JOURNAL OF MULTIDISCIPLINARY SCIENCES AND INNOVATIONS

VOLUME 5, ISSUE 03
MONTHLY JOURNALS

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

CELLULAR AND MOLECULAR BIOLOGY OF BONE AND CARTILAGE: STRUCTURE, REMODELING, PATHOLOGICAL DEGENERATION, AND REGENERATIVE THERAPEUTIC STRATEGIES

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Abstract

Background: Bone and cartilage are specialized connective tissues that form the structural and biomechanical foundation of the vertebrate musculoskeletal system. Despite their apparent rigidity, both tissues are metabolically dynamic, undergoing continuous remodeling throughout life. Disruption of this homeostasis underlies some of the most prevalent and disabling diseases in modern medicine, including osteoporosis—affecting over 200 million people worldwide—and osteoarthritis, estimated to affect 528 million individuals globally.

Objective: To provide a comprehensive, evidence-based review of the cellular and molecular biology of bone and cartilage, encompassing their extracellular matrix composition, key cell types, signaling pathways governing remodeling and degeneration, and current regenerative and pharmacological therapeutic strategies.

Methods: A systematic review of eight primary peer-reviewed sources was conducted, including original research articles, meta-analyses, and authoritative clinical practice guidelines published between 2000 and 2024.

Results: Bone tissue is maintained by the coordinated activity of osteoblasts, osteocytes, and osteoclasts, regulated by the RANK/RANKL/OPG axis, Wnt/β-catenin signaling, and parathyroid hormone (PTH). Articular cartilage, avascular and aneural, relies on chondrocytes and a proteoglycan- and collagen II-rich extracellular matrix for load distribution. In osteoporosis, uncoupled remodeling favors resorption, reducing bone mineral density (BMD) and increasing fracture risk. In osteoarthritis (OA), matrix metalloproteinase (MMP)- and ADAMTS-mediated degradation of aggrecan and type II collagen drives progressive cartilage loss. Pharmacological interventions include bisphosphonates, denosumab, and teriparatide for osteoporosis, and intra-articular corticosteroids and hyaluronic acid for OA. Emerging regenerative strategies encompass mesenchymal stem cell (MSC) transplantation, scaffold-based tissue engineering, and gene therapy.

Conclusion: Advances in molecular biology have transformed understanding of bone and cartilage pathophysiology, enabling targeted therapies that significantly reduce fracture incidence and slow cartilage degeneration. Future progress depends on translating stem cell and gene therapy innovations into safe, scalable clinical protocols.

Keywords

bone remodeling, cartilage degeneration, osteoblast, osteoclast, chondrocyte, RANK/RANKL/OPG, Wnt signaling, osteoporosis, osteoarthritis, tissue engineering, mesenchymal stem cells

1. INTRODUCTION

Bone and cartilage constitute the two principal hard connective tissues of the musculoskeletal system, together providing rigid structural support, protecting vital organs, facilitating locomotion, and serving as metabolic reservoirs for calcium and phosphate homeostasis. Despite their outward similarity as load-bearing tissues, bone and cartilage differ profoundly in their cellular composition, extracellular matrix (ECM) architecture, vascularization, innervation, and regenerative capacity [1]. Bone is a highly vascularized, mineralized tissue capable of continuous self-repair through a tightly regulated remodeling cycle, whereas articular cartilage is avascular, aneural, and alymphatic—properties that critically limit its intrinsic healing potential following injury or disease [2].

The clinical significance of these tissues is enormous. Osteoporosis, defined by the World Health Organization (WHO) as a bone mineral density T-score ≤ -2.5 standard deviations below the young adult mean, affects over 200 million individuals worldwide and is responsible for approximately 8.9 million fragility fractures annually, including 1.6 million hip fractures with a one-year mortality approaching 20–30% [3]. Osteoarthritis (OA), the most prevalent form of arthritis, affects an estimated 528 million people globally as of 2019, with prevalence projected to increase substantially with population aging and the obesity epidemic [2]. Together, these conditions represent a leading cause of pain, disability, and healthcare expenditure in both high- and low-income countries.

At the molecular level, both osteoporosis and OA share a common pathophysiological theme: disruption of the homeostatic balance between anabolic (tissue-building) and catabolic (tissue-degrading) processes. In bone, this manifests as uncoupled remodeling in which osteoclast-mediated resorption outpaces osteoblast-mediated formation, leading to net bone loss [3]. In cartilage, it presents as an imbalance between chondrocyte matrix synthesis and protease-driven ECM degradation, culminating in the progressive loss of articular cartilage that defines OA [4]. The molecular mediators of these imbalances—including the RANK/RANKL/OPG axis, Wnt/β-catenin pathway, matrix metalloproteinases (MMPs), and ADAMTS aggrecanases—have become primary targets for pharmacological intervention and regenerative medicine strategies [5].

Understanding the biology of bone and cartilage at the cellular and molecular level is therefore not merely of academic interest but is the essential foundation for rational drug development, tissue engineering, and regenerative medicine. This review synthesizes evidence from eight primary sources to provide a comprehensive account of the structure, cellular biology, signaling pathways, pathological degeneration, and current and emerging therapeutic approaches in bone and cartilage medicine.

The specific objectives of this review are: (i) to describe the ECM composition and cellular organization of bone and articular cartilage; (ii) to analyze the molecular pathways governing bone remodeling and cartilage homeostasis; (iii) to examine the pathophysiological mechanisms of osteoporosis and osteoarthritis; (iv) to evaluate established pharmacological treatments and their mechanisms of action; and (v) to survey emerging regenerative strategies including MSC-based therapy and scaffold-guided tissue engineering.

2. MATERIALS AND METHODS

2.1 Literature Search and Database Sources

A systematic literature search was conducted between November 2024 and January 2025 using PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials. The following MeSH terms and keywords were used in Boolean combinations: "bone remodeling," "cartilage extracellular matrix," "osteoclast differentiation," "RANK RANKL OPG," "Wnt signaling bone," "chondrocyte apoptosis," "osteoporosis treatment," "osteoarthritis pathophysiology," "mesenchymal stem cell bone," and "cartilage tissue engineering." No date restriction was initially applied; results were subsequently filtered to prioritize publications from 2000 to 2024.

2.2 Inclusion and Exclusion Criteria

Articles were eligible for inclusion if they: (i) were published in peer-reviewed journals with an impact factor ≥5.0 or constituted major clinical practice guidelines issued by recognized international societies; (ii) reported original experimental data, systematic reviews, meta-analyses, or comprehensive narrative reviews on the molecular biology, pathology, or therapy of bone or articular cartilage in humans or directly translatable animal models; and (iii) were published in English. Studies were excluded if they focused exclusively on bone tumors, infectious osteitis, or non-articular fibrocartilage without relevance to bone homeostasis or hyaline cartilage biology. Eight primary sources were selected to provide complementary coverage of structure, pathophysiology, and therapy.

2.3 Data Extraction and Quality Assessment

For each included source, the following data were systematically extracted: study design, principal subject matter, key molecular or clinical findings, patient populations (for clinical studies), and evidence quality ratings. For clinical guidelines, recommendation class (I–III) and evidence level (A–C) were recorded as defined by the originating societies. Data quality was assessed using the GRADE framework for clinical studies and the ARRIVE guidelines for preclinical experimental studies. All extracted data are synthesized narratively; quantitative re-analysis was not performed. Key characteristics of the eight primary sources are summarized in Table 1.

Table 1. Characteristics of the eight primary sources included in this review

Ref.	First Author / Source	Study Type	Focus Area	Key Contribution	Year
[1]	Raggatt & Partridge	Review	Bone cell biology	Osteoblast-osteoclast coupling	2010
[2]	Hunter & Bierma-Zeinstra	Review (Lancet)	Osteoarthritis	OA pathophysiology	2019
[3]	Compston et al.	Clinical Guideline	Osteoporosis	Diagnosis & treatment	2019
[4	Loeser	Review	OA	MMP/ADA	20

Ref.	First Author / Source	Study Type	Focus Area	Key Contribution	Year
]	et al.	(NEJM)	molecular basis	MTS roles	12
[5]	Baron & Kneissel	Review (NRM)	Wnt signaling	Bone mass regulation	2013
[6]	Camacho et al.	Clinical Guideline	Osteoporosis Rx	Pharmacotherapy	2020
[7]	Pittenger et al.	Original Research	MSC therapy	Stem cell properties	2019
[8]	Kon et al.	Systematic Review	Cartilage repair	Tissue engineering	2018

MSC = mesenchymal stem cell; OA = osteoarthritis; MMP = matrix metalloproteinase; ADAMTS = a disintegrin and metalloproteinase with thrombospondin motifs; NRM = Nature Reviews Molecular Cell Biology.

3. RESULTS

3.1 Extracellular Matrix Composition of Bone

Bone is a composite biomaterial consisting of approximately 65% inorganic mineral phase (carbonated hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$) and 35% organic matrix, of which approximately 90% is type I collagen [1]. The remaining organic fraction comprises non-collagenous proteins (NCPs) including osteocalcin, osteopontin, bone sialoprotein, and osteonectin, which coordinate mineral nucleation, cell adhesion, and matrix organization. The hierarchical assembly of bone ECM—from tropocollagen triple helices to collagen fibrils, fibers, lamellae, and osteons—confers the tissue's unique combination of stiffness (elastic modulus ~20 GPa in cortical bone) and fracture toughness. Hydroxyapatite crystals, oriented parallel to collagen fibril axes, resist compressive loading, while collagen fibers absorb tensile and torsional forces—a complementarity that makes bone simultaneously stiff and crack-resistant [1].

Cortical (compact) bone, comprising 80% of the skeletal mass, is organized into cylindrical osteons (Haversian systems) containing concentric lamellae surrounding a central canal with neurovascular supply. Trabecular (cancellous) bone, concentrated at metaphyseal ends of long bones and in vertebral bodies, consists of a three-dimensional network of trabeculae oriented along lines of mechanical stress, providing maximal strength at minimal mass. This architectural optimization is continuously updated through the bone remodeling process, in which old or microdamaged bone is removed by osteoclasts and replaced with new bone by osteoblasts in spatially and temporally coordinated basic multicellular units (BMUs) [1].

3.2 Extracellular Matrix and Zones of Articular Cartilage

Articular (hyaline) cartilage is a specialized connective tissue covering the articulating surfaces of synovial joints, providing a near-frictionless bearing surface (coefficient of friction ~0.001–0.01) and distributing mechanical loads across the underlying subchondral bone [2]. Its ECM is composed predominantly of water (65–80% wet weight), type II collagen (50–60% dry weight), and the large aggregating proteoglycan aggrecan—assembled with link protein and hyaluronic acid into macromolecular complexes that occupy the interfibrillar space. The negatively charged glycosaminoglycan (GAG) side chains of aggrecan (primarily chondroitin sulfate and keratan sulfate) generate a high fixed charge density that drives osmotic swelling, resisting compressive loads through the Donnan equilibrium [4].

Articular cartilage is organized into four distinct zones: the superficial tangential zone (10–20% of thickness), with collagen fibers oriented parallel to the surface and high concentrations of the boundary lubricant lubricin (PRG4); the middle (transitional) zone, with randomly oriented collagen and high proteoglycan content; the deep zone, with radially oriented collagen fibers and the highest proteoglycan concentration; and the calcified cartilage zone, separated from the deep zone by the tidemark and anchoring the tissue to subchondral bone. This zonal organization creates a depth-dependent biomechanical profile that allows cartilage to distribute stress across its thickness and into the subchondral bone, protecting deeper structures from impact loading [2].

3.3 Molecular Regulation of Bone Remodeling

Bone remodeling is governed by a molecular triad: receptor activator of nuclear factor κB (RANK) expressed on osteoclast precursors, its ligand RANKL expressed on osteoblasts and osteocytes, and the decoy receptor osteoprotegerin (OPG) secreted by osteoblasts [1]. RANKL binding to RANK activates NF-κB and MAPK pathways, driving osteoclastogenesis and bone resorption. OPG competitively inhibits RANKL–RANK interaction, suppressing osteoclast differentiation. The RANKL/OPG ratio therefore determines the set point of bone turnover: a high ratio (elevated RANKL or reduced OPG) promotes resorption, while a low ratio favors formation. This axis is modulated by systemic hormones (PTH, estrogen, glucocorticoids, vitamin D), mechanical loading transmitted by osteocytes, and inflammatory cytokines (IL-1β, TNF-α, IL-6, IL-17) [3].

The Wnt/β-catenin signaling pathway is the dominant anabolic signal for osteoblast differentiation and bone formation [5]. Binding of Wnt ligands to Frizzled receptors and co-receptors LRP5/LRP6 inhibits the β-catenin destruction complex (comprising GSK-3β, APC, and axin), allowing β-catenin to translocate to the nucleus and activate TCF/LEF-dependent transcription of osteogenic genes including RUNX2 and osterix. The physiological importance of this pathway is demonstrated by gain-of-function mutations in LRP5 that cause high bone mass syndrome and loss-of-function mutations that cause osteoporosis-pseudoglioma syndrome [5]. Sclerostin (encoded by SOST), secreted by osteocytes under mechanical unloading conditions, is a potent endogenous Wnt antagonist that binds LRP5/6 and suppresses bone formation—a mechanism exploited therapeutically by the anti-sclerostin monoclonal antibody romosozumab [6].

3.4 Molecular Pathogenesis of Osteoporosis

Osteoporosis results from chronic dysregulation of the remodeling cycle in which bone resorption persistently exceeds formation, leading to progressive deterioration of bone microarchitecture and reduced bone mineral density (BMD) [3]. In postmenopausal osteoporosis, estrogen deficiency removes the inhibitory effect of estrogen on RANKL expression and

osteoclastogenesis, and simultaneously reduces OPG production and the proliferative/anti-apoptotic signaling to osteoblasts. The net result is an approximately 2–3-fold increase in bone turnover rate, with each remodeling cycle producing a net bone deficit of approximately 0.5–1% of total bone mass. Over the 5–10 years following menopause, women may lose 20–30% of their trabecular bone mass, reducing the load-bearing cross-sectional area of trabecular struts below the fracture threshold [3].

Age-related (senile) osteoporosis, affecting both sexes after age 70, is characterized by blunted osteoblast function due to reduced IGF-1 signaling, impaired Wnt pathway activity, and accumulation of adipogenic differentiation of skeletal progenitor cells at the expense of osteoblastogenesis [5]. Secondary osteoporosis—arising from glucocorticoid excess, hypogonadism, malabsorption, hyperthyroidism, or chronic kidney disease—accounts for approximately 30% of postmenopausal and 50–80% of male osteoporosis cases and requires treatment of the underlying cause in addition to bone-directed pharmacotherapy. Dual-energy X-ray absorptiometry (DXA) at the lumbar spine and total hip remains the gold-standard diagnostic tool, with the WHO BMD T-score classification (normal ≥ -1.0; osteopenia -1.0 to -2.5; osteoporosis ≤ -2.5) providing the framework for fracture risk assessment and treatment thresholds [3].

3.5 Molecular Pathogenesis of Osteoarthritis

Osteoarthritis is a whole-joint disease characterized by articular cartilage degradation, subchondral bone sclerosis, osteophyte formation, synovial inflammation, and periarticular muscle atrophy [2]. The primary molecular event in OA cartilage is the imbalance between anabolic cytokines (TGF-β, IGF-1, BMP-7) and catabolic mediators (IL-1β, TNF-α, IL-6, IL-17), with catabolic signals predominating in the disease state. Chondrocyte activation by pro-inflammatory cytokines—primarily IL-1β and TNF-α from the inflamed synovium—drives upregulation of matrix metalloproteinases (MMP-1, MMP-3, MMP-13) and aggrecanases ADAMTS-4 and ADAMTS-5, which cleave the collagen network and aggrecan core protein at specific sites, releasing GAG fragments into the synovial fluid [4].

MMP-13 (collagenase-3) is considered the key effector of cartilage collagen degradation in OA: it preferentially cleaves type II collagen at the ¾–¼ Gly-Ile cleavage site, generating denatured collagen (gelatin) fragments that are susceptible to further degradation by gelatinases MMP-2 and MMP-9 [4]. ADAMTS-5 is the dominant aggrecanase in murine OA models, and its genetic deletion protects mice from cartilage proteoglycan loss; its role in human OA is supported by elevated ADAMTS-5 expression in late-stage OA cartilage. Chondrocyte hypertrophy—characterized by type X collagen upregulation, alkaline phosphatase activity, and MMP-13 expression—represents a pathological recapitulation of the terminal differentiation program of growth plate chondrocytes and is a critical step in the vascular invasion and eventual mineralization of OA cartilage [2].

3.6 Pharmacological Management of Osteoporosis and Osteoarthritis

The pharmacological management of osteoporosis is stratified by fracture risk and mechanism of action [6]. Bisphosphonates (alendronate, risedronate, zoledronic acid) remain first-line therapy, functioning as synthetic analogues of pyrophosphate that accumulate in bone mineral and are internalized by osteoclasts, where they inhibit farnesyl pyrophosphate (FPP) synthase in the mevalonate pathway, disrupting prenylation of small GTPases (Ras, Rho, Rac) essential for osteoclast cytoskeletal function and survival. Long-term bisphosphonate use reduces vertebral fracture risk by approximately 40–70% and hip fracture risk by 40–50% in clinical trials. Denosumab, a fully human anti-RANKL monoclonal antibody, achieves a higher degree

of bone turnover suppression than bisphosphonates and is preferred in patients with renal insufficiency (eGFR < 30 mL/min/1.73 m²), showing 68% reduction in vertebral fractures and 40% reduction in hip fractures over 3 years in the FREEDOM trial [6].

Teriparatide (recombinant PTH 1–34) and abaloparatide (PTH-related peptide analogue) are anabolic agents that, when given as once-daily subcutaneous injections, preferentially stimulate bone formation over resorption by direct activation of PTH receptor 1 (PTH1R) on osteoblasts, stimulating IGF-1 and Wnt pathway activity [6]. Romosozumab, a dual-action anti-sclerostin antibody approved in 2019, both stimulates bone formation (by enhancing Wnt signaling) and reduces resorption (by increasing OPG), producing BMD gains approximately twice those of alendronate at the lumbar spine within 12 months. For osteoarthritis, current pharmacotherapy is predominantly symptomatic: topical and oral NSAIDs, intra-articular corticosteroids (triamcinolone, betamethasone), and intra-articular hyaluronic acid viscosupplementation provide pain relief and modest functional improvement, but no approved disease-modifying OA drug (DMOAD) currently exists that demonstrably slows radiographic cartilage loss [2].

3.7 Regenerative and Tissue Engineering Strategies

Mesenchymal stem cells (MSCs), isolated from bone marrow, adipose tissue, synovium, and umbilical cord, possess the capacity for self-renewal and trilineage differentiation into osteoblasts, chondrocytes, and adipocytes, making them the principal cell source for bone and cartilage regenerative medicine [7]. In chondrogenic differentiation protocols, MSCs are cultured as pellets or in three-dimensional scaffolds in serum-free medium supplemented with TGF-β3, BMP-6, and dexamethasone, resulting in upregulation of SOX9 (the master chondrogenic transcription factor), type II collagen, and aggrecan. In osteogenic protocols, BMP-2, BMP-7, dexamethasone, ascorbic acid, and β-glycerophosphate drive RUNX2/SP7 (osterix) expression and matrix mineralization [7].

Scaffold-based tissue engineering for cartilage repair utilizes biocompatible, biodegradable matrices that provide a three-dimensional template for cell attachment, proliferation, and ECM deposition [8]. Natural polymer scaffolds include collagen, fibrin, hyaluronic acid, and alginate hydrogels, which mimic native cartilage ECM and promote chondrogenic gene expression. Synthetic polymer scaffolds—polyglycolic acid (PGA), polylactic acid (PLA), and poly(lactic-co-glycolic acid) (PLGA)—offer tunable mechanical properties and degradation rates but require surface modification for adequate cell adhesion. Osteochondral composite scaffolds featuring a chondrogenic upper layer and an osteogenic mineralized lower layer separated by a tidemark-mimicking interface are under active clinical evaluation for the repair of full-thickness osteochondral defects. First-generation cell-free scaffolds (e.g., MaioRegen, Chondro-Gide) have demonstrated satisfactory clinical outcomes at 5-year follow-up in focal chondral defects of the knee, with MOCART scores indicating good defill and surface integration [8].

4. DISCUSSION

The evidence reviewed in this article reveals that bone and cartilage, despite their structural similarity as load-bearing connective tissues, represent fundamentally distinct biological systems with different cellular hierarchies, ECM compositions, vascularization patterns, and disease vulnerabilities [1, 2]. This biological divergence has direct clinical implications: bone's rich vascularity and periosteum-derived progenitor pool confer considerable

regenerative capacity, such that even major fractures heal spontaneously under optimal conditions, whereas the avascularity of articular cartilage renders full-thickness chondral defects essentially irreparable by intrinsic mechanisms. This asymmetry in regenerative biology explains why pharmacological suppression of bone resorption (bisphosphonates, denosumab) reduces fracture rates by 40–70%, while no pharmacological agent has yet demonstrated convincing disease modification in osteoarthritis [3, 6].

The RANK/RANKL/OPG axis and the Wnt/β-catenin pathway represent arguably the most therapeutically important molecular systems in skeletal medicine, and their elucidation over the past two decades has directly enabled a new generation of targeted biologics [5]. Denosumab, by mimicking endogenous OPG and neutralizing RANKL, achieves a degree of osteoclast suppression not achievable with bisphosphonates, translating into superior BMD gains and fracture risk reduction in head-to-head comparisons [6]. Romosozumab's dual anabolic-antiresorptive mechanism—exploiting the osteocyte sclerostin/Wnt axis—represents the most mechanistically sophisticated bone drug currently available, though cardiovascular safety signals observed in the ARCH trial (higher rates of serious cardiovascular events vs. alendronate in post-MI patients) have necessitated cautious patient selection [6].

The failure to develop disease-modifying OA drugs despite decades of research reflects the biological complexity and multifactorial nature of OA pathogenesis [4]. Single-target approaches directed at individual MMPs (e.g., MMP-13 inhibitors) or cytokines (anti-IL-1β, anti-TNF-α) have consistently failed in phase II/III trials, largely due to the redundancy of catabolic pathways, inadequate drug delivery to the cartilage matrix (particularly after the loss of normal cartilage architecture and fixed charge density), and the challenge of conducting long-term trials with validated structural outcome measures. The recognition that OA is a whole-joint disease involving subchondral bone remodeling, synovial inflammation, and meniscal degeneration—not simply a cartilage-wear condition—has prompted interest in subchondral bone-targeting strategies using bisphosphonates and strontium ranelate, and in synovial anti-inflammatory approaches using intra-articular gene therapy vectors encoding IL-1Ra or IL-10 [2].

MSC-based therapies occupy a critical frontier in musculoskeletal regenerative medicine, offering the theoretical capacity to restore both cellular and matrix components of damaged bone and cartilage [7]. However, translation from preclinical success to robust clinical efficacy has been challenging. Key obstacles include the incomplete understanding of MSC fate after intra-articular injection (with studies demonstrating that <1% of systemically administered MSCs reach cartilage), the immunological and inflammatory milieu of the OA joint that promotes MSC apoptosis and blocks chondrogenic differentiation, and the lack of standardized MSC isolation, expansion, and characterization protocols that enable reproducible clinical outcomes. Emerging strategies to overcome these barriers include the use of synovium-derived MSCs (which demonstrate superior chondrogenic potential), pre-activation of MSCs with TGF-β and hypoxic conditioning to enhance survival and differentiation, and the use of MSC-derived extracellular vesicles (exosomes) as cell-free paracrine delivery vehicles that avoid the immunological and regulatory complexity of live cell therapies [7].

Scaffold-based tissue engineering for osteochondral repair has achieved meaningful clinical translation, with several collagen-based and biphasic scaffolds demonstrating satisfactory outcomes in young, active patients with focal chondral defects of limited size (typically < 4 cm^2) [8]. However, the repair tissue generated by scaffold-based strategies is predominantly fibrocartilage rather than hyaline cartilage, as evidenced by elevated type I collagen expression and reduced proteoglycan content in biopsy specimens. Achieving true

hyaline cartilage regeneration—with its characteristic zonal organization, type II collagen content, and biomechanical properties—remains an unmet goal. Three-dimensional bioprinting of cartilage constructs using chondrocyte- or MSC-laden bioinks incorporating GelMA, methacrylated hyaluronic acid, or decellularized cartilage matrix is emerging as the most promising avenue for achieving zonal cartilage architecture and mechanical properties approaching those of native tissue [8].

Gene therapy approaches for both osteoporosis and OA are at early but promising stages. Adeno-associated virus (AAV) vectors delivering BMP-2 or BMP-7 to fracture sites have demonstrated accelerated healing in animal models, while local delivery of sclerostin siRNA using lipid nanoparticles has enhanced spine fusion success in preclinical models [5]. For OA, intra-articular delivery of IL-1Ra-encoding constructs using retrovirally transduced autologous chondrocytes (the TNF-α stimulated gene/protein 6 approach, TG-C) is currently in phase III trials, representing the most advanced gene therapy program in OA [4]. The integration of gene therapy with smart biomaterial scaffolds that enable spatiotemporally controlled gene expression in response to mechanical loading or inflammatory cues represents the next generation of osteochondral tissue engineering.

5. CONCLUSION

This systematic review has demonstrated that bone and cartilage, as the principal structural tissues of the musculoskeletal system, are maintained by sophisticated molecular networks whose dysregulation produces the highly prevalent and disabling diseases of osteoporosis and osteoarthritis. The cellular biology of bone—centered on the osteoblast–osteocyte–osteoclast triad coordinated by the RANK/RANKL/OPG axis and Wnt/β-catenin signaling—provides mechanistically validated targets for bisphosphonates, denosumab, teriparatide, and romosozumab, enabling substantial reductions in fracture incidence in high-risk populations. The avascular biology of articular cartilage and the redundancy of its catabolic machinery pose greater therapeutic challenges, as no DMOAD has yet succeeded in clinical development.

The emergence of MSC-based cell therapies, scaffold-guided tissue engineering, and gene therapy vectors encoding anabolic or anti-inflammatory factors offers transformative potential for restoring bone and cartilage tissue in patients with structural defects beyond the reach of pharmacological agents. Realizing this potential will require convergence of advances in stem cell biology, biomaterials science, three-dimensional bioprinting, and in vivo gene delivery, together with the development of validated structural and functional outcome measures for clinical trials. The ultimate goal—regenerating mechanically competent, zonal hyaline cartilage and architecturally appropriate bone in vivo—remains technically demanding but scientifically within reach given the pace of current progress.

Future research priorities include: (i) elucidation of the crosstalk between subchondral bone and articular cartilage in OA progression to identify shared therapeutic targets; (ii) development of scaffold-free, self-assembled cartilage constructs that faithfully recapitulate native tissue architecture; (iii) optimization of MSC delivery routes and pre-conditioning protocols for intra-articular applications; and (iv) long-term clinical trials of anabolic bone agents and cell-based cartilage repair technologies with 10-year structural and functional follow-up. These efforts, grounded in the molecular biology reviewed here, will define the future of bone and cartilage medicine.

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