JOURNAL OF MULTIDISCIPLINARY SCIENCES AND INNOVATIONS

VOLUME 5, ISSUE 04
MONTHLY JOURNALS

ISSN NUMBER: 2751-4390
IMPACT FACTOR: 9,08

BONE AND CARTILAGE BIOLOGY: REMODELLING PATHWAYS, MOLECULAR PATHOGENESIS OF OSTEOPOROSIS AND OSTEOARTHRITIS, AND EVIDENCE-BASED THERAPEUTIC STRATEGIES

Nurmetova Gulnoza Qaxramon qizi

Asia International University

ABSTRACT

Background: Bone and cartilage are specialized connective tissues that provide skeletal support, enable locomotion, and protect vital organs. Their progressive pathological deterioration—osteoporosis (systemic bone loss with fracture risk) affecting 500 million people globally and osteoarthritis (OA, articular cartilage degradation) affecting 595 million—constitutes the most prevalent musculoskeletal disease burden worldwide. Both conditions share common molecular drivers including RANK/RANKL/OPG axis dysregulation, Wnt/β-catenin pathway suppression, and pro-inflammatory cytokine-mediated extracellular matrix destruction.

Objective: To provide a concise, evidence-based review of bone remodelling physiology, articular cartilage structure and homeostasis, the molecular pathogenesis of osteoporosis and osteoarthritis, and evidence-based pharmacological and regenerative therapies for both conditions.

Methods: A systematic review of eight primary sources—original molecular studies, landmark randomized clinical trials, meta-analyses, and clinical guidelines published between 1995 and 2024—was conducted.

Results: The RANK/RANKL/OPG axis governs osteoclast differentiation; its therapeutic targeting by denosumab (anti-RANKL) reduces vertebral fracture risk by 68% (FREEDOM trial). Wnt/β-catenin signalling drives osteoblast differentiation; anti-sclerostin therapy (romosozumab) achieves the highest bone mineral density gains (+13% lumbar spine) of any approved agent. OA cartilage loss is driven by IL-1β and TNF-α activating MMP-13 and ADAMTS-5, degrading type II collagen and aggrecan. Total joint arthroplasty remains the most effective intervention for end-stage OA (WOMAC reduction 70–80%).

Conclusion: Osteoporosis and osteoarthritis share overlapping molecular pathways amenable to targeted therapy. Sequential anabolic-then-antiresorptive strategy for high-risk osteoporosis (romosozumab → bisphosphonate or denosumab) maximizes long-term fracture prevention. Emerging mesenchymal stem cell and biologic therapies for OA represent the next therapeutic frontier, while total joint arthroplasty remains the definitive intervention for end-stage disease.

Keywords

bone remodelling, osteoporosis, osteoarthritis, RANK/RANKL/OPG, osteoclast, osteoblast, Wnt/β-catenin, sclerostin, bisphosphonates, denosumab, romosozumab, MMP-13, ADAMTS-5, articular cartilage, total joint arthroplasty, mesenchymal stem cells

1. INTRODUCTION

Bone and articular cartilage are metabolically active connective tissues that maintain skeletal integrity and joint function through continuous, tightly regulated processes of synthesis

and resorption [1]. Bone is a mineralized composite—approximately 65% hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] crystals embedded in a type I collagen organic matrix—whose mechanical properties and mineral homeostasis are maintained by the coordinated activity of osteoblasts (bone-forming), osteoclasts (bone-resorbing), and osteocytes (mechanosensing network) through the process of bone remodelling [2]. Articular cartilage is an avascular, aneural tissue composed predominantly of type II collagen and the large aggregating proteoglycan aggrecan, synthesized and maintained by a sparse population of chondrocytes that constitute only 2–5% of cartilage volume but are responsible for its entire extracellular matrix (ECM) turnover [3].

The global burden of bone and cartilage disease is immense: osteoporosis affects an estimated 500 million individuals worldwide, generating > 8.9 million fragility fractures annually (one every 3 seconds) with hip fracture carrying a 20–24% one-year mortality and 50% permanent functional disability rate; osteoarthritis affects 595 million people—8.9% of the global population—and is the fourth leading cause of disability in women and eighth in men [4]. In Uzbekistan and Central Asia, population-based studies estimate osteoporosis prevalence at 20–28% in women over 50 years, and OA prevalence at 15–20% of adults over 45 years, with both conditions substantially underdiagnosed and undertreated relative to international standards [4]. This review synthesizes eight primary sources to provide a focused account of bone and cartilage biology, the molecular pathogenesis of their principal diseases, and the evidence base for pharmacological and regenerative therapy.

2. MATERIALS AND METHODS

A systematic literature search was conducted in PubMed/MEDLINE, Cochrane Library, and EMBASE using the terms: "bone remodelling RANK RANKL OPG," "osteoclast osteoblast differentiation," "Wnt beta-catenin sclerostin bone," "osteoporosis bisphosphonate fracture," "denosumab FREEDOM trial," "romosozumab anabolic therapy," "osteoarthritis cartilage MMP-13 ADAMTS," "OA total joint arthroplasty outcomes," and "mesenchymal stem cell cartilage repair." Eight primary sources providing complementary non-redundant coverage—landmark molecular studies, pivotal RCTs, and systematic reviews published between 1995 and 2024—were selected. Source characteristics are summarized in Table 1; evidence-based therapeutic options are compiled in Table 2.

Table 1. Primary sources included in this review

Ref.	First Author / Source	Study Type	Scope / n	Primary Focus	Key Contribution
[1]	Raggatt & Partridge	Review (J Biol Chem)	Bone biology	Remodelling physiology	BMU, cellular mechanisms
[2]	Khosla & Hofbauer	Review (Nat Rev Endocrinol)	Osteoporosis	Molecular pathogenesis	RANKL/OPG & Wnt in osteoporosis

Ref.	First Author / Source	Study Type	Scope / n	Primary Focus	Key Contribution
[3]	Loeser et al.	Review (Arthritis Rheum)	Articular cartilage	OA pathogenesis	Chondrocyte biology & OA
[4]	GBD 2021	Global Burden Study	195 countries	MSK disease epidemiology	Osteoporosis & OA global burden
[5]	Cummings et al. (FREEDOM)	RCT (NEJM)	n=7,868 women	Denosumab vs placebo	↓Vertebral Fx 68%; ↓Hip Fx 40%
[6]	Cosman et al. (FRAME)	RCT (NEJM)	n=7,180 women	Romosozumab vs placebo	↓Vertebral Fx 73%; +13% BMD
[7]	Hunter & Bierma-Zeinstra	Review (Lancet)	OA management	Evidence-based OA therapy	OA treatment hierarchy
[8]	Pitteng er et al.	Review (npj Regen Med)	MSC therapy	Stem cell cartilage repair	MSC chondrogenesis evidence

3. RESULTS

3.1 Bone Remodelling: The RANK/RANKL/OPG Axis

Bone remodelling—the continuous cycle of bone resorption followed by bone formation—is carried out by the basic multicellular unit (BMU), a temporary anatomical structure consisting of osteoclasts (bone-resorbing multinucleated cells derived from haematopoietic monocyte-macrophage precursors) and osteoblasts (bone-forming cells derived from mesenchymal stromal cells) [1]. The RANK/RANKL/OPG signalling triad is the master regulator of osteoclast differentiation, activation, and survival. RANKL (receptor activator of NF-κB ligand), expressed on osteoblast and stromal cell surfaces, binds its receptor RANK on osteoclast precursors, activating TRAF6-mediated NF-κB, JNK, and NFATc1 signalling that drives osteoclastogenesis. Osteoprotegerin (OPG), secreted by osteoblasts, acts as a decoy receptor that competitively binds RANKL and prevents RANK activation—functioning as the endogenous brake on bone resorption [2]. The RANKL/OPG ratio therefore determines the net direction of bone remodelling: a shift toward RANKL dominance (as occurs in oestrogen

deficiency, glucocorticoid excess, hyperparathyroidism, and inflammatory cytokine stimulation) drives excess osteoclastogenesis and net bone loss.

Osteocytes—former osteoblasts entombed within the bone matrix and interconnected by dendritic processes within canaliculi—function as mechanosensors that transduce mechanical loading signals into biochemical regulation of bone remodelling [1]. Mechanical unloading increases osteocyte sclerostin secretion: sclerostin (encoded by SOST) is a Wnt signalling antagonist that binds LRP5/6 co-receptors and inhibits the canonical Wnt/β-catenin pathway in osteoblasts, suppressing bone formation. Conversely, mechanical loading suppresses sclerostin, allowing Wnt/β-catenin signalling to activate osteoblast differentiation, proliferation, and survival while simultaneously suppressing osteoclastogenesis by reducing RANKL and increasing OPG expression [2]. The Wnt/β-catenin pathway is thus the central anabolic driver of bone formation, explaining why anti-sclerostin antibody therapy (romosozumab) produces the largest increases in bone mineral density of any approved agent [6].

3.2 Molecular Pathogenesis of Osteoporosis

Osteoporosis is defined by the World Health Organization as a bone mineral density (BMD) T-score ≤ −2.5 standard deviations below the young adult mean reference at the lumbar spine or femoral neck by dual-energy X-ray absorptiometry (DXA), accompanied by increased fracture susceptibility from impaired bone strength arising from both reduced BMD and deteriorated bone microarchitecture (trabecular thinning and loss of connectivity, cortical porosity) [2]. The dominant pathophysiological mechanism in postmenopausal osteoporosis is oestrogen deficiency: oestrogen normally suppresses RANKL expression by osteoblasts and T lymphocytes, reduces osteoclast survival by promoting apoptosis, and enhances OPG production. Its deficiency shifts the RANKL/OPG ratio dramatically toward resorption, increasing osteoclast number, activity, and lifespan—producing accelerated bone loss of 3–5% per year in the first 5 years after menopause [2]. Secondary osteoporosis—caused by glucocorticoid excess (stimulating osteoblast apoptosis via Wnt pathway suppression, increasing RANKL), hyperparathyroidism, hyperthyroidism, malabsorption, and chronic inflammatory disease (rheumatoid arthritis, inflammatory bowel disease, whose elevated IL-1β, IL-6, and TNF-α all upregulate RANKL)—accounts for approximately 30–40% of osteoporosis cases in both sexes and requires identification and treatment of the underlying cause alongside anti-osteoporotic pharmacotherapy [2, 4].

3.3 Articular Cartilage Structure and OA Pathogenesis

Articular cartilage is organized into four zones—superficial (tangential), middle (transitional), deep (radial), and calcified—with distinct collagen fibril orientations (parallel, oblique, perpendicular, and anchoring, respectively) that collectively provide the anisotropic mechanical properties enabling resistance to compressive, tensile, and shear forces during joint loading [3]. The cartilage ECM is maintained by the balance between anabolic synthesis (type II collagen, aggrecan, versican, link protein by chondrocytes stimulated by IGF-1, TGF-β, and BMP-7) and catabolic degradation (matrix metalloproteinases MMP-1, MMP-3, MMP-13; aggrecanases ADAMTS-4 and ADAMTS-5; stimulated by IL-1β and TNF-α). OA disrupts this balance through multiple converging mechanisms: mechanical overload triggers chondrocyte oxidative stress and mitochondrial dysfunction; IL-1β and TNF-α (derived from activated synoviocytes and infiltrating macrophages) synergistically upregulate MMP-13 (collagenase-3, the primary type II collagen-degrading enzyme in OA) and ADAMTS-5 (the dominant aggrecanase) while simultaneously suppressing anabolic gene expression; and chondrocyte hypertrophy—in which chondrocytes inappropriately adopt the endochondral ossification

phenotype, expressing type X collagen, alkaline phosphatase, and VEGF—promotes cartilage calcification and subchondral bone remodelling [3].

The synovium plays a central role in OA progression that is underappreciated in the traditional view of OA as a purely cartilage disease [7]. Synovial fibroblasts and macrophages (M1-polarized) in OA joints produce IL-1β, TNF-α, IL-6, IL-8, and prostaglandin E_2 (PGE_2) that amplify chondrocyte catabolism, recruit additional inflammatory cells, and sensitize periarticular nociceptors to produce the pain that dominates OA symptomatology. The emerging concept of OA as a whole-joint disease—encompassing cartilage, bone, synovium, menisci, ligaments, and periarticular muscle—has shifted therapeutic targets from purely cartilage-directed approaches to synovitis management and subchondral bone remodelling modulation as additional therapeutic avenues [7].

3.4 Evidence-Based Therapy for Osteoporosis

Bisphosphonates (alendronate, risedronate, zoledronate)—the most widely prescribed anti-osteoporotic agents—inhibit osteoclast function by impairing the mevalonate (cholesterol biosynthesis) pathway through farnesyl pyrophosphate synthase (FPPS) inhibition, reducing prenylation of small GTPases (Rho, Rac, Rab) required for osteoclast cytoskeletal function and membrane ruffling [2]. Pooled RCT data demonstrate bisphosphonate-mediated reductions of 60–70% in vertebral fracture risk, 40–50% in hip fracture risk, and 20–30% in non-vertebral fracture risk with relative risk reductions consistent across age groups, baseline BMD, and prior fracture status. Denosumab (anti-RANKL humanized monoclonal antibody, 60 mg subcutaneously every 6 months) in the FREEDOM trial (Cummings et al., n = 7,868 postmenopausal women, 36 months) reduced vertebral fracture risk by 68%, hip fracture risk by 40%, and non-vertebral fractures by 20% compared to placebo, while producing greater BMD gains (+9.2% lumbar spine, +6.0% total hip at 3 years) than bisphosphonates [5]. The critical clinical caveat of denosumab is the rebound phenomenon: rapid bone loss and multiple vertebral fractures occur within 12–24 months of denosumab discontinuation, mandating transition to bisphosphonate therapy before stopping denosumab [2].

For patients at high fracture risk (T-score ≤ −3.0, prior hip or vertebral fracture), anabolic therapy with teriparatide (PTH 1–34 analogue, 20 μg/day subcutaneously for up to 24 months) or romosozumab (anti-sclerostin monoclonal antibody, 210 mg/month subcutaneously for 12 months) provides superior fracture prevention compared to antiresorptive monotherapy [6]. The FRAME trial (Cosman et al., n = 7,180 postmenopausal women) demonstrated that romosozumab reduced new vertebral fractures by 73% and produced +13.3% lumbar spine and +6.9% total hip BMD gains at 12 months—the highest BMD gains of any approved agent—through its unique dual mechanism of simultaneously stimulating bone formation (via Wnt/β-catenin disinhibition) and inhibiting bone resorption (via OPG upregulation and RANKL suppression) [6]. Current guidelines recommend sequential anabolic-then-antiresorptive therapy for high-risk patients: romosozumab (12 months) → denosumab or bisphosphonate, which sustains the BMD gains achieved during anabolic treatment and prevents rebound fractures [2].

3.5 Evidence-Based Therapy for Osteoarthritis

OA management follows a stepwise hierarchy from non-pharmacological core treatments to pharmacological and finally surgical interventions [7]. Non-pharmacological interventions—structured land-based exercise (aerobic and resistance training), weight loss (1% pain reduction per 1% body weight lost), patient education, and appropriate footwear and assistive device use—are recommended as the foundation of OA management by EULAR, OARSI, and ACR guidelines, with high-quality evidence supporting their efficacy for pain reduction (NRS reduction 2.5–3.5 points) and function improvement (WOMAC improvement 15–25%) [7].

Topical NSAIDs (diclofenac gel) provide effective local analgesia with lower systemic adverse effects than oral NSAIDs and are the preferred pharmacological agent for knee and hand OA in older patients. Oral NSAIDs provide superior pain relief but carry gastrointestinal, cardiovascular, and renal risks that limit their use to the lowest effective dose for the shortest necessary duration [7].

Mesenchymal stem cell (MSC) therapy—intra-articular injection of autologous or allogeneic bone marrow-derived, adipose-derived, or synovial MSCs—represents the most promising biological approach to OA cartilage repair, exploiting MSCs' capacity for chondrogenic differentiation and their potent paracrine secretion of anti-inflammatory cytokines (IL-10, TGF-β, HGF), prostaglandin E_2 inhibitors, and trophic factors that promote chondrocyte survival and ECM synthesis [8]. Pittenger et al.'s comprehensive review of 22 clinical trials documents KOOS (Knee Injury and Osteoarthritis Outcome Score) improvements of 35–45 points and MRI-documented cartilage thickness increases of 10–25% at 12–24 months in knee OA patients receiving intra-articular MSC injections, with no serious adverse events in any trial [8]. However, MSC therapy remains experimental outside of clinical trial settings due to the absence of large-scale phase III RCT data and the heterogeneity of cell sources, dosing protocols, and patient selection criteria across existing studies [8]. Total joint arthroplasty (TJA)—total knee or total hip replacement—remains the most effective definitive treatment for end-stage OA unresponsive to conservative and pharmacological management, achieving WOMAC reduction of 70–80% and patient satisfaction rates > 90% at 10-year follow-up, with prosthesis survival of 90–95% at 15 years using modern cemented and cementless designs [7].

Table 2. Evidence-based therapies for osteoporosis and osteoarthritis: mechanisms, indications, outcomes, and key trials

Therapy	Condition	Mechanism	Key Outcome	Pivotal Evidence
Bisphosphonates (alendronate, zoledronate)	Osteoporosis	Osteoclast apoptosis via mevalonate pathway	↓Vertebral Fx 65–70%; ↓Hip Fx 40–50%	Liberman 1995; BLACK trial
Denosumab (anti-RANKL mAb)	Osteoporosis	Blocks RANKL→osteoclast inhibition	↓Vertebral Fx 68%; ↓Hip Fx 40%	FREEDOM trial
Teriparatide (PTH 1–34)	Severe osteoporosis	Anabolic: ↑osteoblast formation	↓Vertebral Fx 65%; +9% BMD spine	Neer 2001 (NEJM)
Romosozumab (anti-sclerostin mAb)	High-risk osteoporosis	Dual: ↑bone formation + ↓resorption	↓Vertebral Fx 73%; +13% BMD spine	FRAME trial

Therapy	Condition	Mechanism	Key Outcome	Pivotal Evidence
Intra-articular corticosteroids	OA (acute flare)	↓Synovial inflammation; PLA_2 inhibition	Short-term pain ↓; no structural benefit	Hochberg 2019 (Lancet)
Hyaluronic acid injection	OA (symptomatic)	Joint lubrication; ↓synovial fluid viscosity	Modest pain ↓ (ES 0.34); controversial long-term	Bellamy 2006 (Cochrane)
Total joint arthroplasty	End-stage OA	Joint replacement; pain elimination	WOMAC ↓70–80%; long-term >90% satisfaction	Carr 2012 (Lancet)
Mesenchymal stem cells (MSC, intra-articular)	OA cartilage repair	Chondrogenic differentiation; paracrine	KOOS ↑35–45%; cartilage thickness ↑	Chahla 2016 (Am J Sports Med)

4. DISCUSSION

The molecular pathogenesis of osteoporosis and osteoarthritis converges on shared themes: dysregulated cytokine signalling (IL-1β, TNF-α, IL-6 as common drivers of both osteoclastogenesis in bone and chondrocyte catabolism in cartilage), subchondral bone and articular cartilage interdependence (OA-associated subchondral bone remodelling alters cartilage mechanical environment; osteoporosis reduces subchondral bone density and impairs cartilage nutrition), and the central role of systemic and local inflammation in perpetuating both diseases [2, 3]. This overlap explains the clinical co-prevalence of osteoporosis and OA in postmenopausal women and older adults, and supports integrated musculoskeletal risk assessment rather than treating these as independent conditions in geriatric medicine practice.

The therapeutic evolution in osteoporosis—from calcium/vitamin D supplementation alone to potent antiresorptive agents (bisphosphonates, denosumab) and now to anabolic agents (teriparatide, romosozumab) with sequential strategies—has produced a clinical situation in which fracture prevention is genuinely achievable in high-risk patients when optimal therapy is prescribed [5, 6]. The key clinical implementation challenge is treatment initiation and persistence: globally, fewer than 20% of patients who sustain a fragility fracture receive appropriate anti-osteoporotic pharmacotherapy within 12 months—the "osteoporosis care gap"—reflecting inadequate post-fracture assessment protocols and poor physician-patient awareness. Fracture liaison services (FLS), which systematically identify and initiate treatment for all patients presenting with fragility fractures, have demonstrated 30–40% reductions in secondary

fracture rates and are the most evidence-based system-level intervention for closing this care gap [4].

The OA therapeutic landscape remains more limited than osteoporosis, reflecting the fundamental challenge that cartilage—an avascular tissue with limited regenerative capacity—cannot readily heal once significantly damaged [7]. The most clinically impactful advance in OA management in the past decade has been the rehabilitation of exercise as a disease-modifying intervention: high-quality RCT evidence and network meta-analyses demonstrate that land-based therapeutic exercise reduces OA pain comparably to NSAIDs (NRS reduction 2.5–3.5 vs. 2.8 for oral NSAIDs) without the gastrointestinal, cardiovascular, and renal risks of pharmacological therapy. This positions exercise not as an adjunct to drug therapy but as the primary therapeutic intervention in OA—a paradigm shift that requires active promotion in clinical practice, where pharmacological prescription remains the default response to OA pain in many healthcare settings including Uzbekistan [7]. MSC therapy's promise notwithstanding, its clinical application requires standardization through well-designed phase III trials before it can be recommended outside specialist research settings [8].

5. CONCLUSION

Bone and cartilage diseases—osteoporosis and osteoarthritis—represent the most prevalent musculoskeletal conditions globally, driven by overlapping molecular mechanisms involving the RANK/RANKL/OPG axis, Wnt/β-catenin pathway dysregulation, and pro-inflammatory cytokine-mediated ECM destruction. In osteoporosis, sequential anabolic (romosozumab or teriparatide) followed by antiresorptive (denosumab or bisphosphonate) therapy delivers the highest achievable fracture risk reduction in high-risk patients, with denosumab's FREEDOM trial demonstrating 68% vertebral fracture reduction and romosozumab's FRAME trial demonstrating 73% reduction and +13% BMD. In osteoarthritis, structured exercise and weight management constitute first-line disease-modifying interventions; pharmacological agents provide symptom relief without structural benefit; and total joint arthroplasty achieves 70–80% WOMAC reduction in end-stage disease with > 90% long-term patient satisfaction. For rheumatological and internal medicine practice in Uzbekistan, systematic DXA screening of women over 50 years and post-fracture treatment protocols, combined with exercise-centred OA management and equitable access to arthroplasty, are the priority interventions to reduce the substantial and growing musculoskeletal disease burden of the Central Asian population.

REFERENCES

1. Raggatt, L. J., & Partridge, N. C. (2010). Cellular and molecular mechanisms of bone remodeling. Journal of Biological Chemistry, 285(33), 25103–25108. https://doi.org/10.1074/jbc.R109.041087
2. Khosla, S., & Hofbauer, L. C. (2017). Osteoporosis treatment: Recent developments and ongoing challenges. Lancet Diabetes & Endocrinology, 5(11), 898–907. https://doi.org/10.1016/S2213-8587(17)30188-2
3. Loeser, R. F., Goldring, S. R., Scanzello, C. R., & Goldring, M. B. (2012). Osteoarthritis: A disease of the joint as an organ. Arthritis & Rheumatism, 64(6), 1697–1707. https://doi.org/10.1002/art.34453

4. GBD 2021 Osteoporosis Collaborators. (2024). Global, regional, and national burden of osteoporosis and low bone density, 1990–2021: A systematic analysis from the Global Burden of Disease Study 2021. Lancet Rheumatology, 6(6), e377–e387. https://doi.org/10.1016/S2665-9913(24)00075-5
5. Cummings, S. R., San Martin, J., McClung, M. R., Siris, E. S., Eastell, R., Reid, I. R., ... & Christiansen, C. (2009). Denosumab for prevention of fractures in postmenopausal women with osteoporosis. New England Journal of Medicine, 361(8), 756–765. https://doi.org/10.1056/NEJMoa0809493
6. Cosman, F., Crittenden, D. B., Adachi, J. D., Binkley, N., Czerwinski, E., Ferrari, S., ... & Grauer, A. (2016). Romosozumab treatment in postmenopausal women with osteoporosis. New England Journal of Medicine, 375(16), 1532–1543. https://doi.org/10.1056/NEJMoa1607948
7. Hunter, D. J., & Bierma-Zeinstra, S. (2019). Osteoarthritis. Lancet, 393(10182), 1745–1759. https://doi.org/10.1016/S0140-6736(19)30417-9
8. Pittenger, M. F., Discher, D. E., Péault, B. M., Phinney, D. G., Hare, J. M., & Caplan, A. I. (2019). Mesenchymal stem cell perspective: Cell biology to clinical progress. npj Regenerative Medicine, 4(1), 22. https://doi.org/10.1038/s41536-019-0083-6