osx, also known as SP7) [34]. RUNX2 directs multipotent BMSCs toward the osteoblastic lineage while inhibiting their differentiation into adipocytes and chondrocytes [35, 36]. The activity of OBs is further modulated through multiple signaling pathways, including TGF-β [37] and the Wnt/β-catenin pathway [38], which control both OB differentiation and function [39].

OCs, which are derived from the monocyte-macrophage lineage, are primarily regulated through the RANK/RANKL/OPG axis [40]. When RANKL binds to its receptor RANK on OC precursors, it triggers multiple downstream signaling cascades, including the NF-κB, JNK, and ERK pathways, which regulate the activation and differentiation of the osteoclastic lineage [41]. OPG serves as a natural brake on this system by acting as a decoy receptor for RANKL [42].

BMSCs represent a critical cell population in bone homeostasis due to their capacity for multipotent differentiation [43]. The balance between osteogenic and adipogenic differentiation of BMSCs is particularly relevant to OP pathogenesis [44]. Peroxisome proliferator-activated receptor-γ (PPARγ) is usually considered the main regulator of adipogenesis, while also inhibiting osteogenesis [45].

Muscular regulation in OP pathogenesis

The intricate relationship between muscle and bone extends beyond mechanical support to include complex molecular and endocrine interactions [46]. Skeletal muscle functions not only as a mechanical actuator but also as an endocrine organ, secreting various myokines that influence bone metabolism [47]. The "mechanostat" theory emphasizes how muscle-generated mechanical forces regulate bone remodeling, with reduced physical activity or reduced muscle mass leading to disturbed bone homeostasis [48].

The interaction between mechanical loading and bone metabolism is primarily mediated through mechanotransduction pathways in the osteocytes and OBs. Specifically, cell-based assays have demonstrated that cytoskeletal microtubules act as crucial mechanosensors, translating mechanical forces into biochemical signals through pathways involving NADPH oxidase 2 (NOX2), transient receptor potential vanilloid 4 (TRPV4), and β-catenin [49,50]. This mechano-transduction process initiates cascades that influence bone cell behavior and matrix mineralization. Moreover, clinical trials have demonstrated that age-related declines in mechanical sensitivity and cellular responsiveness to mechanical loads significantly impact bone health [51], potentially due to reduced stem cell populations [52], altered bone morphology [53], and reduced bone deformation capacity [54].

Muscle-derived factors, including myostatin, irisin, and β-aminoisobutyric acid (BAIBA), significantly influence bone metabolism through multiple pathways [55-57]. Animal experiments have shown that myostatin negatively regulates bone formation by promoting the expression of regulators like sclerostin and DKK1 in osteocytes, which reduces exosomal miR-218 levels and downregulates osteogenic markers, including RUNX2, ALP, and osteocalcin (OCN), by suppressing Wnt signaling [58-60]. In contrast, irisin promotes OB differentiation and bone formation through the activation of Wnt/β-catenin and ERK/MAPK signaling pathways via binding with integrin proteins [61]. The phenotype analysis of FNDC5/Irisin-deficient mice has demonstrated that irisin deficiency leads to reduced OB formation, increased OC formation, and lower bone density, while the presence of irisin stimulates the browning of adipose tissue, indirectly supporting bone formation [62], highlighting irisin's essential role in bone homeostasis. Furthermore, BAIBA, a metabolic by-product of irisin, also stimulates osteoprogenitor cell differentiation through the activation of NAD(P)H/ROS signaling, providing an additional pathway through which muscle factors influence bone metabolism [63].

The complex nature of muscle-bone interactions is further exemplified by myogenin, a key muscle regulatory factor that interacts with transcription factors like MEF2. While myogenin primarily regulates muscle development and function, its effects on muscle mass and strength indirectly influence bone health through both mechanical and biochemical pathways [64]. This intricate relationship between muscle and bone highlights the importance of maintaining muscle function in preventing and treating OP, suggesting that therapeutic strategies should consider both tissues as integral components of musculoskeletal health.

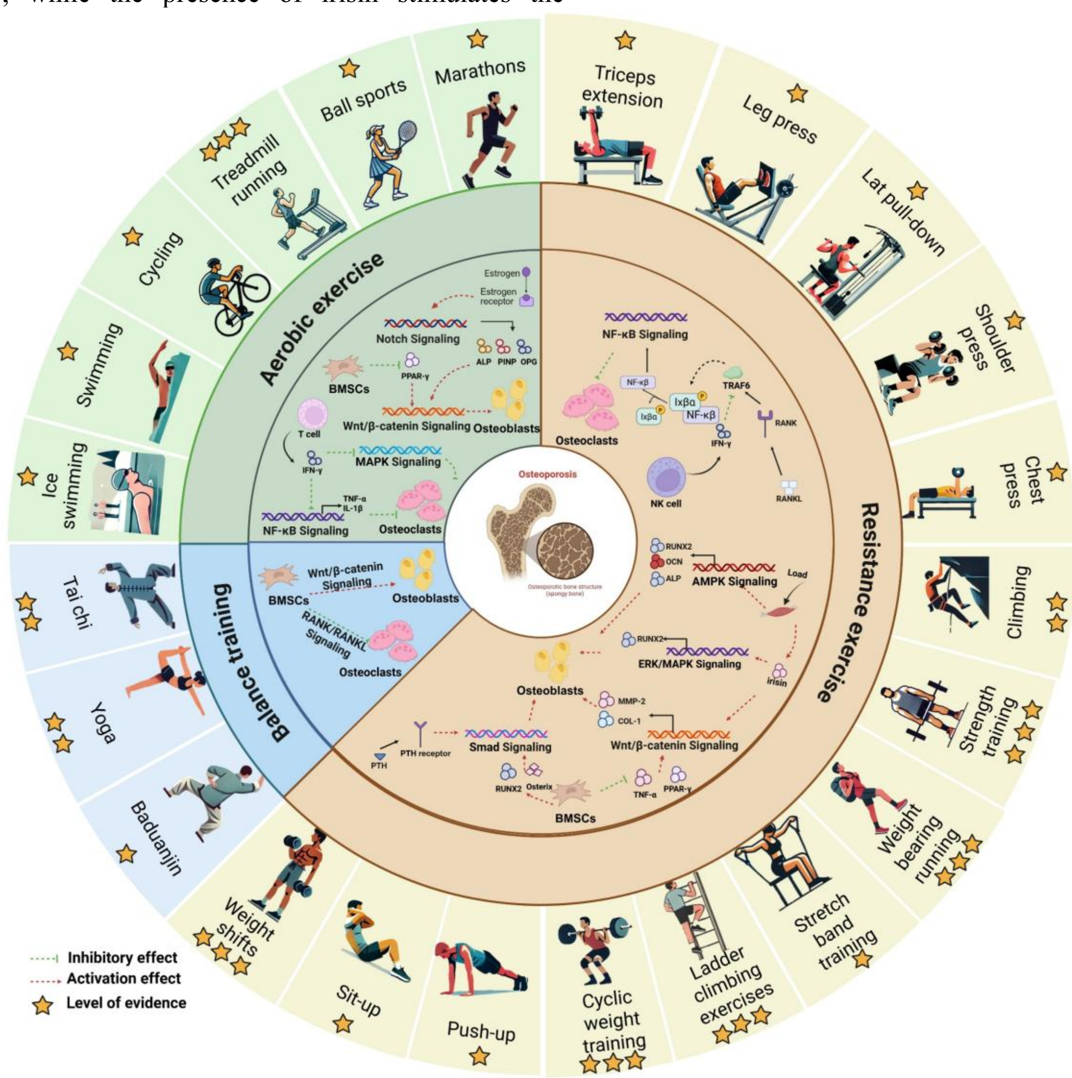

Figure 3. Comprehensive mechanistic overview of exercise modalities and their therapeutic targets in OP management. This circular diagram illustrates the integration of exercise interventions with their cellular and molecular targets across three hierarchical levels, demonstrating the multi-targeted therapeutic mechanisms underlying exercise-mediated bone protection in OP management. Outer ring (exercise modalities): Exercise interventions are categorized by biomechanical characteristics into three main types: aerobic exercise (green sectors, including treadmill running, cycling, swimming, ball sports, marathons, and ice swimming), resistance exercise (orange/beige sectors, including triceps extension, leg press, lat pulldown, shoulder press, chest press, climbing, strength training, weight-bearing running, stretch band training, ladder climbing exercises, cyclic weight training, push-ups, and sit-ups), and balance training (blue sectors, including Tai Chi, Yoga, and Baduanjin). Evidence quality for each specific exercise modality is indicated by stars (⭐⭐⭐ = high-quality evidence; ⭐⭐ = moderate evidence; ⭐ = preliminary or limited evidence). Inner region (mechanistic zones): The inner core is divided into three color-coded zones corresponding to the exercise categories, each depicting distinct molecular mechanisms acting on key bone cell populations—bone marrow mesenchymal stem cells (BMSCs), osteoblasts (bone-forming cells), and osteoclasts (bone-resorbing cells)—as well as osteocytes (mechanosensing cells). Aerobic exercise (green zone): primarily activates osteogenic pathways including Wnt/β-catenin and Notch signaling to promote BMSCs differentiation toward osteoblasts, while suppressing NF-κB-mediated inflammatory responses that reduce pro-inflammatory cytokine production (TNF-α, IL-1β). Additionally, aerobic exercise modulates MAPK pathways, activates estrogen receptor signaling, and inhibits PPARγ expression to prevent adipogenic differentiation. It also enhances immune cell function, with T cells and NK cells releasing IFN-γ to exert systemic anti-inflammatory effects and inhibit osteoclastogenesis. Resistance exercise (yellow/beige zone): exerts dual regulatory effects on bone remodeling (1) suppressing bone resorption through increasing by increasing the OPG/RANKL ratio, which inhibits NF-κB and TRAF6 signaling in osteoclast precusors, thereby reducing osteoclast differentiation and activity; and (2) promoting bone formation through upregulation of master osteogenic transcription factors RUNX2 and SP7 in osteoblasts. Resistance exercise also activates the Wnt/β-catenin and Smad signaling pathways via PTH receptor binding, leading to increased expression of bone matrix proteins (BMP-2, COL-1) and osteoblastic differentiation markers (ALP, OCN). The muscle-derived myokine irisin further contributes to osteogenesis through ERK/MAPK signaling activation. Balance training (blue zone): primarily engages mechanical transduction pathways in osteocytes and BMSCs through activation of Wnt/β-catenin signaling and modulation of RANK/RANKL/OPG axis. These mechanosensing mechanisms enhance the adaptive bone remodeling response to mechanical loading, improving bone microarchitecture and strength. Red dashed arrows indicate activation or promotion effects; green lines with blunt ends (⊣) represent inhibitory effects.

Beyond bone homeostasis and muscle-derived regulators, estrogen itself drives multiple osteogenic routes—by switching on Wnt signaling, boosting the Notch axis, and promoting OB differentiation and function. After menopause, the sharp estrogen drop dismantles these safeguards and accelerates OC-mediated resorption [65-68]. Meanwhile, osteoimmunology has revealed a dense web of crosstalk between the skeleton and the immune system, which is now viewed as a central player in skeletal maintenance and in the pathogenesis of OP [69].

The effects and underlying mechanisms of various exercise modalities in anti-op therapy

Clinical evidence supports the therapeutic potential of various exercise modalities in preventing and treating OP. Among them, running and swimming (aerobic exercise) effectively treat OP by boosting BMD and regulating the metabolism of calcium and phosphorus [70-72]. Resistance exercise, such as ladder climbing and weight-bearing running, enhances muscle strength and modulates hormonal levels, contributing to the prevention and treatment of OP [26,73]. Meanwhile, balance exercise (e.g., Tai Chi) has shown significant clinical effectiveness in both preventing and treating OP [74-76]. The following sections provide the molecular and cellular mechanisms through which different exercise modalities contribute to skeletal health and mitigate OP risk, with a focus on their roles in bone homeostasis, hormone balance, immune modulation, and muscular dynamics (Fig. 3).

Mechanisms of aerobic exercise in OP prevention

Aerobic exercise, also known as cardiovascular or endurance training, is distinguished by its steady rhythm, moderate intensity performed over an extended duration, and elevated oxygen achieved by increasing heart rate, thereby aligning oxygen supply with the body's demands throughout exercise [77-79]. While traditionally recognized for its cardiovascular benefits [80-82], emerging evidence highlights its direct effects on bone metabolism. Specifically, swimming has shown efficacy in counteracting BMD decline and restoring bone microarchitecture in high-fat diet-induced osteoporotic Sprague-Dawley (SD) rats [83]. Moreover, a 9-month study involving treadmill exercises at varying intensities in young mice demonstrated notable improvements in BMD and bone strength [84]. Further supporting this, downhill running exhibits enhanced osteogenic potential due to greater ground reaction forces and eccentric muscle contractions [85].

Effects of aerobic exercise on bone homeostasis

Aerobic exercise regulates bone homeostasis by modulating multiple molecules involved in bone formation, thereby enhancing bone mass. Research using Otsuka Long-Evans Tokushima Fatty (OLETF) rats has shown that sustained voluntary running for 36 weeks can reverse diabetes-related bone deterioration by improving cortical bone composition and mineral content [86]. Additionally, Kim's study demonstrated that a 6-week low-speed intermittent running program produced multiple beneficial effects: it (1) enhanced osteogenic molecules like BMP and SIRT in BMSCs, (2) downregulated RANKL-induced osteoclastogenesis through suppression of the MAPK pathway, and (3) enhanced the skeleton's own antioxidant defenses [87]. Furthermore, low-intensity aerobic training over 14 weeks prevents bone loss primarily through inhibiting PPARγ, activating canonical Wnt/β-catenin signaling, and directing marrow stromal cells toward the bone-forming lineage [88].

Effects of aerobic exercise on endocrine modulation

Aerobic exercise significantly influences bone metabolism through modulation of key endocrine pathways. Endurance activities, like marathons, trigger adaptive responses in both the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-gonadal (HPG) axis, both of which are crucial for hormonal regulation [89]. Clinical studies in perimenopausal women found that regular aerobic exercise (5 sessions weekly) elevated plasma cortisol and estradiol levels [90]. In animal models, swimming intervention demonstrates particularly interesting hormonal effects, with a 9-week program increasing BMD, estradiol, and 1,25-dihydroxyvitamin D3 levels [91].

In addition, the relationship between exercise and PTH regulation appears intensity-dependent, as evidenced by cohort studies of ice swimming participants aged 42-84 years, which showed acute elevations in serum PTH, calcium, and phosphorus levels [92]. Furthermore, PTH influences a range of downstream pathways, including JNK-MAPK and TGF-β, which govern the behavior of various bone cells [93, 94]. Maïmoun et al.'s research has revealed a threshold mechanism for PTH responses, emphasizing that hormonal adaptations occur only when exercise intensity or duration reaches specific thresholds [95, 96].

Enhancement of muscle-bone interaction by aerobic exercise

Aerobic exercise also strengthens the crucial relationship between muscle and bone health. For instance, long-term treadmill exercise effectively preserves skeletal muscle mass and prevents muscle atrophy [97, 98], while an over 12-week program of progressive aerobic cycling in elderly men demonstrates particular promise in reversing age-related muscle deterioration [99]. The molecular basis for these benefits includes reduced inflammatory signaling and enhanced antioxidant activity, as demonstrated in OVX rats. Exercise upregulates key muscle growth factors, including myogenin, p-mTOR, sirtuin (SIRT), and bone morphogenetic protein (BMP) [87]. Even non-weight-bearing exercises like swimming (60 minutes daily, 5 times/week) promote bone formation through muscle contraction-induced mechanical stress, effectively counteracting bone loss and microstructural deterioration in osteoporotic models [100]. Collectively, these findings underscore the value of aerobic exercise in maintaining muscle and bone health, offering a promising therapeutic avenue against muscle loss and OP.

Immunomodulatory effects of aerobic exercise

It is widely acknowledged that aerobic exercise influences bone metabolism by modulating immune responses within the bone microenvironment. Regular running wheel exercise (6 sessions weekly for 3 months) demonstrated potent anti-inflammatory effects, reducing IL-1β and IL-6 levels while increasing trabecular bone volume [101]. Treadmill training specifically inhibits NLRP3/Caspase1/IL-1β signaling, which attenuates low-grade inflammation by blocking NF-κB nuclear translocation and by reducing serum TNF-α and IL-1β levels [102]. Furthermore, consistent exercise activates CD8 T cells to release IFN-γ, which suppresses osteoclastogenesis via modulation of the NF-κB and MAPK pathway, thereby preventing OP [103].

These comprehensive findings underscore the multifaceted benefits of aerobic exercise through regulating signaling pathways from mechanical loading to gene expression in OP prevention and treatment. Table 1 summarizes the key experimental evidence supporting various aerobic exercise modalities, highlighting their specific effects on bone metabolism, immune function, and musculoskeletal health. This growing body of evidence establishes aerobic exercise as a crucial component of comprehensive OP management strategies. However, aerobic exercise has limitations: a substantial proportion of trials report no significant benefits for bone health, primarily due to insufficient mechanical loading intensity [104, 105]. While aerobic exercise maintains cardiovascular and metabolic benefits, without enough mechanical load, its bone-building potential may be limited.

Table 1. Aerobic exercise for the therapy of OP.

Study design	Exercise modalities	Experimental subject	Frequency and duration	Outcomes	Ref.
Randomized Controlled Trial	Treadmill exercises	3 months old male SAMP6 mice	3 d/week; 9 months	Boosts BMD and bone strength	[84]
Randomized Controlled Trial	Voluntary running wheel exercise	4 weeks old male OLETF rats	36 weeks	Reverses the decline in BMD and disruption of bone microarchitecture	[86]
Randomized Controlled Trial	Intermittent running	OVX rats	5 d/week; 6 weeks	Improves BMP and SIRT expression; downregulates RANKL in BMSCs	[87]
Randomized Controlled Trial	Treadmill exercise	3 months old female SD rats	3 d/week; 14 weeks	Prevents bone loss by inhibiting PPARγ expression	[88]
Randomized Controlled Trial	Breathing and progressive muscle relaxation	40-50 years old adults	5 d/week; 8 weeks	Improves plasma cortisol and estradiol levels	[90]
Randomized Controlled Trial	Swimming	15 months old Wistar rats	5 d/week; 9 weeks	Increases BMD, estradiol, and 1.25-dihydroxyvitamin D_3 levels	[91]
Randomized Controlled Trial	Ice swimming	42-82 years old women and men	-	Increases serum PTH, Ca, and phosphorus levels	[94]
Randomized Controlled Trial	Treadmill exercise	42-64 years old Obese Caucasians	9 months	Preserves skeletal muscle mass	[97] [98]
Randomized Controlled Trial	Aerobic cycling	elderly men	4 d/week; 12 weeks	Improves cardiovascular health and quadriceps muscle, including a partial reversal of age-related muscle mass decline	[99]
Randomized Controlled Trial	Interval running	OVX rats	5 d/week; 6 weeks	Suppresses inflammatory molecules expression, and enhance antioxidant activity in the skeletal muscles	[87]
Randomized Controlled Trial	Swimming	18 months old female Fisher 344 rats	5 d/week; 12 weeks	Mitigates bone loss and the deterioration of trabecular microstructure	[100]
Randomized Controlled Trial	Running wheel exercise	200-220 g female Wistar rats	6 d/week; 3 months	Decreases IL-1β and IL-6 mRNA/proteins levels	[101]
Randomized Controlled Trial	Treadmill training	24 months old SD rats	7 d/week; 8 weeks	Downregulates NLRP3, pro-Caspase1, and IL-1β mRNA/proteins levels	[102]
Randomized Controlled Trial	Running wheel exercise	8 weeks old female C57BL/6 mice	Daily; 8 weeks	Activates CD8 T cells to release IFN-γ and activates NF-κB and MAPK signaling pathways	[103]

Mechanisms of resistance exercise in OP prevention

Resistance exercise, defined as physical activity that involves muscle contraction against external resistance, encompasses various forms such as weight-bearing exercise, strength training, and counter-resistance exercise [106], and has demonstrated remarkable efficacy in enhancing tendon and skeletal muscle strength, particularly in aged rats [107-110]. Clinical investigations have further validated its potential as a promising intervention for maintaining bone mass and preventing OP progression [111]. Clinical studies support its therapeutic potential, with 24-week resistance training programs effectively maintaining bone density in elderly women [112]. Moreover, the effectiveness of resistance exercise appears to be intensity- and site-specific [113]. High-intensity progressive resistance training showed particular efficacy in improving lumbar spine BMD in premenopausal women, though its effects on femoral neck density may be less pronounced [114]. It is worth noting that the therapeutic benefits of resistance training for increasing bone mass in early postmenopausal women are highly dependent on 3 factors: the intensity, frequency, and peak resistance load. Particularly, greater emphasis should be placed on intensity and frequency rather than the number of load cycles. Optimal skeletal health outcomes are achieved with mechanical loads at 80% of the maximum resistance coupled with a training frequency of twice per week [115].

Resistance exercise on bone homeostasis

Resistance exercise modulates bone mass through sophisticated molecular mechanisms [116, 117]. Vertical ladder climbing exercise, performed 3 times weekly for 12 weeks, notably reduced SOST gene expression in elderly rats. This downregulation activates the Wnt signaling pathway, enhancing bone formation while improving bone toughness by upregulating matrix metalloproteinase-2 (MMP-2) and collagen type I (COL-1) expression, which are key elements of bone matrix production [118]. Similarly, a 16-week strength training program reduced PPARγ and TNF-α expression in BMSCs while increasing osteogenic transcription factors RUNX2 and OSX, thereby promoting the osteogenic differentiation capacity of BMSCs[119]. In addition, mechanical load studies further demonstrated reduced OC differentiation in femoral bone marrow and lowered the RANKL/OPG ratio in the maxillary bone, indicating effective inhibition of bone resorption [120].

Resistance exercise on immune system regulation

Resistance exercise has been shown to positively modulate immune function, which is particularly beneficial in elderly populations. A 12-week tailored exercise program featuring leg extensions, leg presses, and hip abduction/adduction exercises enhanced immune markers by upregulating CD28 on cytotoxic T cells and CD80 on monocytes [121]. In line with these findings, animal experiments with ladder climbing training showed a significant reduction in pro-inflammatory cytokines TNF-α and IL-6, thus improving the inflammatory microenvironment [122]. In parallel, weight-bearing running exercise enhanced IFN-γ secretion and activated Wnt signaling pathway components, such as Wnt1, Wnt3a, and β-catenin, thereby promoting bone formation [123]. Moreover, studies show that IFN-γ, which is released by NK and activated T cells, disrupts RANKL-RANK signaling to curb osteoclast formation, drives pre-OCs toward apoptosis by boosting FasL on osteoblasts, and strengthens new bone formation [124-126].

Adiponectin is also an important anti-inflammatory marker, which is beneficial for delaying the progression of OP. Notably, 30 minutes of strength training increases adiponectin levels, which in turn inhibits OC activity and activates osteogenesis [127]. These effects are particularly beneficial in mitigating age-related chronic low-grade inflammation associated with OP.

Resistance exercise on endocrine adaptations

Resistance training induces substantial hormonal adaptations that benefit skeletal health. A 12-week cyclic weight training program involving diverse exercises (chest press, leg extension, shoulder press, leg curl, lat pull-down, leg press, arm curl, and triceps extension), performed 3 times weekly, significantly elevated growth hormone, estrogen, PTH, and testosterone levels [128]. Specific exercises like climbing modulate PTH signaling by upregulating PTH1 receptor expression, thereby promoting osteogenesis while inhibiting adipogenic differentiation of BMSCs [129]. Furthermore, resistance training targeting knee extension and flexion effectively counteracted age-related declines in sex steroidogenic enzymes and muscle androgen levels in elderly men, illustrating its potential to address hormonal imbalances associated with aging and OP [130].

Resistance exercise on musculoskeletal benefits

Resistance exercise is also vital for maintaining strong musculoskeletal strength and reducing the risk of fracture [131]. The mechanical stress induced by resistance training activates key signaling pathways that directly affect the cytoskeleton reorganization in OBs and osteocytes. For instance, stretch band training programs enhance grip strength and muscle power while potentially elevating circulating irisin, which is produced by cleavage of fibronectin type III domain-containing protein 5 (FNDC5) [131-134]. It could promote OB differentiation and bone formation through activation of Wnt/β-catenin and ERK/MAPK signaling pathways via binding with integrin proteins [61]. A resistance running program effectively combats STZ-induced femoral atrophy in diabetic rats by downregulating myostatin (MSTN) expression [135], while weight-bearing treadmill exercise activates the Wnt/GSK3β/β-catenin pathway to improve bone microstructure [136]. A separate study in sarcopenic rats demonstrated that a resistance training program modulates key regulatory proteins, including Akt, mTOR, and FoxO3a phosphorylation, while increasing AMP-activated protein kinase (AMPK) activation and mitochondrial quality control [137]. All of these molecular adaptations suggest resistance exercise's crucial role in maintaining musculoskeletal integrity and preventing age-related deterioration.

The extensive body of evidence presented above demonstrated the importance of resistance exercises in maintaining musculoskeletal health and preventing OP through mechanotransduction and anabolic signaling cascades, especially. Through its effects on molecular signaling pathways, immune function, hormonal regulation, and muscle-bone interactions, resistance training offers a comprehensive approach to skeletal health maintenance. These exercises have demonstrated benefits in enhancing bone formation, reducing fracture risk, and improving muscle strength, underscoring their value in OP management. Multiple studies also hint at a dose–response relationship for resistance training: higher loads delivered less often appear to give the strongest osteogenic stimulus [138]. However, high-load resistance training may increase the risk of fracture in elderly individuals with compromised bone quality. Therefore, moderate, carefully titrated training intensities appear to offer the optimal balance between efficacy and safety. Table 2 summarizes the diverse resistance exercise protocols and their specific therapeutic effects in OP prevention and treatment, providing evidence-based guidance for clinical applications.

Table 2. Resistance exercise for the therapy of OP.

Study design	Exercise modalities	Experimental subject	Frequency and duration	Outcomes	Ref.
Randomized Controlled Trial	Vertical ladder climbing	3 month-old male rats	3 d/week; 12 weeks	Down-regulates SOST gene expression; increases bone formation via MMP2 and COL-1	[118]
Randomized Controlled Trial	Progressive load ladder movement	5-month-old female Wistar rats	3 d/week; 16 weeks	Reduces BMSCs' osteogenic differentiation; reduce PPARγ and TNF-α expression	[119]
Randomized Controlled Trial	Ladder climbing + treadmill run	C57BL/6 mice	Daily; 2 weeks	Reduces RANKL/OPG ratio; decreases OC differentiation	[120]
Randomized Controlled Trial	Resistance exercise program	61-79 years old people	2 d/week; 12 weeks	Enhances CD28 in Tc cells and CD80 in monocytes	[121]
Randomized Controlled Trial	Ladder- climbing Training	Obese Rats	2 times/day; 8 weeks	Inhibits pro-inflammatory cytokines TNF-α and IL-6	[122]
Randomized Controlled Trial	Weight-bearing running	Balb/C mice	3 d/week; 8 weeks	Enhances IFN-γ secretion; upregulates Wnt pathway	[123]
Randomized Controlled Trial	Strength + treadmill running	12-18 years old obese adolescents	3 d/week; 1 year	Increases adiponectin, inhibits osteoclastogenesis, and activates osteogenesis	[127]
Randomized Controlled Trial	Weight training	22-28 years old sedentary females	3 d/week; 12 weeks	Boosts growth hormone, estrogen, PTH, and testosterone levels	[128]
Randomized Controlled Trial	Voluntary climbing exercise	young and older men	4 weeks	Promotes PTHR1 expression and osteogenesis; inhibits terminal differentiation of adipocyte progenitor cells	[129]
Randomized Controlled Trial	Stretch band training	male C57BL/6 mice	2 d/week; 12 weeks	Correlates exercise strength with circulating Irisin levels	[132]
Randomized Controlled Trial	Weight-bearing running	200-220g male SD rats	6 d/week; 6 weeks	Downregulates MSTN expression; ameliorate femoral atrophy in diabetic rats	[135]
Randomized Controlled Trial	Weight-bearing running	OVX rats	6 d/week; 10 weeks	Upregulates Wnt1 and β-catenin mRNA/protein, and activates Wnt/GSK3β/β-catenin pathway	[136]
Randomized Controlled Trial	Ladder-climbing training	3 months old female SD rats	3 d/week; 12 weeks	Decreasing Akt, mTOR, and FoxO3a phosphorylation; and increases AMPK activity	[137]

The mechanisms of balance exercise in OP prevention

Balance exercises, characterized by their emphasis on postural stability and controlled movement, represent an innovative and effective approach to OP management. Traditional forms such as Yoga, Baduanjin, and Tai Chi are distinguished by their low-intensity, controlled movements and integration of breathing techniques, offering a unique combination of physiological and psychological benefits [139]. These exercises are particularly valuable for addressing OP-related challenges, such as reducing the risk of falls, correcting postural deformities (e.g., kyphosis), and mitigating bone loss[28, 140, 141]. By promoting proper anatomical alignment, particularly of the spine, balance exercises evenly distribute skeletal stress, prevent damage, and improve overall structural stability [142]. Furthermore, these low-intensity and accessible modalities are especially suited for elderly individuals or patients with limited physical capacity, ensuring broad applicability in diverse populations. For institutionalized individuals with OP who experience fear of falling, a 12-week balance training program conducted twice weekly using the Biodex Balance System significantly reduced fear of falling, improved dynamic balance, and enhanced isometric strength, highlighting the feasibility and efficacy of balance exercises in promoting stability and physical resilience among institutionalized individuals with OP [143]. Beyond these biomechanical benefits, recent studies underscore the role of balance exercises (such as Baduanjin and Yoga) in modulating inflammatory responses and improving bone metabolism, marking them as valuable therapeutic tools for OP management. Table 3 summarizes the specific mechanisms of balance exercises in addressing OP-related pathophysiology.

Baduanjin

Baduanjin, a traditional Chinese mind-body exercise, combines slow, symmetrical body movements with controlled breathing and meditative focus [144]. This practice is particularly beneficial for elderly individuals or those with OP who may be unable to engage in high-intensity physical activity. Mechanistically, Baduanjin promotes moderate mechanical loading that activates pathways involving NOX2, TRPV4, and β-catenin. This activation promotes osteogenic differentiation of BMSCs through three mechanisms: (1) inhibiting adipogenic differentiation, (2) promoting OB proliferation, and (3) inhibiting OC-mediated bone resorption, ultimately facilitating bone formation and mitigating bone loss [145]. Clinical evidence underscores the therapeutic efficacy of Baduanjin in OP management. For instance, a 24-week randomized clinical trial involving 160 OP patients demonstrated that Baduanjin practice significantly reduced pain scores, increased BMD, and elevated serum levels of bone turnover markers such as procollagen I N-terminal propeptide (PINP) and β-CTX [146]. Similarly, a 12-week trial focused on middle-aged women found that participants practicing Baduanjin exhibited remarkably lower IL-6 levels and higher BMD compared to the control group, suggesting its dual role in reducing systemic inflammation and improving skeletal health [147]. These findings collectively highlight Baduanjin's multifaceted contributions to bone homeostasis and its potential as a low-cost, accessible intervention for OP patients.

Yoga

Yoga, a widely practiced form of exercise, combines balancing poses, breath control, and meditation, offering comprehensive benefits for physical and mental well-being [148]. For OP patients, Yoga serves as a therapeutic option that not only reduces the risk of falls and strengthens the skeletal muscles but also promotes relaxation, alleviates stress, and supports recovery from bone loss [29]. Clinical trials provide robust evidence of Yoga's efficacy in improving bone health [149, 150]. Specifically, in a 6-month trial, participants who practiced Yoga 4 times a week for 1 hour each session experienced substantial increases in BMD and improvements in T-score [151]. Another investigation reported that just 12 minutes of daily Yoga improved BMD in the spine, hip, and femur of OP patients [152]. Beyond these physical benefits, Yoga also modulates inflammatory responses; a comparative study involving 208 subjects showed that individuals who practiced Yoga regularly for over 5 years had lower serum levels of pro-inflammatory cytokines, including TNF-α and IL-6, compared to non-practitioners [153]. Furthermore, Yoga programs have been shown to elevate estrogen levels in middle-aged women [154], providing additional protection against bone resorption associated with hormonal imbalances. By enhancing muscle activity, Yoga amplifies mechanical load on skeletal muscle, thereby rectifying the imbalance in bone homeostasis and preventing further deterioration [155].

Tai Chi

Tai Chi, a traditional Chinese discipline, is frequently utilized for its meditative qualities and is recognized for its potential health benefits [156, 157]. This practice involves a series of complex movements, including squats paired with deep breathing, designed to foster relaxation and alleviate pain [158]. Previous research has indicated that Tai Chi can effectively reduce the deterioration of BMD [159]. Song's research suggests that the influence of Tai Chi on BMD is significantly tied to the length of engagement. Individuals who practiced for 40 minutes daily over 1 year exhibited markedly superior improvements in lower limb muscle mass and BMD compared to those who practiced for only 4 months [160]. Moreover, a randomized controlled trial involving women with diminished bone mass revealed that a 6-month regimen of Tai Chi enhanced various markers of skeletal health, including increased bone alkaline phosphatase (BAP) levels, an elevated BAP/TRAP ratio, and heightened serum PTH levels, in addition to a significant boost in muscle strength [161]. Regular Tai Chi practice for 24 weeks has also been shown to ameliorate lipid metabolism and bolster vascular endothelial function [162]. In line with these findings, a study demonstrated that a 3-month Tai Chi program, with three one-hour sessions per week, effectively reduced whole-body oxidative stress, decreasing ROS through Wnt and RANK/RANKL signaling, shifting the balance toward osteoblasts and away from osteoclasts, which in turn improved OP [163].

Balance exercises link neuromuscular control to bone metabolism, providing a multifaceted approach to the management of OP by addressing critical issues such as spinal deformities, fall risk, inflammatory modulation, and bone metabolism. These practices integrate physical, mental, and biochemical benefits, providing a comprehensive therapeutic strategy for skeletal health improvement. Evidence from clinical trials consistently demonstrates their efficacy in improving bone density, reducing systemic inflammation, and enhancing the overall quality of life for OP patients. Interestingly, the benefit of balance exercise may scale with time: continued practice for months allows the bone to respond [160]. Because the movements integrate easily into daily life, they suit chair-bound or load-limited OP patients who cannot tolerate high-impact exercise. Table 3 summarizes the specific mechanisms, intervention protocols, and outcomes of balance exercises in OP therapy. As research into these traditional practices continues to expand, a clearer understanding of their molecular mechanisms and broader applications in osteobiology will solidify their role as essential components of comprehensive OP management strategies. Incorporating balance exercises into individualized treatment plans offers patients a safe, accessible, and effective means to improve their skeletal health and overall well-being.

Table 3. Balance exercise for the therapy of OP.

Study design	Exercise modalities	Experimental subject	Frequency and duration	Outcomes	Ref.
Randomized Controlled Trial	Balance training program	76 years old people	2 d/week; 12 weeks	Improves dynamic balance and isometric strength in older adults	[143]
Randomized Controlled Trial	Baduanjin	breast cancer patients	-	Inhibits adipogenic differentiation and promotes BMSCs' osteogenic differentiation	[145]
Randomized Controlled Trial	Baduanjin	45-70 years old women 50-70 years old men	3 d/week; 24 weeks	Increase BMD; elevates PINP and β-CTX levels	[146]
Randomized Controlled Trial	Baduanjin	45 years old women	3 d/week; 12 weeks	Lowers IL-6 levels; enhances BMD	[147]
Randomized Controlled Trial	Yoga	45-62 years old women	4 d/week; 6 months	Increase BMD; reduces T-score	[151]
Randomized Controlled Trial	Yoga	Individuals aged 68.2 years	5 years	Improves BMD in spine, hip, and femur	[152]
Randomized Controlled Trial	Yoga	20-60 years old adults	1 h/day; Long term	Lowers serum TNF-α and IL-6 levels	[153]
Randomized Controlled Trial	Yoga	postmenopausal women	2 sessions (1 h each)/week; 16 weeks	Increases estrogen	[154]
Randomized Controlled Trial	Yoga	women	Daily	Enhances skeletal muscle load; and rectifies bone homeostasis imbalance	[155]
Randomized Controlled Trial	Tai Chi	55-65 years old women	Daily; 1 year	Enhances limb muscle mass and BMD	[160]
Randomized Controlled Trial	Tai Chi	at least 2 years after menopause	1 h/day; 3 d/week; 6 months	Increases BAP and BAP/TRAP ratio; heightenes serum PTH levels; boosts muscle strength	[161]
Randomized Controlled Trial	Tai Chi	54 years old women	1 h/day; 4 d/week; 24 weeks	ameliorates lipid metabolism and bolsters vascular endothelial function	[162]
Randomized Controlled Trial	Tai Chi	at least 2 years after menopause women	1 h/day; 3 d/week; 6 months	lowers the body's oxidative stress levels	[163]

Influence of other factors on exercise outcomes

Direct comparisons across studies remain challenging due to heterogeneity in participant characteristics, including age, sex, and comorbidities. Recent studies show that aged osteocytes lose mechanosensitivity, display blunted cellular responsiveness, and suffer from defective lacuno-canalicular remodeling [164]. This age-related decline in mechanical reactivity can dampen the protective effect of exercise against OP [165]. However, the aging skeleton can be activated by brief bouts of high-impact loading, after which even low-moderate activities yield greater benefits, demonstrating that re-engineering the loading pattern can make exercise more efficient in older adults [166].

Additionally, gender-specific influences, particularly those mediated by the endocrine milieu, constitute a non-negligible source of heterogeneity. Epidemiological and mechanistic evidence indicate that males maintain a stronger correlation between muscle mass and bone architecture as well as biomechanical competence, whereas the abrupt decline in estrogen concentrations after menopause attenuates the mechanosensitivity of the female skeleton to a greater extent than age alone affects males. In men, exercise-induced skeletal adaptation appears to be partly IGF-1-dependent; the progressive reduction in circulating and muscle-derived IGF-1 with advancing age may therefore underlie the attenuated osteogenic response to mechanical loading observed in elderly male cohorts [167].

Lifestyle-related disorders, such as type 2 diabetes mellitus (T2DM), obesity, and sarcopenia, may modulate the skeletal response to exercise interventions in OP. Individuals with T2DM frequently exhibit normal or even modestly elevated BMD, a phenomenon largely attributed to hyperinsulinemia, which exerts direct anabolic effects on osteoblast lineage cells [168]. Combined weight-bearing aerobic and resistance training has been shown to mitigate excessive bone loss in this population [169]. Concurrently, accumulating evidence links compromised muscle integrity to accelerated bone loss; the myo-adipose metabolic perturbations characteristic of sarcopenic obesity disrupt the coupling between bone formation and resorption, thereby amplifying OP risk [170]. Caloric restriction, when implemented without nutrient deficiency, augments skeletal muscle mass, attenuates muscle wasting, and reduces excess adiposity. Consequently, an integrated exercise–nutritional support paradigm appears optimally suited for OP patients with concurrent sarcopenia [171].

Comparative clinical efficacy of exercise modalities in op management

Although exercise is an established strategy for preserving postmenopausal bone mass and decelerating bone loss, with mechanistic evidence substantiating its feasibility, not all exercise modalities or dosages elicit equivalent skeletal benefits [106]. The following synthesis critically compares the clinical efficacy of distinct exercise paradigms in OP management, with particular emphasis on understanding the differential responses across modalities and identifying optimal intervention parameters. Table 4 summarizes the therapeutic efficacy of distinct exercise modalities in the treatment of OP.

Table 4. Comparative Clinical Efficacy of Exercise Modalities in OP Management.

Study design	Exercise modalities	Experimental subject	Frequency and duration	Outcomes	Ref.
Randomized Controlled Trial	swimmers maintaining	43 female competitive swimmers (mean age 40.4)	>2 h/week; 5 years	No differences in BMD	[172]
Randomized Controlled Trial	low-repetition light-load power training	OP patients younger than 65 years	2 times/week; 6 weeks	Improves pelvic BMD and knee-extensor strength	[174]
Randomized Controlled Trial	progressive resistance training	43 older men with sarcopenia (aged 73-91)	2 times/week; 1 year	Preserves BMD and improves muscle strength	[175]
Randomized Controlled Trial	high-intensity resistance training	101 women with low bone mass (T-score < -1.0, aged 65 ± 5 years)	2 sessions (30 min each)/week; 8 months	Raises BMD and bone strength and enhances neuromuscular performance indices	[176]
Randomized Controlled Trial	impact-plus-resistance training and low-intensity Pilates	women with low bone mass who had discontinued anti-resorptive therapy	2 times/week; 8 months	Improves proximal-femur geometry; Pilates yields no measurable benefit	[179]
Randomized Controlled Trial	Baduanjin for 30-60 min every time	44 OP patients	3 times/week; 12 weeks	Reduces IL-6 and maintains BMD	[147]
Randomized Controlled Trial	Tai Chi	105 urban older women with habitual inactivity	1 year	Increased lower-limb muscle mass and strength, BMD, and balance capacity	[160]
Randomized Controlled Trial	one-hour circuit incorporating both strength and balance exercises	150 out-patients with OP	2 times/week; 12 weeks	Improves gait speed, functional capacity, overall health status and quality of life	[106]
meta-analysis	Combined aerobic and resistance training	2230 postmenopausal women aged 50–60 years	Regular exercise	Mitigating bone loss and promoting skeletal health	[181]

A prevailing clinical perception posits that aerobic exercise may not constitute the most appropriate regimen for OP prevention and treatment. In a seminal investigation, Abrahin et al. conducted a comparative analysis of 43 female competitive swimmers and 44 age-matched controls (mean age 40.4 vs 43.8 years). Despite swimmers maintaining > 2 h/week of swimming over 5 years while controls remained sedentary, no differences in bone mineral content were detected at any skeletal site between groups [172]. This apparent lack of benefit may be explained by the concept that low-impact aerobic activities impose habitual mechanical loads insufficient to surpass the mechanostat threshold required for osteogenic adaptation. Substantial skeletal benefits manifest only when exercise-induced loading deviates markedly from habitual mechanical stimuli [173]. These findings suggest that while aerobic exercise offers cardiovascular and metabolic benefits, its osteogenic potential may be limited without adequate mechanical loading intensity.

Resistance exercise is currently recommended as an effective strategy to increase and maintain BMD in postmenopausal women[112]. Hamaguchi's team demonstrated that wearing a weighted vest while performing low-repetition, light-load strength training for only 6 weeks significantly improved pelvic BMD and knee-extensor strength in OP patients younger than 65 years [174]. Similarly, in sedentary community-dwelling older men with sarcopenia, twice-weekly progressive resistance training not only preserved BMD but also produced marked gains in muscle strength [175]. A meta-analysis concluded that higher-intensity, lower-frequency dosing—by generating large compressive, shear, and bending loads—delivers a stronger osteogenic stimulus [138]. In a cohort of 101 women aged 65 years, 8 months of high-intensity resistance training (two sessions/week, 30 min/sessions) raised BMD and bone strength while simultaneously enhancing neuromuscular performance indices [176]. Nevertheless, heavy loading carries an increased fracture risk in older adults, necessitating careful consideration of individual risk profiles. Therefore, clinical guidelines favor moderate-intensity protocols that balance osteogenic benefits with safety concerns [73]. Importantly, the skeletal response is site-specific rather than systemic: progressive back-extension resistance preferentially boosts lumbar BMD, whereas 2-3 sessions per week of high-impact jumping for 12 months improved proximal-femur BMD without altering lumbar values [177, 178]. This site-specificity underscores the importance of targeting exercise protocols to regions at the highest fracture risk.

Balance exercise is viewed clinically as a potential therapeutic tool, yet its efficacy remains debated. In a comparative study of postmenopausal women with low bone mass who had discontinued anti-resorptive therapy, 8 months of impact-plus-resistance training twice a week improved proximal-femur geometry, whereas low-intensity Pilates yielded no measurable benefit [179]. However, other data are more encouraging: after 12 weeks of Baduanjin, 44 OP patients exhibited reduced IL-6 and maintained BMD [147]. Notably, the benefit of balance exercise appears tightly linked to intervention duration. Among 105 urban older women with habitual inactivity, daily Tai Chi produced no short-term skeletal gains, yet extending practice to 8–12 months significantly increased lower-limb muscle mass and strength, BMD, and balance capacity [160]. Because Tai Chi requires no high mechanical loads and can be readily incorporated into daily routines, it is particularly suitable for sedentary adults at risk of OP or those unable to perform high-intensity exercises.

Moreover, sex-specific responses must be factored into clinical decision-making. In men, the tighter covariance between muscle mass and skeletal architecture renders resistance training particularly effective at averting bone loss. In women, however, the sharp postmenopausal decline in bone mechanosensitivity suggests that early initiation of resistance exercise during the pre-menopausal period offers the greatest protective benefits [167, 180]. These sex-specific patterns underscore the need for personalized, life-stage-appropriate exercise interventions to optimize skeletal health outcomes.

Current clinical consensus favors multi-modal programs that combine two or more exercise types—such as resistance plus aerobic, or resistance plus balance—to prevent OP and fractures, as these approaches positively influence multiple skeletal and fall-related risk factors [106]. In a 12-week randomized controlled trial (RCT) of 150 outpatients with OP, a twice-weekly, 1-hour circuit incorporating both strength and balance exercises improved gait speed, functional capacity, overall health status, and quality of life compared with usual care [181]. Furthermore, a meta-analysis of 2230 postmenopausal women aged 50–60 years concluded that regular combined aerobic and resistance exercise is an effective non-pharmacological strategy for mitigating bone loss and promoting skeletal health [182]. These findings collectively support the integration of multiple exercise modalities to maximize therapeutic benefits and address the multifaceted nature of OP pathophysiology.

Conclusion and prospect

OP is a widespread systemic metabolic bone disease, particularly among the elderly, that profoundly diminishes the quality of life. It arises from disrupted bone homeostasis driven by hormonal imbalances, immune dysregulation, muscle atrophy, and vascular changes. Exercise therapy has emerged as a safe and promising intervention, offering substantial benefits in mitigating bone loss, enhancing bone strength, and improving patient quality of life [183]. Notably, clinical trials and preclinical studies have demonstrated the efficacy of aerobic, resistance, and balance exercises in addressing various facets of OP pathogenesis. For instance, aerobic exercises like swimming and running increase BMD and bone mineral content [23, 184], while resistance training activates mechanotransduction pathways to stimulate bone formation [64]. Additionally, balance exercises such as Tai Chi and Yoga improve posture, reduce fall risk, and prevent fractures in OP patients [155, 185].

The integration of exercise and other therapeutic methods has gained increasing attention in OP care, with the combination of traditional anti-OP drugs with exercise interventions showing promising outcomes [186-189] (Fig. 4A). Emerging evidence from clinical studies has demonstrated the efficacy of coupling aerobic exercise with bisphosphonate therapy in significantly reducing serum bone resorption markers, such as type I collagen C-terminal peptide (CTX-1) and PINP, while elevating bone turnover markers and BMD. This combined approach not only improves bone health but also enhances the overall quality of life for OP patients [190]. For example, a study revealed that low-amplitude whole body vibration (WBV) in conjunction with alendronate sodium (ALE) over 12 weeks results in greater bone volume and improved trabecular structure compared to ALE alone, highlighting WBV's potential to augment the therapeutic effects of alendronate [191].

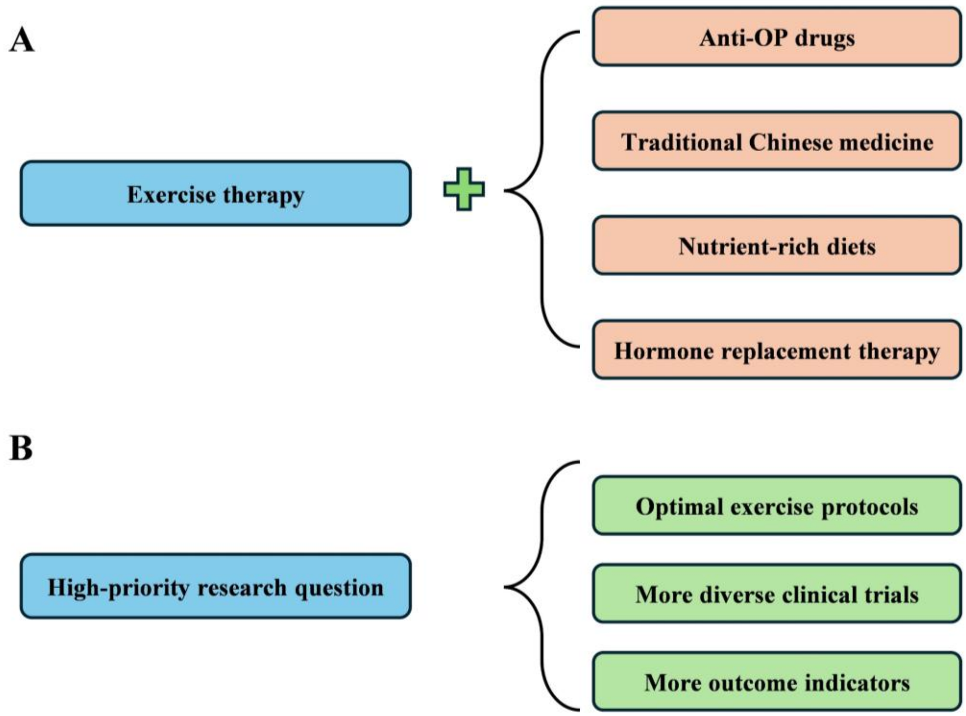

Figure 4. Integrative therapeutic paradigm for OP management and high-priority research questions. The schematic depicts the synergistic integration of exercise therapy with evidence-based pharmacological and lifestyle interventions, encompassing anti-osteoporotic drugs, traditional Chinese medicine formulations, nutrient-dense dietary regimens, and hormone-replacement therapy. High-priority research questions center on (i) defining the optimal exercise prescription, (ii) expanding clinical trials to more diverse cohorts, and (iii) broadening the spectrum of outcome measures.

In addition, the integration of traditional Chinese medicine (TCM) formulas with exercise therapy holds significant promise in the management of OP. TCM formulas, known for their multi-component synergistic effects, have been extensively used to support bone health for centuries. For instance, Fuzi decoction modulates the NF-κB pathway to inhibit OC differentiation [192], while Qianggu Decoction promotes BMSCs differentiation and upregulates osteogenic markers such as RUNX2, OPN, and OCN, thereby effectively mitigating OP [193]. Recent progress in understanding the material basis and compatibility mechanisms of TCM formulas provides a scientific basis for their modernization and internationalization [194, 195]. Furthermore, clinical trials and animal studies have also indicated that combining TCM formulas with exercise therapy enhances therapeutic outcomes. For example, a 2-month regimen of naringin with treadmill exercise in OVX-induced OP rats reduced CTX-1 levels and increased OCN expression [196]. Similarly, pairing Erxian Tang with Baduanjin exercise demonstrated efficacy and safety in managing postmenopausal OP participants [197]. Therefore, such integrative approaches emphasize the potential of combining non-pharmaceutical and pharmaceutical therapies to minimize fracture risks and improve overall skeletal health [198].

Additionally, pairing a nutrient-rich diet with exercise emerges as a safe and cost-effective therapeutic strategy for musculoskeletal health. Supplements containing protein, vitamin D, and calcium, combined with tailored exercise regimens, address inflammation and oxidative stress and promote muscle protein synthesis. This dual approach mitigates the complex interaction between muscle and bone deterioration associated with OP, ultimately improving skeletal strength and functionality [199].

For postmenopausal women, estrogen deficiency profoundly influences OP progression, making hormone replacement therapy (HRT) a conventional therapeutic intervention. Comparative studies have shown that supervised exercise is more effective than HRT in enhancing BMD. Furthermore, the combination of aerobic exercise and estrogen therapy offers synergistic therapeutic effects while mitigating the risks associated with HRT by improving metabolic health [200].

The integration of diverse therapeutic modalities with targeted exercise regimens offers a promising strategy for comprehensive OP management. By integrating the unique properties of each adjunctive therapy with the empirically validated benefits of physical activity, these multimodal programs enhance clinical outcomes, boost patient adherence, and may ultimately lighten the economic burden of OP. As ongoing investigative efforts continue to unravel the complex mechanisms underlying these therapies, the development of precision-targeted and personalized treatment protocols becomes increasingly feasible. Such advancements are anticipated to herald a new era of OP management, fostering better skeletal health and improved quality of life for affected individuals.

Despite the compelling evidence supporting exercise as a cornerstone of OP therapy, challenges remain in optimizing exercise protocols. Variability within study populations and limited outcome measures have contributed to inconsistencies regarding reported efficacy. Further clinical trials with larger, more diverse cohorts and expanded outcome indicators are essential to consolidate the evidence base and refine exercise regimens (Fig. 4B). By addressing these gaps, the field can advance toward more effective and tailored therapeutic strategies. Ultimately, exercise therapy holds the potential to serve as a central pillar in the comprehensive, multidisciplinary management of OP, offering a sustainable and impactful solution to this pervasive health challenge.

Author contributions

Conceptualization, H.R., L.C., K.F.; data curation, Y.X., S.X., R.D., G.X., H.B., X.D., H.R., L.C., K.F.; validation, Y.X., S.X., R.D., G.X., H.B., X.D., H.R., L.C., K.F.; writing–original draft preparation, Y.X., S.X., R.D., G.X., H.B., X.D., H.R., L.C., K.F.; writing–review and editing, Y.X., S.X., R.D., G.X., H.B., X.D., H.R., L.C., K.F.; supervision, H.R., L.C., K.F.; funding acquisition, K.F.. All the authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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