

Exercise Intervention Effects and Related Mechanisms of Post-stroke Osteoporosis

Hongyi Xu, Yanzhen Wang*

School of Rehabilitation Medicine, Shandong University of Traditional Chinese Medicine, Jinan, China

**Corresponding Author. Email: 2784739465@qq.com*

Abstract. Post-stroke osteoporosis (PSO) is a common complication in stroke patients, characterized by rapid bone loss and impaired bone microstructure, which significantly increases the risk of fracture and mortality. Limb disuse and muscle weakness are the core inducing factors, and the daily physical activity of patients is far below the recommended standard. This study aimed to summarize existing research and develop an optimal exercise intervention program for PSO patients. We integrated relevant clinical studies, meta-analyses and basic experimental results through literature review, and analyzed the implementation strategies of different exercise interventions and their effects on bone health. The results showed that aerobic exercise was the core intervention for PSO, and programs such as cycle ergometer at 50%~80% of maximum heart rate could improve patients' cardiorespiratory function and walking ability. Comprehensive exercise combining aerobic exercise with muscle strengthening and skeletal loading (e.g., FAME program) could maintain the bone mineral density (BMD) of the femoral neck on the affected side and improve tibial bone geometric parameters. The low-intensity walking program had high compliance, and 12-week aerobic plus resistance training could significantly optimize BMD and bone metabolic markers. The efficacy of exercise was affected by training duration and gender. It is concluded that exercise intervention is a safe and effective method for improving PSO, and comprehensive exercise programs are superior to single aerobic exercise. Community-based individualized exercise programs are worthy of promotion. Future research needs to further explore the mechanism of exercise on bones in different parts of the body.

Keywords: stroke, Osteoporosis, Exercise, Mechanisms, bone

1. Introduction

Bone density serves as a key indicator of skeletal health and structural integrity [1]. Post-stroke osteoporosis (PSO) commonly occurs after stroke, characterized by rapid bone mass reduction and deteriorated bone microarchitecture, which markedly raises the risk of fracture [2]. Stroke patients exhibit a fourfold higher risk of femoral neck fracture than age-matched controls without stroke [2]. Such osteoporosis can result in disability and even mortality, representing a leading cause of death in stroke patients [3]. Stroke patients have a more than 8% fracture risk within five years after onset.

Mild stroke severity and osteoporosis are strongly associated with post-stroke fracture susceptibility [4]. Approximately one in 12 stroke patients sustains a femoral fracture within 5 years post-stroke [5]. Stroke-related fracture risk ranges from 1.5 to four times higher [6]. Post-stroke fractures hinder the recovery of independent walking and elevate mortality, highlighting the necessity of fracture prevention for this high-risk population [7].

Earlier DXA-based investigations demonstrated a 10–12% decrease in proximal femoral aBMD on the paretic side during the first post-stroke year [8, 9]. Bone property alterations are also pronounced in the chronic stroke phase (mean duration: 4 years). pQCT detected a substantial reduction in trabecular vBMD of the paretic distal tibia as early as 1 year post-stroke [10]. TBone loss occurred at nearly 10 times the rate seen in healthy individuals [11]. Preclinical studies indicate that stroke induces altered bone vascularization, featuring increased branching, fewer small vessels, and reduced periosteal vessels—key elements in bone remodeling [12]. Peripheral injuries such as fractures may trigger neuroinflammation and cognitive dysfunction [13, 14]. Pre-stroke tibial fracture aggravated microglia and macrophage infiltration, impaired hippocampal CA1 blood-brain barrier, and exacerbated basal ganglia white matter damage in stroke mice, which may contribute to persistent memory impairment in such combined injury models [15]. Tibial fracture combined with internal fixation aggravates cerebral inflammation and impairs cognitive performance in stroke mice [16].

Thus, effective interventions to alleviate post-stroke bone loss are essential. Management approaches include pharmacotherapy, nutritional support, physical activity and rehabilitation training. Aerobic exercise denotes structured, repetitive movement that relies on oxidative metabolism for energy production. It enhances cardiovascular oxygen uptake and delivery efficiency, typically performed at 70–80% of the age-predicted maximal heart rate. As the core of endurance training, it involves moderate energy output sustained over time, with aerobic endurance quantified by maximal oxygen uptake (VO_{2max}) [17]. Earlier investigations have shown aerobic training helps maintain or increase BMD in postmenopausal women [18, 19]. Most exercise programs for stroke survivors still rely mainly on aerobic exercise, with cycle ergometry as the primary modality [20]. Physical activity helps preserve or enhance BMD and bone structure in healthy older adults, potentially lowering fracture risk [1].

Research by Hanne, N.J., et al. demonstrated that exercise did not enhance bone microstructure post-stroke, yet elevated mineral-to-matrix ratio in stroke animals rather than sham controls [21]. A meta-analysis suggests exercise interventions can prevent hip bone loss following stroke. Its effects on bone health in the tibia and radius, as well as serum bone turnover markers, remain unclear. Exercise efficacy may be modulated by training duration and sex [22]. Combined aerobic, resistance and weight-bearing training benefits bone health alongside cardiopulmonary function [23], muscle weakness [10] and insufficient weight-bearing [24] correlate with adverse bone health in stroke individuals. This study thus aims to propose an optimized exercise program for post-stroke osteoporosis patients.

2. Inducing factors of post-stroke bone loss and clinical evidence of exercise intervention

Research by Abo Elyazed, T.I., et al. indicates that inactivity post-stroke is a key contributor to bone loss, especially during the prolonged rehabilitation period. Stroke patients exhibit marked BMD reduction on the paretic side [25]. Evidence suggests bone mineral loss is more severe in the upper limbs than lower limbs. Within the first post-stroke year, BMD declines by over 10% in the paretic leg and 20% in the paretic arm [26]. This phenomenon may be attributed to the much lower frequency of upper limb activity in daily life, especially among individuals with chronic mild

hemiplegia following stroke, who exhibit obvious inter-limb discrepancies. Even though bone mineral density is relatively higher on the unaffected side, generalized mild osteoporosis may still develop as a result of reduced overall physical activity. Importantly, a substantial decline in the use of the paralyzed arm among some stroke patients is closely associated with a notable reduction in bone mass [27].

Post-stroke bone loss is linked to paretic limb disuse and muscle weakness. Exercise interventions may thus effectively preserve or enhance post-stroke bone health by targeting these factors [28–34]. Post-stroke physical activity enhances mobility, function [35], muscle strength [36] and fitness [37], thereby conferring skeletal benefits. Accordingly, aerobic exercise training intensities on cycle ergometers are lower than treadmill protocols (50%–70% HRmax vs. 50%–85% HRmax), and this should be applied clinically. In mild-to-moderate stroke patients, AE programs lasting 8–12 weeks (50%–80% HRmax, 3–5 sessions/week, 20–40 min) improve cardiorespiratory fitness.^{9,34} The relative increase in VO₂max is comparable to that in healthy sedentary adults and cardiac rehabilitation participants (12.5% vs. 10%–30% vs. 13%–15%, respectively).³⁵ Even absolute improvements remain modest (≈ 1 mL/kg/min) ³⁶ [38].

Alajam et al. noted a strong positive correlation between physical activity and BMD, especially at the ankle, indicating that exercise may enhance bone health in stroke survivors and lower osteoporosis and fracture risk, frequent post-stroke secondary complications [39]. Seven RCTs covering 480 participants were pooled in this meta-analysis. Interventions used 50%–80% heart rate reserve, 20–40 min per time, 3–5 times weekly. Such training improves cardiorespiratory fitness at all stroke rehabilitation phases. Homogeneous effect sizes indicated aerobic exercise significantly boosted peak VO₂ (SES=0.42, 95%CI 0.15–0.69, $p=0.001$) and peak load (SES=0.50, 95%CI 0.26–0.73, $p<0.001$). It also evidently enhanced walking speed and endurance with corresponding positive effect values [40].

A total of 63 community-based chronic stroke survivors were randomly assigned to two groups. The intervention group underwent a 19-week, 3 times weekly program including skeletal loading, aerobic, strength and balance training, while the control group performed seated upper limb exercises. Peripheral quantitative computed tomography (pQCT) assessed tibial bone geometry and volumetric BMD at the distal 4% and midshaft 50% sites pre and post intervention. After training, the intervention group showed a significantly greater percentage increase in paretic trabecular bone content at the 4% site $p = 0.048$. At the paretic 50% site, the intervention group also exhibited a larger cortical thickness gain $p = 0.026$, with no between-group difference in polar stress strain index (p-SSI). No obvious intergroup disparities existed in paretic-side trabecular (4%) and cortical (50%) BMD improvements. No relevant index variations were observed in non-paretic-side bone sites [41].

Dr. Marco Y. C. Pang et al. enrolled 63 community-dwelling older adults (≥ 50 years) with chronic stroke (≥ 1 year post-stroke), randomized into intervention $n = 32$ and control $n = 31$ groups. The intervention completed a 19-week FAME program (1 h, 3 $\times$ weekly) targeting cardiorespiratory fitness, mobility, leg strength, balance and hip BMD; the control performed seated upper-limb exercises. Outcomes included VO₂max, 6-minute walk distance, isometric knee extension strength, Berg Balance Scale, physical activity scale, and femoral neck BMD (DXA). The intervention group showed obvious improvements in cardiopulmonary function, motor ability and affected limb muscle strength. Paretic femoral neck BMD was preserved in the intervention group but decreased significantly in controls. No significant group-time interactions were found for balance, activity, non-paretic strength or non-paretic BMD. The FAME program is feasible and beneficial, mitigating inactivity-related secondary complications in older stroke patients, and can

serve as a community fitness model for chronic disease prevention [28]. The basic characteristics of the included studies and their main outcome indicators are summarized in Table 1.

Table 1. Basic information and outcome indicators of main exercise intervention studies

First Author + Year of Publication	Key Participant Characteristics (Mean ± Standard Deviation)	Intervention Protocol	Outcome Measures
Marco Y. C. Pang, 2005 [1]	Age: Intervention group 65.8±9.1 years, Control group 64.7±8.4 years; Post-stroke duration: Intervention group 5.2±5.0 years, Control group 5.1±3.6 years; MMSE score: Intervention group 27.6±2.3, Control group 28.2±1.9	Intervention group: Community-based Fitness and Mobility Exercise (FAME) program, 1 hour per session, 3 sessions per week for 19 weeks (aerobic exercise, balance training, leg strength training); Control group: Seated upper extremity training	Measured indicators included peak oxygen uptake for cardiopulmonary capacity, 6-minute walk test for walking performance, isometric knee extension for lower limb muscle strength, Berg Balance Scale for balance ability, DXA-detected femoral neck BMD, and PASIPD-assessed daily activity and social involvement.
M. Y. C. Pang, 2006 [2]	Age: Intervention group 63.9±7.0 years (4% site), Control group 63.7±7.6 years (4% site); Intervention group 65.2±8.8 years (50% site), Control group 64.7±8.5 years (50% site); Post-stroke duration: Intervention group 6.1±6.1 years (4% site), Control group 4.7±3.5 years (4% site)	19-week comprehensive exercise program (consistent with the FAME protocol): 1 hour per session, 3 sessions per week, including weight-bearing aerobic exercise, balance training and leg strengthening training	Tibial morphological indices were measured via pQCT. At the 4% site: total bone area, trabecular density and area. At the 50% site: total bone area, cortical area, cortical density, cortical thickness, polar section modulus and p-SSI.
Marco YC Pang, 2008 [3]	Age: 65.7 ± 9.2 years (males), 63.4 ± 7.4 years (females); Peak VO ₂ : 23.3 ± 4.2 ml/kg/min (males), 20.5 ± 5.2 ml/kg/min (females); Lean mass of the affected limb: 9081.8 ± 1452.2 g (males), 5960.0 ± 1107.9 g (females)	Cross-sectional study with no intervention measures; Focus on analyzing factors influencing tibial geometry and bone strength	Tibial geometric parameters (pQCT: total bone area, cortical bone area, medullary cavity area, cortical bone mineral content, cortical BMD, cortical thickness, bone surface index); peak oxygen uptake; leg lean mass; spasticity grade (Modified Ashworth Scale); functional mobility (leg lift test)
Yang Zhenhui, 2021 [4]	Age: 20 Hz group 60.4±5.9 years, 30 Hz group 59.0±7.0 years; Post-stroke duration: 20 Hz group 4.6±3.7 years, 30 Hz group 4.5±3.4 years;	Whole-body vibration (WBV) training: comparison between the 20 Hz group and 30 Hz group, amplitude 0.6 mm, 3 sessions per week for 8 weeks;	Isokinetic concentric/eccentric knee extension work;

Table 1. (continued)

Yang Zhenhui, 2021 [4]	
Fugl-Meyer Assessment (FMA) lower extremity function score: 20 Hz group 24.6±2.8 points, 30 Hz group 23.2±4.1 points Age: 60.8±7.7 years;
Post-stroke duration: 5.8±4.0 years;
FMA-upper extremity (FMA-UE) score: 35.9±18.9;
Clonus and Spasticity Scale (CSS) score: 8.6±2.5;
Motor Activity Log-Amount of Use (MAL-AOU) score: 1.3±1.3	
Each training session included 12 sets of 1-minute vibration (20 Hz) or 8 sets of 1-minute vibration (30 Hz) with a 1-minute rest between sets	serum bone resorption marker (N-telopeptide, NTx); walking endurance (6-minute walk test)
Tiev Miller, 2021 [5]	
Cross-sectional study with no intervention measures;
Focus on analyzing factors influencing distal radial bone properties and estimated failure load	Distal radial bone parameters (high-resolution quantitative CT: volumetric BMD, trabecular/cortical microarchitecture, geometric parameters); estimated failure load (micro-finite element, μFE analysis); motor function (FMA); paretic limb use (MAL); spasticity status (CSS)	
Ursula Foger-Samwald, 2020 [6]	No specific sample (review based on existing studies);
Target population: Patients with osteoporosis (including post-stroke osteoporosis)	Review of therapeutic protocols: antiresorptive drugs (bisphosphonates, denosumab, raloxifene), anabolic agents (teriparatide, romosozumab), combination therapy and non-pharmacological interventions	Bone mineral density (BMD); bone metabolic markers (bone resorption/formation markers); fracture risk

A 2011 systematic review on post-stroke exercise skeletal effects found physical activity significantly improved paretic lower limb tibial cortical thickness and femoral neck BMD [1]. Physical exercise correlates with enhanced skeletal strength. Multiple studies verify that exercise increases bone density and mitigates bone loss in elderly individuals of both genders. While exercise exerts the strongest impact on bone mass among young adults, it remains beneficial across all age groups [42-45].

3. Structure pathogenesis, bone metabolic markers and exercise regulation of post-stroke osteoporosis

Post-stroke osteoporosis (PSO) arises from multiple pathogenic factors, including oxidative stress, inflammation, neurological injury, prolonged immobilization, and hormonal disorders, leading to disrupted bone metabolism [46].

Bone metabolic markers comprise formation indicators (serum alkaline phosphatase, osteocalcin, C-terminal telopeptide of type I collagen) and resorption markers (tartrate-resistant acid phosphatase, C-telopeptide of type I collagen, urinary deoxypyridinoline, hydroxyproline) [47]. These markers comprehensively reflect skeletal status and are vital for fracture risk evaluation and early osteoporosis diagnosis [48]. In stroke patients, bone formation markers tend to decrease while resorption markers rise, uncovering the mechanisms of osteoporosis. Numerous studies report elevated C-telopeptide of type I collagen and calcitonin, alongside reduced osteocalcin and 25-hydroxyvitamin D in such patients [48].

Nicholas J. Hanne's research team studied 27 male C57Bl/6J mice aged 12 weeks. The rodents underwent either stroke modeling or sham surgery, then received four weeks of daily treadmill training or sedentary rearing. All subjects maintained normal locomotion after stroke, with no motor coordination deficits during exercise, keeping mechanical loading consistent across groups. Stroke alone caused no direct deterioration of bone microarchitecture. Exercise triggered skeletal adaptive changes solely in sham-operated mice, presenting elevated bone volume fraction and trabecular thickness within the distal femoral metaphysis. By contrast, no such benefits occurred in stroke mice. Additionally, stroke specifically diminished cortical bone area of the impaired hindlimb and lowered endosteal bone formation rate in the affected tibial shaft [49].

Intense nonweightbearing cycling elevated serum bone ALP isoforms B1/B2 and phosphate in postmenopausal women [50]. Aerobic training for 8 weeks significantly raised osteocalcin levels ($p=0.001$) [51]. Alqahtani enrolled 9 nonambulatory stroke survivors (age 61.8 ± 13.6 years; 5 males; 8 ischemic) who completed 8week aerobic walking ($3 \times / \text{week}$). Postintervention, osteocalcin (OC) increased from 8.51 ± 2.28 to 9.39 ± 2.97 ng/ml ($p < 0.1$), and ICTP rose from 4.45 ± 2.58 to 5.31 ± 2.92 ng/ml ($p < 0.1$). Lowintensity aerobic walking may enhance bone health via elevated formation markers. Nonetheless, severe baseline disability and exercise type may delay bone remodeling initiation.

A prospective study included 108 stroke patients with osteoporosis, randomly divided into two groups (54 each) [52]. The control group received conventional treatment, and the experimental group added aerobic + resistance training. BMD and BGP, P1NP, β -CTX were compared before treatment, 8 and 12 weeks after treatment, with SPSS 26.0 for analysis ($P < 0.05$ for statistical significance). Finally, 101 patients were included (50 in experimental group, 51 in control group), with no baseline differences ($P > 0.05$). After 8 weeks, only β -CTX had significant inter-group difference ($P < 0.05$); after 12 weeks, the experimental group had more significant improvement in BMD and bone metabolism indicators ($P < 0.05$), with no difference in adverse events ($P > 0.05$). Conclusion: Conventional treatment combined with aerobic + resistance training is better, faster and safer for post-stroke osteoporosis [53]. The regulatory effects of exercise on myokine and adipokine expression, as well as their impacts on bone metabolism, are presented in Table 2.

Table 2. Regulatory effects of exercise on myokine and adipokine expression and their impacts on bone metabolism

Molecular Type	Molecular Name	Tissue Source	Effect of Exercise on Its Expression	Main Effect on Bone Metabolism
Myokine	IL-6	Liver, immune cells, skeletal muscle	Chronic exercise reduces chronic inflammation levels; strenuous exercise increases it significantly	Reduces inflammation levels and improves bone status; increases bone turnover markers
Myokine	IL-7	Skeletal muscle, immune system	Strength training increases it; training can induce its expression	Similar effect to muscle-derived IL-6; indirectly activates osteoclast differentiation through immune cells
Myokine	IL-8	Monocytes and macrophages	Strenuous endurance exercise increases it	Promotes bone resorption
Myokine	LIF	Working muscle groups	Mild exercise increases it	Increases bone turnover rate

Table 2. (continued)

Myokine	IGF-I	Liver, extrahepatic tissues	Strenuous exercise increases it	Increases NTx, TRAP-5b and osteocalcin (OC); promotes bone anabolism
Myokine	Irisin	Skeletal muscle	Exercise increases it	Induces browning of white adipose tissue and enhances thermogenesis (direct effect on bone metabolism needs further clarification)
Myokine	BDNF	Nervous tissue, muscle cells	Exercise increases it	Expressed by osteoblasts during fracture healing and involved in bone repair
Adipokine	Leptin	Adipose tissue	Increased during sedentary/lack of exercise; increased when physical activity is reduced	Promotes the expression of pro-inflammatory cytokines; enhances osteoclast activity; increases total osteocalcin (OC) and glutamylated osteocalcin (GluOC)
Adipokine	Adiponectin	Adipose tissue	Regular exercise increases it; single exercise has no significant effect	Autocrine/paracrine effect enhances osteoblast stimulation; systemic effect promotes osteoclast formation
Adipokine	Visfatin	Skeletal muscle, adipose tissue	Exercise increases intracellular form; decreases extracellular form	Increases NAD ⁺ levels; improves insulin sensitivity (direct effect on bone metabolism needs further clarification)

4. Conclusion

Post-stroke osteoporosis (PSO), a common and severe complication driven by limb disuse and muscle weakness, leads to rapid bone loss and elevated fracture and mortality risks, with stroke patients' daily physical activity far below recommended standards. This study synthesized clinical studies, meta-analyses and basic experiments to explore exercise interventions for PSO, confirming that exercise is a safe and effective non-pharmacological approach, with its efficacy affected by training duration and gender. Aerobic exercise acts as the core intervention, with cycle ergometer training at 50%~80% of maximum heart rate improving cardiorespiratory function and walking ability, and low-intensity walking boasting high patient compliance; notably, comprehensive exercise programs integrating aerobic exercise, muscle strengthening and skeletal loading (e.g., the FAME program) outperform single aerobic exercise, as they can maintain the affected femoral neck bone mineral density (BMD), optimize tibial bone geometric parameters, and 12-week aerobic plus resistance training significantly improves BMD and bone metabolic markers. Exercise exerts bone-protective effects by regulating myokine and adipokine expression, modulating bone metabolic markers, and alleviating limb disuse and muscle weakness, though stroke may inhibit exercise-induced bone microstructure improvement, and the regulatory mechanisms of exercise on different skeletal sites remain unclear. In clinical practice, community-based individualized comprehensive exercise programs are worthy of promotion, and future research should further explore the tissue-specific mechanisms of exercise on bone health, the synergistic effects of exercise combined with pharmacological and nutritional interventions, and strategies to enhance patients' long-term exercise

adherence, so as to develop more targeted and effective PSO intervention programs, reduce fracture risks, and improve the physical function and quality of life of stroke survivors.

Rehabilitation programs for stroke survivors increasingly integrate aerobic training (treadmill, cycle ergometer, recumbent stepper, chest-deep water, functional training) to enhance cardiorespiratory fitness, muscle strength and mobility [54]. Alqahtani et al. verified an 8-week low-intensity walking program (30 min, 3×/week) as feasible, with 100% adherence and 10% dropout among 9 nonambulatory stroke patients (5 males, mean age 61.8±13.6 years, 8 ischemic) [52]. A meta-analysis found stroke patients averaged only 4355.2 daily steps, far below healthy elders (6000 steps/day [55]) and chronic disability recommendations (6500–8500 steps/day [56]). Active survivors need ≥3000 steps at ≥100 steps/min to meet 30 min daily moderate-intensity exercise guidelines [56, 57]. Current evidence supports combined cardiorespiratory (including walking) and strength (especially upperbody) training in group settings. While general exercise improves fitness and cognition, task-specific training better retains benefits and yields functional gains [58].

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