Regenerative Medicine in Orthopaedic Surgery: Pioneering Advances and Their Applications

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Abstract

Regenerative medicine has significantly impacted orthopaedic surgery by introducing biological therapies aimed at repairing, restoring, or replacing damaged musculoskeletal tissues. Recent advancements in stem cell therapies, platelet-rich plasma (PRP), and tissue engineering have paved the way for improved treatments for cartilage, bone, tendon, and ligament injuries. Mesenchymal stem cells (MSC) and induced pluripotent stem cells (iPSC) are gaining attention for their ability to regenerate tissues, while PRP shows promise in accelerating tendon and cartilage healing. Innovations in cartilage regeneration, including autologous chondrocyte implantation and biomimetic scaffolds, address the limitations of self-repair, and bone regeneration is being enhanced through growth factors like bone morphogenetic proteins (BMP) and synthetic grafts. In tendon and ligament repair, biological augmentation with scaffolds and growth factors is emerging as a novel approach. Moreover, regenerative approaches are making strides in spinal surgery and joint preservation, particularly in osteoarthritis treatment. However, challenges such as regulatory hurdles, cost, and the need for further clinical evidence remain. As the field progresses, the integration of cutting-edge techniques like 3D printing and gene therapy could further revolutionise orthopaedic regenerative medicine.

Key Points

1. Orthopaedic injuries and degenerative conditions, such as osteoarthritis, tendon damage, and cartilage damage are common, and often lead to reduced mobility, chronic pain, and long-term disability. While traditional surgical treatments can involve prolonged recovery times, risk of complications, and incomplete healing, regenerative medicine holds great potential.

2. This review highlights recent advancements in regenerative medicine within orthopaedic surgery, focusing on key areas such as stem cell therapies, platelet-rich plasma, cartilage and bone regeneration, tendon and ligament repair, and the use of biologics in spinal procedures.

3. Regenerative medicine is transforming the future of orthopaedic surgery by offering less invasive, biologically driven treatments that promote long-term tissue healing. While challenges remain, the continued research into stem cells, biomaterials, and tissue engineering is poised to improve patient recovery and revolutionise musculoskeletal care.

INTRODUCTION

Regenerative medicine is a rapidly growing field within orthopaedic surgery, focusing on harnessing the body's natural healing mechanisms to repair and regenerate musculoskeletal tissues. The rapid growth of orthopaedic injuries and degenerative diseases such as osteoarthritis makes conventional approaches, which frequently end with an invasive surgery or prosthetic implant, limited in temporary relief or in restoring the original function of the musculoskeletal tissues. The regenerative therapies like stem cells, biomaterials, and growth factors have emerged as a new hope to tackle these challenges. These therapies aim to not only treat symptoms but also promote long-term healing by stimulating tissue regeneration. This article examines the latest advancements in regenerative medicine and their applications in orthopaedic surgery, highlighting key advances and future directions.

ORTHOPAEDIC STEM CELL THERAPIES

Stem cell therapies have emerged as a breakthrough in orthopaedic surgery by providing various innovative solutions for musculoskeletal disorders. Because of their capacity to differentiate into multiple cell lineages, stem cells possess regenerative properties and are therefore considered a fundamental platform for regenerative medicine within the field of orthopaedics. Mesenchymal stem cells (MSC), induced pluripotent stem cells (iPSC), and allogeneic stem cells are among the most studied sources of stem cells for therapeutic applications in orthopaedics.

Mesenchymal Stem Cells

MSCs are commonly harvested from bone marrow (BM-MSC) or adipose tissue (ADSC), widely used for cartilage and bone regeneration. The harvested tissue is processed in a lab to isolate the MSCs and grown in culture to the required number of cells for use.[1] The MSCs are injected directly into the injured or degenerated area, such as a joint cartilage repair or bone fracture healing. This procedure is typically done under ultrasound or imaging guidance for precise delivery. According to recent research, MSCs can improve osteoarthritis, tendon injuries, and bone abnormalities. MSCs have demonstrated great promise in the treatment of bone deformities and other orthopaedic disorders. These cells can be produced from a variety of sources, including bone marrow, adipose tissue, and umbilical cord. According to research, MSCs can improve tissue regeneration by secreting bioactive substances that promote healing and reduce inflammation and by their differentiation abilities.[2,3] For instance, studies have demonstrated that MSCs can be effectively harvested from the forearm and utilised in hand surgeries to address conditions like scaphoid non-union and osteoarthritis.[4] Furthermore, the regenerative capacity of umbilical cord-derived MSCs has been emphasised; these cells offer a non-invasive cell therapy source that can enhance patient outcomes in orthopaedic surgery.[3]

The deeper understanding of stem cell function and differentiation mechanisms has been a significant advancement. For example, studies have shown that Wnt signalling pathways are essential for coordinating MSC identification and function during skeletal regeneration.[5] This makes it possible to specifically manipulate stem cell behaviour to boost bone repairing procedures. Furthermore, the identification of specific markers, such as Emilin2, has been linked to the accumulation of MSCs at bone regeneration sites, providing new therapeutic targeting options.[6]

Induced Pluripotent Stem Cells

iPSCs are reprogrammed from adult cells and offer the potential for patient-specific therapies. They can be programmed to become osteocytes (bones), chondrocytes (cartilage), myocytes (muscle), or other relevant cells for orthopaedic applications. They are generated from the patient's somatic cells, typically taken from skin or blood samples. These cells are reprogrammed to a pluripotent state similar to embryonic stem cells by a genetic reprogramming process. This involves introducing transcription factors such as Oct-4, SOX2, KLF4, and c-MYC into the somatic cells, turning them into iPSCs.

Research on iPSCs for joint and bone regeneration is encouraging, offering another cutting-edge direction in orthopaedic regenerative medicine, even though it has not been widely used clinically yet. Transplanted from somatic cells, iPSCs can develop into any type of cell, including those required for musculoskeletal repair.[7,8] Their use in regenerative therapies is particularly advantageous as they can be derived from the patient's own cells, thus minimising the immune rejection risks.[9] Recent studies have explored the potential of iPSCs in generating functional tissues for musculoskeletal regeneration, demonstrating their versatility and effectiveness in preclinical models.[10] Furthermore, the effectiveness of producing specific cell types from iPSCs has increased due to developments in differentiation methods, which is crucial for targeted therapy in orthopaedic applications.[11]

Allogeneic Stem Cells

Donor stem cells are being explored for large-scale use in treating conditions like degenerative joint diseases and spinal cord injuries. The harvested stem cells are processed, purified, and cryopreserved (frozen) for future use, offering a readily available source for transplantation compared to autologous cells from the patients, especially when patient conditions or previous surgeries may limit the availability of autologous sources.[7] However, their use raises concerns regarding immunogenicity and the need for immunosuppression, which can complicate treatment protocols.[9] Therefore, ongoing research is focused on optimising the use of allogeneic stem cells with these challenges to overcome.

APPLICATION OF PLATELET-RICH PLASMA

Platelet-rich plasma (PRP) therapy uses a patient's blood, concentrated with platelets and growth factors, to accelerate healing in injured tissues. The therapy has emerged as a promising treatment modality in orthopaedics, particularly for tendon and ligament injuries, cartilage repair, and post-surgical recovery. PRP is characterised by a high concentration of platelets and growth factors, which are critical for tissue healing and regeneration process. PRP's capacity to promote angiogenesis, cellular proliferation, and the healing process in general by releasing different growth factors, including PDGF, VEGF, and TGF-β, makes it highly effective.[12,13]

Each of these growth factors play a distinct role in PRP applications. VEGF mainly functions as an angiogenesis promoter, stimulating new blood vessel development through enhanced endothelial cell movement and growth, which plays a vital role in supplying nutrients and oxygen to healing tissues.[14,15] They also modulate the immune response by causing a transition from inflammatory state environment of macrophages (M1) to repairing macrophages (M2). PDGF functions as a powerful growth factor that drives mesenchymal cell division, boosts extracellular matrix (ECM) synthesis, and facilitates cellular migration, which contributes to tissue reconstruction and healing process.[16–18] These growth factors stimulate fibroblast proliferation and collagen synthesis, which is critical for supplying nutrients and oxygen to initiate wound healing. By enhancing the deposition of proteins such as collagen and elastin, PRP promotes remodelling of the ECM and ensures the tissue restoration and their functions. TGF-β regulates key cellular activities including, differentiation and ECM production; it exhibits a dual effect on tissue regeneration and fibrosis, depending on specific cellular concentration and environment.[19,20]

Tendon and Ligament Injuries

PRP is commonly used to treat chronic conditions like tennis elbow, Achilles tendinopathy, and anterior cruciate ligament (ACL) injuries. PRP encourages the regeneration of tendons and ligaments, which aids in their repair. Studies show that platelet-rich plasma (PRP) can enhance recovery from injuries, including rotator cuff tears and Achilles tendon tears. For example, a study showed that PRP injections improved pain scores and shortened recovery periods for individuals having arthroscopic surgery to repair damaged rotator cuffs.[21,22] Additionally, PRP has been found to augment tendon healing by reducing scar tissue formation, which is a common complication in traditional surgical interventions.[22] However, the clinical effectiveness of PRP may vary, with some studies reporting mixed results regarding its benefits in ligament and tendon repair.[23,24]

Cartilage Repair

PRP injections have the potential to help heal cartilage, as well as relieve pain and inflammation in osteoarthritis patients by stimulating cartilage regeneration. They contain growth factors such as TGF-β, IGF-1, PDGF, BMPs, and fibroblast growth factor (FGF), which can promote chondrocyte proliferation and improve the synthesis of ECM components critical for cartilage regeneration. Studies have indicated that the application of PRP in conjunction with other treatments, such as bone grafts or scaffolds, can lead to significant improvements in cartilage repair. [25,26] The use of PRP in osteoarthritis management has also been explored; according to findings, it may aid in relieving symptoms and enhance joint function by enhancing tissue regeneration.[13,26]

Post-Surgical Recovery

PRP is used in conjunction with surgical interventions to enhance post-surgical recovery and tissue healing after procedures like rotator cuff repairs and knee surgeries. The application of PRP in surgical settings has also shown to reduce inflammation, lead to quicker recoveries, and improved surgical wound healing. For example, PRP has been utilised effectively in dental and oral surgeries, where it has shown quicker wound healing and reduced post-surgery complications.[27,28] The autologous nature of PRP also minimises the risk of adverse reactions, making it a safe option for enhancing recovery across various surgeries.[29] PRP therapy is a biologically active method that stimulates the body's healing mechanisms. Its use in cartilage repair, tendon and ligament injuries, and post-surgical healing highlights its potentials and advantages.

CARTILAGE REGENERATION METHODS

Cartilage regeneration in orthopaedic surgery remains significantly challenging due to the limited intrinsic healing capacity of cartilage tissue. Recent developments in regenerative medicine have mainly focused on implementing approaches such as autologous chondrocyte implantation (ACI) and the development of scaffolds and biomaterials that improve cartilage healing.

Autologous Chondrocyte Implantation

ACI is a well-established surgical procedure used for cartilage regeneration in the treatment of cartilage defects in the knee, particularly on the femoral condyle and trochlea. It involves harvesting a patient's own cartilage cells, culturing them *in vitro*, and reimplanting them into the damaged joint. The procedure involves a small piece of periosteum tissue which covers the bone, or a synthetic membrane placed over the defect and sutured in place. The cultured chondrocytes are then injected below the periosteal flap or membrane into the defect. This membrane helps contain the chondrocytes and integrates them into the tissue. ACI promotes the growth of hyaline-like cartilage, and like the native cartilage it is more durable than fibrocartilage formed through other procedures.[30,31]

Recently, this method has evolved into more sophisticated approaches such as matrix-associated autologous chondrocyte implantation (MACI), which also combines chondrocytes with biomimetic scaffolds

to improve integration and support the regeneration process.[32,33] In order to promote cellular adhesion and growth, scaffolds are used to mimic the natural ECM and to provide a structural framework for cell attachment.[32,34] Recent studies have shown that the incorporation of stem cells and growth factors into these scaffolds can significantly enhance the regenerative potential of the implanted cells, which improved cartilage repair.[34,35]

Scaffolds and Biomaterials

Scaffold materials can be natural (collagen, hyaluronic acid, chitosan, and alginate), synthetic (polylactic acid [PLA], polyglycolic acid [PGA], and polycaprolactone [PCL])' or hybrid scaffolds (a combination of natural and synthetic). In cartilage regeneration, scaffolds can be made from natural or synthetic materials and are often combined with chondrocytes, stem cells, or growth factors to enhance cartilage repair. Recent innovations include biomimetic scaffolds, which mimic the structure and properties of natural cartilage, enhancing cellular adhesion and growth. These are often combined with growth factors or stem cells to promote regeneration.

Biomimetic scaffolds designed to replicate the mechanical and biochemical properties of natural cartilage have shown promise in enhancing the regeneration process.[32,36] For instance, oriented scaffolds have been shown to regulate hyaline cartilage regeneration, which is crucial in restoring the joint's functional characteristics.[35] The integration of growth factors such as TGF-β and BMPs into these scaffolds has shown to promote chondrogenesis in combination, hence improving the quality of the regenerated cartilage.[34,37]

Several investigations emphasised the role of mechanical loading and bioreactor systems in optimising the conditions for cartilage regeneration. It was also demonstrated that mechanical stimulation promotes chondrocyte differentiation and proliferation. This approach shows that the mechanical environment plays a vital role in cartilage tissue regeneration.[38] These strategies not only aim to restore the structural integrity of cartilage but also seek to enhance its functional properties, ultimately improving patient outcomes in joint repair.

BONE REGENERATION METHODS

The use of regenerative medicine in bone healing has seen promising developments, especially with techniques like the use of BMPs, synthetic bone grafts and bioceramics, and 3D printing technologies. Each of these methods contributes uniquely to enhancing bone healing and regeneration.

Bone Morphogenetic Proteins

BMPs are a group of growth factors that stimulate bone formation and repair. They stimulate the recruitment of MSCs to injured bones and signal them to differentiate into osteoblasts to initiate bone formation. Their osteoinductive nature triggers bone-forming cells to make new bone tissue, making them valuable in natural bone healing and clinical bone regeneration process, such as in spinal fusion surgeries or healing large bone fractures.

BMP-2 in particular has gained prominence for its osteoinductive properties, shown to induce differentiation of MSCs into osteoblasts, thereby promoting bone regeneration.[39-41] Clinical applications of BMP-2 have shown improved fusion rates in spinal surgeries compared to traditional iliac crest bone grafts, reducing the need for additional surgeries.[39,42] However, adverse effects like inflammation and heterotopic ossification have been reported. Therefore, careful optimisation of these delivery methods is required.[43,44]

Synthetic Bone Grafts and Bioceramics

Materials like calcium phosphate, hydroxyapatite, and bioactive glass are employed to mimic the natural bone matrix. These materials support bone cell proliferation and are often used alongside biological agents like BMPs or MSCs. They are vital substitutes for autologous bone grafts, which are limited by availability and donor site morbidity. Materials like

hydroxyapatite and calcium phosphate are made to mimic the natural bone matrix, acting as a scaffold to promote the integration and proliferation of bone cells.[45,46] These materials can be combined with BMPs to enhance their osteogenic potential, creating a synergistic effect that promotes more effective bone healing.[47] The incorporation of bioceramics with growth factors has significantly improved outcomes in cases of large bone defects and non-unions.[47]

3D Printing and Tissue Engineering

3D printing technologies are being used to create patient-specific scaffolds for bone regeneration that are tailored to patients' needs. These scaffolds can be engineered to include BMPs or MSCs to increase their efficacy in bone regeneration.[48] The ability to produce customised scaffolds through 3D printing facilitates better integration with the host tissue and improves the overall success rate of bone healing procedures. Research indicates that 3D-printed scaffolds can outperform traditional graft materials in terms of osteogenic activity and structural support.[48]

The integration of BMPs, synthetic grafts, and advanced 3D printing technologies is transforming orthopaedic surgery. While BMPs provide critical biological signals for bone healing, synthetic materials and 3D-printed scaffolds enhance the mechanical and structural aspects of bone repair. Further research and clinical trials are essential in these technologies to address any potential complications.

APPROACHES IN TENDON AND LIGAMENT REPAIR

Tendon and ligament injuries are also prevalent in both sports and trauma, leading to significant challenges in orthopaedic surgery. Recent advancements in regenerative medicine have introduced innovative therapies aimed at enhancing the healing process of these injuries. The most important approaches to tendon and ligament repair are biological augmentation, growth factor therapy, and cell-based therapies.

Biological Augmentation

Scaffolds made from biological materials like collagen or synthetic polymers are used to enhance the repair of tendons and ligaments. They provide a structural framework that can facilitate cellular attachment and proliferation, which is essential for effective healing. ECM scaffolds, when sterilised appropriately, do not impair ligament healing and can support the formation of a fibrovascular scar, which is crucial for recovery.[49] Additionally, the use of collagen-based compounds was demonstrated to enhance the morpho-functional properties of tenocytes, which suggests they can improve the healing for tendon injuries.[50]

Growth Factor Therapy

Growth factor therapy, particularly for tendon and ligament repair, can enhance the biological healing process. TGF-β and vascular endothelial growth factor (VEGF) are also being used to stimulate tendon regeneration. To stimulate tendon regeneration, they utilise specific proteins to play critical roles in the processes of proliferation and differentiation. TGF-β has been noted for its ability to modulate tenocyte activity and accelerate collagen synthesis, which is vital for tendon repair.[51] The application of PRP, which is rich in growth factors like PDGF and TGF-β, has been shown to promote the differentiation of tendon stem cells into active tenocytes, which accelerated the healing process.[52] Many studies have proved that PRP can significantly improve tendon healing by increasing tenocyte proliferation and collagen production.[53,54]

Cell-Based Therapies

Use of MSCs and tenocytes in cell therapies can improve healing outcomes and reducing re-injury rates in tendinopathies and ligament reconstructions. MSCs have the potential to differentiate into tenocytes and aid in the tendon repair process. Different approaches in combination with cell therapies have been introduced in studies to improve outcomes. For example, the combination of tendon-derived stem cells (TDSC) with PRP has been shown to enhance tendon healing,

thus emerging as a preferable option in cell therapy.[51,54] Tenocytes also play a crucial role in the healing process by secreting ECM components and signalling molecules that recruit other cells to the injury site.[55] The intrinsic healing capacity of tenocytes makes them essential for the regeneration of the tendon matrix and the overall repair process.[56]

USE OF BIOLOGICS IN SPINAL SURGERY

Regenerative approaches in spinal surgeries, particularly in intervertebral disc repair and spinal fusion, have gained significant attention due to their potential to enhance recovery outcomes and less invasive procedures. Recent studies have focused on using biologics, including stem cells, growth factors, and injectable hydrogels.

Intervertebral Disc Repair

The application of stem cells and growth factors represents a promising approach for the repair and function restoration of degenerated intervertebral discs. Research indicates that bone marrow MSCs have better efficacy in repairing the annulus fibrosus of intervertebral discs. A study demonstrated that transplantation of bone marrow MSCs significantly improved collagen type II levels in the repaired tissue.[57] Another study shows that the use of TGF-β suppresses inflammation and promotes chondrogenesis in intervertebral disc cells, which aids in disc function restoration.[58]

Injectable hydrogels, which provide a scaffold for cell growth and nutrient diffusion, are also being explored. These hydrogels can also be loaded with growth factors and stem cells, creating a conducive environment for tissue regeneration. A recent study shows the potential of chitosan hydrogels combined with decellularised nucleus pulposus matrix and growth factor microspheres to prevent intervertebral disc degeneration.[59] This approach helps cell viability and enhances the capacity of the injected cells to regenerate.[59]

Exosomes, types of extracellular vesicles derived from stem cells, have also emerged recently as a novel therapy. They supply target cells with bioactive molecules that improve tissue repair and cell communication. Stem cell-derived exosomes have also improved ECM formation and nucleus pulposus cell proliferation to help intervertebral disc degeneration.[60,61] This cell-free approach can be a less invasive option for traditional stem cell therapies.

Spinal Fusion

BMPs and other biologics are being used to enhance bone fusion in spinal surgeries, which can reduce the use of autografts and invasive methods. BMPs play a critical role in enhancing bone fusion rates. They have been widely used in clinical practice for their capacity to stimulate osteogenesis and reduce autograft reliance, which can lead to donor site morbidity.[62] The incorporation of BMPs into spinal fusion procedures has shown surgical outcomes and less complications.[62]

Use of PRP in spinal fusion with high concentration of growth factors was also investigated for its potential to enhance healing in spinal fusion surgeries. Studies suggest that PRP can improve bone healing, provide faster recovery, and enhance the fusion process.[63,64] However, application methods for PRP remain challenging and subjects of further research. The integration of biologics in spinal surgery, particularly with stem cells, growth factors, and innovative scaffold technologies, holds promise for improving patient outcomes.

METHODS IN JOINT PRESERVATION AND OSTEOARTHRITIS

Joint preservation methods have become attractive alternatives to traditional surgical procedures for maintaining joint function and avoiding total knee replacements, as understanding of osteoarthritis (OA) developed. The most used approaches in current research are gene therapy, stem cell and platelet injections, and microfracture and drilling.

Microfracture and Drilling

Microfracture and drilling involve creating small fractures in the subchondral bone to stimulate the repair of articular cartilage. Recent studies indicate that these methods can perform better by integrating cell-based therapies and scaffolds, which improve the quality of the repaired cartilage.[65,66] For instance, combining core decompression with new adjuvant therapies can lead to better postoperative outcomes, and development of these techniques is crucial for effective joint preservation.[65] The incorporation of scaffolds can provide a supportive environment for chondrocyte proliferation and differentiation, potentially leading to more robust cartilage repair.[66]

Stem Cell and Platelet-Rich Plasma Injections

The combination of stem cell therapy and PRP injections has shown better results in the progression of OA and cartilage repair compared to conventional treatments in recent studies. A clinical trial demonstrated that patients receiving PRP combined with arthroscopic debridement provided better results than using PRP alone.[67] Another study showed significant improvement in joint conditions by using the combination of stem cells with PRP.[68] The ability of MSCs to transform into cartilage-forming cells, as well as their anti-inflammatory nature and regenerative properties, make them attractive options to address the underlying pathophysiology of OA.[69]

Gene Therapy

Gene therapy is an innovative approach in the treatment of OA, particularly in targeting inflammatory pathways. Although this is currently experimental, gene therapies that are able to inhibit pro-inflammatory cytokines such as IL-1 and TNF-α show promise in modifying the disease. Recent studies have indicated that targeting inflammatory mediators can reduce cartilage degradation and improve joint function.[70] Gene therapy may alter the inflammation in OA and provide a multifaceted approach to treatment.

Joint preservation strategies for OA, including microfracture and drilling, stem cell and PRP injections, and gene therapy, represent huge developments in OA treatment. By focusing on the preservation and restoration of joint function, these techniques aim to relieve symptoms and address the underlying causes of OA. Further research and clinical trials will be essential to establish their long-term safety and efficacy.

DISCUSSION

Regenerative medicine in orthopaedic surgery has made significant advances in recent years; however, many challenges remain for widespread adoption and efficacy. Numerous studies have shown improvements in the application of regenerative therapies. The review of these studies points out several challenges yet to overcome. The long-term efficacy and safety of these therapies are critical to consider. These studies also need to consider demographic factors such as age, race, and sex in patient groups receiving therapies, as the outcomes may vary depending on an individual's immune system. These therapies require critical analysis of the methodologies employed.

The long-term safety and efficacy of regenerative techniques like PRP remain critical areas of investigation due to mixed outcomes and challenges with existing therapies. Reports on PRP use in orthopaedics showed variable results, with some studies showing benefits like pain reduction and functional improvement, but the evidence base remains limited. Despite its growing clinical use, there is a significant lack of high-quality prospective randomised studies to confirm long-term efficacy and safety.[71] The American Academy of Orthopaedic Surgeons (AAOS) highlights the need for rigorous biological characterisation of PRP preparations, as standardisation is essential for reliable treatment protocols. Variability in PRP preparation methods contributes to inconsistent outcomes, making it difficult to assess the therapy's long-term effectiveness.[72] The heterogeneity in PRP

preparation techniques results in variable concentrations of bioactive molecules which can impact efficacy.

Stem cell therapies offer a cellular component that directly participates in tissue regeneration compared to PRP, which primarily focuses on growth factor-mediated effects. However, the safety profiles of MSC therapies raises concerns, including risks of tumour formation and immune reactions to allogeneic MSCs.[73] A systematic review of umbilical cord-derived Wharton's Jelly as an MSC source also shows the lack of robust clinical data on safety and efficacy.[74] Patient responses to therapies like PRP and MSCs are highly variable, with documented risks such as infection and adverse reactions to injected materials.[71,72] Large-scale, randomised trials are essential to establish the long-term safety and efficacy of MSCs and other regenerative treatments.[75,76] The current lack of robust evidence limits the ability of orthopaedic surgeons to confidently recommend these therapies for widespread clinical use.[77]

ACI has been recognised as an effective treatment for full-depth chondral defects, particularly in the knee. Long-term studies show that ACI can provide lasting clinical improvement, but its success depends on factors like patient age and activity level, with younger patients often requiring more durable solutions. Challenges with ACI include the risk of chondrocyte dedifferentiation during *in vitro* expansion, which may affect cartilage quality.[78] The procedure is complex, requiring skilled surgery and careful patient selection to achieve the best outcomes.[79] Biomimetic scaffolds, made from materials like collagen and hydroxyapatite, have shown promise in enhancing cartilage repair by supporting cell attachment and growth. While these scaffolds can aid osteochondral regeneration, their long-term effectiveness is unclear, as studies report mixed outcomes and highlight the need for further research. Additionally, BMPs have shown potential in promoting bone healing and cartilage regeneration, but their role in improving ACI outcomes still needs to be fully explored. Some studies of BMPs observed potential complications, including ectopic bone formation and inflammatory responses, which requires careful consideration for long-term results. Application of iPSCs offer a promising approach for generating chondrocytes for cartilage repair, but their long-term safety and efficacy remain uncertain. Concerns include the potential for tumour formation and the stability of differentiated cells.[73] Since iPSCs can be derived from a patient's own cells, they reduce the risk of immune rejection.

A critical analysis of the methodologies employed in the studies reveals several limitations that warrant consideration. One key issue is the lack of standardised protocols for PRP preparation, which contributes to variability in treatment outcomes. The study of Gholami et al.[80] highlighted that variations in PRP preparation methods, such as single versus double spinning techniques, differences in platelet concentrations, and the inclusion of coagulants, can significantly influence treatment efficacy. Similarly, Zavarro et al.[71] emphasised the importance of thorough biological characterisation of PRP, recommending adherence to guidelines like the Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO) to enhance the reliability of study findings. The absence of such standardisation across various studies complicates the interpretation of results and limits the ability to draw definitive conclusions regarding the effectiveness of PRP in orthopaedic applications.

Demographic factors significantly influence the applicability of findings from PRP studies. Many trials focus on specific groups, such as professional athletes, which may not represent the broader population undergoing orthopaedic procedures. For instance, Bubnov et al.[81] studied ultrasound-guided PRP injections in professional athletes, but these results may not be applicable to older adults or individuals with comorbidities. Some studies have relatively small sample sizes, raising concerns about the statistical validity and robustness of their conclusions. Growth factors in PRP, such as PDGF and VEGF, interact in complex ways to enhance healing in injuries

and surgeries. These effects can vary widely due to the multidimensional nature of their activity.[19,82] The variability in outcomes, combined with limited demographic diversity and small sample sizes, challenges the ability to generalise PRP therapies across diverse patient populations.

Many research studies exhibit methodological limitations, particularly regarding follow-up duration and the outcome measures employed. Several investigations focused on short-term outcomes, which may not accurately reflect the long-term benefits or risks of PRP interventions. Murrell et al.[83] emphasise that the existing evidence often lacks comprehensive long-term follow-up data, which is crucial for assessing the sustained efficacy of these treatments. Additionally, the reliance on subjective outcome measures, such as patient-reported pain scores, introduces potential bias and variability in evaluating treatment success. As noted by Jacobs et al.[84] adopting a more standardised approach to outcome measurement is essential to compare across studies and improving the overall quality of evidence. Addressing these methodological limitations must be considered to enhance the validity and applicability of research findings.

The regulatory and approval processes for emerging regenerative therapies, especially involving biological products like stem cell therapies and gene therapies, can be very lengthy and complex. They require extensive data on safety and efficacy for approval, which can cause delays in the process.[85,86] The need for alignment between regulatory processes and reimbursement strategies is critical, and regulatory bodies must facilitate the integration of these therapies into clinical practice. To overcome these hurdles in the process, regulatory bodies can apply pathways to allow conditional approvals based on early, promising clinical data while also gathering long-term evidence. Establishing clear, specific guidelines tailored to regenerative therapies can reduce hurdles and ensure quicker development of therapies. Collaboration between regulators, academic researchers, and industry stakeholders can create standardised protocols for safety, efficacy, and manufacturing processes. Accelerating the use of real-world evidence and advanced analytics can support market surveillance, enhancing trust without delaying approvals. Use of advanced analytics with real-world evidence can expedite market surveillance while maintaining timely approvals.

Cost and accessibility also pose substantial barriers to the implementation of regenerative medicine in orthopaedic surgery. The high costs of cell-based therapies and other advanced treatments limit their availability to all patients equally.[86] The cost of these therapies may discourage patients and healthcare professionals from seeking them, which would limit access to potentially life-changing treatments.[87]

In the near future, advancements in tissue engineering, gene editing technologies such as clustered regularly interspaced short palindromic repeats (CRISPR), and 3D bioprinting may provide more personalised and effective regenerative medicine solutions.[3,86] These innovations could lead to the development of tailored treatments that not only enhance the regenerative capacity of tissues but also significantly improve patient outcomes. The integration of biological, synthetic, and mechanical solutions in orthopaedic surgery is anticipated to restore function and provide better quality of life for patients with musculoskeletal conditions.[83] In order to overcome current challenges and achieve the full potential of regenerative medicine, orthopaedic surgery, continued research, and stakeholder collaboration are essential.

CONCLUSION

Recent advances in stem cell therapies for orthopaedic surgery have involved deeper insights into stem cell biology, improved biomaterials, and innovative delivery methods. The integration of these advances with PRP injections has enhanced treatment outcomes due to better tissue healing and regeneration. Recent literature highlights the efficacy of umbilical cord-

derived Wharton's jelly and other MSCs, which have emerged as promising sources for regenerative applications due to their regenerative capabilities.[3,88,89] The application of orthobiologics uses a range of biologically derived materials, offering tailored solutions for bone, ligament, tendon, and cartilage healing.[90,91] Innovative technologies like AI and 3D printing further enhance the precision and effectiveness of regenerative methods in orthopaedic surgery, allowing for more personalised approaches and improved outcomes.[92-94]

Regenerative medicine is reshaping the landscape of orthopaedic surgery by introducing innovative, biologically driven therapies that aim to repair and regenerate damaged tissues rather than merely treating symptoms. Advances in stem cell therapies, PRP, growth factors, and tissue engineering are paving the way for more effective and less invasive treatments for conditions like osteoarthritis, tendon injuries, and bone defects. While challenges related to regulatory approval, cost, and long-term clinical efficacy remain, ongoing research and technological innovations are becoming more refined, offering hope for better overall patient outcomes, with shorter recovery times and improved quality of life for patients with musculoskeletal conditions.

In the near future, orthobiologics may be employed as intermediate care, placed between surgery and conservative therapies like steroid injection. Clinicians could even witness a complete change in how joint replacement is performed by shifting from ceramic and metal replacements to biological regeneration. In the future, biologic injection may be used as a preventative measure for degenerative joint conditions. While challenges in storing and rapidly growing stem cells for grafting remain, the transformative potential of regenerative medicine is exciting. It could expand the landscape of minimally invasive treatment and potentially even cure conditions that cannot be cured with current treatment options. However, the size and consistency of recent studies is still a hurdle. While enough evidence exists to support regenerative medicine techniques in specific conditions such as osteoarthritis and tendinopathy, broader evidence-based studies will be required before these treatments can be accepted as standard practice in wider clinical settings.

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