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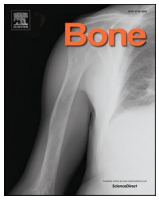

Review Article

Hyperbaric oxygen therapy for osteoporosis: A systematic review of preclinical evidence and mechanisms

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ABSTRACT

Hyperbaric oxygen therapy (HBOT) has been proposed as a direct anti-osteoporotic intervention rather than solely an adjunctive therapy. We systematically synthesized preclinical in vivo evidence and underlying mechanisms following PRISMA, with prospective registration (PROSPERO CRD42024525038), by searching PubMed, Embase, Cochrane Library, and Web of Science to November 2025. Of 3281 records, six studies (2016–2025) met inclusion across ovariectomy, hindlimb unloading, spinal cord transection, and D-galactose–induced aging models in Wistar and Sprague-Dawley rats. HBOT protocols most used 2.0–2.2 atm absolute with 85–100 % oxygen for 40–60 min per session. Across studies, HBOT improved bone mineral density and trabecular microarchitecture (e.g., BV/TV, Tb.Th, Tb.N), enhanced biomechanical strength, increased formation markers (e.g., procollagen type I N-terminal propeptide, bone-specific alkaline phosphatase, osteocalcin), and reduced resorption markers (e.g., C-terminal telopeptide of type I collagen, tartrate-resistant acid phosphatase-5b). Mechanistic signals converged on remodeling and vascular–metabolic pathways: modulation of the osteoprotegerin (OPG)/receptor activator of nuclear factor-κB ligand (RANKL) axis; restoration of Wnt/β-catenin signaling with reduced sclerostin; attenuation of oxidative and inflammatory stress (e.g., tumor necrosis factor-α); pro-angiogenic support (vascular endothelial growth factor, basic fibroblast growth factor); and neuropeptide-related effects (calcitonin gene-related peptide). Risk-of-bias profiles were mixed and heterogeneity precluded meta-analysis. Collectively, preclinical data indicate that HBOT mitigates osteoporotic bone loss primarily through coordinated, mechanisms of action that rebalance bone remodeling and improve the osteovascular milieu, while underscoring the need for standardized dosing parameters and rigorously designed human studies powered for clinically meaningful endpoints.

1. Introduction

Osteoporosis, characterized by low bone mass and microarchitectural deterioration, confers a high and age-dependent fracture risk and a substantial societal burden [1,2]. Approximately 10 million adults aged over 50 years in the United States are affected with 1.5 million fragility fractures annually [3], while lifetime fracture risk approaches one in two women and one in five men in the United Kingdom [4], incurring direct costs of roughly $17.9 billion (U.S.) and £4 billion (U.K.) each year [5]. Current management spans pharmacologic agents—bisphosphonates, denosumab, selective estrogen receptor modulators, and teriparatide—and non-pharmacologic strategies (nutrition, exercise, fall prevention), which reduce fracture risk but are constrained by suboptimal adherence, tolerability issues, rare yet

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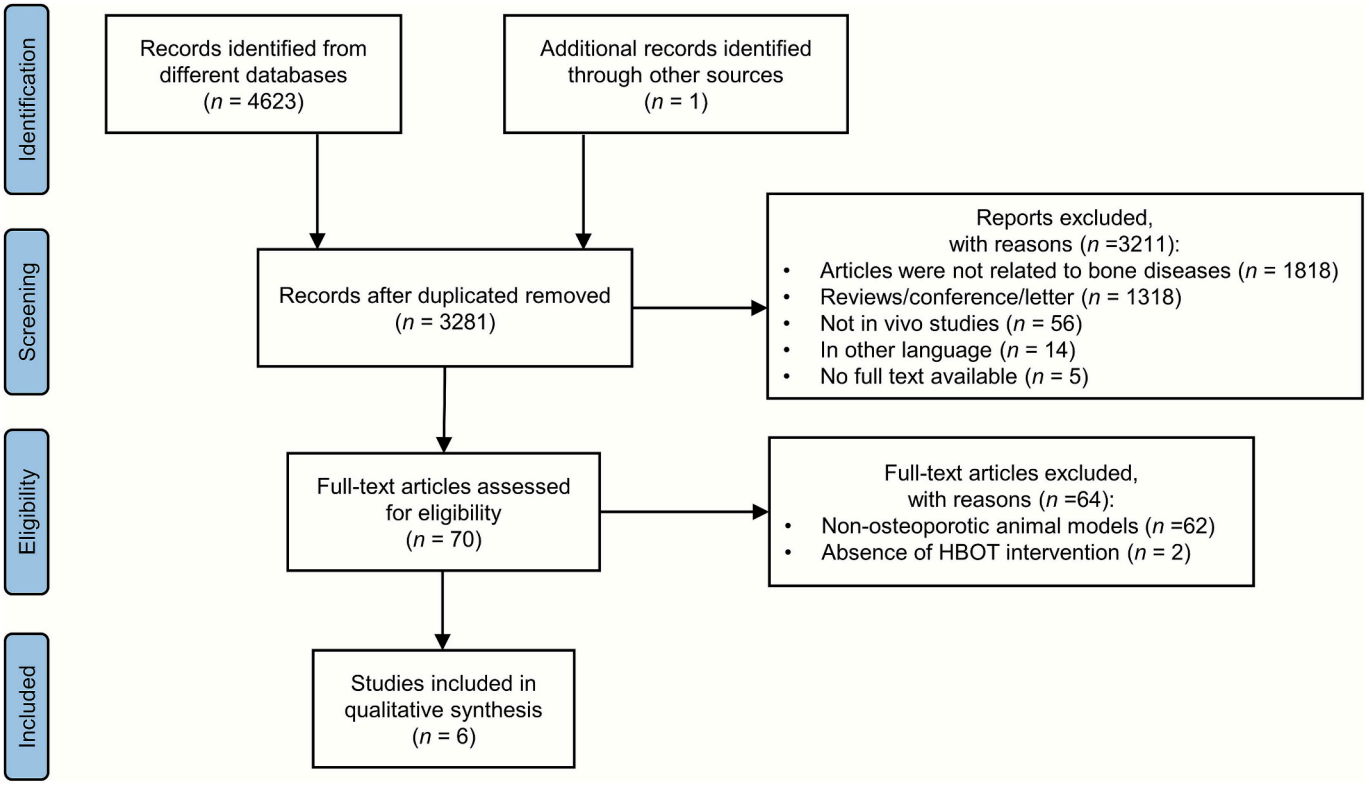

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram including study algorithm.

serious adverse events (e.g., medication-related osteonecrosis of the jaw), and long-term safety concerns, particularly in multimorbid older adults [6–8]. These limitations underscore a clear unmet need for additional, broadly applicable, and safe therapeutic options.

Hyperbaric oxygen therapy (HBOT), involving the inhalation of pure oxygen under elevated atmospheric pressure, has been utilized as an adjunctive treatment for a variety of medical conditions including open fractures, chronic non-healing wounds, carbon monoxide poisoning, and diving accidents [9–11]. Besides as a therapy for bisphosphonate-related osteonecrosis of the jaw [12,13], emerging clinical evidence indicates HBOT's direct utility in treating osteoporosis by promoting osteogenic differentiation, however with limited data reported by in vitro studies [14,15]. Experimental studies using in vivo (animal) models of osteoporosis have reported beneficial effects of HBOT in promoting bone metabolism through mechanisms involving improved oxygenation, antioxidation, anti-inflammatory pathways, and regulation of critical signaling cascades involved in osteogenesis and bone remodeling [16–18], with improved bone mineral density and altered expression of osteoprotegerin (OPG)/receptor activator of nuclear factor kappa-B ligand (RANKL) in osteocytes, suggesting the therapy's multifaceted biological activities [19]. While the in vivo studies have validated the results of clinical case reports, Although in vivo studies have verified the results of in vitro studies based on a limited number of clinical cases, and suggest that HBOT has a therapeutic effect on osteoporosis, its methods, results and mechanisms are heterogeneous, making it difficult to translate clinically [20].

This systematic review aims to (i) identify and critically appraise in vivo preclinical studies of hyperbaric oxygen therapy for osteoporosis; (ii) synthesize quantitative effects across key bone outcomes (bone mineral density, microarchitecture, histology, serologic markers, and biomechanics); (iii) clarify putative mechanisms relevant to bone remodeling, and (iv) collate protocol parameters (oxygen concentration, chamber pressure, session duration and frequency, and total sessions) to contextualize efficacy, and delineate priorities for subsequent clinical evaluation.

2. Methods

2.1. Systematic literature search strategy

A comprehensive systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Fig. 1) and was prospectively registered in PROSPERO (CRD42024525038) [21]. The focused question was “Does hyperbaric oxygen therapy have a therapeutic effect on osteoporosis?” and was formulated with the Participants, Interventions, Control, and Outcomes (PICO) framework [22], as follows: (P) participant: in vivo (animals) models with osteoporosis; (I) intervention: HBOT administration; (C) control group: sham-exposed or untreated control animals; (O) outcome: quantitative or qualitative indicators of bone status (i.e., histomorphometry, X-ray, micro-CT, biochemical markers and biomechanics).

To filter studies relevant to the focused question, A comprehensive electronic database search was performed through PubMed, Embase, Cochrane Library, and Web of Science up to November 2025. The search strategy utilized combinations of the following keywords with Boolean logic: (osteoporosis OR osteopenia OR “bone loss” OR bone OR “low bone density” OR “metabolic bone disease” OR “bone remodeling” OR “bone turnover” OR OP) AND (“hyperbaric oxygen therapy” OR “hyperbaric oxygen” OR HBO OR HBOT). Reference lists of eligible articles and relevant reviews were screened manually for additional citations. Three reviewers (H.W., X.M. and Y.S.) independently screened titles and abstracts, followed by full-text assessment. The inter-rater agreement was assessed using mean Cohen's kappa statistic. Disagreements were resolved through discussion with a third senior reviewer (M.S.). The search strategy is shown in Fig. 1.

2.2. Exclusion and inclusion criteria

In vivo peer-reviewed studies evaluating the bone-related outcomes of HBOT were included in this systematic review. In vivo was defined as animal studies investigating bone-related outcomes after HBOT treatment for osteoporosis. Each animal study was classified according to the Centre for Evidence-Based Medicine (CEBM) system for assigning levels of evidence, with all studies in this review being considered basic science studies (level 5). Inclusion criteria for in vivo studies were animal studies of bone-related outcomes after HBOT treatment. The exclusion criteria for all studies (in vivo) were as follows: (1) articles not written in English; (2) review and expert opinion articles, conference proceedings, and presentations; (3) ex vivo studies; (4) full text was unavailable and (5) studies that did not evaluate the bone-related outcomes after HBOT or did not perform HBOT treatment (HBOT is applied after the establishment of animal models). Studies were also excluded if bone defects or osteonecrosis or fractures were included in the intervention. The characteristics of the included studies, the interventions, the comparisons, the measurements, and the relevant outcomes were reviewed and discussed.

2.3. Data extraction

From each included study we extracted: animal species, gender, age, osteoporosis induction method, HBOT protocol (pressure, oxygen fraction, session duration, frequency, total number of sessions), co-interventions, follow-up length, and all reported bone-related outcomes. We then generated an effect direction plot to visually synthesize the findings across studies. When data were presented graphically, numerical values were estimated using WebPlotDigitizer 4.7.

2.4. Risk of bias and quality assessment

The methodological quality and risk of bias of included studies were assessed independently by three reviewers (H.W., X.M. and Y.S.) using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool [23] and the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines [24], and disagreements were resolved after consensus-oriented discussions. If disagreement occurred, the senior author (M.S.) was consulted.

3. Results

3.1. Identification and selection of studies

Electronic database searches identified 3281 articles (Fig. 1). After screening titles and abstracts for relevance, 3211 articles were deemed irrelevant based on the inclusion and exclusion criteria. Out of the 70 full texts of the in vivo animal studies assessed for eligibility, 6 papers were selected and reviewed after applying the criteria. Among the articles that were further excluded, 62 were not osteoporotic models and 2 did not involve HBOT (Table S1). The average Cohen's Kappa value among the three researchers was 0.87, indicating good agreement. The included studies were published between 2016 and 2025 and involved various animal osteoporosis models, including ovariectomy, spinal cord transection, hindlimb unloading, and D-galactose-induced aging. Meta-analysis was not conducted due to the scarcity and heterogeneity of the studies. Fig. 2 shows the frequency of publications over the past decades, reflecting the growing interest in the field of HBOT treatment for osteoporosis (Fig. 2).

3.2. Study characteristics

The general characteristics of the selected in vivo studies are shown in Table 1. Three studies used Wistar rats [19,25,26], and three used Sprague-Dawley rats [27–29], with sample sizes ranging from 18 to 75 animals. They utilized diverse osteoporosis animal models: ovariectomized rats [29], D-galactose-induced aging models [19,26], hindlimb unloading models [25], and complete spinal cord transection models [27,28]. Among the studies we included, three used male animal models [19,25,26], while the other three used female ones [27–29]. Follow-up periods ranged from 6 to 22 weeks. Micro-CT scan, molecular biology analysis, histological analysis, and mechanical tests were formed to comprehensively evaluate the anti-osteoporosis outcomes of HBOT. Regarding micro-CT scanning, one study sampled the metaphyseal region of the tibia and used a region-of-interest manager to select multiple measurement points within the target area [19] (micro-CT system: Quantum GX, PerkinElmer, Waltham, MA, USA; reconstruction software: PerkinElmer Analyze 12.0). Another study specifically sampled the distal femoral metaphysis and manually defined regions of interest for multi-point measurements [29] (micro-CT system: *E*-Class VECTor6 CT, MILabs, Netherlands; reconstruction software: MILabs Rec version 12).

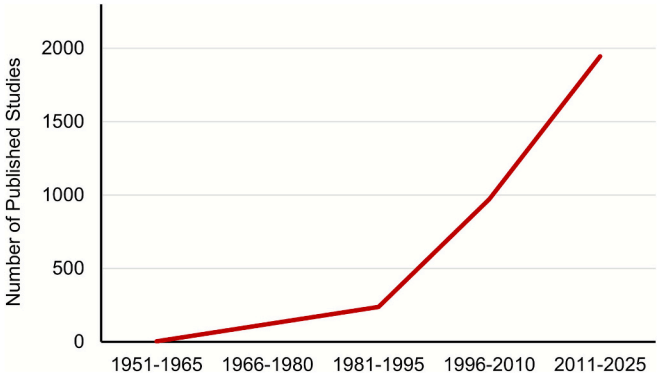

Fig. 2. Frequency of studies evaluating the outcome of HBOT treatment for osteoporosis per 15 years.

↑Increase; ↓Decrease; *Abbreviations: AAS* Atomic Absorption Spectroscopy, *ALP* Alkaline phosphatase, *B-HYP* Bone hydroxyproline, *BV/TV* Bone volume/total volume, *CGRP* Calcitonin gene-related peptide, *Col1a1* Collagen type I alpha 1 chain, *CTX-I* C-terminal telopeptide of type I collagen, *DC-STAMP* Dendritic cell-specific transmembrane protein, *ELISA* Enzyme-linked immunosorbent assay, *HBOT* Hyperbaric oxygen therapy, *HPLC* High-performance liquid chromatograph, *MDA* Malondialdehyde, *NFATc1* Nuclear factor of activated T cells 1, *Oc.S/BS %* Osteoclast surface/bone surface percentage, *Osx* Osterix, *PGC-1α* Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, *PINP* Procollagen type I N-Terminal propeptide, *qPCR* quantitative PCR, *RANKL* Receptor activator of nuclear factor kappa-B ligand, *RT-PCR* Real-time quantitative reverse transcription polymerase chain reaction, *sBAP* Serum bone-specific alkaline phosphatase, *sNTX* Serum N-Terminal telopeptide of type I collagen, *sOC* Serum osteocalcin, *SOD* Superoxide dismutase, *sRAGE* Soluble receptor for advanced glycation end products, *Tb.N* Trabecular number, *Tb.Sp* Trabecular spacing, *Tb.Th* Trabecular thickness, *TRACP-5b* Tartrate-resistant acid phosphatase 5b, *uDPD* Urinary deoxypyridinoline.

The bone volume (BV), bone volume fraction (BV/TV, %), trabecular thickness (Tb.Th, μm), trabecular separation (Tb.Sp, μm) were analyzed by micro-CT analysis. Bone-related mRNA expression was evaluated via real-time PCR (RT-PCR). Serological markers related to inflammation and bone metabolism (tumor necrosis factor-alpha (TNF-α), procollagen type I N-terminal propeptide (PINP), C-terminal telopeptide of type I (CTX—I)) were assessed through Enzyme-Linked Immunosorbent Assay (ELISA). Mechanical testing, particularly three-point bending assay, was utilized to measure bone biomechanical strength. Histological analysis included osteoclast counting, osteoclast surface area per total bone surface area (OC. S/BS), and bone mineralization. Atomic absorption

Table 1
General Characteristics of the Selected Studies.

Authors (Year)	Osteoporosis model	Study animals (n, gender)	Study groups	Treatment period	Sampling sites	Analysis methods	Bone-related indicators	HBOT anti-osteoporosis effects
Imerb et al. (2023) [25]	D-galactose-induced aged model	Wistar rats ($n = 30$, male)	Group 1: Normal diet + vehicle injection + sham treatment (NDVS) Group 2: Normal diet + D-galactose injection + sham (NDDgalS) Group 3: Normal diet + D-galactose injection + HBOT (NDDgalH) Group 4: High-fat diet + D-galactose injection + sham (HFDgalS) Group 5: High-fat diet + D-galactose injection + HBOT (HFDgalH)	14 days	Left tibia Left tibia Right femur	AAS Micro-CT RT-PCR	Bone mineral content BV/TV, Tb.Th, Tb.Sp, Tb.N Osteoclast differentiation (RANKL, NFATc1, DC–STAMP), osteogenesis (Osx, ALP, Col1a1)	Restored bone microarchitecture, increased bone mineralization, improved bone remodeling markers (RANKL↓, Osx↑, ALP↑, Col1a1↑) and suppressed inflammation (TNF-α, IL-6).
Peng et al. (2023) [35]	Ovariectomized model	Sprague-Dawley rats ($n = 40$, female)	Group 1: Sham control (Control) Group 2: Ovariectomy (OVX) Group 3: OVX + treadmill exercise (OVX + EX) Group 4: OVX + HBOT (OVX + HBO) Group 5: OVX + combined HBOT and treadmill exercise (OVX + HBO + EX)	12 weeks	Blood Left femur Right femur	ELISA Micro-CT RT-PCR	Bone formation marker (PINP), bone resorption marker (CTX—I), antioxidant enzyme (SOD), sclerostin BV/TV, Trabecular bone volume, Tb.N, Tb.Th Osteoblast-related gene (PGC-1α), osteoclast-related gene (RANKL)	Improved bone microarchitecture (increased trabecular bone volume, number, thickness), reduced osteoclast activity (CTX—I, RANKL), increased osteoblast-related (PGC-1α) and antioxidant gene expression (SOD).
Imerb et al. (2022) [32]	D-galactose-induced aged model	Wistar rats (n = 30, male)	Group 1: Normal diet + vehicle injection + sham treatment (NDVS) Group 2: Normal diet + D-galactose injection + sham (NDDS) Group 3: Normal diet + D-galactose injection + HBOT (NDDH) Group 4: High-fat diet + D-galactose injection + sham (HFDDS) Group 5: High-fat diet + D-galactose injection + HBOT (HFDDH)	14 days	Left tibia Blood Right tibia Right femur Blood Left femur	Biomechanical testing ELISA Histomorphometry HPLC Western blot RT-PCR	Bone biomechanical strength (maximum loading, elasticity) CTX-I, TRACP-5b, TNF-α, MDA Bone volume fraction (BV/TV), Trabecular thickness (Tb.Th), Trabecular separation (Tb.Sp), Trabecular number (Tb.N) Serum and bone malondialdehyde (MDA) quantification sRAGE and TNF-α protein expression Sclerostin (SOST) mRNA expression	Reduced bone resorption, improved bone microarchitecture, decreased inflammation and oxidative stress (CTX—I, TRACP-5b, TNF-α, MDA).

(*continued on next page*)

Table 1 (*continued*)

Authors (Year)	Osteoporosis model	Study animals (n, gender)	Study groups	Treatment period	Sampling sites	Analysis methods	Bone-related indicators	HBOT anti-osteoporosis effects
Liu et al. (2018) [33]	Spinal cord transection model	Sprague-Dawley rats ($n = 75$, female)	Group 1: Sham operation Group 2: Complete spinal cord transection (CSCT) Group 3: CSCT + HBOT started 3 h post-injury (HBO1) Group 4: CSCT + HBOT started 12 h post-injury (HBO2)	30 days	left tibia	ELISA	Bone formation markers (sBAP, sOC), bone resorption markers (sNTX, uDPD)	Enhanced CGRP synthesis, increased bone formation (sBAP, sOC), reduced bone resorption (sNTX, uDPD).
					Right tibia	Immunohistochemistry	CGRP-positive cells	
					Blood	qPCR	CGRP mRNA expression	
Liu et al. (2016) [34]	Spinal cord transection model	Sprague-Dawley rats (n = 75, female)	Group 1: Sham operation Group 2: Complete spinal cord transection (CSCT) Group 3: CSCT + HBOT started 3 h post-injury (HBO1) Group 4: CSCT + HBOT started 12 h post-injury (HBO2)	30 days	Blood	Biomechanical testing	Structural/material mechanics parameters (stiffness, strength, Modulus)	Increased femoral biomechanical strength, higher calcium and hydroxyproline content, improved trabecular continuity.
					Left femur	Biochemical assay	Bone calcium, bone hydroxyproline (B-HYP)	
					Right femur	Histology	Bone trabecular continuity, collagen alignment	

Table 2
Intervention Characteristics of the Selected Studies.

Authors (Year)	Oxygen Concentration (%)	Chamber Pressure (ATA)	Pressure Rise Time	Stabilization Time per Session	Pressure Drop Time	Frequency of Treatment	Total Number of Treatments	Anti-osteoporosis outcomes
Imerb et al. (2023) [25]	100 %	2.0 ATA	N/A	60 min/ session	~10 min	1 session/day, daily	14 sessions	HBOT exhibited anti-osteoporotic effects in aging conditions (lean and obese), restoring bone microarchitecture, mineral content, and remodeling markers.
Peng et al. (2023) [35]	85–90 %	2.0 ATA	30 min	40 min/ session	20 min	1 session/day, 5 days/week	60 sessions (12 weeks total)	HBOT effectively ameliorated ovariectomy-induced osteoporosis, preserving bone microarchitecture, reducing bone resorption, and enhancing osteoblast activity.
Imerb et al. (2022) [32]	100 %	2.0 ATA	N/A	60 min/ session	~10 min	1 session/day, daily	14 sessions	HBOT effectively improved age- and obesity-related bone dyshomeostasis, restoring bone remodeling, microstructure, and mechanical strength.
Takemura et al. (2020) [31]	40 %	~1.3 ATA	N/A	3 h/session	N/A	1 session/day, daily	10 sessions	Mild HBOT partially protected against disuse osteoporosis, preserving cortical/ trabecular bone and reducing osteoclast-mediated resorption.
Liu et al. (2018) [33]	97 % ~ 99 %	2.2 ATA	~20 min	40 min/ session	N/A	1 session/day, 10-day treatment courses (2 session/day at first course)	3 courses (40 treatments total)	Ultra-early HBOT significantly promoted bone formation, inhibited bone resorption, and improved overall bone turnover after spinal injury.
Liu et al. (2016) [34]	97 % ~ 99 %	2.2 ATA	~20 min	40 min/ session	N/A	1 session/day, 10-day treatment courses (2 session/day at first course)	3 courses (40 treatments total)	Ultra-early HBOT significantly improved bone biomechanical properties, enhanced bone mass, and improved bone structural integrity after spinal injury.

Abbreviations: ATA atmospheric pressure absolute, 1 ATA = 760 mmHg (101.32Kpa), *HBOT* Hyperbaric oxygen therapy.

spectroscopy was used to evaluate the bone demineralization.

The characteristics of HBOT are presented in Table 2. One study used mild hyperbaric oxygen (the pressure applied was 1.3ATA, and the oxygen concentration was 40 %) [25]. The pressure of HBOT in the remaining studies was 2.0 ATA to 2.2 ATA, and the oxygen concentration was 85 % to 100 % [19,26–29]. The duration of each HBOT in all studies mainly was 40 to 60 min, while the mild treatment lasted to 3 h. The number of treatments applied varied from 14 to 60 times. Three experiments detailed the pressurization times [27–29], while decompression times were documented across three experiments [19,26,29]. Notably, neither pressurization nor decompression times were reported in the study administering mild HBOT [25]. Only one study utilized a combined intervention regimen consisting of HBOT alongside treadmill exercise [29]. The parameters for the treadmill exercise were as follows: speed 20 m/min, duration 40 min/day, incline 5°, frequency 5 days/week, over a period of 12 weeks.

The effect of HBOT on rats of osteoporosis are summarized in the effect direction plot (Fig. S1). Current evidence is predominantly concentrated on bone-related outcomes. All studies consistently report positive effects on anti-bone resorption. In addition, five studies report improvements in bone microstructure and bone mass [19,25,26,28,29], and two studies demonstrate enhanced bone strength [26,28]. Regarding bone formation, evidence is inconsistent: four studies report positive effects [19,27–29], while two others indicate minor effects [25,26]. For outcomes not directly related to bone, positive effects are reported in two studies each on anti-aging and anti-inflammatory properties [19,26]. Regarding antioxidant effects, three studies report positive outcomes [19,26,29], whereas one study describes a minor effect [25].

3.3. Risk of bias and quality assessment

The included studies presented heterogeneous levels of risk of bias, which are presented in Fig. 3A. The details are as follows: 1. Selection Bias: All studies reported random allocation of animals; however, none described allocation concealment; 2. Performance Bias: Four studies maintained uniform feeding for all animals [19,25,26,29], two studies employed different diets (normal vs. high-fat) for inducing obesity, with randomization to dietary groups [19,26]. None of the studies mentioned whether blinding was used during the intervention by researchers; 3. Detection Bias: Due to the nature of the differing interventions, no study implemented blinding of outcome assessors or random outcome assessment, and this may particularly introduce detection bias when subjective judgments are involved, such as in computed tomography imaging and histological analyses; 4. Attrition Bias: Two studies [28,29], reported animal deaths after randomization without specifying how these were handled analytically. The resulting unequal group sizes led to a high risk of bias; 5. Reporting Bias: All studies analyzed the collected data without selective reporting; 6. Other Biases: No other specific sources of bias were identified; 7. Publication bias: All studies reported positive outcomes, but the limited number of studies precluded a formal statistical assessment. Upon our individual review, we found no evidence of negative results from the same animal cohorts or any registered but unpublished related studies. All studies appropriately included a blank control group, the data from which served as the baseline for comparison. The risk of bias was low in 43.4 % of items, unclear in 53.3 %, and high in 3.3 %. After conducting a weighted risk assessment for the studies included, the overall risk level was moderate to low (Fig. 3B).

The assessment of the methodological quality of each study was summarized in Table S2. The quality of the selected studies (ARRIVE [Animal Research: Reporting of In Vivo Experiments] guidelines) achieved a mean score of 18.83 but only one research mentioned that they followed the ARRIVE guidelines, other studies followed national or institutional guidelines.

4. Discussion

The systematic evaluation of the preclinical evidence demonstrates that hyperbaric oxygen therapy (HBOT) exerts significant therapeutic effects on osteoporosis-related bone remodeling. Across diverse animal models, HBOT consistently enhanced bone mineral density and microarchitecture, attenuated bone resorption, and promoted bone formation [19,25–29]. The observed beneficial outcomes predominantly arise from enhanced tissue oxygenation, antioxidative mechanisms, and suppression of inflammatory pathways [19,25,26,29]. These findings are consistent with established clinical applications of HBOT in conditions characterized by tissue hypoxia, such as osteomyelitis and diabetic wounds, underscoring its recognized clinical efficacy [30–32]. While the current clinical application of HBOT for osteoporosis management remains exploratory, the consistent positive outcomes observed across diverse animal models provide a compelling preclinical foundation for future clinical translation.

HBOT exerts its osteogenic effects primarily through angiogenesis stimulation, osteoblast activation, osteoclast suppression, and modulation of critical signaling pathways involving growth factors such as vascular endothelial growth factor VEGF and basic fibroblast growth factor (bFGF) [33–35]. This multifaceted mechanism positions HBOT not only as adjunctive therapy but potentially as a primary non-pharmacological treatment for osteoporosis, especially for cases unresponsive to conventional therapies [36,37]. Compared with traditional pharmacotherapy—which frequently carries adverse effects and limitations—HBOT offers broader applicability, fewer contraindications, and minimal adverse events [38]. Moreover, HBOT potentially enhances overall patient well-being, particularly beneficial in elderly individuals with multiple comorbidities, reinforcing its suitability for osteoporosis management [39–41].

The systematic review of preclinical evidence robustly underscores the efficacy of HBOT in mitigating osteoporosis by targeting multiple pathogenic pathways (Fig. 4). Estrogen deficiency significantly influences osteoporosis through mechanisms such as increased osteoblast apoptosis and disruption of osteoblast differentiation, primarily via the RANKL/OPG imbalance [42–44]. HBOT effectively counters these detrimental processes, notably by promoting the synthesis of OPG through modulation of the RANK-RANKL signaling and Wnt/β-catenin signaling pathways via multiple factors to inhibit osteoclastogenesis-an effect observed in multiple included studies [29, 27, 25, 19]-thereby favorably adjusting the OPG/RANKL ratio critical for bone remodeling [19,45]. Furthermore, HBOT's role in attenuating osteoclast differentiation, particularly in estrogen deficiency models, reinforces its therapeutic potential [46,47]. Additionally, an included study using ovariectomized animal models identified that HBOT inhibits the production of serum C-terminal telopeptide of type I collagen (CTX—I), a marker indicative of bone resorption [48]. This further aligns with previous findings and supporting the beneficial impacts of HBOT [46,47]. However, given the significant influence of estrogen on osteoporosis pathogenesis, subsequent attempts to establish osteoporosis models independent of hormone deficiency should involve either evaluating variations in estrogen levels within a cohort of female animals or utilizing male animals. This strategy is critical to minimize the confounding effect of inter-individual estrogen variability on experimental outcomes.

Oxidative stress represents another pivotal factor driving osteoporosis pathology by promoting osteoclast activation and bone resorption [49–51]. HBOT initiates a paradoxical hyperoxia-hypoxia response, transiently increasing reactive oxygen species (ROS) but subsequently inducing robust antioxidative responses that mitigate oxidative stress over time [30,52,53]. This antioxidative effect of HBOT is confirmed through observed enhancements in endogenous antioxidant enzyme activities, such as superoxide dismutase (SOD), thereby ameliorating

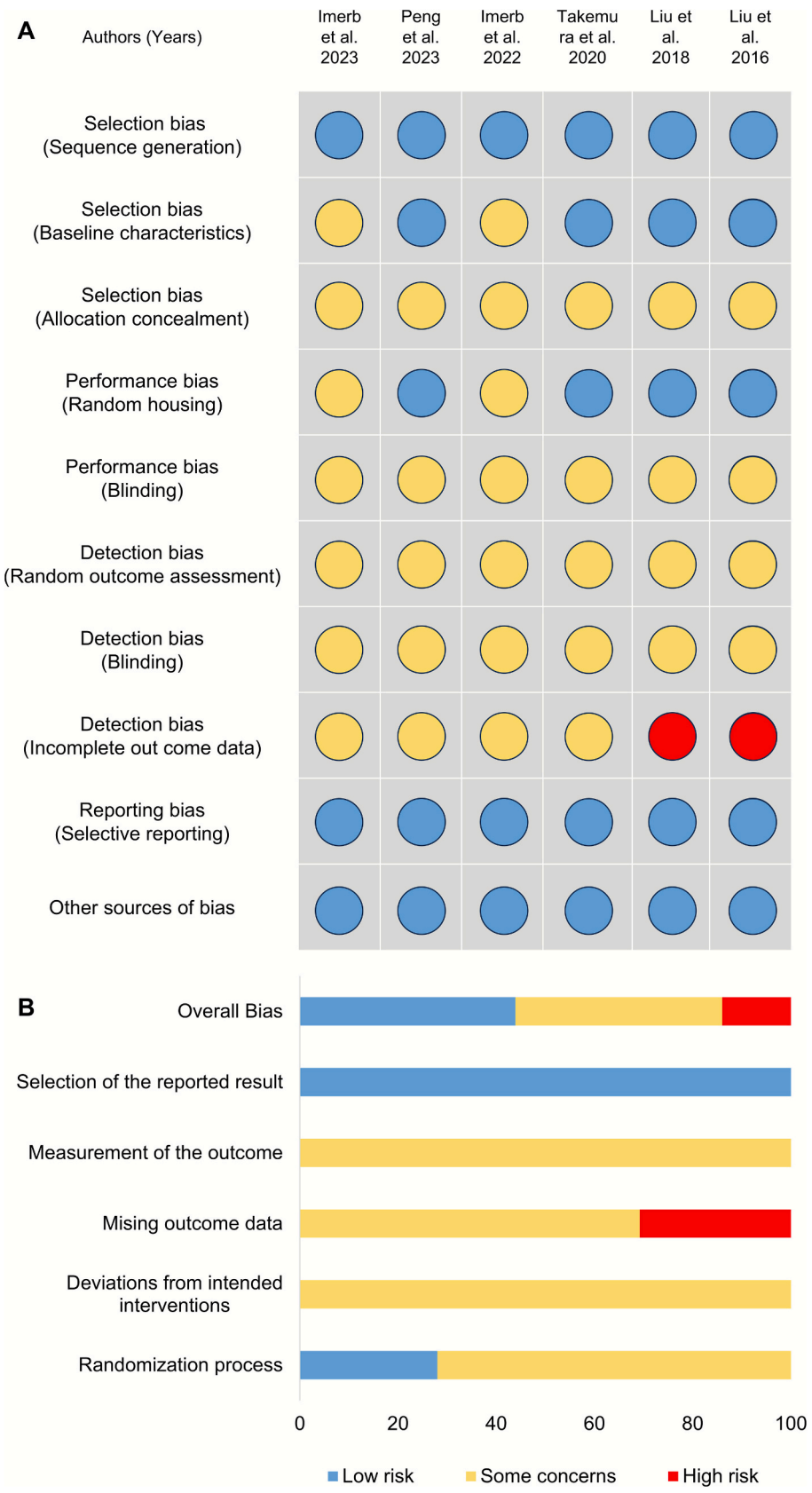

Fig. 3. Risk of bias of the included studies based on SYRCLE's (Systematic Review Centre for Laboratory Animal Experimentation) risk of bias tool and weighted risk bar chart.

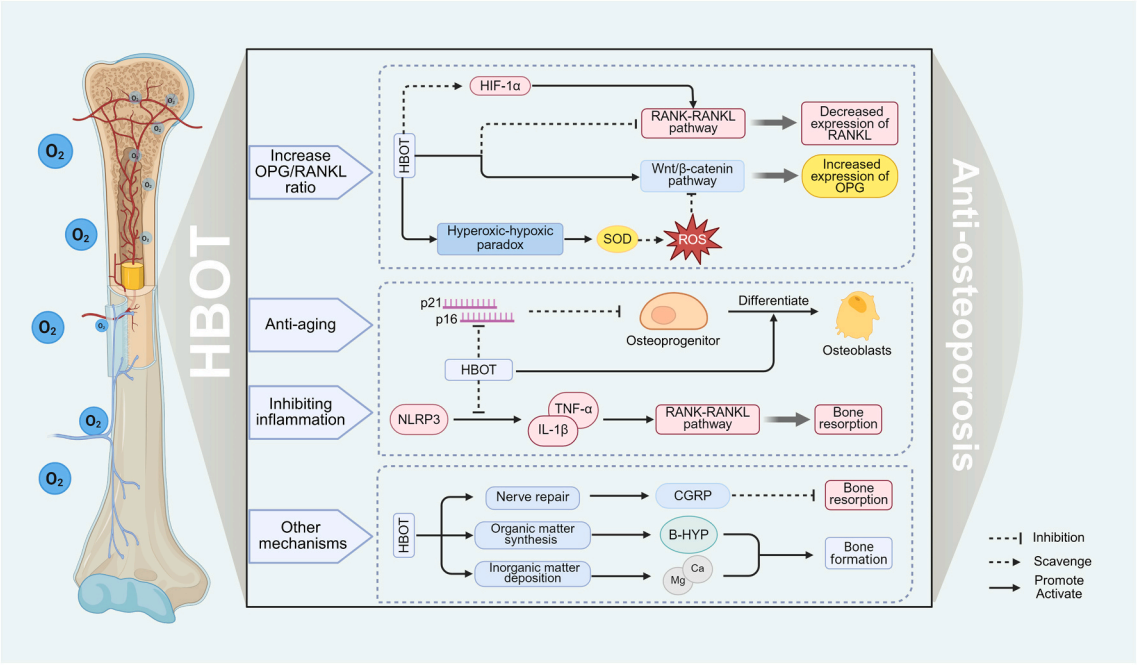

Fig. 4. Hyperbaric oxygen therapy exerts anti-osteoporosis effects through various pathways such as regulating the OPG/RANKL ratio, anti-aging, inhibition of inflammatory responses, and others mechanisms. Abbreviations: B-HYP: bone hydroxyproline content, Ca: calcium, CGRP: calcitonin gene-related peptide, HBOT: hyperbaric oxygen therapy, HIF-1α: hypoxia-inducible factor-1 alpha, IL-1β: interleukin-1 beta, Mg: magnesium, NLRP3: nucleotide-binding oligomerization domain-like receptor protein 3, OPG: osteoprotegerin, p16, CDKN2A, p21: CDKN1A, RANK: receptor activator of nuclear factor kappa-B, RANKL: receptor activator of nuclear factor kappa-B ligand, ROS: reactive oxygen species, SOD: superoxide dismutase, TNF-α: tumor necrosis factor alpha, Wnt/β-catenin: Wnt (wingless-type)/β-catenin signaling pathway. Figure was created using BioRender.

oxidative stress-related bone pathology [19,29] (Fig. 4). Additionally, the antioxidant response can attenuate the increase in RANKL protein levels induced by oxidative stress [54]. Concurrently, ROS scavenging by HBOT mitigates oxidative inhibition of the Wnt/β-catenin signaling, leading to upregulated OPG production [19]. Moreover, in hindlimb unloading models, HBOT reduced sclerostin (SOST) production, thereby relieving inhibition of the Wnt/β-catenin pathway [25]; this mechanism synergizes with the aforementioned antioxidant effects via the same signaling pathway to modulate the OPG/RANKL ratio.

HBOT has also demonstrated efficacy in delaying cellular aging, particularly relevant to osteoporosis due to impaired osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) during aging [55,56]. Experimental studies included in this review demonstrated HBOT's ability to reduce aging markers (e.g., p21 and p16 mRNA expressions) in aged animal models, promoting osteogenic differentiation and osteogenesis by mitigating cellular senescence (Fig. 5A1) [19,57,58]. Furthermore, studies suggest HBOT may indirectly alleviate obesity-induced bone loss, underscoring its potential role in addressing complex metabolic influences on bone metabolism [19,29].

Emerging evidence highlights the role of inflammation in osteoporosis pathogenesis, particularly through activation of nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome and subsequent secretion of pro-inflammatory cytokines, such as TNF-α and IL-1β, leading to bone resorption and impaired osteoblast function [56,59,60]. Included studies demonstrate HBOT's capability to normalize serum TNF-α levels, supporting previous findings of its broader anti-inflammatory effects and confirming its therapeutic relevance in inflammatory bone loss scenarios (Fig. 5A2) [19,26]. A prospective cohort study (level 2) based on human subjects confirmed this point [61].

Neurological factors, particularly neuropeptides like calcitonin gene-related peptide (CGRP), have been increasingly recognized as influential mediators of bone metabolism and remodeling [62–64]. HBOT enhances CGRP synthesis in spinal cord transection models, improving local blood supply and bone metabolism, thereby mitigating osteoporosis-related bone deterioration post-injury [27,28]. In another study using aging models, it was observed via micro-CT that HBOT could improve the microstructure of bone trabeculae (Fig. 5B), and this finding was corroborated by bone tissue sections (Fig. 5C) [19]. The observed enhancement in calcium deposition and collagen fiber integrity further supports HBOT's therapeutic potential through neurogenic mechanisms in osteoporosis treatment (Fig. 5A3, A4) [28].

Moreover, HBOT promotes inorganic mineral deposition critical for bone integrity, notably calcium and magnesium, which are essential for bone mineralization and homeostasis maintenance (Fig. 5A5) [19,65,66]. For bone mineralization disorders caused by factors such as obesity and aging, HBOT can improve overall oxygenation, thereby reducing HIF-1α and HIF-2α levels, correcting bone metabolic derangements, accelerating bone formation, and restoring mineralization capacity [26]. These findings align with previous studies demonstrating HBOT's positive influence on bone mineralization processes [67,68].

The systematic review has underscored HBOT as a promising intervention for osteoporosis management, highlighting several underlying biological mechanisms. However, the heterogeneous outcomes reported among the included studies underscore the need for standardized protocols to ensure consistent therapeutic efficacy. For instance, discrepancies were observed regarding the effects of HBOT on osteocalcin (OCN) expression. While one study demonstrated no significant elevation in OCN mRNA expression following HBOT application, another documented notable increases in both OCN gene expression and serum procollagen type I N-terminal propeptide (PINP) levels when HBOT was administered at a higher frequency and duration (90 min per session, 60 sessions total) [19,29]. These differences suggest that treatment parameters such as duration, oxygen concentration, and atmospheric pressure significantly influence therapeutic outcomes, highlighting the necessity for clearly defined treatment regimens in future research.

Furthermore, the synergistic potential of HBOT combined with other non-pharmacological therapies, such as exercise and weight control,

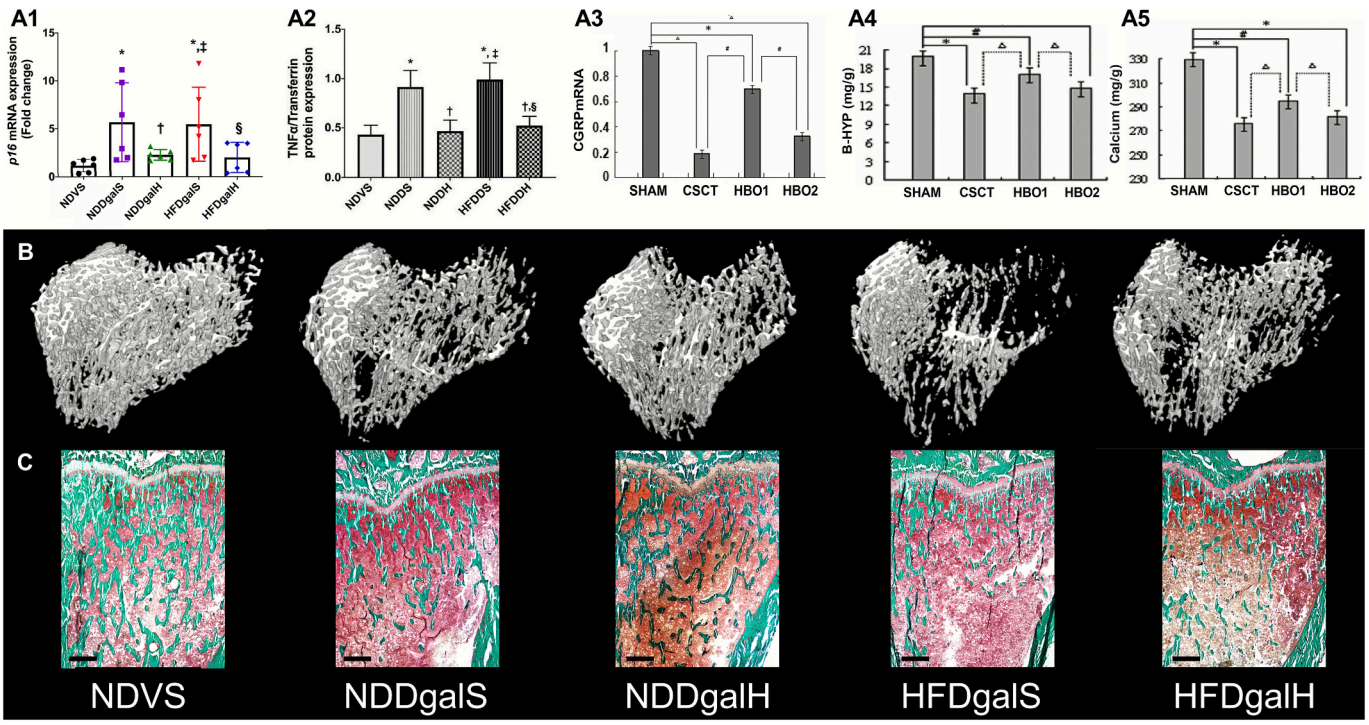

Fig. 5. Evidence of hyperbaric oxygen therapy in anti-osteoporosis. A1, A2: Compared with the aging rats that did not receive HBOT, those that received HBOT had lower expression levels of p16 mRNA and TNF-α, approaching the levels of the blank control rats. *$P < 0.05$ vs NDVS group, †P < 0.05 vs NDDgalS/NDDS group, ‡P < 0.05 vs NDDgalH/NDDH group, §P < 0.05 vs HFDgalS/HFDDS group. A3: Number of CGRP-positive cells in femurs of rats is more in HBO groups than sham group, $\Delta P < 0.01$ and *P < 0.05 compared with sham group, #P < 0.05 compared with HBO1 group. A4, A5: The content of B-HYP and bone calcium in femurs of rats is higher in HBO groups than sham group, *P < 0.01 and #P < 0.05 compared with rats in the sham group, ΔP < 0.05 compared with rats in CSCT and HBO2 groups. B, C: Therapeutic effects of HBOT on attenuation of bone loss and improvement of bone microarchitecture in D-galactose accelerated aging with and without obesity. Grouping: NDVS: normal diet + saline injection + sham treatment group, NDDgalS/NDDF: normal diet + D-galactose injection + sham treatment group, NDDgalH/NDDH: normal diet + D-galactose injection + HBOT group, HFDgalS/HFDDS: high-fat diet + D-galactose injection + sham treatment group, HFDgalH/HFDDH: high-fat diet + D-galactose injection + HBOT group, SHAM: sham-operated group, CSCT: complete spinal cord transection group, HBO1: HBOT after spinal cord injury 3 h group, HBO2: HBOT after spinal cord injury 12 h group. Abbreviations: B-HYP: bone hydroxyproline content, CGRP: calcitonin gene-related peptide, p16, CDKN2A, TNF-α: tumor necrosis factor alpha.

emerged as particularly promising in the reviewed studies. Specifically, evidence indicated that the combination of HBOT and physical exercise was more effective in preventing bone loss and preserving bone microarchitecture than either intervention alone [29]. Such findings suggest a combinatory approach might optimize therapeutic outcomes in osteoporosis management, potentially translating into more significant clinical benefits. Future clinical trials should rigorously investigate these synergistic effects to develop comprehensive osteoporosis management protocols.

Finally, an "Effect Direction Plot" (Fig. S1) was utilized to systematically summarize the reported direction of HBOT effect. The plot visually illustrates consistent positive evidence across the included studies for effects on anti-bone resorption, bone mass, bone microstructure, and bone strength. Similarly, positive effects were observed regarding anti-aging, antioxidant, and anti-inflammatory outcomes. However, in one study utilizing a mild HBOT protocol, neither bone formation promotion nor antioxidant effects reached statistical significance, a finding that may be attributable to the lower pressure and oxygen concentration parameters employed. Future research should further explore the optimal ranges of oxygen concentration and pressure, as well as the minimum effective number of treatment sessions.

While preclinical evidence is promising, the existing studies have several important limitations. First, the number of studies is limited, and there is substantial methodological heterogeneity. This includes the use of diverse animal models (e.g., spinal cord transection, ovariectomy, D-galactose-induced aging, and hindlimb unloading), inconsistent intervention protocols (with hyperbaric oxygen pressures ranging from 1.3 to 2.2 ATA, sometimes combined with exercise therapy), and varied outcome measures (encompassing bone biomechanics, bone metabolism markers, and molecular biomarkers). This heterogeneity complicates direct comparisons between studies and precludes a meaningful meta-analysis, necessitating a cautious interpretation of the findings. Second, although a comprehensive literature search was performed, limiting the review to include English-language publications may have omitted relevant studies, potentially introducing publication bias. These limitations highlight the need for future standardization in preclinical research methodology and validation through more rigorous, large-scale studies.

Despite the aforementioned heterogeneity, HBOT has consistently demonstrated beneficial effects in promoting osteogenesis and inhibiting bone resorption across various osteoporosis models, indicating its potential broad-spectrum therapeutic value across different etiologies. Although this review did not include in vitro studies, the mechanisms revealed remain of reference value. Our research provides a theoretical reference for subsequent human trials. Future studies should design rigorous clinical trials based on existing mechanistic clues to further explore the specific mechanisms and optimized protocols of hyperbaric oxygen as a non-pharmacological strategy for treating osteoporosis.

5. Conclusions

Across preclinical models, HBOT mitigates osteoporotic bone loss through convergent, mechanisms of action that rebalance bone remodeling. HBOT modulates the OPG/RANKL axis and restores Wnt/β-catenin signaling-with concomitant reductions in sclerostin-thereby suppressing osteoclastogenesis while supporting osteoblast–osteocyte

function. In parallel, attenuation of oxidative stress—reflected by enhanced endogenous antioxidant activity and reactive oxygen species scavenging—relieves inhibition of osteogenic pathways; suppression of inflammatory drivers, stimulation of angiogenic support (VEGF, bFGF), and neuropeptide-related effects (CGRP) further promote mineral deposition and bone formation. HBOT also mitigates cellular senescence, aligning with observed improvements in bone mineral density, trabecular microarchitecture, and reductions in resorption markers such as CTX—I. Interpretation should remain cautious given the limited number of studies, methodological heterogeneity, and identified risks of bias. Future work should advance to rigorously designed human studies that define indications, dose parameters (pressure, session frequency and duration), safety, and comparative effectiveness versus established therapies, using clinically meaningful endpoints such as fracture events, bone mineral density, and functional outcomes. Harmonized protocols and standardized reporting across preclinical and clinical investigations will be essential to enable robust synthesis and guide translation, thereby clarifying HBOT's appropriate role within evidence-based osteoporosis management.

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CRediT authorship contribution statement

Hao Wang: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Xiao Ma:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yang Sun:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Zhihao Guo:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Jincheng Wang:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mingli Sun:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Ethics approval

Not applicable.

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Declaration of competing interest

The authors declare no conflicts of interest.

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Data availability

No data was used for the research described in the article.

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