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Regenerative Therapies for Articular Cartilage: Current Concepts, Clinical Outcomes, and Future Directions

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ABSTRACT

Introduction and purpose. Articular cartilage injuries represent a significant clinical challenge due to the tissue's limited intrinsic healing capacity, often progressing to osteoarthritis and chronic disability. Traditional treatments remain largely symptomatic, prompting extensive research into regenerative therapies aimed at restoring functional cartilage tissue.

Description of the state of knowledge. We conducted a systematic analysis of recent literature (2020-2026) encompassing randomized controlled trials, systematic reviews, meta-analyses, and prospective cohort studies. Evidence was synthesized across multiple therapeutic modalities including mesenchymal stem cells (MSCs), autologous chondrocyte implantation (ACI/MACI), platelet-rich plasma (PRP), osteochondral transplantation, tissue engineering scaffolds, and emerging technologies such as 3D bioprinting, gene therapy, and exosome-based treatments. Matrix-associated autologous chondrocyte implantation (MACI) demonstrates

significant long-term efficacy with large effect sizes (>0.8) in patient-reported outcomes at 2-15 years follow-up. Mesenchymal stem cells from various sources (bone marrow, adipose tissue, synovium, umbilical cord) show promise in clinical trials, with synovium-derived MSCs exhibiting particularly high chondrogenic potential. Comparative studies indicate that ACI/MACI and expanded MSC transplantation outperform microfracture for focal cartilage defects.

Summary. Regenerative therapies have evolved significantly, with cell-based approaches demonstrating superior outcomes compared to traditional marrow stimulation techniques. However, challenges persist regarding optimal cell source, dosage, delivery methods, and long-term durability. Standardized protocols, large-scale randomized trials, and integration of emerging technologies are essential to advance the field toward personalized, effective cartilage regeneration strategies.

Keywords: Articular cartilage regeneration; Mesenchymal stem cells; Tissue engineering; Regenerative medicine; Cartilage repair; Osteoarthritis

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1. INTRODUCTION

Articular cartilage injuries and degenerative joint diseases represent a major global health burden, affecting millions of individuals worldwide and contributing significantly to disability and reduced quality of life [1], [2], [3], [4]. The unique biological characteristics of articular cartilage—including its avascular nature, low cellularity, and limited metabolic activity—severely restrict its intrinsic capacity for self-repair following injury [5], [6], [7], [8]. Consequently, even minor cartilage lesions can progress to extensive degenerative changes, ultimately leading to osteoarthritis (OA), a chronic and debilitating condition characterized by progressive cartilage degradation, subchondral bone remodeling, synovial inflammation, and persistent pain [4], [30], [31], [32].

Traditional treatment approaches for cartilage defects have been largely palliative, focusing on symptom management through pharmacological interventions, physical therapy, and ultimately joint replacement surgery in advanced cases [1], [2], [33]. While these strategies provide temporary relief, they fail to address the underlying pathophysiology or restore native cartilage structure and function [7], [8], [34]. The limitations of conventional therapies have catalyzed intensive research into regenerative medicine approaches that aim to promote true biological repair and functional restoration of damaged cartilage tissue [6], [10], [35], [36].

Over the past three decades, significant advances have been made in regenerative cartilage therapies, encompassing cell-based treatments, biological augmentation strategies, tissue engineering approaches, and emerging technologies [10], [11], [12], [37]. Cell-based therapies, particularly autologous chondrocyte implantation (ACI) and mesenchymal stem cell (MSC) transplantation, have demonstrated promising clinical outcomes and represent the most extensively studied regenerative modalities [1], [2], [13], [14], [38]. Concurrently, advances in biomaterial science, scaffold design, and delivery systems have enhanced the feasibility and efficacy of tissue engineering strategies [8], [39], [40], [41].

More recently, cutting-edge technologies such as 3D bioprinting, gene therapy, exosome-based treatments, and CRISPR-mediated gene editing have emerged as potentially transformative approaches for cartilage regeneration [30], [31], [42], [43], [44]. These innovations offer unprecedented opportunities for precise control over cellular behavior, tissue architecture, and therapeutic outcomes [45], [46], [47]. However, significant challenges remain in translating these promising technologies from bench to bedside, including issues related to scalability, standardization, regulatory approval, and cost-effectiveness [48], [49], [50].

This comprehensive review synthesizes current evidence on regenerative therapies for articular cartilage defects, with particular emphasis on clinical outcomes, comparative effectiveness, and future directions. We critically evaluate established cell-based and biological therapies, examine emerging technologies, and discuss the challenges and opportunities that will shape the future of cartilage regeneration.

2. BIOLOGICAL CHARACTERISTICS OF ARTICULAR CARTILAGE AND CHALLENGES IN REGENERATION

Articular cartilage is a highly specialized connective tissue that provides a smooth, lubricated surface for joint articulation and distributes mechanical loads across the joint [5], [6], [7], [30]. The tissue exhibits a unique zonal architecture, with distinct superficial, middle (transitional), and deep zones, each characterized by specific cellular organization, extracellular matrix (ECM) composition, and biomechanical properties [4], [8], [31], [32]. The superficial zone contains flattened chondrocytes aligned parallel to the articular surface and produces lubricin for joint lubrication [5], [30]. The middle zone features rounded chondrocytes and abundant proteoglycans, while the deep zone contains columnar chondrocytes oriented perpendicular to the subchondral bone and anchors the cartilage to the underlying calcified cartilage layer [6], [7], [31].

The extracellular matrix of articular cartilage is composed primarily of type II collagen (providing tensile strength), proteoglycans such as aggrecan (providing compressive resistance through water retention), and various non-collagenous proteins and glycoproteins [4], [5], [8], [32]. This highly organized ECM structure is maintained by chondrocytes, which represent the sole cellular component of cartilage and account for only 1-5% of the tissue volume [6], [7], [30]. Chondrocytes are responsible for synthesizing and maintaining the ECM, but their metabolic activity is relatively low due to the avascular and aneural nature of the tissue [31], [33].

The limited regenerative capacity of articular cartilage stems from several fundamental biological constraints [5], [6], [7], [8]. First, the avascular nature of cartilage restricts the delivery of nutrients, oxygen, growth factors, and progenitor cells to sites of injury, severely limiting the tissue's ability to mount an effective healing response [4], [30], [31]. Second, the low cellularity and limited proliferative capacity of mature chondrocytes prevent adequate cellular repopulation of defects [32], [33], [34]. Third, the dense ECM structure impedes cell migration and tissue remodeling [5], [6]. Fourth, the lack of access to systemic inflammatory and immune responses—which play crucial roles in tissue repair in vascularized tissues—further compromises healing potential [7], [8], [30].

When cartilage injury occurs, the body's repair response varies depending on whether the lesion is confined to the cartilage (chondral defect) or extends into the subchondral bone (osteochondral defect) [4], [31], [32]. Chondral defects that do not penetrate the subchondral bone fail to elicit a significant healing response and typically do not heal spontaneously [5], [6], [33]. In contrast, osteochondral defects that breach the subchondral bone plate allow access to bone marrow-derived cells and growth factors, initiating a fibrocartilaginous repair response [7], [8], [30]. However, the resulting fibrocartilage tissue is biomechanically and biochemically inferior to native hyaline cartilage, lacking the organized zonal structure and appropriate ECM composition [31], [34], [35]. This fibrocartilage is prone to degeneration under normal joint loading, often leading to progressive cartilage loss and osteoarthritis [4], [32], [36].

The progression from focal cartilage injury to osteoarthritis involves complex molecular and cellular mechanisms, including inflammatory cytokine production, matrix metalloproteinase (MMP) activation, chondrocyte apoptosis, and alterations in subchondral bone metabolism [4], [30], [31], [32]. Pro-inflammatory mediators such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) drive catabolic processes that accelerate cartilage degradation [4], [32]. Additionally, mechanical factors such as joint instability, malalignment, and abnormal loading patterns contribute to disease progression [5], [6], [36].

Understanding these fundamental biological characteristics and healing limitations is essential for developing effective regenerative strategies. Successful cartilage regeneration must address multiple challenges: providing appropriate cellular sources with chondrogenic potential, delivering bioactive factors to promote matrix synthesis and inhibit degradation, creating biomechanically suitable scaffolds to support tissue formation, and establishing a favorable microenvironment that recapitulates native cartilage development [7], [8], [30], [31], [37].

3. CURRENT REGENERATIVE THERAPIES

3.1 Cell-Based Therapies

3.1.1 Autologous Chondrocyte Implantation (ACI/MACI)

Autologous chondrocyte implantation (ACI) represents one of the first clinically successful cell-based therapies for cartilage repair and has undergone significant evolution since its introduction in the 1990s [1], [2], [9], [10]. The procedure involves harvesting healthy cartilage from a non-weight-bearing area of the joint, isolating and expanding chondrocytes in vitro, and subsequently implanting the expanded cells into the cartilage defect [11], [12], [13]. First-generation ACI utilized a periosteal flap to cover the defect and retain the cell suspension, while second-generation techniques employed collagen membranes to improve handling and reduce complications [1], [9], [14].

Matrix-associated autologous chondrocyte implantation (MACI), representing third-generation ACI technology, involves seeding expanded chondrocytes onto a three-dimensional scaffold (typically collagen or hyaluronic acid-based) prior to implantation [1], [2], [10], [11]. This approach offers several advantages over earlier generations, including improved surgical handling, more uniform cell distribution, enhanced chondrocyte phenotype maintenance, and reduced risk of periosteal hypertrophy [9], [12], [13], [14]. The scaffold provides a three-dimensional environment that supports chondrocyte differentiation and matrix production while facilitating arthroscopic implantation techniques [1], [10], [38].

Clinical evidence demonstrates that MACI is effective for treating symptomatic focal cartilage defects, particularly in young to middle-aged patients with traumatic lesions [1], [2], [9], [11], [27]. The procedure is most commonly applied to femoral condyle defects but has also shown efficacy for patellar and trochlear lesions [10], [12], [13]. Optimal outcomes are typically achieved in patients with isolated defects, stable joints, and appropriate limb alignment [1], [14], [38]. Patient selection criteria generally include defect size >2-4 cm^2, age <50 years, body mass index <30-35 kg/m^2, and absence of advanced degenerative changes [9], [11], [27].

The biological mechanisms underlying ACI/MACI efficacy involve the production of hyaline-like cartilage tissue by the implanted chondrocytes, with gradual integration into surrounding native cartilage and subchondral bone [1], [2], [10]. Histological studies have demonstrated that MACI-treated defects can produce tissue with characteristics approaching native hyaline cartilage, including type II collagen expression, proteoglycan content, and zonal organization [11], [12], [13]. However, complete restoration of native cartilage architecture remains

challenging, and the regenerated tissue often exhibits mixed hyaline and fibrocartilaginous features [9], [14], [38].

Recent advances in ACI/MACI technology include the development of characterized chondrocyte implantation, which involves quality control testing of expanded cells to ensure appropriate phenotype and potency [18], [39], [40]. Additionally, combination approaches incorporating growth factors, gene therapy, or co-culture with mesenchymal stem cells are being investigated to enhance chondrogenic differentiation and tissue quality [30], [31], [41], [42].

3.1.2 Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) have emerged as a promising alternative to chondrocytes for cartilage regeneration due to their multipotent differentiation capacity, immunomodulatory properties, paracrine effects, and relative ease of isolation and expansion [2], [3], [4], [14]. MSCs can be derived from multiple tissue sources, including bone marrow (BM-MSCs), adipose tissue (AD-MSCs), synovium (SM-MSCs), umbilical cord (UC-MSCs), and peripheral blood [3], [4], [6], [7], [38]. Each source exhibits distinct characteristics in terms of proliferation rate, chondrogenic potential, immunophenotype, and paracrine factor secretion [2], [14], [42], [43].

Bone marrow-derived MSCs represent the most extensively studied cell source and have been widely used in clinical trials for cartilage repair [2], [3], [4], [15]. BM-MSCs demonstrate robust chondrogenic differentiation capacity when cultured in appropriate conditions with transforming growth factor-β (TGF-β) superfamily members [6], [7], [14], [44]. However, BM-MSC harvesting requires invasive bone marrow aspiration, yields relatively low cell numbers, and shows age-dependent decline in proliferative and differentiation capacity [3], [4], [38], [42].

Adipose-derived MSCs offer advantages of abundant availability, minimally invasive harvesting via liposuction, and high cell yields [3], [4], [6], [7]. AD-MSCs exhibit comparable or superior proliferation rates to BM-MSCs and demonstrate chondrogenic potential, though some studies suggest slightly lower chondrogenic capacity compared to BM-MSCs [2], [14], [38], [43]. Clinical studies have investigated AD-MSCs for cartilage repair, with promising early results, though long-term comparative data remain limited [3], [17], [42].

Synovium-derived MSCs have garnered increasing attention due to their superior chondrogenic potential compared to other MSC sources [2], [3], [4], [30]. SM-MSCs can be harvested arthroscopically from synovial tissue, exhibit high proliferation rates, and demonstrate robust cartilage matrix production in vitro and in vivo [6], [7], [14], [38]. Preclinical studies have shown that SM-MSCs produce more cartilage-like tissue with higher type II collagen and

proteoglycan content compared to BM-MSCs or AD-MSCs [3], [42], [43]. Clinical translation of SM-MSC therapy is advancing, with early-phase trials demonstrating safety and preliminary efficacy [2], [30], [44].

Umbilical cord-derived MSCs represent an attractive allogeneic cell source with advantages including non-invasive collection, high proliferation capacity, low immunogenicity, and potential for off-the-shelf availability [3], [4], [6], [7]. UC-MSCs exhibit strong immunomodulatory properties and secrete abundant trophic factors that may enhance cartilage repair through paracrine mechanisms [2], [14], [38], [42]. Clinical trials have investigated UC-MSC therapy for osteoarthritis and cartilage defects, with encouraging safety profiles and preliminary efficacy data [3], [8], [43].

The mechanisms by which MSCs promote cartilage regeneration extend beyond direct chondrogenic differentiation and include paracrine signaling, immunomodulation, and trophic support [2], [3], [4], [14]. MSCs secrete a wide array of bioactive factors, including growth factors (TGF-β, IGF-1, FGF-2), anti-inflammatory cytokines (IL-10, IL-1Ra), and extracellular vesicles containing microRNAs and proteins [6], [7], [38], [42], [43]. These paracrine factors can modulate the local microenvironment, reduce inflammation, inhibit apoptosis, stimulate endogenous progenitor cell recruitment, and enhance matrix synthesis by resident chondrocytes [2], [14], [30], [44].

Clinical applications of MSCs for cartilage repair include direct intra-articular injection, arthroscopic implantation with or without scaffolds, and combination with marrow stimulation techniques such as microfracture [2], [3], [4], [15]. Dosing strategies vary widely across studies, ranging from 1-100 million cells per treatment, with some protocols employing single injections and others using multiple doses [6], [7], [14], [38]. Optimal cell dose, delivery method, and treatment frequency remain areas of active investigation [3], [42], [43].

3.2 Biological Therapies

Biological therapies for cartilage regeneration encompass a range of approaches that utilize growth factors, cytokines, and blood-derived products to enhance the body's intrinsic repair mechanisms [4], [5], [6], [30]. Platelet-rich plasma (PRP) represents one of the most widely studied biological therapies, consisting of autologous blood plasma with concentrated platelets that release growth factors including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and insulin-like growth factor-1 (IGF-1) [5], [17], [31], [38]. These growth factors promote chondrocyte proliferation, matrix synthesis, and anti-inflammatory effects [4], [30], [39], [40].

Clinical applications of PRP for cartilage pathology include intra-articular injections for osteoarthritis and augmentation of surgical cartilage repair procedures [5], [17], [31], [38]. Multiple randomized controlled trials and meta-analyses have evaluated PRP efficacy for knee osteoarthritis, with most studies demonstrating short- to medium-term improvements in pain and function compared to placebo or hyaluronic acid injections [4], [30], [39], [40]. However, significant heterogeneity exists in PRP preparation methods, platelet concentrations, activation protocols, and treatment regimens, making direct comparisons challenging [5], [31], [38], [41]. The composition and preparation of PRP significantly influence its biological activity and clinical efficacy [4], [17], [30], [39]. Leukocyte-rich PRP (LR-PRP) contains white blood cells that may contribute pro-inflammatory mediators, while leukocyte-poor PRP (LP-PRP) minimizes inflammatory components [5], [31], [38], [40]. Some evidence suggests that LP-PRP may be more appropriate for intra-articular applications due to reduced inflammatory potential, though comparative studies have yielded mixed results [4], [30], [41], [42].

Growth factor therapies beyond PRP have been investigated for cartilage regeneration, including recombinant proteins and gene therapy approaches to deliver sustained growth factor expression [30], [31], [43], [44]. Transforming growth factor-β (TGF-β) superfamily members, particularly TGF-β1, TGF-β3, and bone morphogenetic proteins (BMPs), are potent chondrogenic factors that promote MSC differentiation and cartilage matrix production [4], [45], [46], [47]. Insulin-like growth factor-1 (IGF-1) enhances chondrocyte proliferation and matrix synthesis while inhibiting catabolic processes [30], [31], [48]. Fibroblast growth factor-2 (FGF-2) and fibroblast growth factor-18 (FGF-18) promote chondrocyte proliferation and have been investigated in clinical trials [17], [39], [40], [49].

Combination approaches that integrate biological therapies with cell-based or surgical treatments have shown promise in enhancing cartilage repair outcomes [4], [5], [17], [30]. For example, PRP or growth factors can be combined with microfracture, MSC therapy, or scaffold implantation to provide a more favorable regenerative microenvironment [31], [38], [39], [40]. These combination strategies aim to synergistically address multiple aspects of cartilage regeneration, including cell recruitment, proliferation, differentiation, and matrix production [4], [30], [41], [42].

3.3 Tissue Engineering and Scaffolds

Tissue engineering approaches for cartilage regeneration combine cells, scaffolds, and bioactive signals to create functional tissue constructs that can integrate with native cartilage and restore joint function [7], [8], [39], [40]. Scaffolds serve multiple critical functions in cartilage tissue engineering, including providing structural support, guiding cell organization,

facilitating nutrient and waste exchange, delivering bioactive factors, and promoting integration with surrounding tissue [8], [30], [31], [41]. The ideal scaffold should possess appropriate mechanical properties, biocompatibility, biodegradability, porosity, and surface characteristics to support chondrogenesis [7], [39], [40], [42].

Natural biomaterials commonly used for cartilage scaffolds include collagen, hyaluronic acid, chitosan, alginate, fibrin, and silk fibroin [7], [8], [30], [31]. Collagen scaffolds, particularly type I and type II collagen, are widely used due to their biocompatibility, biodegradability, and ability to support cell adhesion and chondrogenic differentiation [39], [40], [41], [42]. Collagen-based scaffolds are employed in commercial MACI products and have demonstrated clinical efficacy [1], [9], [11], [27]. Hyaluronic acid, a major component of cartilage ECM, provides excellent biocompatibility and can be chemically modified to create hydrogels with tunable properties [7], [8], [30], [31].

Synthetic biomaterials offer advantages of reproducibility, tunable properties, and scalable manufacturing [7], [8], [39], [40]. Commonly used synthetic polymers include poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), and poly(ε-caprolactone) (PCL) [30], [31], [41], [42]. These materials can be fabricated into various scaffold architectures using techniques such as electrospinning, 3D printing, freeze-drying, and solvent casting [7], [8], [39], [40]. Synthetic scaffolds can be designed with specific degradation rates, mechanical properties, and surface modifications to optimize cellular responses [30], [31], [43].

Composite scaffolds that combine natural and synthetic materials aim to leverage the advantages of both material classes [7], [8], [39], [40]. For example, PLGA scaffolds can be coated with collagen or hyaluronic acid to enhance cell adhesion while maintaining mechanical strength [30], [31], [41]. Bilayer and multilayer scaffolds have been developed to recapitulate the zonal architecture of native cartilage or to address osteochondral defects by incorporating distinct cartilage and bone layers [7], [8], [42], [43].

Hydrogels represent a particularly promising scaffold platform for cartilage tissue engineering due to their high water content, similarity to native cartilage ECM, and ability to encapsulate cells in three dimensions [7], [8], [30], [31]. Injectable hydrogels offer minimally invasive delivery and can conform to irregular defect geometries [39], [40], [41], [42]. Photocrosslinkable hydrogels enable in situ gelation and precise spatial control of scaffold formation [7], [8], [30], [43]. Stimuli-responsive hydrogels that respond to temperature, pH, or enzymatic activity provide additional functionality for controlled drug release and dynamic mechanical properties [31], [39], [40].

Decellularized extracellular matrix (dECM) scaffolds derived from native cartilage or other tissues represent a biomimetic approach that preserves the complex composition and architecture of natural ECM [7], [8], [30], [31]. Decellularization processes remove cellular components while retaining ECM proteins, growth factors, and structural organization [39], [40], [41]. dECM scaffolds have demonstrated promising results in preclinical studies, promoting chondrogenic differentiation and tissue integration [7], [8], [42], [43].

Scaffold functionalization strategies enhance biological activity through incorporation of bioactive molecules, surface modifications, and controlled release systems [7], [8], [30], [31]. Growth factors such as TGF-β, BMP-2, and IGF-1 can be physically adsorbed, covalently attached, or encapsulated within scaffolds for sustained delivery [39], [40], [41], [42]. Cell adhesion peptides such as RGD (arginine-glycine-aspartate) sequences can be conjugated to scaffold surfaces to promote cell attachment and spreading [7], [8], [30], [43]. Nanoparticle incorporation enables controlled release of drugs, genes, or proteins to modulate cellular behavior [31], [39], [40].

3.4 Osteochondral Transplantation

Osteochondral transplantation techniques address cartilage defects by transferring intact osteochondral units (cartilage with underlying subchondral bone) to the defect site, providing immediate structural restoration with viable chondrocytes and native ECM architecture [20], [26]. Two primary approaches exist: osteochondral autograft transplantation (OAT, also known as mosaicplasty) and osteochondral allograft transplantation (OCA) [20], [26], [53].

Osteochondral autograft transplantation involves harvesting cylindrical osteochondral plugs from non-weight-bearing areas of the patient's own joint (typically the lateral femoral condyle or intercondylar notch) and transplanting them into the defect [20], [26]. Single or multiple plugs can be used depending on defect size, with the mosaicplasty technique employing multiple small plugs to fill larger defects [53]. OAT offers advantages of using autologous tissue (eliminating immunological concerns), providing immediate structural support with viable cartilage, and achieving good integration of the bone component [20], [26]. However, limitations include donor site morbidity, limited availability of graft tissue, and challenges in achieving smooth articular surface restoration with multiple plugs [53].

Osteochondral allograft transplantation utilizes fresh or fresh-frozen osteochondral tissue from cadaveric donors, enabling treatment of larger defects (>2-4 cm^2) that exceed the capacity of autograft harvest [20], [26], [53]. Fresh allografts, stored at 4°C for up to 28-42 days, maintain high chondrocyte viability (>70%) and are preferred for optimal biological outcomes [26], [53]. Fresh-frozen allografts offer logistical advantages and longer storage but have reduced

chondrocyte viability [20], [26]. OCA is particularly valuable for large traumatic defects, osteochondritis dissecans, and salvage procedures following failed previous cartilage repairs [26], [53].

Clinical outcomes of osteochondral transplantation vary based on defect characteristics, surgical technique, and patient factors [20], [26], [53]. OAT demonstrates good short- to medium-term results for small to medium-sized focal defects (<2-4 cm^2), with success rates of 75-90% at 5-10 years [20], [26]. OCA shows favorable outcomes for larger defects, with graft survival rates of 75-85% at 10 years and 60-75% at 15-20 years [26], [53]. Factors associated with better outcomes include younger age, lower body mass index, focal traumatic lesions, and absence of bipolar (kissing) lesions [20], [26], [53].

Complications of osteochondral transplantation include graft subsidence, incomplete integration, donor site morbidity (for OAT), disease transmission risk (for OCA), and immune rejection (for OCA, though rare due to the immunoprivileged nature of cartilage) [20], [26], [53]. Technical challenges include achieving precise graft sizing and positioning, ensuring adequate graft fixation, and restoring congruent articular surface geometry [20], [26]. Advances in imaging, surgical instrumentation, and graft preservation techniques continue to improve outcomes [53].

4. CLINICAL OUTCOMES AND COMPARATIVE EFFECTIVENESS

4.1 Long-Term Outcomes of ACI/MACI

Long-term clinical outcomes of autologous chondrocyte implantation and matrix-associated autologous chondrocyte implantation have been extensively documented, with follow-up studies extending to 10-20 years demonstrating sustained improvements in patient-reported outcomes and functional scores [1], [9], [13], [21], [27]. Multiple systematic reviews and meta-analyses have confirmed the durability and effectiveness of ACI/MACI for treating symptomatic focal cartilage defects [1], [9], [11], [13], [27].

A prospective study with 15-year follow-up of arthroscopic matrix-assisted autologous chondrocyte transplantation reported significant and sustained improvements in International Knee Documentation Committee (IKDC) scores, Knee injury and Osteoarthritis Outcome Score (KOOS), and Tegner activity scores [21]. The study demonstrated that 78% of patients achieved clinically meaningful improvements, with graft survival rate of 89% at 15 years [21]. Magnetic resonance imaging (MRI) evaluation showed good defect fill and integration in the majority of cases, though some patients exhibited incomplete integration or graft hypertrophy [16], [21].

Systematic reviews of minimum 10-year outcomes after MACI have reported overall success rates of 71-87%, with failure defined as revision surgery or conversion to arthroplasty [13], [27], [29]. Patient-reported outcome measures showed large effect sizes (Cohen's d > 0.8) for improvements in pain, function, and quality of life [1], [9], [27]. Factors associated with superior long-term outcomes included younger age (<40 years), lower body mass index, smaller defect size, femoral condyle location, traumatic etiology, and absence of concomitant pathology such as meniscal deficiency or malalignment [13], [21], [27], [29].

Comparative studies between first-generation ACI with periosteal cover and third-generation MACI have demonstrated advantages of the matrix-associated technique, including reduced periosteal hypertrophy (occurring in 10-25% of periosteal ACI versus <5% of MACI), improved surgical handling, and potential for arthroscopic implantation [19], [21], [27]. A prospective long-term comparison found similar clinical outcomes between periosteal ACI and MACI at 10-15 years, but MACI showed lower complication rates and fewer revision procedures [19], [21].

Real-world data from post-market surveillance studies have corroborated the efficacy and safety of MACI in diverse patient populations [5], [27]. A large-scale analysis of MACI outcomes in Japan reported significant improvements in patient-reported outcomes at 2-5 years, with low rates of treatment failure and adverse events [5]. The study confirmed that MACI is effective across a range of defect sizes (2-10 cm^2) and locations, though outcomes were optimal for isolated femoral condyle lesions [5], [27].

Magnetic resonance imaging-based assessment of MACI-treated defects has provided insights into structural repair quality and its correlation with clinical outcomes [16], [21]. The MOCART (Magnetic Resonance Observation of Cartilage Repair Tissue) scoring system is commonly used to evaluate defect fill, integration with adjacent cartilage, surface congruity, and signal intensity characteristics [16]. Studies have shown that better MOCART scores at 12-24 months correlate with superior long-term clinical outcomes, though the relationship is not absolute [16], [21]. Complete defect fill and good integration are associated with better functional results, while incomplete fill or graft hypertrophy may predict suboptimal outcomes [16].

The concept of patient acceptable symptomatic state (PASS) has been applied to evaluate clinically meaningful outcomes after MACI [29]. A study examining PASS thresholds at 10 years post-MACI found that 68-74% of patients achieved acceptable symptomatic states across various outcome measures (IKDC, KOOS subscales, Lysholm score) [29]. PASS thresholds

provide valuable benchmarks for counseling patients regarding expected outcomes and defining treatment success [29].

4.2 MSC Therapy Outcomes

Clinical outcomes of mesenchymal stem cell therapy for cartilage defects have been evaluated in numerous trials, with evidence supporting safety and preliminary efficacy across various MSC sources and delivery methods [2], [3], [4], [15]. Systematic reviews and meta-analyses have synthesized data from randomized controlled trials and cohort studies, providing insights into the comparative effectiveness of different MSC approaches [3], [15], [24].

Bone marrow-derived MSC therapy has demonstrated improvements in pain and function scores in patients with knee osteoarthritis and focal cartilage defects [2], [3], [4], [15]. A systematic review and meta-analysis of dose-response relationships found that higher MSC doses (>40-50 million cells) were associated with greater improvements in clinical outcomes, though optimal dosing remains debated [15]. The study also identified that multiple injections may provide superior results compared to single-dose treatments [15]. Adverse events were generally mild and transient, including temporary pain, swelling, and stiffness at the injection site [3], [15].

Adipose-derived MSC therapy has shown promising results in clinical trials, with several studies reporting improvements in pain, function, and quality of life measures [3], [17]. A pilot study combining adipose-derived MSCs with PRP and microfracture demonstrated feasibility and safety, with encouraging preliminary efficacy data [17]. However, comparative studies directly evaluating AD-MSCs versus other cell sources remain limited [3].

Allogeneic umbilical cord blood-derived MSC therapy has been investigated as an off-the-shelf treatment option for cartilage regeneration [8]. A comparative study of UC-MSC implantation versus microfracture combined with high tibial osteotomy for cartilage regeneration in patients with varus malalignment reported superior outcomes in the UC-MSC group at 2-year follow-up [8]. The allogeneic MSCs were well-tolerated without evidence of immune rejection or serious adverse events [8].

Synovium-derived MSC therapy represents an emerging approach with high chondrogenic potential [2], [3], [30]. While clinical data remain limited compared to BM-MSCs and AD-MSCs, early-phase trials have demonstrated safety and preliminary efficacy [2], [30]. The superior chondrogenic capacity of SM-MSCs observed in preclinical studies suggests potential advantages for clinical translation [3], [30].

MRI-based assessment of cartilage repair following MSC therapy has provided structural outcome data to complement clinical measures [3], [8], [15]. Studies have reported

improvements in cartilage thickness, defect fill, and MOCART scores following MSC treatment, though the quality of regenerated tissue varies [3], [15]. Second-look arthroscopy and biopsy studies have shown that MSC therapy can produce fibrocartilaginous or mixed hyaline-fibrocartilaginous repair tissue, though achieving pure hyaline cartilage remains challenging [2], [3].

4.3 Comparative Studies

Comparative effectiveness research has provided critical insights into the relative merits of different cartilage repair strategies, informing clinical decision-making and treatment algorithms [22], [23], [24], [25]. Network meta-analyses and systematic reviews have synthesized data from randomized controlled trials to compare multiple treatment modalities simultaneously [22], [23], [25].

A comprehensive network meta-analysis of randomized controlled trials comparing various cartilage repair treatments to microfracture found that ACI/MACI, characterized chondrocyte implantation, and osteochondral autograft transplantation all demonstrated superior clinical outcomes compared to microfracture alone [22]. The analysis reported that MACI showed the highest probability of being the most effective treatment for improving IKDC scores and KOOS subscales [22]. Effect sizes were largest for MACI (standardized mean difference 0.8-1.2), followed by characterized chondrocyte implantation and OAT [22].

Systematic reviews specifically comparing third-generation autologous chondrocyte implantation (cells cultured within collagen membrane) versus microfracture for focal chondral defects have consistently demonstrated superiority of ACI/MACI at minimum 2-year follow-up [23], [25]. A systematic review of randomized controlled trials reported that ACI/MACI resulted in significantly better IKDC scores (mean difference 8.5-12.3 points), KOOS scores, and Tegner activity levels compared to microfracture [23]. The benefits of ACI/MACI were most pronounced for larger defects (>4 cm^2) and at longer follow-up periods (>5 years) [23], [25].

Meta-analyses comparing autologous chondrocyte implantation versus microfracture have confirmed the superiority of ACI for focal cartilage defects, particularly in younger patients with larger lesions [25]. The analysis found that ACI demonstrated better clinical outcomes, higher rates of return to sports, and lower failure rates compared to microfracture at 2-10 year follow-up [25]. However, ACI was associated with higher costs and more complex surgical procedures [25].

Comparative studies of expanded mesenchymal stem cell transplantation versus marrow stimulation alone have demonstrated advantages of the cell-based approach [24]. A systematic

review and meta-analysis found that expanded MSC transplantation following marrow stimulation resulted in significantly better clinical outcomes and MRI-based structural repair compared to marrow stimulation alone [24]. The combination approach showed improvements in IKDC scores (mean difference 7.8 points), KOOS scores, and defect fill percentage [24].

Comparative effectiveness research has also evaluated different MSC sources, though direct head-to-head clinical trials remain limited [2], [3], [14]. Systematic reviews synthesizing preclinical and clinical data suggest that synovium-derived MSCs may offer superior chondrogenic potential compared to bone marrow or adipose-derived MSCs, though clinical validation is needed [2], [3], [30]. Allogeneic versus autologous MSC comparisons have shown similar safety and efficacy profiles, supporting the feasibility of off-the-shelf allogeneic products [3], [8].

Osteochondral allograft transplantation has been compared to other cartilage repair techniques for large defects [20], [26], [53]. Systematic reviews indicate that OCA provides effective treatment for defects >4 cm^2 where other techniques may be insufficient [26], [53]. While direct comparative trials are limited, observational studies suggest that OCA outcomes are comparable to or better than MACI for large defects, with the advantage of single-stage surgery [20], [26].

5. EMERGING TECHNOLOGIES AND FUTURE DIRECTIONS

5.1 3D Bioprinting

Three-dimensional bioprinting represents a transformative technology for cartilage tissue engineering, enabling precise spatial control over cell placement, biomaterial distribution, and architectural design to recapitulate the complex zonal structure of native articular cartilage [34], [37], [40], [49]. Bioprinting technologies utilize computer-aided design and layer-by-layer fabrication to create patient-specific constructs with controlled geometry, mechanical properties, and biological functionality [34], [37], [40], [57], [58].

Multiple bioprinting modalities have been developed for cartilage applications, each with distinct advantages and limitations [34], [37], [40], [49]. Extrusion-based bioprinting uses pneumatic or mechanical pressure to dispense cell-laden bioinks through a nozzle, offering high cell density, compatibility with viscous materials, and scalability for large constructs [34], [37], [57], [58]. Inkjet bioprinting employs thermal or piezoelectric actuators to deposit precise droplets of bioink, providing high resolution and speed but limited to low-viscosity materials [34], [40], [49]. Laser-assisted bioprinting uses focused laser pulses to transfer cells and materials from a donor ribbon to a substrate, achieving high resolution and cell viability but

with lower throughput [37], [40], [58]. Stereolithography and digital light processing utilize photopolymerization to create structures with exceptional resolution and complex geometries [34], [37], [49], [57].

Bioink formulation is critical for successful bioprinting and must balance printability, biocompatibility, mechanical properties, and biological functionality [34], [37], [40], [49]. Natural polymer-based bioinks including alginate, gelatin, hyaluronic acid, collagen, and chitosan offer excellent biocompatibility and cell-instructive properties [34], [37], [57], [58]. Alginate provides rapid gelation through ionic crosslinking and good printability but limited cell adhesion [34], [40]. Gelatin methacryloyl (GelMA) combines the bioactivity of gelatin with photocrosslinkable functionality, enabling precise spatial control and tunable mechanical properties [34], [37], [49], [56], [57]. Hyaluronic acid-based bioinks recapitulate native cartilage ECM composition and support chondrogenesis [34], [40], [58].

Composite bioinks that combine multiple materials aim to optimize both printability and biological performance [34], [37], [40], [49]. For example, alginate-gelatin composites leverage alginate's printability and gelatin's cell adhesion properties [34], [57]. Nanocomposite bioinks incorporating nanoparticles (nanoclay, carbon nanotubes, graphene oxide) enhance mechanical strength and provide additional functionality [34], [40], [56], [58]. Decellularized extracellular matrix-based bioinks preserve native tissue composition and architecture while offering excellent biological activity [34], [37], [49].

Advanced bioprinting strategies for cartilage regeneration include multi-material printing to create zonal structures that mimic native cartilage architecture [34], [37], [40], [49], [57]. By varying bioink composition, cell types, and growth factor incorporation across different zones, bioprinted constructs can recapitulate the superficial, middle, and deep zones of articular cartilage [34], [58]. Gradient bioprinting enables smooth transitions in composition and properties, potentially improving integration and biomechanical function [37], [40], [49].

Osteochondral bioprinting addresses the challenge of regenerating both cartilage and underlying subchondral bone through bilayer or gradient constructs [34], [37], [40], [49], [57], [58]. The cartilage layer incorporates chondrocytes or MSCs with chondrogenic bioinks, while the bone layer contains osteogenic cells and mineralized bioinks [34], [37], [58]. Interface design is critical for achieving integration between layers and recapitulating the native osteochondral junction [40], [49], [57].

In situ bioprinting represents an emerging approach where bioprinting is performed directly into the defect site during surgery, enabling patient-specific defect filling and immediate integration [58], [60]. Handheld bioprinting devices have been developed for intraoperative use,

though clinical translation remains in early stages [58], [60]. In situ bioprinting offers advantages of precise defect matching, minimally invasive delivery, and elimination of in vitro culture periods [58], [60].

Bioprinted constructs incorporating bioactive cargos such as growth factors, drugs, or extracellular vesicles provide additional functionality for enhancing cartilage regeneration [57], [59]. Controlled release systems can be integrated into bioprinted structures to deliver therapeutic agents with spatial and temporal precision [57], [59]. For example, bioprinted scaffolds with encapsulated exosomes have demonstrated enhanced chondrogenic differentiation and cartilage matrix production [57], [59].

Despite significant advances, several challenges must be addressed for clinical translation of bioprinted cartilage [34], [37], [40], [49], [58]. Achieving adequate mechanical strength to withstand joint loading remains difficult, as bioprinted constructs typically exhibit inferior mechanical properties compared to native cartilage [34], [37], [58]. Vascularization of thick constructs is challenging due to the avascular nature of cartilage, though this may be less critical for cartilage than for other tissues [40], [49]. Scalability and manufacturing standardization are needed for clinical production [34], [37], [58]. Regulatory pathways for bioprinted tissue products are still evolving [49], [58], [60].

5.2 Gene Therapy

Gene therapy for cartilage regeneration aims to deliver therapeutic genes to cells within or surrounding cartilage defects, enabling sustained local production of chondrogenic growth factors, anti-inflammatory molecules, or matrix proteins to enhance tissue repair [1], [11], [24], [25], [30], [31], [43], [44], [45], [46], [47]. Gene therapy approaches offer advantages over recombinant protein delivery, including prolonged therapeutic effect, reduced dosing frequency, and localized expression that minimizes systemic exposure [1], [11], [24], [25], [30], [31], [43].

Viral vector-mediated gene delivery utilizes modified viruses to efficiently transduce target cells with therapeutic genes [1], [11], [24], [25], [31], [43], [44], [45]. Adeno-associated virus (AAV) vectors are widely used for cartilage gene therapy due to their excellent safety profile, low immunogenicity, broad tropism, and ability to transduce both dividing and non-dividing cells [1], [24], [25], [31], [44], [45], [47]. Recombinant AAV (rAAV) vectors have been extensively studied for delivering chondrogenic genes such as TGF-β, SOX9, IGF-1, and BMP-2 to enhance cartilage repair [1], [24], [25], [44], [45], [47]. Studies have demonstrated that rAAV-mediated overexpression of SOX9 and TGF-β enhances chondrogenic differentiation of bone marrow-derived MSCs and promotes cartilage matrix production [44], [45], [47].

Adenoviral vectors offer high transduction efficiency and large transgene capacity but elicit stronger immune responses and provide only transient gene expression [11], [24], [25], [31], [43]. Adenoviral vectors have been used in preclinical studies for cartilage gene therapy, though safety concerns have limited clinical translation [11], [24], [31], [43]. Lentiviral vectors enable stable, long-term gene expression through chromosomal integration and can transduce non-dividing cells, but integration carries theoretical risks of insertional mutagenesis [11], [24], [25], [31], [43].

Non-viral gene delivery methods offer advantages of lower immunogenicity, easier manufacturing, and better safety profiles compared to viral vectors, though typically with lower transfection efficiency [11], [24], [25], [31], [43], [46]. Plasmid DNA delivery can be achieved through direct injection, electroporation, or incorporation into biomaterial scaffolds [11], [24], [25], [43], [46]. Lipid-based nanoparticles and polymeric nanoparticles protect nucleic acids from degradation and facilitate cellular uptake [11], [24], [25], [31], [43], [46]. Physical methods such as electroporation and sonoporation enhance cell membrane permeability to enable gene transfer [11], [24], [43].

Biomaterial-mediated gene delivery combines gene therapy with tissue engineering scaffolds to provide sustained, localized gene expression within cartilage defects [11], [24], [25], [43], [46], [51]. Scaffold-based gene delivery systems can incorporate viral vectors, plasmid DNA, or nanoparticles within hydrogels, electrospun fibers, or porous scaffolds [11], [24], [25], [43], [46], [51]. This approach enables controlled release kinetics, protects vectors from degradation, and concentrates therapeutic genes at the defect site [11], [24], [43], [46], [51]. Studies have demonstrated that scaffold-guided rAAV delivery enhances chondrogenic activities in human bone marrow aspirates and MSCs [45], [47], [51].

Target genes for cartilage regeneration gene therapy include chondrogenic transcription factors, growth factors, anti-inflammatory molecules, and matrix proteins [1], [11], [24], [25], [30], [31], [43], [44], [45], [46], [47]. SOX9, the master transcription factor for chondrogenesis, promotes chondrocyte differentiation and cartilage-specific gene expression [1], [44], [45], [47]. TGF-β superfamily members (TGF-β1, TGF-β3, BMP-2, BMP-7) are potent chondrogenic factors that enhance MSC differentiation and cartilage matrix production [1], [24], [25], [31], [44], [45], [47]. IGF-1 promotes chondrocyte proliferation, matrix synthesis, and survival while inhibiting catabolic processes [1], [30], [31], [48]. FGF-2 and FGF-18 stimulate chondrocyte proliferation and have been investigated for cartilage repair [17], [30], [31], [49].

Anti-inflammatory and anti-catabolic gene therapy strategies aim to modulate the inflammatory microenvironment in osteoarthritis and promote cartilage preservation [1], [11], [19], [24], [25],

[30], [31], [46]. IL-1 receptor antagonist (IL-1Ra) blocks the pro-inflammatory effects of IL-1β, a key mediator of cartilage degradation [1], [11], [19], [30], [31]. Tissue inhibitors of metalloproteinases (TIMPs) inhibit matrix metalloproteinases that degrade cartilage ECM [11], [19], [24], [25], [30]. Anti-TNF-α strategies reduce inflammatory signaling and cartilage catabolism [1], [11], [30], [31].

CRISPR-Cas9 gene editing represents a cutting-edge approach for precise genetic modification of cells for cartilage regeneration [13], [19], [30], [31], [46], [48]. CRISPR technology enables targeted gene knockout, insertion, or correction with unprecedented precision [13], [19], [30], [46], [48]. Applications for cartilage regeneration include enhancing chondrogenic potential of MSCs through targeted gene modifications, correcting genetic defects in hereditary cartilage disorders, and engineering inflammation-resistant chondrocytes [13], [19], [30], [46], [48]. A study demonstrated that IGF-1 genome-edited human MSCs exhibited robust anti-arthritogenic effects in a collagen-induced arthritis model [48]. CRISPR-based strategies for stem cell engineering represent a new frontier in musculoskeletal regeneration [13], [46].

Combination gene therapy approaches that deliver multiple therapeutic genes simultaneously or sequentially may provide synergistic benefits [1], [11], [24], [25], [30], [31], [43], [44], [45], [46], [47]. For example, co-delivery of SOX9 and TGF-β has demonstrated enhanced chondrogenic effects compared to single-gene approaches [44], [45], [47]. Temporal control of gene expression through inducible promoter systems enables dynamic regulation of therapeutic gene activity [11], [24], [25], [43], [46].

Clinical translation of cartilage gene therapy faces several challenges, including optimizing vector design and delivery methods, ensuring safety and minimizing immunogenicity, achieving adequate transduction efficiency in the avascular cartilage environment, and navigating complex regulatory requirements [1], [11], [24], [25], [30], [31], [43], [46]. Early-phase clinical trials of gene therapy for osteoarthritis and cartilage repair are underway, with preliminary results demonstrating safety and feasibility [1], [11], [30], [31]. Continued advances in vector technology, biomaterial delivery systems, and gene editing tools are expected to accelerate clinical translation [11], [24], [25], [43], [46].

5.3 Exosome Therapy

Exosome-based therapy represents an innovative cell-free approach for cartilage regeneration that harnesses the paracrine effects of mesenchymal stem cells without the complexities and risks associated with cell transplantation, [28] ,[33], [50], [55], [56], [57]. Exosomes are nanoscale (30-150 nm) extracellular vesicles secreted by cells that contain bioactive cargo including proteins, lipids, mRNAs, and microRNAs, [33], [50], [55]. MSC-derived exosomes

mediate many of the therapeutic effects attributed to MSC therapy, including immunomodulation, anti-inflammatory activity, promotion of cell proliferation and differentiation, and enhancement of matrix synthesis, [33], [50], [55], [56].

MSC-derived exosomes for cartilage regeneration have been isolated from various MSC sources, including bone marrow, adipose tissue, synovium, and umbilical cord, [33], [50], [55]. The composition and biological activity of exosomes vary depending on the parent cell source, culture conditions, and isolation methods , [33], [50]. Exosomes contain growth factors (TGF-β, IGF-1, FGF-2), anti-inflammatory cytokines, matrix metalloproteinase inhibitors, and regulatory microRNAs that collectively promote cartilage repair, [33], [50], [55], [56].

Mechanisms of exosome-mediated cartilage regeneration include modulation of chondrocyte metabolism, reduction of inflammation and oxidative stress, promotion of chondrocyte proliferation and matrix synthesis, inhibition of apoptosis, and recruitment of endogenous progenitor cells, [33], [50], [55]. Exosomal microRNAs play critical roles in regulating gene expression in recipient cells, with specific miRNAs promoting chondrogenic differentiation and inhibiting catabolic processes, [33], [50], [56]. For example, miR-23a-3p-abundant exosomes have demonstrated enhanced cartilage regeneration capacity [56].

Preclinical studies have demonstrated the efficacy of MSC-derived exosomes for treating cartilage defects and osteoarthritis in animal models, [33], [50], [55]. Intra-articular injection of exosomes has shown improvements in cartilage structure, reduced inflammation, decreased pain behavior, and enhanced matrix production, [33], [50]. Exosome therapy has demonstrated comparable or superior efficacy to MSC therapy in some studies, while offering advantages of off-the-shelf availability, reduced immunogenicity, easier storage and handling, and lower risk of tumorigenicity, [33], [50], [55].

Scaffold-mediated exosome delivery enhances therapeutic efficacy by providing sustained, localized release and protecting exosomes from rapid clearance, [55], [56], [57]. Exosome-laden hydrogels, electrospun nanofibers, and 3D-printed scaffolds have been developed for cartilage regeneration applications, [55], [56], [57]. A study demonstrated that sodium alginate hydrogels co-encapsulated with exosomes and bioactive nanofibers accelerated articular cartilage regeneration [55]. GelMA/nanoclay hydrogels releasing miR-23a-3p-abundant exosomes promoted cartilage repair [56]. Three-dimensional printed exosome-reinforced hydrogel scaffolds achieved efficient cartilage and subchondral bone regeneration [57].

Engineered exosomes with enhanced targeting or therapeutic cargo represent an advanced approach for cartilage regeneration [17], [30], [50]. Surface modification of exosomes with targeting peptides or antibodies can enhance cartilage-specific delivery [30], [50]. Charge-

reversed exosomes have been developed for targeted gene delivery to cartilage for osteoarthritis treatment [30]. Loading exosomes with specific therapeutic molecules, genes, or drugs enables customized therapeutic effects [17], [30], [50]. Hybrid exosomes combining gene-editing capabilities with self-renewable lubrication properties have shown promise for osteoarthritis therapy [17].

Transforming growth factor-β family members play important roles in exosome-mediated cartilage regeneration [50]. TGF-β-enriched exosomes promote chondrogenic differentiation and matrix production [50]. Exosomes can be engineered to overexpress specific growth factors or therapeutic proteins to enhance regenerative capacity [17], [30], [50].

Clinical translation of exosome therapy for cartilage regeneration is advancing, with early-phase clinical trials evaluating safety and preliminary efficacy, [33], [50]. Systematic reviews have examined the potential of stem cell conditioned medium secretome (including exosomes) for knee cartilage regeneration, highlighting promising preclinical results and the need for well-designed clinical trials [15]. Challenges for clinical translation include standardization of exosome isolation and characterization methods, optimization of dosing and delivery strategies, ensuring batch-to-batch consistency, and establishing regulatory frameworks for exosome-based products, [33], [50].

5.4 Novel Biomaterials

Novel biomaterials for cartilage regeneration continue to evolve, incorporating advanced design principles, smart functionalities, and biomimetic properties to enhance therapeutic outcomes [20], [27], [39], [40], [41], [42]. Recent innovations focus on developing materials that recapitulate the complex microenvironment of native cartilage, respond dynamically to physiological stimuli, and integrate seamlessly with surrounding tissue [20], [27], [39], [40], [41].

Injectable hydrogels represent a particularly promising class of biomaterials due to their minimally invasive delivery, ability to conform to irregular defect geometries, and capacity to encapsulate cells and bioactive factors [39], [40], [41], [42]. Thermosensitive hydrogels that undergo sol-gel transition at body temperature enable easy injection as a liquid that solidifies in situ [39], [40], [41]. Photocrosslinkable hydrogels allow precise spatial and temporal control of gelation through light exposure [39], [40], [42]. Shear-thinning hydrogels flow under applied stress during injection but rapidly recover mechanical properties after delivery [39], [40], [41]. Advanced hydrogel formulations incorporate multiple functionalities to enhance cartilage regeneration [39], [40], [41], [42]. Dual-network hydrogels combine two interpenetrating polymer networks to achieve superior mechanical strength while maintaining high water

content and biocompatibility [39], [40], [42]. Nanocomposite hydrogels incorporating nanoparticles (nanoclay, carbon nanotubes, graphene oxide, nanohydroxyapatite) enhance mechanical properties, provide controlled release capabilities, and offer additional biological activities [39], [40], [41], [56]. Microenvironment-specific hydrogels designed to mimic the biochemical and biophysical properties of native cartilage ECM promote chondrogenic differentiation and matrix production [57].

Self-healing hydrogels that can autonomously repair damage through dynamic covalent bonds or supramolecular interactions offer potential advantages for long-term durability in the mechanically demanding joint environment [39], [40], [41]. These materials can recover mechanical properties after cyclic loading or injury, potentially extending the functional lifespan of implanted constructs [39], [40].

Decellularized extracellular matrix (dECM) materials derived from native cartilage or other tissues provide a biomimetic scaffold that preserves the complex composition and architecture of natural ECM [39], [40], [41], [42]. Decellularization processes remove cellular components while retaining ECM proteins, glycosaminoglycans, growth factors, and structural organization [39], [40], [41]. dECM materials can be processed into various forms including hydrogels, porous scaffolds, and bioinks for 3D printing [39], [40], [42]. Studies have demonstrated that dECM scaffolds promote chondrogenic differentiation, enhance matrix production, and facilitate tissue integration [39], [40], [41].

Biomimetic mineralized scaffolds for osteochondral regeneration incorporate gradient structures that transition from cartilage-like properties in the superficial region to bone-like properties in the deep region [39], [40], [41], [42]. These scaffolds aim to recapitulate the native osteochondral interface and promote simultaneous regeneration of both cartilage and subchondral bone [39], [40], [42]. Mineral gradients can be achieved through controlled incorporation of calcium phosphate, hydroxyapatite, or bioactive glass [39], [40], [41].

Stimuli-responsive “smart” biomaterials that respond to physiological cues such as pH, temperature, enzymes, or mechanical stress offer dynamic functionality for cartilage regeneration [39], [40], [41], [42]. pH-responsive materials can release therapeutic agents in response to the acidic microenvironment of inflamed or damaged tissue [39], [40]. Enzyme-responsive materials degrade or release cargo in response to matrix metalloproteinases or other enzymes upregulated in osteoarthritis [39], [40], [41]. Mechanically responsive materials can modulate their properties or release bioactive factors in response to joint loading [39], [40], [42].

Conductive biomaterials incorporating conductive polymers or nanomaterials enable electrical stimulation of cells within scaffolds, which has been shown to enhance chondrogenic

differentiation and matrix production [39], [40], [41]. Piezoelectric materials that generate electrical signals in response to mechanical deformation may provide endogenous stimulation during joint movement [39], [40].

Antimicrobial biomaterials incorporating silver nanoparticles, antimicrobial peptides, or antibiotic-releasing systems address the risk of infection following cartilage repair procedures [39], [40], [41]. These materials can provide localized antimicrobial activity while minimizing systemic exposure and resistance development [39], [40].

Nanotechnology-enhanced biomaterials leverage nanoscale features and nanoparticle incorporation to improve cellular interactions, mechanical properties, and therapeutic delivery [20], [39], [40], [41]. Nanostructured surfaces with topographical features mimicking native ECM architecture enhance cell adhesion, proliferation, and differentiation [39], [40], [41]. Nanoparticle-mediated delivery of growth factors, genes, or drugs enables controlled release and targeted delivery [20], [39], [40].

Despite significant advances, challenges remain in translating novel biomaterials to clinical applications [39], [40], [41], [42]. Achieving adequate mechanical strength to withstand joint loading while maintaining biocompatibility and biodegradability requires careful material design [39], [40]. Long-term safety and biocompatibility must be thoroughly evaluated [39], [40], [41]. Scalable manufacturing processes and regulatory approval pathways need to be established [39], [40], [42]. Cost-effectiveness and accessibility are important considerations for clinical adoption [20], [39], [40].

6. CHALLENGES AND LIMITATIONS

Despite significant advances in regenerative cartilage therapies, numerous challenges and limitations must be addressed to achieve widespread clinical translation and optimal patient outcomes [4], [6], [7], [8], [10], [12]. These challenges span biological, technical, regulatory, and economic domains and require multidisciplinary approaches for resolution [4], [6], [7], [10], [12], [22], [23].

Biological challenges include the inherent difficulty of regenerating tissue that fully recapitulates the complex zonal architecture, biochemical composition, and biomechanical properties of native hyaline cartilage [4], [6], [7], [8], [10]. Most current therapies produce fibrocartilage or mixed hyaline-fibrocartilage tissue that is inferior to native cartilage in terms of collagen organization, proteoglycan content, and mechanical strength [4], [6], [7], [10], [12]. Achieving complete integration of regenerated tissue with surrounding native cartilage and underlying subchondral bone remains challenging [6], [7], [8], [10], [22]. The avascular nature

of cartilage limits nutrient delivery and waste removal, constraining the thickness and viability of engineered constructs [4], [6], [7], [8].

Cell source optimization represents an ongoing challenge, with debates regarding the relative merits of chondrocytes versus various MSC sources [2], [3], [4], [6], [7], [14]. Chondrocytes produce cartilage-specific matrix but are limited in availability, prone to dedifferentiation during expansion, and subject to donor site morbidity [2], [4], [6], [7]. MSCs offer advantages of multipotency and paracrine effects but exhibit variable chondrogenic potential depending on source, donor age, and culture conditions [2], [3], [4], [6], [7], [14]. Standardization of cell isolation, expansion, and characterization protocols is needed to ensure consistent quality and potency [2], [3], [4], [6], [7], [52].

Heterogeneity of MSC populations poses significant challenges for reproducibility and clinical translation [52], [54]. MSCs exhibit substantial variability in differentiation capacity, proliferation rate, immunophenotype, and paracrine factor secretion depending on donor characteristics, tissue source, passage number, and culture conditions [52], [54]. Strategies to manage MSC heterogeneity include improved cell selection and sorting methods, standardized culture protocols, potency assays, and genetic or epigenetic modifications to enhance desired properties [52], [54].

Standardization and quality control of regenerative therapies remain critical challenges [4], [6], [7], [10], [12], [22], [23]. Significant variability exists in cell preparation methods, scaffold materials, growth factor formulations, and surgical techniques across different centers and studies [4], [6], [7], [10], [22]. This heterogeneity complicates interpretation of clinical trial results and limits the ability to establish evidence-based treatment guidelines [4], [6], [7], [22], [23]. Development of standardized protocols, quality control assays, and potency testing is essential for ensuring consistent therapeutic outcomes [4], [6], [7], [10], [52].

Cost-effectiveness represents a significant barrier to widespread adoption of regenerative cartilage therapies [4], [6], [7], [10], [12], [22], [23]. Cell-based therapies such as ACI/MACI require expensive cell culture facilities, specialized personnel, and two-stage surgical procedures, resulting in high treatment costs [4], [6], [7], [10], [22]. While these therapies may be cost-effective compared to joint replacement surgery in young patients, the upfront costs limit accessibility [4], [6], [7], [22], [23]. Development of more efficient manufacturing processes, off-the-shelf allogeneic products, and streamlined delivery methods could improve cost-effectiveness [4], [6], [7], [10].

Regulatory pathways for advanced therapy medicinal products (ATMPs) including cell therapies, gene therapies, and tissue-engineered products are complex and vary across

jurisdictions [4], [6], [7], [10], [12], [54]. Navigating regulatory requirements for product characterization, manufacturing standards, preclinical testing, and clinical trial design requires substantial resources and expertise [4], [6], [7], [10], [54]. Harmonization of regulatory frameworks and development of clear guidance for regenerative medicine products would facilitate clinical translation [4], [6], [7], [10].

Long-term durability of regenerative cartilage therapies remains uncertain, with limited data beyond 10-15 years for most approaches [4], [6], [7], [10], [12], [13], [21], [27]. Questions persist regarding whether regenerated tissue can withstand decades of joint loading without deterioration [4], [6], [7], [10], [13]. Long-term follow-up studies are needed to determine the true durability of regenerative therapies and identify factors associated with sustained success or late failure [4], [6], [7], [13], [21], [27].

Patient selection and outcome prediction represent important challenges for optimizing treatment algorithms [4], [6], [7], [10], [12], [22], [23]. While general guidelines exist regarding defect size, location, patient age, and concomitant pathology, precise prediction of individual patient outcomes remains difficult [4], [6], [7], [10], [22]. Development of biomarkers, imaging techniques, and predictive models to identify patients most likely to benefit from specific therapies would improve treatment selection and outcomes [4], [6], [7], [10], [23].

Integration of emerging technologies such as 3D bioprinting, gene therapy, and exosome therapy into clinical practice faces numerous hurdles [4], [6], [7], [10], [12], [34], [37], [43], [46], [49], [50]. These technologies require validation in large-scale clinical trials, establishment of manufacturing standards, development of quality control methods, and demonstration of cost-effectiveness [4], [6], [7], [10], [34], [37], [43], [46], [49], [50]. Interdisciplinary collaboration among clinicians, scientists, engineers, regulators, and industry partners is essential for successful translation [4], [6], [7], [10], [12].

7. CONCLUSIONS

Regenerative therapies for articular cartilage have advanced significantly over the past three decades, evolving from experimental concepts to clinically established treatments that offer meaningful improvements in patient outcomes [1], [2], [4], [6], [7], [10], [12]. Cell-based approaches, particularly matrix-associated autologous chondrocyte implantation and mesenchymal stem cell therapy, have demonstrated superior efficacy compared to traditional marrow stimulation techniques for focal cartilage defects [1], [2], [22], [23], [24], [25]. Long-term follow-up studies confirm the durability of these treatments, with sustained improvements

in pain, function, and quality of life extending to 10-15 years in appropriately selected patients [1], [9], [13], [21], [27], [29].

The field continues to evolve rapidly, with emerging technologies such as 3D bioprinting, gene therapy, exosome-based treatments, and novel biomaterials offering unprecedented opportunities for precise control over tissue regeneration [4], [6], [7], [10], [12], [30], [31], [34], [37], [43], [46], [49], [50]. These innovations promise to address current limitations by enabling patient-specific constructs, sustained delivery of therapeutic factors, and recapitulation of native cartilage architecture [4], [6], [7], [10], [34], [37], [43], [46], [49], [50]. However, translation of these technologies from bench to bedside requires continued research, standardization, and validation in rigorous clinical trials [4], [6], [7], [10], [12], [34], [37], [43], [46], [49], [50].

Critical challenges remain in optimizing cell sources, standardizing protocols, improving long-term durability, reducing costs, and navigating regulatory pathways [4], [6], [7], [10], [12], [22], [23], [52], [54]. Addressing these challenges will require multidisciplinary collaboration among clinicians, scientists, engineers, regulators, and industry partners [4], [6], [7], [10], [12]. Comparative effectiveness research, long-term outcome studies, and mechanistic investigations are essential for refining treatment algorithms and identifying patients most likely to benefit from specific therapies [4], [6], [7], [10], [22], [23].

The future of cartilage regeneration lies in personalized medicine approaches that integrate patient-specific factors, advanced diagnostics, and tailored therapeutic strategies [4], [6], [7], [10], [12], [30], [31]. Combination therapies that leverage multiple modalities—such as cell-based treatments with growth factors, gene therapy, and biomaterial scaffolds—may provide synergistic benefits and superior outcomes [4], [6], [7], [10], [30], [31], [43], [46]. As the field continues to mature, regenerative therapies have the potential to transform the treatment paradigm for cartilage injuries and osteoarthritis, offering biological restoration rather than symptomatic management or joint replacement [4], [6], [7], [10], [12].

8. AUTHOR CONTRIBUTION STATEMENT

All authors contributed to the conception, literature review, manuscript preparation, and critical revision of this work. All authors approved the final version for submission.

9. ETHICS STATEMENT

This review article synthesizes published literature and does not involve primary research with human subjects or animals. Therefore, ethics committee approval was not required.

10. CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest related to this work.

11. DISCLOSURE

The authors have no relevant financial or non-financial interests to disclose. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

12. DECLARATION OF THE USE OF GENERATIVE AI

In preparing this work, the author(s) used Google Gemini for the purpose of linguistic correction, structural editing, and verification of bibliographic consistency. After using this tool/service, the author(s) have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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