

Review

Concept of exosome therapy as a treatment for sports injuries to ligaments in the field of orthopaedics: a brief review

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Abstract

Exosome therapy has emerged as a promising treatment option for sports-related ligament injuries within the field of orthopaedics. Ligament injuries, commonly sustained during physical activities involving rapid or high-impact movements such as running, jumping, or twisting, can lead to pain, swelling, and limited joint mobility. These injuries, if not appropriately managed, can result in long-term functional impairment. Exosomes, small extracellular vesicles rich in proteins, RNA, and growth factors, play a crucial role in cellular communication and tissue regeneration. This study explores the potential of exosome therapy to enhance ligament healing by modulating inflammatory responses, stimulating fibroblast proliferation, and promoting angiogenesis. These mechanisms work synergistically to accelerate tissue repair and improve the biomechanical strength of ligaments, making exosome therapy a more effective treatment option compared to conventional approaches. Unlike traditional stem cell therapy, exosome therapy does not carry the same high immunogenic risks and technical challenges. Preclinical studies have demonstrated the ability of exosomes to reduce inflammation, prevent fibrosis, and improve ligament regeneration. Moreover, exosome therapy can be combined with biomaterials like hydrogels to optimize stability and retention at the injury site, further enhancing its therapeutic potential. Despite promising results in preclinical trials, further research is required to determine optimal dosages, delivery methods, and long-term safety profiles. This review aims to provide insights into the concept of exosome therapy and its potential as a novel, low-risk, and effective treatment for ligament injuries in orthopaedic practice.

Keywords: Exosome; ligament; sports injury; orthobiologic therapy

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Introduction

Ligament injury on sports are common, particularly among athletes and active individuals, as ligaments are crucial for maintaining joint stability and function by connecting bones. Ligament injury on sports, particularly anterior cruciate ligament (ACL) ruptures represent a major burden in active populations worldwide. Recent data from elite European football report an ACL injury incidence of around 0.40 ruptures per 1,000 match hours, while professional Asian leagues show overall injury rates of approximately 5.1 per 1,000 exposure hours with ACL ruptures contributing disproportionately to time-loss.^{1,2} Hospital-based and national reports from Indonesia similarly indicate that ligament injuries constitute a substantial proportion of knee pathologies in young, physically active individuals, especially those participating in football, basketball and martial arts.³ Ligament injuries often result from excessive mechanical trauma, such as sudden acceleration, deceleration, abrupt rotation, or hard impacts. A common example is ACL injuries in the knee, typically caused by pivoting movements involving rotation and excessive valgus stress. The pathophysiology involves collagen fiber rupture, local inflammation, extracellular matrix degradation, and immune cell recruitment, leading to joint instability and a higher risk of complications like osteoarthritis over time.⁴ Traditional treatment includes conservative methods like immobilization, physical therapy, and anti-inflammatory medications, with surgical reconstruction for complete ruptures. However, ligament healing is often slow and incomplete due to limited vascularization and the complex tissue structure. Recent advances in regenerative therapies, such as stem cells, growth factors, and biomaterials, aim to accelerate healing by enhancing ligament integrity and reducing excessive inflammation that impedes tissue regeneration.^{5,6} Exosome therapy has emerged as a promising innovation in orthobiologic therapy, with exosomes extracellular vesicles containing proteins, RNA, and growth factors—acting as mediators to stimulate tissue regeneration. In ligament injuries, exosomes promote fibroblast proliferation, angiogenesis, and inflammation modulation, improving healing speed

and quality compared to conventional therapies.⁵ Recent studies suggest that exosome application improves the biomechanical strength of healed ligaments and enhances tissue integration with bone, offering a safer and more effective treatment. However, further research is necessary to optimize isolation methods, dosage, and long-term safety for broader clinical application.⁷

Sports Injuries to Ligaments

Ligament injuries are a common issue in orthopaedics, particularly in athletes and active individuals. Ligaments are connective tissues made primarily of type I collagen and elastin, connecting bones and limiting joint movement. These structures are vulnerable to damage from repetitive trauma or direct impact during sports, leading to partial or complete tears, joint dysfunction, pain, and limited movement. Injuries often result from excessive torsional forces that exceed the ligament's elastic capacity. Post-injury inflammation can hinder natural healing, making proper treatment crucial to prevent long-term complications like joint instability and osteoarthritis.⁸

Pathophysiology of Ligament Injuries

Ligament injuries occur when mechanical forces exceed the elastic capacity of the ligament tissue, causing partial or complete tears in the collagen fibers. These injuries often involve excessive rotation, valgus load, or abnormal bone translation in the joint, leading to micro- to macroscopic disruption of the ligament structure. This damage triggers bleeding, swelling, and an inflammatory response, releasing mediators like histamine and prostaglandins, which cause pain and edema. Infiltrating inflammatory cells, such as neutrophils and macrophages, further damage the ligament by releasing proteolytic enzymes that degrade the extracellular matrix. This inflammatory process exacerbates tissue degradation and alters the ligament's microenvironment, impairing its function. Ligament injuries also result in biomechanical dysfunction, particularly the loss of passive stability, which increases the risk of further damage to supporting structures like the meniscus and articular cartilage, potentially leading

Table 1. Ligament Injury Grading Classification¹¹

Grade	I	II	III
Description	Strain – stretch Mild Injury	Partial tear Moderate injury • IIa – mild partial tear <50% • IIb – severe partial tear >50%	Complete tear Serious injury
Fiber continuity	Intact ligament fibers	Incomplete fiber disruption	Complete fiber disruption
Ligament caliber	Dense ligament fibers are normal or thickened	Ligament thickening or thinning	No ligament fibers at the site of the tear
Tension	Tense	Partial loss	Complete disappearance with retraction
Avulsion fragment	-	Possibly	Possibly
Findings in the early acute stage	-	Ligament edema thickening	Ligament edema thickening

to post-traumatic osteoarthritis. Risk factors such as weak muscles, neuromuscular imbalances, and improper dynamic movements contribute to the high incidence of ligament injuries by increasing mechanical stress on the ligament, highlighting the importance of evaluating biomechanical and neuromuscular risk factors to prevent injuries, especially in athletes or physically active individuals.^{9,10,12}

Clinical Sports Injuries on Ligaments

Ligament injuries in sports are common, especially in activities involving rapid and sudden movements like football, basketball, tennis, and badminton. These injuries typically present with sudden severe pain, swelling around the injured joint, bruising, and limited range of motion. Patients often feel instability or a “giving way” sensation in the joint and may hear a “pop” at the time of injury. These symptoms indicate damage to the ligament’s collagen fibers and local inflammation, resulting in pain and edema. Swelling may also be accompanied by hemarthrosis (blood accumulation in the joint), increasing discomfort and limiting function.^{12,13} Ligament injury grading is based on the severity of the

tear and loss of function, with Grade I (mild) injuries involving small tears without joint instability, Grade II (moderate) injuries causing partial tears and some instability, and Grade III (severe) injuries involving complete tears with total loss of function and stability. Grading is important for determining treatment and prognosis, with Grade III injuries typically requiring more aggressive management, including potential reconstructive surgery.¹⁰ The European Society of Radiology (EPOS) outlines the classification of ligament injuries based on grading, as shown in (Table 1).

Ligament Therapy For Sports Injuries

Conventional therapy for ligament injuries typically involves both conservative and operative approaches tailored to the type and severity of the injury. Non-operative management includes pain modulation, swelling control, physiotherapy modalities, and a gradual rehabilitation exercise program, while operative intervention is reserved for severe injuries that require reconstruction. A multidisciplinary approach and individualized therapy are crucial for optimal outcomes and to minimize long-term complications like joint

instability and osteoarthritis.¹⁴ Physiotherapy rehabilitation plays a key role in restoring joint function and strengthening supporting muscles, with exercises focusing on increasing range of motion (ROM), strengthening the quadriceps and hamstrings, and improving neuromuscular control. These exercises begin with comfortable movement and progress to functional activities such as balance training, proprioception, and closed-chain exercises to enhance joint stability. The goal is to prevent muscle atrophy and reduce re-injury risk by improving knee joint mechanics and stability.¹⁵ In cases of severe ligament injuries, such as total tears of the anterior cruciate ligament (ACL), ligament reconstruction using tendon grafts (e.g., patellar or hamstring tendon) is often necessary to restore mechanical stability and allow patients to resume normal activities. Post-operative rehabilitation is critical for achieving maximum functional recovery, starting with pain reduction, swelling control, and range of motion maintenance, followed by muscle strengthening, balance training, and preparation for return to competitive sports. The success of this therapy depends on accurate diagnosis, patient adherence to rehabilitation, and the selection of appropriate treatment methods for the injury.^{10,14}

Definition and Characteristics of Exosomes

Exosomes are nano-sized extracellular vesicles (ranging from 40 to 160 nm) produced by nearly all eukaryotic cell types through an endosomal biogenesis pathway. They form from the invagination of the plasma membrane and the creation of multivesicular bodies (MVBs), which release intraluminal vesicles into the extracellular space via exocytosis (Figure 1). With a lipid bilayer membrane similar to cells, exosomes contain biomolecules like proteins, lipids, DNA, mRNA, and microRNA, serving as agents of intercellular communication that facilitate the exchange of materials and biological signals, influencing target cell behavior in various physiological and pathological processes such as cancer development, neurodegeneration, and infections. Due to the protection of the lipid bilayer, the proteins and RNA within exosomes remain intact during their journey through biological fluids, making them an effective means of delivering functional molecules to target cells. The composition of exosomes can

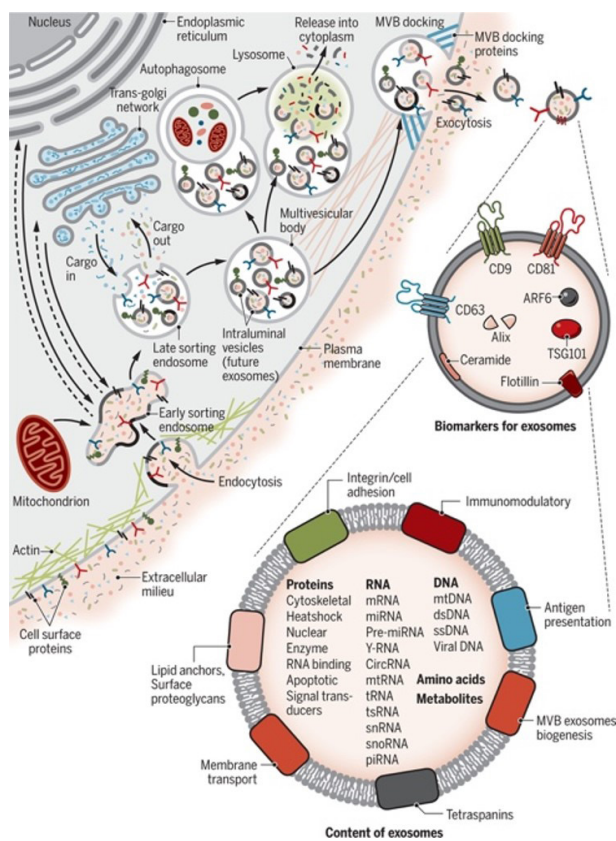


Figure 1. Exosome Biogenesis and Identification. Exosome surface proteins include tetraspanins, integrins, immunomodulatory proteins, and more. Exosomes can contain various types of cell surface proteins, intracellular proteins, RNA, DNA, amino acids, and metabolites. Fluid and extracellular constituents such as proteins, lipids, metabolites, small molecules, and ions can enter the cell, along with cell surface proteins, through endocytosis and plasma membrane invagination.¹⁶

be influenced by the microenvironment and metabolic status of the parent cell, making them a key subject in modern therapies and liquid biopsy diagnostics. Exosome products play a crucial role in intercellular communication, reflecting the physiological or pathological state of their parent cells, and are isolated using methods like differential ultracentrifugation, size-exclusion chromatography, immunoprecipitation, and polymer precipitation, each with varying advantages and limitations regarding quality and purity. Standard characterization includes size and morphology analysis using electron microscopy or nanoparticle tracking analysis, along with the identification of protein

markers such as CD9, CD63, and CD81 using Western blotting and flow cytometry, as per the International Society for Extracellular Vesicles (ISEV) guidelines. The development of effective isolation and characterization techniques is crucial for ensuring reproducibility and quality in exosome products for diagnostic and therapeutic applications, including regenerative therapy and orthobiologic therapy.^{16,17,18}

Exosome Working Mechanism in Ligament Regeneration

In the context of ligament regeneration, exosomes function as carriers of biological signals that regulate cell proliferation, migration, and differentiation at the site of ligament injury. By delivering messenger RNA (mRNA) and microRNA (miRNA), exosomes stimulate the synthesis of proteins necessary for repairing and replacing damaged ligament tissue, while also regulating immune responses and reducing excessive inflammation to create a favorable healing environment.^{19,20} Exosome mechanisms in ligament regeneration include stimulating angiogenesis (formation of new blood vessels), which is essential for supplying nutrients and oxygen to regenerating tissue. Exosomes from mesenchymal stem cells (MSCs) contain growth factors such as VEGF (vascular endothelial growth factor), TGF- β (transforming growth factor-beta), and FGF (fibroblast growth factor), which support the growth and maintenance of ligament tissue. Additionally, exosomes inhibit apoptosis (programmed cell death) and fibrosis, which can disrupt regeneration, while enhancing collagen production and extracellular matrix components vital for ligament strength and elasticity.^{20,21} Moreover, exosomes regulate local immune modulation by increasing anti-inflammatory cytokines like IL-10 and suppressing pro-inflammatory cytokines, contributing to reduced inflammation and fibrosis that could damage ligament structure. This anti-inflammatory effect is essential for accelerating regeneration and restoring the mechanical function of ligaments. Recent studies suggest that MSC-derived exosomes in ligament regenerative therapy accelerate recovery while reducing inflammatory complications commonly seen after ligament injuries.^{20,21}

Exosome Therapy in Sports Ligament Injuries

Exosome therapy for sports ligament injuries is a groundbreaking innovation in regenerative medicine that utilizes small extracellular vesicles produced by cells, particularly mesenchymal stem cells (MSCs). These exosomes serve as carriers of biological signals, delivering molecules like proteins, RNA, and growth factors that regulate tissue repair processes. In ligament injuries, exosomes modulate the inflammatory process, which is crucial in early healing stages, and support fibroblast proliferation and differentiation for extracellular matrix synthesis, essential for reconstructing damaged ligaments.^{5,7} Preclinical studies show that exosome administration can enhance biomechanical strength by stimulating angiogenesis (new blood vessel formation) and promoting osteogenesis at the tendon-ligament interface, reducing the risk of graft failure or tissue reconstruction failure.²¹ Exosomes also regulate macrophage polarity towards an anti-inflammatory phenotype, helping to suppress excessive inflammation that can impede healing.^{7,20} This therapy offers advantages over direct stem cell treatments, such as reduced immunogenicity and technical complications, and can be combined with biomaterials like hydrogels to enhance stability and retention at the injury site, improving clinical effectiveness and recovery time.^{20,23} Overall, exosome therapy shows great potential as an alternative and adjunct in treating sports ligament injuries, with mechanisms that modulate inflammation, stimulate tissue regeneration, and repair microstructures of damaged ligaments. Further clinical trials are needed to evaluate dosages, administration methods, and safety profiles, so this therapy can be widely adopted in clinical sports medicine.²⁴ In orthobiologic therapy, exosome therapy offers a new alternative for repairing musculoskeletal tissues, including bones, ligaments, tendons, and cartilage, and shows promise for treating conditions such as osteoarthritis, ligament injuries, and bone fractures. It can become a standard adjunctive treatment, promoting tissue regeneration, improving biomechanical function, and enhancing patients' quality of life, although challenges remain in developing stable exosome products, optimal dosages, and best delivery methods.²⁵ Additionally, combining exosomes with scaffolds or

hydrogels could enhance therapy targeting, enabling personalized treatment designs based on injury type and severity.²⁶ Exosome therapy is expected to revolutionize orthobiologic therapy, especially for acute and chronic injuries, with better regenerative outcomes and minimal side effects.²⁷ Despite still being in development, its potential as a low-risk, effective regenerative therapy makes it a primary focus for research in the coming decade.²⁸

Conclusion

Sports ligament injuries are common in activities involving sudden movements like running, jumping, or twisting. These injuries can cause pain, swelling, and limited joint function. Exosome therapy, an innovative approach, offers potential for faster and better healing of ligament tissue. Exosomes, small vesicles containing proteins, RNA, and growth factors, promote cell communication, fibroblast proliferation, angiogenesis, and

inflammation regulation, improving ligament regeneration compared to conventional therapies. Exosome therapy has advantages, such as modulating local inflammation and stimulating ligament repair without high immunogenic risks seen in stem cell therapy. Preclinical studies show its effectiveness in improving ligament strength and reducing post-injury complications, but more research is needed to determine optimal dosages, administration, and long-term effects for broader clinical use.

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Conflict of Interest

The authors declared no conflicts of interest.

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