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Contents

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EDITORIAL

Evidence-based orthobiologic practice: Current evidence review and future directions

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Abstract

The field of orthopedic and regenerative medicine is rapidly evolving with the increasing utilization of orthobiologic. These biologically derived therapies, including platelet-rich plasma, mesenchymal stem cells, bone marrow aspirate concentrate, stromal vascular fraction (SVF), and autologous chondrocyte implantation, are gaining traction for their potential to enhance the body's natural healing processes. They offer a promising alternative to traditional surgical interventions for musculoskeletal injuries and degenerative conditions. Current evidence suggests significant benefits of orthobiologics in treating conditions like osteoarthritis, tendon injuries, and spinal disorders, yet inconsistencies in treatment protocols and outcomes persist. The global market for orthobiologics is projected to grow substantially, driven by advancements in biologic therapies such as adipose-derived stem cells and SVF, and the demand for minimally invasive treatments. Despite their promise, regulatory and ethical challenges, as well as the need for high-quality, standardized research, remain significant obstacles. Future directions in the field include advancements in delivery systems, personalized medicine approaches, and the exploration of novel sources like induced pluripotent

stem cells, aiming for more targeted and effective treatments. Collaborative efforts are crucial to overcoming these challenges and ensuring the safe and effective application of orthobiologics in clinical practice.

Key Words: Orthobiologics; Platelet-rich plasma; Stem cells; Musculoskeletal regeneration; Regenerative medicine; Evidence-based medicine

Core Tip: Orthobiologics, including platelet-rich plasma, mesenchymal stem cells, bone marrow aspirate concentrate, stromal vascular fraction, and autologous chondrocyte implantation, show significant potential in enhancing musculoskeletal healing and reducing the need for invasive surgeries. Despite their growing popularity, inconsistencies in treatment protocols and evidence levels highlight the need for standardized, high-quality research. Future advancements in delivery systems, personalized medicine, and novel cell sources may further optimize their efficacy and safety.

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INTRODUCTION

The field of orthopedic and regenerative medicine is witnessing a surge in interest and application of orthobiologics. These biologically derived therapies, such as platelet-rich plasma (PRP), Adipose tissue-derived Mesenchymal Stem Cells (AD-MSCs), and Bone Marrow Aspirate Concentrate (BMAC), are being recognized for their potential to significantly improve the treatment outcomes of musculoskeletal injuries and degenerative conditions. The promise of these therapies lies in their ability to enhance the body's natural healing processes, offering a less invasive alternative to traditional surgical methods.

Orthobiologics is a dynamic and rapidly advancing field dedicated to the application of biologically derived substances and techniques to enhance healing and regeneration in musculoskeletal tissues. This domain encompasses a diverse range of therapies, including cell-based treatments such as MSCs and cultured chondrocytes, blood-derived products like PRP, tissue grafts, growth factors, hormones, and extracellular matrix components such as hyaluronic acid. While the focus of this paper is primarily on specific cell-based therapies and blood-derived products, it is crucial to recognize the broader and continually evolving nature of the orthobiologics landscape.

Orthobiologics involves using biological substances to promote the repair and regeneration of musculoskeletal tissues. These therapies are increasingly employed to address a wide array of conditions, including osteoarthritis, tendon and ligament injuries, cartilage defects, muscle injuries, and bone fractures[1-4]. To provide a comprehensive understanding of the field, it is essential to outline the major categories of orthobiologics currently in use or under investigation:

Autologous peripheral blood-derived orthobiologics

Utilized in the form of PRP, platelet-rich fibrin, platelet lysate, autologous conditioned serum, autologous protein solution, autologous conditioned plasma, hyperacute serum, growth factor concentrates, plasma rich in growth factors, and gold-indued cytokines.

MSCs

These multipotent cells can be harvested from several sources namely: (1) Autologous (bone marrow, adipose tissue, umbilical cord, amniotic fluid, dental pulp, hair follicle, periosteum, menstrual blood, peripheral blood, and synovial fluid); and (2) allogenic.

Bone marrow-derived biologics

Utilized in the form of BMA and BMAC.

Adipose tissue-derived biologics

Utilized in the form of adipose-derived stem cells, stromal vascular fraction (SVF), micro-fat, nano-fat, microvascular fragments, and exosomes.

CULTURED CELLS

Autologous chondrocyte implantation

The patient's chondrocytes are cultured and reimplanted.

Cultured MSCs

Expanded under laboratory conditions to increase cell numbers.

Growth factors

Including bone morphogenetic proteins (BMPs), which are utilized to enhance bone healing.

Tissue grafts

Autologous or allogeneic grafts used for tissue repair and regeneration.

The clinical use of these orthobiologic techniques varies across the globe, influenced by differing regulatory frameworks. In the United States, the Food and Drug Administration has approved certain forms of PRP, Autologous Chondrocyte Implantation (ACI)/Matrix-Induced ACI (MACI), and specific growth factors such as some BMPs for orthopedic use. Stem cell therapies, particularly those involving significant manipulation of cells, remain largely experimental in many jurisdictions and are subject to ongoing clinical trials. In Europe, the regulatory landscape mirrors that of the United States, with approved applications for PRP, ACI/MACI, and specific growth factors. However, some countries, like Japan and South Korea, have more permissive regulations regarding stem cell therapies, enabling earlier clinical application of these treatments. It is important to note that the regulatory status and clinical adoption of these therapies are continuously evolving, with practices varying not only between countries but also among different medical institutions within the same country.

Despite the growing popularity and enthusiasm surrounding these therapies, the scientific validation of their efficacy and safety remains inconsistent and often controversial. Recent studies have shown promising results for the use of orthobiologics. For instance, PRP therapy has demonstrated significant potential in managing early knee osteoarthritis[5] and enhancing the healing process following rotator cuff repairs[6]. Similarly, stem cell therapies are being explored for their ability to regenerate cartilage in osteoarthritic joints[7] and improve recovery from tendon injuries[8]. However, the field faces challenges such as variability in treatment protocols, inconsistent outcomes, and regulatory concerns. The clinical application of orthobiologics also extends to chronic wound healing, where therapies like PRP have shown effectiveness in promoting tissue regeneration and reducing healing time[9]. Moreover, advancements in molecular biology and drug delivery systems are paving the way for more targeted and controlled release of bioactive molecules, enhancing the therapeutic potential of orthobiologics. This editorial aim to provide a concise overview of the current evidence levels in the field of orthobiologics.

CURRENT UTILIZATION OF ORTHOBIOLOGICS

Clinical applications

Orthobiologics are increasingly being utilized in various clinical scenarios to promote the healing and regeneration of musculoskeletal tissues. They are particularly prominent in the treatment of sports injuries, osteoarthritis, and spinal disorders. PRP, in particular, has demonstrated effectiveness in treating tendinopathies like tennis elbow and patellar tendinitis. It achieves this by delivering growth factors that promote healing and reduce inflammation. Similarly, stem cell therapies, especially those involving MSCs, are being explored for their potential to repair and regenerate damaged ligaments and tendons. These therapies show promise in accelerating recovery and reducing the necessity for surgical interventions[9,10]. In osteoarthritis management, orthobiologics offer a promising alternative to conventional treatments. PRP injections aim to reduce pain and inflammation, potentially delaying the need for joint replacement, while MSCs are being investigated for their cartilage regeneration potential[3,11-13]. Orthobiologics are gaining traction in the treatment of spinal disorders. BMP, for instance, are utilized in spinal fusion procedures to enhance bone growth and increase the success rate of the surgery. PRP and stem cell therapies are also being investigated for their potential to repair intervertebral discs and alleviate chronic back pain associated with degenerative disc disease[14].

Popularity and market growth

The popularity and market growth of orthobiologics are driven by several factors, including the increasing prevalence of musculoskeletal conditions, advancements in biological therapies, and a growing preference for minimally invasive treatments. The global orthobiologics market is projected to surpass USD 11.4 billion by 2032. This expansion is fueled by the increasing prevalence of musculoskeletal conditions and sports injuries, advancements in biologic therapies, a growing preference for minimally invasive treatments, and the aging population's shift towards more active lifestyles. Additionally, the demand for treatments that offer faster recovery and fewer complications compared to traditional surgical methods further bolsters the market's growth, establishing orthobiologic treatments as promising alternatives in regenerative medicine. Orthobiologics play an essential role in soft tissue healing, enhancing the repair of ligaments, tendons, and cartilage. For instance, viscosupplementation using hyaluronic acid derivatives is becoming a popular treatment for knee osteoarthritis, providing lubrication and cushioning for arthritic joints. Similarly, stem cell-based therapies are being adopted to treat various orthopedic conditions, including osteoarthritis and degenerative disc disease,

due to their potential to regenerate damaged tissues and improve joint function. Despite the promising potential and growing market, the clinical efficacy of orthobiologics is still under investigation. The need for high-quality, reproducible research is critical to establishing standardized treatment protocols and ensuring the safety and effectiveness of these therapies in clinical practice.

Current evidence base

Table 1 summarizes the indications for orthobiologic products and the level of evidence supporting their usage across various musculoskeletal conditions. We used the Level of Evidence table to ascertain the level of evidence of the studies available for a given orthobiologic[15]. Further, we graded the studies for their quality, based on the bias in their study design into high, moderate, and low[16,17]. For example: Despite the availability of randomized controlled trials (RCTs) for a given orthobiologic if the quality parameters are not satisfied they are downgraded by one level. Orthobiologics such as PRP, BMAC/Microfragmented Adipose Tissue/(SVF/MFAT/AD-MSC), allogeneic MSC, and cultured chondrocytes are utilized in treating a range of disorders, including knee osteoarthritis, avascular necrosis of the femoral head, tendinopathies, adhesive capsulitis, plantar fasciitis, degenerative disc disease, fractures, anterior cruciate ligament (ACL) augmentation, meniscus repair, rotator cuff repair augmentation, ankle sprains, acute muscle injuries, ankle osteoarthritis, and carpal tunnel syndrome[18-78].

For knee osteoarthritis, multiple orthobiologics such as PRP, BMAC, SVF/MFAT/AD-MSC, allogeneic MSC, and cultured chondrocytes demonstrate a high level of evidence (Level 1). Similarly, PRP and BMAC show strong support (Level 1) in the treatment of conditions like lateral epicondylitis, Achilles tendinopathy, patellar tendinopathy, adhesive capsulitis, plantar fasciitis, degenerative disc disease, fractures, ACL augmentation, and meniscus repair (with MFAT also showing Level 1 evidence). In contrast, avascular necrosis of the femoral head shows high-level evidence (Level 1) for BMAC, but a lower level of evidence (Level 4) for SVF/MFAT/AD-MSC and cultured osteoblasts. Other conditions like plantar fasciitis treated with SVF and meniscus repair with BMAC exhibit Level 4 evidence, suggesting the need for further research to validate their efficacy. The data suggest that PRP and BMAC are extensively supported by high-quality evidence across multiple indications, particularly in tendinopathies and joint-related conditions. SVF/MFAT/AD-MSC and cultured cells, while promising, require more rigorous research to establish their efficacy conclusively. This evidence highlights the progressive adoption and validation of orthobiologics in clinical practice, yet underscores the variability in the level of support depending on the specific condition as shown in Figure 1, and treatment modality as shown in Table 1. It is important to note that 'cultured chondrocytes' in the context of knee osteoarthritis treatment refers to techniques such as ACI or MACI, where a patient's cartilage cells are cultured and then reimplanted to repair cartilage defects.

Challenges and future directions

The development and application of orthobiologics face significant regulatory challenges. Regulatory bodies like the European Medicines Agency and the United States Food and Drug Administration require extensive clinical data to ensure safety and efficacy, but the rapid advancement of these therapies often outpaces regulatory frameworks. This mismatch can lead to delays in approval and commercialization[79-81]. Ethically, the use of stem cells and other biological materials raises concerns about patient safety, informed consent, and potential exploitation. For instance, the sourcing of stem cells, whether from autologous (self) or allogeneic (donor) origins, necessitates strict ethical oversight to prevent misuse and ensure that patients are fully aware of the risks and benefits. Additionally, there is an ongoing debate regarding the commercialization of stem cell therapies, with concerns about equity and access to these potentially life-changing treatments[82].

Despite the promising potential of orthobiologics, several research gaps need to be addressed. One of the key gaps is the lack of standardized protocols for the preparation and application of these therapies. The variability in methods for isolating and concentrating biological materials, such as PRP and stem cells, leads to inconsistent results across studies, making it challenging to draw definitive conclusions about their efficacy. Moreover, long-term safety and efficacy data are scarce. Most studies focus on short-term outcomes, and there is a need for longitudinal studies that follow patients over several years to understand the durability of the benefits and any potential long-term adverse effects. There is also a need for more high-quality RCTs to provide robust evidence that can guide clinical practice.

The future of orthobiologics is promising, driven by advancements in biotechnology and personalized medicine. One exciting prospect is the development of more sophisticated delivery systems that can target biological materials precisely to the site of injury or disease. For instance, advances in nanotechnology and drug delivery systems could enhance the efficacy of growth factors and stem cells by ensuring sustained and controlled release. Personalized medicine also holds great potential for orthobiologics. By leveraging genomic and proteomic data, clinicians can tailor biologic therapies to the individual patient's biological profile, improving outcomes and reducing the risk of adverse reactions. This approach aligns with the broader trend in medicine towards more personalized and precision-based treatments.

iPSCs represent a promising frontier for future orthobiologic therapies, offering several key advantages that could revolutionize the field. Derived from adult somatic cells, iPSCs circumvent the ethical concerns associated with embryonic stem cells while providing a patient-specific, autologous source that minimizes the risk of immune rejection and eliminates the need for immunosuppression. The scalability of iPSCs is another significant benefit, as established iPSC lines can be expanded indefinitely, potentially offering an unlimited source of cells for therapeutic applications. Moreover, iPSCs possess the capacity for directed differentiation into various cell types relevant to orthopedic tissues, such as osteoblasts, chondrocytes, and tenocytes. Additionally, patient-derived iPSCs enable the creation of *in vitro* models of orthopedic conditions, facilitating drug discovery and personalized treatment approaches. Future research directions in the field may focus on developing efficient and safe methods for generating clinical-grade iPSCs, optimizing protocols for their differentiation into specific orthopedic cell types, investigating the use of iPSC-derived organoids in tissue en-

Table 1 Orthobiologic usage indications and the level of evidence supporting its usage

Indication	Orthobiologic product	Level of evidence	Ref.
Knee osteoarthritis	PRP	1	[18-20]
	BMAC	1	[21,22]
	SVF/MFAT/AD-MSC	1	[23-25]
	Allogeneic MSC	1	[26-28]
	Cultured chondrocytes (ACI/MACI)	1	[29]
Avascular necrosis of femoral head	BMAC	1	[30-32]
	SVF/MFAT/AD-MSC	4	[33,34]
	Cultured osteoblasts	4	[35-37]
Lateral epicondylitis	PRP	1	[1,38]
	BMAC	1	[39]
Achilles tendinopathy	PRP	1	[40,41]
	BMAC	1	[39]
Patellar tendinopathy	PRP	1	[42,43]
	BMAC	1	[39]
Adhesive capsulitis	PRP	1	[44,45]
Plantar fasciitis	PRP	1	[46,47]
	SVF	4	[48]
Degenerative disc disease	PRP	1	[49,50]
	BMAC	1	[51-53]
Fracture	PRP	1	[54-56]
	BMAC	1	[57-59]
ACL augment	PRP	1	[60,61]
	BMAC	1	[62]
Meniscus repair	PRP	1	[63-65]
	BMAC	4	[66,67]
	MFAT	1	[68]
Rotator cuff repair augment	PRP	1	[69,70]
	BMAC	1	[39,71,72]
Ankle sprain	PRP	1	[73]
Acute muscle injuries	PRP	1	[74]
Ankle osteoarthritis	PRP	1	[75,76]
Carpal tunnel syndrome	PRP	1	[77,78]

ACL: Anterior cruciate ligament; PRP: Platelet-rich plasma; BMAC: Bone Marrow Aspirate Concentrate; SVF: Stromal vascular fraction; MFAT: Microfragmented Adipose Tissue; AD-MSC: Adipose tissue-derived Mesenchymal Stem Cells; MACI: Matrix-Induced Autologous Chondrocyte Implantation.

gineering, and exploring the integration of gene editing technologies like CRISPR to correct genetic defects in patient-derived cells before transplantation. Furthermore, long-term safety studies are essential to assess the risks of tumorigenicity and other potential adverse effects associated with iPSC-based therapies. Ongoing research into the mechanisms of action of different orthobiologic materials will likely yield new insights that can be translated into clinical practice. Understanding how these materials interact with the body at a molecular level will enable the development of more effective and safer treatments.

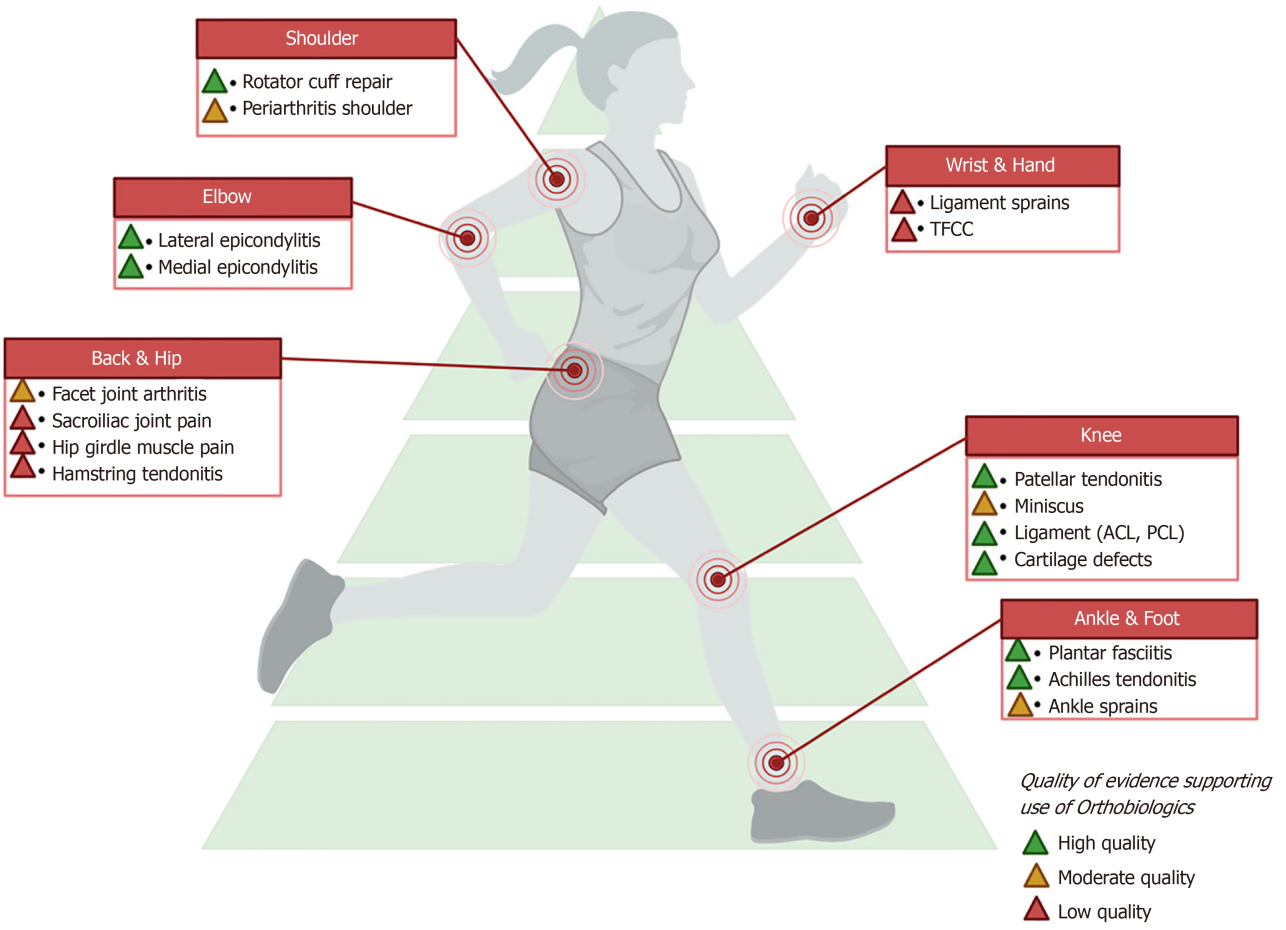

Figure 1 Strength of evidence supporting the use of orthobiologics in various inflammatory conditions. ACL: Anterior cruciate ligament; PCL: Posterior cruciate ligament; TFCC: Triangular fibrocartilage complex.

CONCLUSION

The field of orthobiologics shows immense potential in enhancing musculoskeletal healing and regeneration. Despite promising clinical applications and market growth, the evidence supporting their efficacy remains variable and sometimes inconsistent. High-quality, standardized research is critical to address these gaps, validate treatment protocols, and ensure safety and effectiveness. Regulatory and ethical challenges also demand attention to facilitate the responsible development and use of these therapies. Future advancements in delivery systems and personalized medicine hold promise for more targeted and effective treatments. The orthopaedic and regenerative medicine communities must prioritize rigorous, high-quality research to establish standardized protocols and robust evidence for orthobiologics. Regulatory bodies should streamline approval processes without compromising safety. Collaborative efforts are essential to overcome existing challenges and fully realize the therapeutic potential of orthobiologics, ultimately improving patient outcomes.

FOOTNOTES

Author contributions: Jeyaraman M conceptualized the manuscript; Jeyaraman N, Ramasubramanian S and Balaji S performed data analysis and wrote the manuscript; Muthu S performed image analysis. All authors have read and approved the final version of the manuscript.

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