E-ISSN: 3068-3726
Journal of Orthopaedic Science and Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Review Article

Orthoregeneration in Modern Orthopedic: Biological Strategies for Musculoskeletal Repair and Regeneration

Bilal Mohamad Ali Obeid[1*]

[1]Orthopedic Department, Gardenia Medical Centre, Doha, Qatar

***Correspondence author:** Bilal Mohamad Ali Obeid, MD, MBA, PHD, FACS, Orthopedic Department, Gardenia Medical Centre, Doha, Qatar; Email: biobeid6@hotmail.com

Citation: Obeid BMA. Orthoregeneration in Modern Orthopedic: Biological Strategies for Musculoskeletal Repair and Regeneration. J Ortho Sci Res. 2025;6(2):1-12. https://doi.org/10.46889/JOSR.2025.6205

Received Date: 22-05-2025

Accepted Date: 09-06-2025

Published Date: 16-06-2025

Abstract

Orthoregeneration has emerged as a transformative paradigm in regenerative medicine, shifting the focus from mechanical interventions to biologically driven strategies for musculoskeletal tissue repair. This approach leverages the therapeutic potential of Mesenchymal Stem Cells (MSCs), growth factors and bioengineered scaffolds to overcome the inherent limitations of traditional orthopedic treatments. While preclinical and early clinical studies demonstrate promise, the field faces significant challenges in standardization, mechanistic clarity and reproducible efficacy-issues that must be addressed to solidify its clinical relevance.

This review critically evaluates the biological foundations, clinical applications and emerging technologies in orthoregeneration, with a focus on tissue-specific strategies and the synergistic integration of biologics and physical therapies. Through an integrative analysis of peer-reviewed literature, we examine the roles of MSCs derived from bone marrow, adipose tissue and umbilical cord, alongside orthobiologics such as Platelet-Rich Plasma (PRP), extracellular vesicles, ozone therapy, gene therapy and scaffold-based tissue engineering. These modalities are assessed for their efficacy in regenerating bone, cartilage, tendon, ligament and intervertebral disc tissues.

Current evidence suggests that MSC-based therapies promote regeneration through immunomodulation, extracellular matrix remodeling and cellular differentiation. Adjunctive treatments, including PRP and ozone therapy, appear to enhance these effects, though their clinical benefits remain inconsistently documented. Tissue-specific approaches, such as Matrix-Induced Autologous Chondrocyte Implantation (MACI) and scaffold-assisted bone regeneration, show potential but are hindered by variability in outcomes and a lack of standardized protocols.

Despite these advances, the translation of orthoregenerative therapies into routine practice is hampered by unresolved questions. The mechanisms underlying MSC homing and differentiation, the optimal combinations of biologics and the long-term durability of engineered tissues demand further investigation. Moreover, the field must reconcile the gap between promising *in-vitro* results and the heterogeneous responses observed in clinical settings.

Orthoregeneration represents a multidisciplinary frontier in addressing complex musculoskeletal disorders. Its success will depend on rigorous mechanistic studies, standardized therapeutic protocols and robust clinical validation-steps essential for establishing these strategies as reliable alternatives to conventional treatments.

Keywords: Orthoregeneration; Mesenchymal Stem Cells (MSCs); Platelet-Rich Plasma (PRP); Tissue Engineering; Cartilage Repair; Bone Regeneration; Growth Factors; Extracellular Vesicles (EVs); Scaffolds; Orthobiologics; Ozone Therapy

Abbreviations

MSCs: Mesenchymal Stem Cells; BM-MSCs: Bone Marrow-derived Mesenchymal Stem Cells; AT-MSCs: Adipose Tissue-derived Mesenchymal Stem Cells; UC-MSCs: Umbilical Cord-derived Mesenchymal Stem Cells; UCB-MSCs: Umbilical Cord Blood-derived Mesenchymal Stem Cells; PRP: Platelet-Rich Plasma; L-PRP: Leukocyte-rich Platelet-Rich Plasma; P-PRP: Leukocyte-poor Platelet-Rich Plasma; PRF: Platelet-Rich Fibrin; GFC: Growth Factor Concentrate; EVs: Extracellular Vesicles; ECM: Extracellular Matrix; MACI: Matrix-induced Autologous Chondrocyte Implantation; ACI: Autologous Chondrocyte

Implantation; TGF-β: Transforming Growth Factor-beta; IGF-1: Insulin-like Growth Factor-1; VEGF: Vascular Endothelial Growth Factor; PDGF: Platelet-Derived Growth Factor; FGF-2: Fibroblast Growth Factor-2; IL-1, IL-6, IL-10, IL-11: Interleukin-1, -6, -10, -11; TNF-α: Tumor Necrosis Factor-alpha; IFN-γ: Interferon-gamma; SOX9: SRY-Box Transcription Factor 9 (critical for chondrogenesis); HIF1: Hypoxia-Inducible Factor 1; Nrf2: Nuclear Factor Erythroid 2-Related Factor 2 (antioxidant pathway); PI3K/Akt: Phosphoinositide 3-Kinase/Protein Kinase B (cell survival pathway); MAPK: Mitogen-Activated Protein Kinases (signaling pathway); ROS: Reactive Oxygen Species; OA: Osteoarthritis; 3D: Three-Dimensional

Introduction

Orthoregeneration refers to the restoration and regeneration of musculoskeletal tissues by combining biomaterials, growth factors and stem cells particularly Mesenchymal Stem Cells (MSCs). Given the inherently limited regenerative capacity of musculoskeletal tissues, there is a compelling need for more sophisticated, biologically-informed strategies. Tissue engineering has responded to this challenge with the development of bioinspired scaffolds designed to emulate the structural and biochemical cues of native tissues, thereby promoting lineage-specific cell differentiation and enhancing tissue integration [1,2]. However, despite promising *in-vitro* outcomes, clinical translation remains constrained by the complexity of replicating an optimal *in-vivo* microenvironment. It is increasingly evident that the success of such therapies is not solely dependent on the implanted cells or scaffolds, but on modulating host responses particularly by minimizing inflammation and establishing anabolic signaling pathways [3].

The use of orthobiologics, including MSCs and various growth factors, has been explored as a means to restore tissue microarchitecture and function. While preliminary findings suggest these agents may improve clinical outcomes, the variability in therapeutic efficacy across studies raises questions about standardization, dosing and long-term impact [4]. Nonetheless, the convergence of bioengineering, cell therapy and molecular biology represents a significant evolution in regenerative medicine, aiming not merely to repair, but to biologically restore musculoskeletal function [5].

This evolution reflects a paradigm shift in orthopedic treatment philosophy-from traditional mechanical repair to biologically augmented regeneration. Historically, interventions were largely focused on structural stabilization, often without regard for the underlying biological milieu. Such approaches were particularly inadequate for tissues like cartilage and ligaments, which have limited intrinsic healing potential [6,7]. In contrast, modern regenerative therapies aim to enhance the body's own reparative mechanisms, often by delivering MSCs and bioactive molecules directly to the injury site [8]. However, while tissue engineering technologies especially those involving 3D bioprinting and biomimetic scaffolds have introduced groundbreaking possibilities, their efficacy in complex clinical environments remains under critical examination [9,10].

The integration of biological strategies into orthoregeneration is particularly pertinent for chronic or multifactorial injuries that fall outside the effective reach of conventional orthopedic treatments. Regenerative modalities, especially orthobiologics, have demonstrated encouraging outcomes in terms of tissue repair and symptom relief. Yet, the current enthusiasm must be tempered by the lack of large-scale, long-term studies validating these benefits across diverse patient populations. In foot and ankle pathologies, for instance, the clinical utility of interventions such as cartilage grafting, MSC injections and PRP remains under scrutiny due to inconsistent protocols and outcomes [11]. Similarly, in the management of elbow and upper extremity disorders, agents like hyaluronic acid, botulinum toxin and MSCs are employed with varying success, often lacking rigorous comparative data [12]. Although regenerative therapies are increasingly applied in knee osteoarthritis and ligament repair, the absence of standardized treatment protocols continues to limit reproducibility and broader clinical adoption [13]. The spine, too, has become a frontier for biologic treatments, with early results suggesting symptomatic improvement following MSC and PRP injections. Yet these findings require cautious interpretation pending more robust evidence [14].

In conclusion, the field of orthopedic regenerative medicine is advancing through novel applications of stem cells and engineered scaffolds. Despite the transformative potential these strategies hold, their widespread implementation is contingent upon resolving critical issues related to biological variability, clinical standardization and mechanistic understanding. The current body of research underscores both the promise and the limitations of these emerging therapies, highlighting the need for continued rigorous inquiry [15].

The Biological Basis of Orthoregeneration

Orthoregeneration addresses the regeneration of musculoskeletal tissues bone, cartilage, tendons, ligaments and intervertebral discs-through the strategic combination of biological therapies and engineering techniques. Among these tissues, bone and cartilage have drawn the most research attention due to their complex healing requirements and high clinical burden.

Tissue-Specific Regeneration Dynamics

Bone possesses an innate regenerative ability, transitioning from woven to lamellar architecture under mechanical stimuli to restore integrity [16]. However, in cases of large defects or systemic disease, endogenous healing becomes inadequate, necessitating exogenous biological augmentation. Conversely, articular cartilage, particularly in load-bearing joints such as the knee and shoulder, suffers from poor vascularization and limited cell turnover. Treatments employing orthobiologics-such as hyaluronic acid, Platelet-Rich Plasma (PRP) and Mesenchymal Stem Cells (MSCs) have shown varying degrees of success in promoting matrix repair and modulating inflammation, though clinical consistency remains elusive [17,18].

Tendon and ligament regeneration remains a challenge due to their fibrous nature and low cellularity. Cell-based approaches using tenocyte-like cells and MSCs aim to improve structural organization and reduce chronic fibrosis [19]. In the intervertebral disc, regenerative efforts focus on chondrogenic and MSC therapies to restore matrix hydration and mitigate degeneration, but long-term efficacy and delivery optimization are still under active investigation [20]. Despite growing interest and clinical trials, the reproducibility of outcomes in orthoregeneration remains uneven, emphasizing the need for standardized protocols, robust clinical endpoints and a deeper understanding of patient-specific responses (Table 1) [21,22].

Tissue	Key Challenges	Biological Interventions	Major Limitations
Bone	Structural restoration	MSCs, BMPs, scaffold integration	Delayed healing in large defects [16]
Cartilage	Avascularity, limited repair	PRP, HA, MSCs	Variable matrix integration [17,18]
Tendon/Ligament	Low cell turnover, fibrosis	MSCs, tenocytes	Suboptimal mechanical properties [19]
Intervertebral Disc	Degeneration, low hydration	Chondrogenic cells, MSCs	Delivery challenges, relapse risk [20]

Table 1: Overview of tissue targets and regenerative strategies.

Cellular Contributors: MSCs, Chondrocytes and Tenocytes

Cell-based therapies form the backbone of musculoskeletal regenerative medicine, with Mesenchymal Stem Cells (MSCs) occupying a central role due to their multipotency, paracrine signaling and immunomodulatory capabilities. However, while the theoretical versatility of MSCs is widely recognized, their therapeutic translation is far from straightforward.

Mesenchymal Stem Cells (MSCs): Promise and Pitfalls

MSCs are attractive therapeutic agents for musculoskeletal repair because of their ability to differentiate into multiple mesodermal lineages-including chondrocytes and tenocytes-as well as their secretion of bioactive factors that modulate inflammation, support angiogenesis and remodel extracellular matrix [23,24]. These properties position MSCs as critical mediators in the repair of cartilage and tendon tissues, both of which lack robust intrinsic healing capacity.

Yet, the assumption that MSC-based therapies offer universally consistent outcomes has been challenged by clinical variability. Differences in donor age, tissue source (e.g., bone marrow, adipose, synovium) and *in-vitro* expansion protocols lead to significant heterogeneity in cellular behavior and therapeutic efficacy [27]. Furthermore, the mechanisms governing MSC homing, engraftment and phenotypic stability *in-vivo* remain only partially understood, presenting key obstacles to predictability and reproducibility in clinical outcomes [28].

Chondrocytes and Tenocytes: Specialized but Limited

Chondrocytes, the resident cells of cartilage, maintain extracellular matrix homeostasis through balanced production of proteoglycans and type II collagen. However, during *in-vitro* expansion-a necessary step for most clinical applications chondrocytes is prone to dedifferentiation, losing their phenotypic profile and chondrogenic potential [25]. This compromises their utility for Autologous Chondrocyte Implantation (ACI) and limits scalability.

Tenocytes, by contrast, are specialized fibroblasts critical to the structural integrity of tendons. Efforts to drive MSCs toward a tenogenic phenotype have shown preclinical promise, yet protocols for consistent differentiation and mechanical integration remain underdeveloped and unstandardized (Table 2) [26].

Cell Type	Primary Function	Advantages	Key Limitations
MSCs	Differentiation, immunomodulation	Multi-lineage potential, trophic effects, immunoprivilege	Source variability, poor homing, limited *in-vivo* stability [23,24,27,28]
Chondrocytes	Matrix synthesis and cartilage integrity	Native cartilage phenotype	Dedifferentiation during culture, scalability issues [25]
Tenocytes	Tendon ECM maintenance and repair	High collagen production, tissue-specific functions	Limited availability, challenges in MSC-to-tenocyte induction [26]

Table 2: Comparative summary of cellular contributors in orthoregeneration.

Molecular Mediators: Growth Factors, Cytokines and the Extracellular Matrix

Musculoskeletal regeneration is driven by a complex and interdependent network of growth factors, cytokines and Extracellular Matrix (ECM) components. These molecular mediators coordinate critical aspects of tissue repair, including cell proliferation, migration, differentiation and matrix remodeling. While their roles in physiological healing are well characterized, translating these insights into controlled and effective therapies remains a significant scientific and regulatory challenge.

Growth Factors: Biochemical Activators with Clinical Complexity

Key growth factors-TGF-β, BMPs, IGF, PDGF and FGFs-are fundamental to orchestrating the cellular events of fracture healing. They facilitate progenitor cell activation, direct chemotaxis and angiogenesis and stimulate extracellular matrix synthesis. Despite their essential biological functions, the therapeutic application of recombinant growth factors has faced critical barriers, including short half-lives, dose-dependent toxicity and potential for ectopic tissue formation. Clinical trials using BMPs, for instance, have raised concerns about inflammation, heterotopic ossification and inconsistent efficacy [29].

Cytokines: Inflammatory Gatekeepers with Dual Potential

Pro-inflammatory cytokines such as IL-1, IL-6 and IL-11 play integral roles in the early inflammatory phase of wound healing by modulating immune responses and stimulating tissue turnover. However, their sustained or dysregulated activity can hinder resolution and promote fibrotic remodeling or chronic inflammation. While cytokine modulation offers a strategy to fine-tune tissue repair, the narrow therapeutic window and systemic effects present a substantial translational hurdle [29].

Extracellular Matrix: Structural Scaffold and Signaling Reservoir

The ECM serves not merely as a physical framework but also as a dynamic signaling platform that modulates cellular behavior. ECM components such as heparan sulfate, tenascin-C and laminin interact with growth factors like FGF-2, enhancing their local stability and bioavailability [30]. These interactions can potentiate signal transduction via specific receptors, guiding processes such as fibroblast migration and matrix deposition. However, engineering synthetic ECM analogs that recapitulate these biochemical and mechanical cues remains a formidable challenge.

Pathway Activation and Homeostatic Balance

Growth factors and cytokines function via receptor-mediated pathways that activate intracellular signaling cascades and modulate gene expression-events central to effective wound healing and tissue regeneration [31]. However, disturbances in these signaling networks, particularly during the inflammatory phase, can derail regenerative processes, leading to chronic wounds or fibrosis. This underscores the precarious balance between activation and resolution of tissue responses (Table 3) [32].

Mediator Type	Examples	Primary Roles	Translational Challenges
Growth Factors	TGF-β, BMPs, IGF, PDGF, FGFs	Progenitor activation, angiogenesis, ECM production	Short half-life, off-target effects, ectopic calcification
Cytokines	IL-1, IL-6, IL-11	Inflammation modulation, immune cell recruitment	Risk of fibrosis, chronic inflammation, narrow therapeutic window
ECM Components	Heparan sulfate, tenascin-C, laminin	Growth factor binding, cell migration and adhesion	Synthetic ECM replication, degradation control

Table 3: Summary of molecular mediators in musculoskeletal regeneration.

Key Interventions and Techniques

MSCs: Bone Marrow, Adipose and Umbilical Sources

Mesenchymal Stem Cells (MSCs) from bone marrow, adipose tissue and umbilical sources represent central pillars in orthoregenerative strategies, yet their comparative efficacy remains context-dependent and inadequately resolved. Bone Marrow-Derived MSCs (BM-MSCs), while historically preferred due to their well-documented osteogenic differentiation capacity, are limited by invasive harvesting procedures and donor-dependent variability-factors that constrain their translational scalability and consistency in therapeutic outcomes.

Adipose Tissue-derived MSCs (AT-MSCs), often lauded for their high clonogenicity and angiogenic support, offer an attractive alternative, particularly in early tissue remodeling phases. However, their regenerative potency in orthopedics has not been uniformly demonstrated, with discrepancies in preclinical and clinical performance suggesting an underlying heterogeneity in cellular quality and bioactivity [33].

Umbilical cord-derived MSCs (UC-MSCs), including those from cord blood and Wharton's jelly, have emerged as biologically potent candidates due to their superior proliferative dynamics, minimal senescence and immunological naivety [34]. In tendon regeneration, UC-MSCs have shown greater tenogenic differentiation and matrix organization relative to BM-MSCs, pointing to their potential advantage in certain niche applications [35]. Nevertheless, such findings are derived predominantly from preclinical studies and their translatability to human models remains insufficiently substantiated.

Despite their biological promise, all MSC types face a shared limitation: the transient and often unpredictable nature of their therapeutic impact in chronic conditions like osteoarthritis. While short-term functional improvements have been reported, long-term durability and mechanistic clarity remain elusive [36]. Until robust head-to-head clinical trials and standardized cell characterization protocols are established, the selection of MSC source will continue to be guided more by logistical feasibility than by definitive evidence of superior clinical efficacy.

Extracellular Vesicles (EVs) / Exosomes

Extracellular vesicles (EVs) and particularly exosomes, have emerged as compelling candidates in orthoregenerative therapies. Their appeal lies largely in the potential to recapitulate the beneficial paracrine effects of parent cells most notably MSCs without the inherent risks of cell-based interventions such as tumorigenicity or immunogenic complications. While this cell-free approach offers an attractive alternative, it is not without significant caveats. Chief among these is the persistent ambiguity regarding the standardization of isolation protocols and the functional reproducibility of exosome preparations across studies and production batches.

Exosomes are nano-sized, membrane-enclosed particles secreted by a variety of cell types. They encapsulate a diverse payload of proteins, microRNAs and lipids reflective of their cellular origin, which significantly influences their downstream biological activity. MSC-derived exosomes, for example, have demonstrated regenerative potential across a spectrum of non-orthopedic conditions including liver fibrosis, pulmonary diseases and myocardial injury-indicating their broader systemic bioactivity [37]. However, extrapolating these findings to musculoskeletal tissues is not straightforward. The heterogeneous nature of exosome content, even among MSCs from different sources or donors, poses challenges for reproducibility and mechanistic predictability.

Further complicating their clinical deployment is the issue of cargo engineering. While the ability to enrich exosomes with specific microRNAs or proteins offers customization for disease-specific applications, this bioengineering raises new regulatory questions. Unlike small-molecule drugs or recombinant proteins, exosomes lack a well-defined pharmacokinetic profile and their mechanisms of action remain only partially elucidated. This uncertainty undermines efforts to meet safety and efficacy benchmarks required for clinical translation [38].

In addition to regulatory complexity, scalability remains a formidable barrier. Manufacturing exosomes at clinical-grade quality and quantity, with consistent potency, is still an unmet challenge. Current bioprocessing techniques are labor-intensive and yield low volumes, impeding widespread clinical application. Furthermore, characterization standards for exosome purity, cargo integrity and batch-to-batch consistency have yet to be universally adopted.

Platelet-Rich Plasma (PRP) Formulations

Platelet-Rich Plasma (PRP) therapies including Leukocyte-rich PRP (L-PRP), leukocyte-Poor PRP (P-PRP), Platelet-Rich Fibrin (PRF) and Growth Factor Concentrates (GFC) represent a diverse yet inconsistently standardized class of biologics in orthopedic applications. Despite their wide clinical adoption, the heterogeneity of PRP composition and ambiguous regulatory classification continue to limit rigorous interpretation of their therapeutic value.

L-PRP formulations, enriched with both platelets and leukocytes, are designed to leverage inflammatory signaling for early tissue repair. While this approach theoretically supports immunomodulation and subsequent regeneration, the presence of leukocytes also introduces variability in cytokine release, raising concerns about potential catabolic effects in certain inflammatory conditions. Conversely, P-PRP, with reduced leukocyte content, is thought to favor anabolic responses, promoting type II collagen and aggrecan synthesis key targets in cartilage restoration [39]. However, the actual clinical relevance of leukocyte content remains debated, with some studies reporting equivalent long-term outcomes in knee osteoarthritis regardless of PRP subtype [40].

One of the most underexamined aspects of PRP therapy is the inconsistency in growth factor release kinetics. Factors such as Fibroblast Growth Factor-2 (FGF-2), Vascular Endothelial Growth Factor (VEGF) and Transforming Growth Factor-Beta (TGF-β) exhibit time-sensitive activity profiles that affect synovial cell behavior and hyaluronic acid production [41]. Yet, most clinical protocols overlook this dynamic aspect, treating PRP as a biologically static entity. Without tailoring PRP formulations to the temporal demands of specific tissue types and injury phases, therapeutic efficacy is likely to remain suboptimal [42].

At the molecular level, key bioactive constituents of PRP include Platelet-Derived Growth Factor (PDGF), TGF-β, Insulin-Like Growth Factor-1 (IGF-1) and VEGF. PDGF enhances early wound healing by recruiting fibroblasts and macrophages and stimulating collagen synthesis [43]. VEGF is indispensable for neovascularization, but its effect may be transient and heavily context-dependent [44]. TGF-β supports matrix remodeling and cell migration, although it can paradoxically contribute to fibrosis under chronic exposure. IGF-1 aids fibroblast activation and collagen production, yet its temporal window of action remains narrow and susceptible to degradation [45].

When PRP is combined with Mesenchymal Stem Cells (MSCs), a synergistic enhancement of regenerative potential is observed. This pairing amplifies MSC survival, proliferation and lineage-specific differentiation through a favorable biochemical milieu provided by PRP-derived growth factors such as PDGF, TGF-β and VEGF [46]. MSCs further contribute by modulating local immune responses and differentiating into tissue-specific phenotypes [47].

Notably, PRP appears to upregulate genes involved in MSC migration, adhesion and proliferation, including ESM1, PDGFB and ITGA6, while also stimulating exosome release-another mechanism implicated in immunoregulation and angiogenesis [48]. These interactions engage core intracellular signaling pathways such as PI3K/Akt and MAPK, both critical to MSC fate determination and function [49]. Additionally, PRP induces metabolic shifts in MSCs, enhancing biosynthetic activity and upregulating pathways related to amino acid and lipid metabolism, thus priming the cells for active tissue reconstruction [48].

Ozone Therapy

Ozone therapy has gained traction in orthoregeneration, particularly for Osteoarthritis (OA) and cartilage-related disorders, due to its reported analgesic, anti-inflammatory and antioxidant properties. While these effects are frequently cited in support of its clinical utility, a closer inspection reveals a substantial gap between mechanistic promise and standardized therapeutic implementation. Despite preliminary evidence of improved joint function and pain mitigation, the biological mechanisms underpinning ozone's effects remain only partially delineated and clinical application is often hampered by protocol variability and limited comparative data [50].

Biochemically, ozone exerts its therapeutic actions by inducing transient oxidative stress that stimulates endogenous antioxidant defense systems. This includes the upregulation of key enzymes such as Glutathione (GSH), Superoxide Dismutase (SOD) and Catalase (CAT), which serve to mitigate Reactive Oxygen Species (ROS) accumulation and restore redox homeostasis [51]. However, the threshold between therapeutic and cytotoxic oxidative stress is narrow, raising questions about dosage standardization and long-term safety, especially with repeated intra-articular applications.

Its immunomodulatory capacity, particularly the suppression of pro-inflammatory mediators like IL-6, IL-1β and TNF-α, suggests a favorable environment for tissue regeneration [52]. Nevertheless, the precise kinetics and durability of this modulation remain under-characterized *in-vivo*. Similarly, ozone's ability to stimulate IL-2 and IFN-γ, while potentially beneficial in acute responses, could have unintended consequences in autoimmune-prone or systemically inflamed individuals [53]. The therapy's enhancement of oxygenation and blood flow is theoretically advantageous for tissue metabolism and healing [54], but this physiological benefit has not been conclusively validated across patient populations or injury types.

The integration of ozone therapy with Mesenchymal Stem Cells (MSCs) has been proposed as a synergistic strategy, aiming to augment MSC survival, differentiation and trophic signaling. MSCs are inherently capable of regenerating bone and cartilage structures through both direct differentiation and paracrine mechanisms [55]. When combined with ozone, these cells exhibit upregulation of genes such as SOX9 and HIF-1, both pivotal in chondrogenesis and adaptation to hypoxia [56]. However, these findings are largely preclinical and extrapolation to human pathologies must be approached with caution.

Evidence also suggests that ozone enhances subchondral bone repair and promotes vascularization by increasing trabecular bone volume, yet the reproducibility of these outcomes under clinical conditions is uncertain [57]. The interplay between ozone and MSC-derived exosomes or other secretory elements remains mechanistically attractive but poorly defined in terms of dose-response and temporal dynamics [58,59].

Importantly, the activation of the Nrf2 pathway by ozone represents a critical link between redox signaling and MSC functionality, potentially enhancing therapeutic efficacy by reducing oxidative cellular damage [51,60]. However, the precise modulation of this pathway, especially in chronic or comorbid populations, demands further scrutiny.

Ozone autohemotherapy-a systemic application increases key growth factors such as VEGF, TGF-β and PDGF [61]. These factors, already abundant in PRP formulations, suggest a rationale for combining ozone with PRP to potentiate regenerative outcomes. Yet, despite promising *in-vitro* and animal data, clinical trials assessing the combined use of PRP and ozone remain scarce, lacking rigorous controls and long-term outcome metrics [60-62].

Grafts: Autografts, Allografts and Synthetic Scaffolds

Grafting strategies remain a foundational component of orthopedic regeneration, yet each modality-autografts, allografts and synthetic scaffolds-carries distinct trade-offs that challenge their broad applicability and standardization. While autografts are often hailed as the gold standard due to their intrinsic osteoinductive, osteogenic and osteoconductive properties, their clinical use is not without caveats. The morbidity associated with donor site harvest, limited graft volume and variability in biological activity depending on patient factors significantly restrict their scalability and long-term viability as a universal solution.

Allografts offer a compelling structural alternative, mitigating the morbidity of autologous tissue harvest. However, their immunogenic profile and the potential for disease transmission introduce both safety concerns and regulatory complications [63]. Moreover, the processing methods used to sterilize and decellularize allografts essential for safety often compromise their

biomechanical integrity and diminish their biological activity. This trade-off underscores a persistent dilemma: safety versus regenerative efficacy.

Synthetic scaffolds, developed to circumvent the limitations of biologic grafts, are engineered to replicate the mechanical and architectural properties of native bone or soft tissue. While they offer unmatched design flexibility and are free from immunogenic or infectious risks, their regenerative capacity is inherently limited by the absence of living cells or native growth factors. Consequently, these materials are often reliant on secondary augmentation such as incorporation of bioactive molecules or stem cells-to achieve meaningful osteointegration or tissue remodeling [60]. However, this biofunctionalization introduces additional complexity in terms of manufacturing consistency, cost and regulatory classification.

Despite their potential, synthetic scaffolds remain largely empirical in their clinical implementation. There is a lack of consensus on the optimal composition, degradation rate and surface architecture needed to support specific tissue types or pathologies. Without standardized benchmarks for mechanical performance and biological compatibility, their role in orthoregeneration remains promising but not yet fully substantiated.

ACI: Matrix-Based Cartilage Restoration

Matrix Autologous Chondrocyte Implantation (MACI), as a third-generation advancement of Autologous Chondrocyte Implantation (ACI), has been widely promoted as a refined technique for addressing full-thickness articular cartilage defects. By employing a collagen membrane pre-seeded with autologous chondrocytes, MACI offers technical advantages over earlier ACI iterations, such as eliminating the need for periosteal flaps and reducing complications like graft hypertrophy. Despite these procedural improvements, the assumption that MACI represents a definitive solution for cartilage repair warrants closer scrutiny.

Although clinical studies have reported favorable mid- to long-term outcomes for MACI in the knee especially in lesions of medium to large size the actual superiority of this approach over alternative techniques is less clear-cut [65]. Much of the supporting evidence originates from trials with limited cohort sizes and variable methodological rigor. Moreover, patient-reported outcome measures, though generally improved, do not always correlate with durable tissue integration or restoration of native cartilage biomechanics.

A systematic review and meta-analysis comparing MACI with other restoration techniques, including osteochondral autograft transplantation, concluded that while MACI does lead to significant functional and pain-related improvements, it does not offer a statistically superior benefit over competing interventions [61]. This lack of differentiation raises concerns about cost-effectiveness, particularly given the logistical complexity and resource intensity of MACI including the need for two-stage procedures, chondrocyte expansion and scaffold implantation.

Furthermore, the biological underpinnings of MACI remain incompletely understood. Chondrocytes, when expanded in vitro, risk dedifferentiation and phenotypic drift, potentially compromising their capacity to generate durable hyaline-like cartilage. The long-term behavior of the implanted constructs in weight-bearing joints, especially under high mechanical stress, is still under investigation and the potential for fibrocartilage formation instead of true hyaline cartilage remains a critical limitation.

Gene Therapy (Emerging)

Gene therapy is frequently positioned as a next-generation tool in orthoregenerative medicine, offering theoretical precision and durability that conventional therapies often lack. By enabling localized, long-term modulation of specific biological pathways, gene therapy holds promise for musculoskeletal repair across diverse tissue types including bone, tendon, cartilage and muscle [67]. However, this emerging field is not without substantial translational and practical barriers that challenge its integration into standard orthopedic practice.

The appeal of gene therapy in orthopedics lies in its capacity for anatomical targeting particularly within avascular or hard-to-access tissues such as joints where conventional therapeutics often fail to achieve sustained or tissue-specific effects [68]. Recent developments in understanding the molecular basis of skeletal disorders have accelerated interest in genetic modulation as a minimally invasive, potentially cost-effective alternative to surgical or biologic interventions [64]. Yet, much of this optimism

rests on preclinical data or early-phase trials, with limited demonstration of efficacy and safety in large, well-controlled human studies.

A major limitation remains the reliance on viral vectors for gene delivery. While these vectors offer efficient transduction, they also trigger host immune responses and raise concerns regarding off-target effects, insertional mutagenesis and long-term vector persistence. These immunological and genomic risks have been particularly problematic in orthopedic contexts where repeat dosing may be required due to biomechanical wear or inflammatory recurrence. Non-viral approaches, though safer, often suffer from low transfection efficiency and transient gene expression, undermining their therapeutic viability.

One proposed solution involves the integration of gene therapy with tissue engineering constructs using biomaterial scaffolds or stem cells as delivery vehicles to mitigate immune activation and enhance site-specific transgene expression [62.63]. While conceptually compelling, this approach introduces another layer of complexity in terms of regulatory approval, manufacturing and quality control. Moreover, scalability and reproducibility remain unresolved in the context of clinical grade bioproducts. Although gene therapy is gradually expanding from its roots in rare monogenic diseases to more prevalent orthopedic conditions such as osteoarthritis and bone nonunion, the pace of clinical translation is slow. Ongoing trials aim to evaluate its role as both primary and adjunctive treatment, yet none have achieved widespread regulatory approval, underscoring the need for robust efficacy data and long-term safety profiles (Table 4) [64].

Technique	Mechanism of Action	Advantages	Challenges
BM/AT/UC-MSCs	Differentiation, immunomodulation, trophic signaling	Versatility, tissue-specific effects	Source heterogeneity, regulatory complexity [33-36]
EVs/Exosomes	Paracrine signaling via miRNAs and proteins	Cell-free, low immunogenicity	Isolation, dosing and manufacturing scalability [37-38]
PRP (L-PRP, P-PRP, PRF, GFC)	Growth factor delivery, inflammation modulation	Easy to obtain, customizable	Composition variability, uncertain long-term outcomes [39-49]
Ozone Therapy	Redox modulation, anti-inflammatory, metabolic support	Non-invasive, immunomodulatory	Protocol standardization, mechanism validation [50-62]
Grafts and Scaffolds	Structural replacement, osteoconduction/induction	Structural integrity, biological activity	Donor risks (grafts), bioinactivity (scaffolds) [63-64]
MACI	Cell-based cartilage restoration	Long-term durability, scaffold-guided delivery	Cost, surgical complexity [63]
Gene Therapy	Targeted gene modulation (anti-inflammatory/anabolic)	Site-specific, durable molecular effect	Vector safety, immune response, regulatory barriers [64]

Table 4: Comparative overview of regenerative orthopedic interventions.

Conclusion

Orthoregeneration signifies a fundamental departure from conventional orthopedic approaches, shifting focus from mechanical repair to biologically mediated tissue restoration. While this paradigm leverages Mesenchymal Stem Cells (MSCs), growth factors, Extracellular Vesicles (EVs) and engineered biomaterials to overcome the limitations of traditional interventions, its clinical translation remains fraught with inconsistencies. Preclinical enthusiasm has not yet translated into widespread therapeutic success, as evidenced by the variable outcomes in bone, cartilage, tendon, ligament and intervertebral disc regeneration. The field's progress is hindered by a lack of standardized protocols, incomplete mechanistic insights and unreliable reproducibility issues that cast doubt on the immediate clinical applicability of these strategies.

Key interventions, including MSC-based therapies, PRP formulations, ozone therapy and MACI, have demonstrated only modest and inconsistent efficacy, raising questions about their true regenerative potential. MSC therapies, for instance, suffer from donor variability, poor engraftment and undefined differentiation pathways, while PRP's clinical benefits remain unpredictable due to poorly controlled growth factor release kinetics. Ozone therapy, despite its anti-inflammatory and pro-regenerative properties, lacks rigorous dose-response standardization and its long-term safety profile remains inadequately characterized. Similarly, MACI, though technically refined compared to earlier cartilage repair methods, fails to consistently

outperform alternative treatments in functional or structural outcomes. These limitations underscore a critical gap between experimental promise and real-world clinical utility.

Emerging technologies-such as gene therapy and bioengineered scaffolds-offer theoretically precise and durable solutions but face formidable translational barriers. Viral vector-mediated gene delivery, despite its efficiency, introduces risks of immunogenicity and insertional mutagenesis, while non-viral alternatives struggle with transient gene expression. Synthetic scaffolds, though customizable, lack intrinsic biological activity and require exogenous augmentation to achieve meaningful regeneration. Beyond scientific hurdles, regulatory complexities, manufacturing scalability and ethical concerns (e.g., MSC sourcing, genetic modification) further impede progress. The absence of universally accepted benchmarks for efficacy, safety and quality control exacerbates these challenges, leaving many regenerative therapies in a state of clinical limbo.

The future of orthoregeneration depends on addressing these translational bottlenecks through coordinated multidisciplinary efforts. Mechanistic studies must clarify cellular behaviors and molecular interactions to optimize therapeutic protocols, while large-scale, well-controlled clinical trials are essential to validate long-term efficacy and safety. Regulatory frameworks must evolve to accommodate the unique complexities of biologics and gene therapies without stifling innovation. Until these issues are resolved, orthoregeneration will remain a promising yet unproven frontier in musculoskeletal medicine-one that demands cautious optimism rather than premature clinical adoption.

Conflict of Interests

The authors declare no conflict of interest.

Funding/Sponsorship

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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