

Role of Tissue Engineering and Regenerative Medicine in Treatment of Sport Injuries

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Abstract

Managing sports injuries is clinically challenging. Although new techniques can delay musculoskeletal deterioration and promote tissue restoration, they are not widely used. Thus, there is a critical need to promulgate these new methods. In recent years, "tissue engineering" approaches have been developed for improving the regeneration of cartilage by transplanting cells or engineered constructs into injured tissue. The mechanical environment affects the biology of a tissue and is necessary for the development and maintenance of load-bearing tissues. Platelets can be combined with other healing factors as a new therapeutic modality. Platelet-rich plasma (PRP) can be introduced as an autologous blood product that may improve wound healing. In this regard, stem cell therapy that focuses on mesenchymal stem cells (MSCs) has been proposed as a new treatment method in sports medicine. MSCs are multipotent; they have the ability to differentiate into other cells, notably osteoblasts, chondrocytes, adipocytes, myoblasts, and fibroblasts, depending on a variety of factors. In summary, recent advances in tissue regeneration have provided new perspectives for the use of tissue engineering to enhance tissue healing after sports injuries namely the microfracture method, the mechanical stimuli method, PRP therapy, and stem cell therapy

Keywords: Sport medicine; Stem cell therapy; PRP therapy; Microfracture method; Tissue healing.

Introduction

Physical injury is common in sports and, in severe cases, may result in permanent handicaps in mobility, compromised physical and mental health, increased medical costs, and a reduced incentive for athletes to continue sports activities. Sport injuries constitute 10–19% of all acute injuries (Figure-1).^{1,2} Regular physical activity reduces the risk of premature mortality in general and coronary heart disease. It also helps prevent sports injuries and complications from injuries, and is promoted by many physicians and sports medicine specialists. The most important risk factors for sport injury includes inappropriate environment for exercise, use of non-standard equipment, lack of appropriate physical fitness, and severity of physical collisions between athletes.³

Tissue engineering

Tissue engineering is based on the development of biological substitutes used to reconstruct injured tissues or

organs. The ultimate goal of tissue engineering is to restore the normal functions of organs.⁴ Toward this goal, some biomaterials, notably collagen gels, ceramics, polymers of lactic and glycolic acid, and other polymers, have been explored *in vitro* for tissue engineering. Some methods like stem cell and platelet-rich plasmas (PRP) therapy have been combined with tissue engineering to optimize regeneration of injured tissues.^{5,6}

Biomaterials for skeletal muscle tissue engineering

Biomaterials with high biocompatibility characteristics *in vitro* and *in vivo* are important for tissue engineering and regenerative medicine. The aim of biomimetic scaffolds for skeletal muscle tissue engineering is to preserve the major cellular and tissue functions. Musculoskeletal engineered scaffolds can accomplish this by regulating the cellular attachment, survival, and differentiation of normal regenerated muscle tissue.^{7,8} Most important biomaterials commonly used for skeletal muscle tissue engineering are

extra cellular matrix (ECM) components such as collagen, fibrin, gelatin, hyaluronic acid, chitosan, and keratin.^{9,10} In addition to the naturally components of ECM, synthetic polymers like polycaprolactone, poly-L-lactic acid, and polylactic-co-glycolic acid are used widely by researchers in musculoskeletal tissue engineering.^{11,12} However, these synthetic polymers have some disadvantages, including poor cellular attachment, toxicity, and potential degradation into byproducts that prevent regeneration.¹³ A main goal for tissue engineering is *in vivo* transplantation as a therapeutic pathway to restoring injured muscles. There has already been successful preclinical progress in constructing skeletal muscle *in vitro* upon bioengineered scaffolds with acceptable tissue viability. Acellular biological scaffolds have produced and maintained muscle volume with little loss over six months after transplantation. This tissue has been successfully regenerated with contractile response superior to the original injured tissue.^{14,15}



Figure-1. New techniques for regeneration after a sport injury

Recovery of musculoskeletal injuries

Musculoskeletal injuries may develop gradually due to prolonged exposure to causative agents or suddenly due to an abrupt and severe strike to part of the musculoskeletal system.¹⁶ The management of articular cartilage defects is one of the most challenging clinical problems for orthopedic surgeons. Cartilage has little capacity for regeneration after injury, and disease or injury of the joints related to cartilage damage is one of the most common complaints of orthopedic patients.¹⁷ In recent years, some tissue engineering approaches have been developed for improving the

regeneration of cartilage by transplanting cells or engineered constructs into the injured tissue.¹⁸ Also, another approach for tissue engineering involves implantation of cartilaginous tissue created synthetically from articular chondrocytes and biodegradable polymer scaffolds.¹⁹

In some studies, osteochondral progenitor cells have been used to regenerate tissue to fill large defects of the articular cartilage in rabbit knee.²⁰ Currently, one of the most important clinical treatments for articular cartilage injury is to create microfractures within the subchondral bone to stimulate cartilage regeneration.²¹ However, the repair tissue in these conditions lacks the biomechanical properties of normal articular cartilage and regeneration is rarely successful. Thus, researchers continue to explore new strategies using cell therapy.²²

The inconsistent outcomes of the microfracture method prompted the development of the autologous chondrocyte implantation (ACI) technique. To perform this technique, a full-thickness sample from a low-weight-bearing region of the joint is first collected by biopsy. This tissue provides chondrocytes that are then cultured *in vitro*. The chondrocytes are then implanted into the cartilage defect and covered by a membrane ([Figure-2](#)).²³ This method has two major benefits: using a patient's own cells avoids potential immune response or viral infections from transplanting allogeneic cells or foreign materials, and a small biopsy of cartilage minimizes complications at the chondrocyte donor site.²³

Among the different types of stem cells in the body, bone marrow mesenchymal stem cells (MSC) have many potential advantages for treating skeletal injuries. They are comparatively easy to isolate and proliferate. They are also capable of differentiating into both cartilage and bone and have been shown to be adequate for regenerating cartilage.^{24,25} Most cartilage regeneration work using MSC has been with bone marrow MSC. Bone marrow aspiration can be painful; thus, harvesting stem cells from other sources is beneficial.²³ Adipose-derived stem cells are easier to access, isolate, and culture. Multi-lineage potential, immunosuppressive activities, and limited immunogenicity are their positive features, and they have been used widely for regeneration.^{6,22} Similarly, human adipose tissue-derived stromal cells can be used to induce expression of gene and matrix markers of cartilage for regeneration and repair of cartilage lesions.²⁶

Mechanical stimuli for meniscus regeneration

The menisci of the knee protect the articular cartilage and function in load transmission, stabilization, and shock absorption.^{27,28} Injuries to the menisci are very common and one of the more challenging problems in sports medicine.²⁹ The mechanical environment has an essential effect on the biological features of a tissue and is necessary for the development and maintenance of load-bearing tissues.³⁰ Changes in the loading of a joint may alter the biochemical

composition, gene expression, and mechanical properties of tissues.^{31,32}

In several studies, reduced mechanical stimulation was shown to compromise the mechanical properties and function of the menisci.³³ Gentle motion may prevent adverse effects of immobilization and promote meniscal repair. These findings show the important role of mechanical stimulation in the development, growth, repair, and regeneration of a damaged menisci.^{34,35}

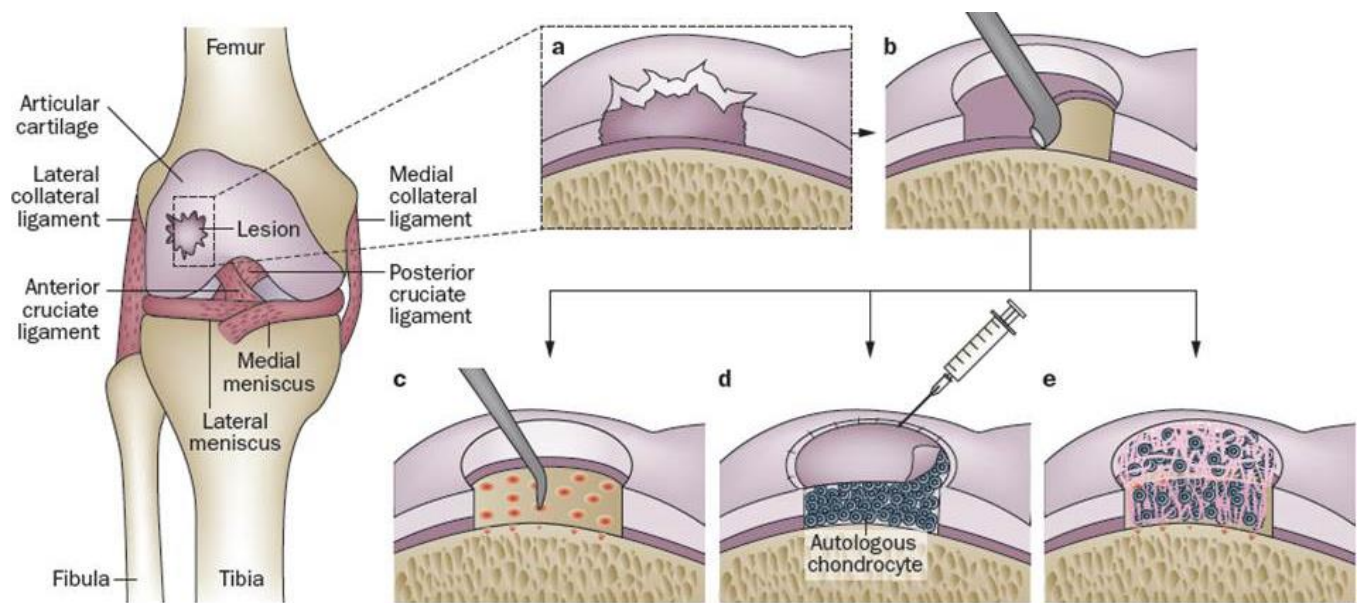


Figure-2. Microfracture techniques for regeneration of cartilage. (a) Shows the full-thickness focal chondral lesion. (b) The lesion is debrided to ensure healthy, stable margins for integration of the host tissue with the neotissue. (c) Microfracture channels are created using a 45° awl. The channels allow MSC to migrate from the marrow to the cartilage defect. (d) ACI. The debrided lesion is filled with 12–48 million autologous chondrocytes and covered with a periosteal flap or mixed collagen type I and type III membrane. (e) MACI. The autologous chondrocyte population is expanded *in vitro* and then seeded for 3 days onto an absorbable 3D (collagen types I and III or hyaluronic acid) matrix prior to implantation. The cell-seeded scaffold is then secured into the lesion with fibrin glue. Abbreviations: ACI, autologous chondrocyte implantation; MACI, matrix-assisted autologous chondrocyte implantation; MSC, mesenchymal stem cell.²³

Platelet-rich plasma (PRP) therapies in sports medicine

Platelet-rich plasma (PRP) is widely used clinically for various sport-related injuries due to its potential healing properties for tendons and ligaments through the employment, proliferation, and differentiation of cells.^{36, 37} The use of platelets in regeneration combined with other healing factors has been a therapeutic treatment since the late 1990s. After PRPs were introduced as autologous blood products, they came to play a pivotal role in wound healing.³⁸

Platelet-rich plasma therapies in tendon injuries

Tendons have a low metabolic rate that causes slow healing

after injury. Some agents, such as growth factors, can stimulate tendon repair.³⁹ Several studies have demonstrated that like PRP, a pool of growth factors released after an injury significantly promotes the proliferation of human tendon cells and stimulates them to produce additional growth factors, such as vascular endothelial growth factor and hepatocyte growth factor,⁴⁰ which have paracrine effects that promote angiogenesis and directly contribute to tendon repair.⁴¹ Further research with animal models established that repetitive injection of PRP into an injured tendon improves tendon regeneration by increasing cell number and angiogenesis.⁴² Other researchers have shown that PRP

injections for one week after surgery increase tendon regeneration.⁴³ Others have recently reported that local injected PRP is an effective activator of cells for amplification of the initial tendon regeneration process.⁴⁴

Tendon injuries are usually traumatic and acute, but in some cases they can become chronic. One important example in sports medicine is tendinopathy, which is characterized by tendon pain, localized tenderness, and inflammation that impairs athletic performance.³⁹ It has been suggested that PRP injections might be useful for restoring the normal tissue composition and avoiding further degeneration in this condition.⁴⁵ Some studies have reported that PRP injections can be effective in treating severe medial epicondylitis, reducing pain, and increasing performance.⁴⁶

Platelet-rich plasma therapies in joint injuries

Risks of joint damage have increased in athletes, and a wide array of joint disorders have been observed. Anterior cruciate ligament (ACL) rupture is a particularly common sports injury.⁴⁷ For ACL injury, surgical reconstruction is the best therapeutic choice; however, with this repair there is often persistent laxity and instability of the knee. In view of this poor recovery, and given its clinical importance, clinicians and researchers have attempted to prepare tissue-engineered ligaments using natural biomaterials.⁴⁸ One novel method for better regeneration of the injuries structure is using tissue-engineered scaffolds that are enriched with PRP. The role of PRP in a tissue-engineered scaffold is to provide biological cues for cell migration, proliferation, angiogenesis, and remodeling.⁴⁸ Research has demonstrated that the intra-articular administration of PRP to avulsed articular cartilage in a young soccer player produced good results.⁴⁹ In a rabbit model, cartilage defects that were treated with PRP showed better mechanical properties.⁴⁹ Mishra et al. showed pain reduction in chronic severe elbow tendinosis after PRP treatment.⁴⁵

Platelet-rich plasma therapies in treating osteoarthritis

Osteoarthritis, the most common joint disease,⁵⁰ often presents in athletes after they retire from competition, but following earlier traumatic injury.⁵¹ Soccer players have an increased prevalence of osteoarthritis compared to other athletes. PRP therapies can restore hyaluronic acid concentration within the joint and promote angiogenesis, which may be helpful for these individuals.⁵² Treatments with

PRP can also maintain tissue homeostasis, regulate inflammation, inhibit chondrocyte apoptosis, and promote collagen synthesis.^{53,54} Because of these properties, PRP can be a feasible treatment option for patients suffering from osteoarthritis of the knee.⁵⁵

When platelets are activated, growth factors are secreted rapidly.⁵⁶ These growth factors, along with other factors like cytokines, chemokines, and proteins stored within the platelet, have been shown to stimulate chondrocyte and proliferation of chondrogenic mesenchymal stem cells.⁵⁷ Exercise is one of the first treatments for osteoarthritis and is also a safe and effective method for reducing pain and improving functional recovery in osteoarthritis patients.⁵⁸ However, exercise has some limitations. In particular, exercise can be painful for patients with osteoarthritis. Therefore, intra-articular PRP injection may be better tolerated by osteoarthritis patients.⁵⁹

Platelet-rich plasma therapies in muscle tears

Musculoskeletal injuries are relatively common problems in sports medicine and can lead to physical disability and severe pain.⁶⁰ Muscle lesions occur in one third of all sports injuries, while muscle strain has a 12–16% prevalence among athletes.⁶¹

The regeneration of strained muscle occurs slowly, and muscle injuries keep athletes out of action for approximately 4–12 weeks.⁶² Some standard therapeutic interventions for this condition include rest, compression, ice, photothermal therapy, hyperbaric oxygen therapy, and use of nonsteroidal anti-inflammatory medications.⁶³ However, clinical evidence to support the efficacy of these treatments is sparse, and they are commonly used as empirical medicine.⁶³ In these cases, PRP therapy is applied for general remedies, because of its potential in accelerating muscle healing.³⁹ One important property of PRP is that it stimulates platelets to release growth factors that can aid in the healing process.⁶⁴ Research has further shown that PRP therapy can promote the proliferation of skeletal muscle cells and upregulate the protein expressions of cyclin B1, cyclin A2, PCNA, cdk1, and cdk2.⁶⁵ Terada et al. showed that the addition of an anti-fibrotic agent like the angiotensin II receptor blocker losartan to PRP therapy can enhance muscle healing after injury by stimulating muscle regeneration and angiogenesis while preventing fibrosis in muscle tissue.⁶⁶

New methods in stem cells therapy for treating osteoarthritis

Stem cell therapy with MSC has been proposed as a treatment for osteoarthritis.⁶⁷ MSC are multipotent, which means they have ability to differentiate into other cells like osteoblasts, chondrocytes, adipocytes, myoblasts, and fibroblasts, depending on the conditions and their potential for differentiation.^{6,68} Bone marrow MSC are popular cells for use in cell therapy, which is approved by the FDA.⁶⁹ However, using these cells is difficult because of donor site morbidity, pain, and a low number of cells after harvest.⁷⁰ Thus, researchers have been led to use other sources of MSC.⁷¹ Potential sources for MSC include muscle, synovial membrane, periosteum, and adipose tissue. All MSC have similar characteristics and, depending on their differentiation potential, can mature into wide variety of cells.^{6,71} Adipose-derived stem cells (ASC) are an easily accessible source of adult stem cells that are particularly promising candidates for regenerative medicine.⁷² Adipose tissue is a mesodermally-derived complex tissue that contains adipocytes as well as a stromal population which includes non-adipocyte cells, such as stem cells.⁷³ The ability of ASC to differentiate into chondrocytes makes them an excellent candidate for use in treating osteoarthritis patients.⁷⁴ The properties of ASC also make them attractive for tissue engineering and regenerative medicine.⁷⁵

Conclusions

This review focuses on new techniques for treating sport injuries. Recent advances in tissue regeneration techniques after sports injuries include stem cell therapy, PRP therapy, the microfracture method, and the mechanical stimuli method. These new therapeutic techniques accelerate physiological healing by supporting cellular viability and binding and reducing pain and inflammation. Such strategies are needed for improving long-term, functional outcomes for injured athletes. It is clear that more research is needed before these therapies can be widely applied in the context of sports medicine.

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Authors' Contribution

AA conceived the review, wrote and edited significant sections of the manuscript, and assisted with the literature review. SZ wrote and edited sections of the manuscript, ASA wrote and edited sections of the manuscript and contributed expertise to the written material. RW edited significant sections of the manuscript and contributed expertise to the written material. All authors reviewed and approved the final manuscript.

Conflict of Interests

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