Utilizing mesenchymal stem cells to improve the healing process of the medial collateral ligament in the knee

Basem Ali Zogel¹, Hussam Masoud Darraj², Zenat Ahmed Khired¹*, Fahad Yahya AlArishi³

ABSTRACT

The healing process of the medial collateral ligament (MCL) in the knee is often slow, resulting in adverse outcomes such as scar tissue formation, joint instability, limited range of motion, and an increased risk of re-injury. Consequently, novel therapeutic strategies are imperative to enhance MCL healing. Mesenchymal stem cells (MSCs) have emerged as a promising treatment modality due to their robust proliferative ability, reparative potential, and ability to differentiate into various cell types. Although preclinical studies have shown encouraging results for MSC-based approaches in MCL injuries, clinical studies in the orthopedic literature remain scarce. This review provides an overview of the MCL, conventional treatments for MCL injuries, and recent advances in MSC research for augmenting MCL healing. MSC-based approaches hold promise as a future therapeutic option to improve MCL healing. Nonetheless, further research is warranted to establish the effectiveness and safety of this emerging treatment modality.

Keywords: Medial collateral ligament (MCL), mesenchymal stem cells (MSCs), healing, injury.

Introduction

The medial collateral ligament (MCL) is a vital structure in the knee joint, connecting the femur to the tibia and playing a key role in joint stability [1]. MCL injuries are commonly caused by direct trauma or excessive stress during physical activity, ranging from minor sprains to complete tears depending on the severity of the injury [2]. These injuries can result in pain, swelling, instability, and long-term disability [2]. Current treatment options for MCL injuries primarily involve rest, ice compression, physical therapy, and surgical intervention for severe cases [3]. However, these treatments often yield suboptimal outcomes, particularly in cases of complete tears, leading to prolonged recovery times and reduced quality of life [3]. Mesenchymal stem cells (MSCs) have emerged as a promising therapeutic avenue for MCL injuries due to their regenerative potential and ability to differentiate into various cell types [4]. Additionally, MSCs have been shown to modulate the immune response, reduce inflammation, and promote tissue repair, making them an attractive option for MCL injury treatment [5]. This review provides a comprehensive overview of the MCL, including its anatomy, biomechanics, and existing treatment methods, while highlighting its limitations. Moreover, this paper presents the latest research advancements in MSC-based approaches aimed at enhancing the biological function of the MCL, a complex ligament. The literature search encompassed various databases such as PubMed, Google Scholar, and CINAHL, utilizing keywords like MCL, MSCs, ligament healing, cell-based treatment, and MCL. Ten articles were initially identified, with three duplicates being removed, resulting in the inclusion of seven articles published between 2002 and 2018.

Anatomy

The MCL is a wide ligament located on the inner side of the knee joint, extending from the femur’s medial epicondyle to the medial tibial plateau [6,7]. It consists of
two layers with distinct fiber orientations. The superficial layer comprises short parallel bundles of collagen fibers, while the deep layer consists of longer oblique collagen fibers [6-8]. These layers are separated by a thin layer of connective tissue [8]. Surrounding the MCL is a synovial sheath that connects to the knee’s joint capsule, reducing friction during knee movement [6]. The MCL is adjacent to the pes anserinus, which is formed by the combined tendon of the sartorius, gracilis, and semitendinosus muscles [1,2]. Innervation to the MCL is provided by the saphenous nerve, supplying sensory innervation to the knee’s medial aspect [9]. Blood supply to the MCL is derived from the medial geniculate artery and the descending genicular artery [10]. Crucially, the MCL plays a vital role in stabilizing the knee joint, particularly during valgus stress, by preventing excessive valgus motion and lateral displacement of the tibia relative to the femur [1,6].

Biomechanics of the (MCL)

The MCL serves as the primary restraint against valgus stress at the knee joint, as well as contributing to the resistance of anteromedial and posterior lateral rotation of the tibia [6,11]. Its tension is highest during full extension and reduces during flexion. Similarly, it is taut during internal rotation and less taut during external rotation. The MCL exhibits impressive tensile strength, capable of withstanding loads up to 230 N/mm² before failure [12]. Notably, it demonstrates a nonlinear stress-strain relationship, enabling it to withstand substantial loads at low deformation levels but leading to failure at higher levels of deformation. The ultimate tensile strength of the MCL is estimated to be around 1,500 N [6,12].

Collaborating with other static and dynamic stabilizers of the knee joint, the MCL plays a crucial role in maintaining joint stability throughout various movements. Additionally, the medial meniscus and the posterior oblique ligament (POL) contribute to the resistance against valgus stress [13]. The POL, which thickens the deep layer of the MCL, extends from the posterior aspect of the femoral condyle to the intercondylar notch of the tibia, providing additional stability during rotational movements. It is most taut during flexion and internal rotation [13]. Similarly, the meniscofemoral ligament, another thickening of the MCL’s deep layer, connects the posterior horn of the medial meniscus to the medial femoral condyle, contributing to the stabilization of the medial meniscus during knee flexion [14].

MCL injuries often occur concomitantly with other knee injuries, such as anterior cruciate ligament (ACL) injuries, and the severity of MCL injuries can vary significantly. Management approaches for MCL injuries encompass nonoperative methods, surgical repair, or reconstruction, depending on the injury’s severity [2,15].

Etiology and Mechanism of MCL Injury

Traumatic injuries to the MCL commonly occur when a direct valgus force is applied to the knee joint, often observed in contact sports or motor vehicle accidents [16]. Conversely, non-traumatic MCL injuries typically stem from chronic overuse, repetitive microtrauma, or degenerative changes in the ligament [17]. The primary mechanism underlying MCL injury is the application of valgus stress to the knee joint. Valgus stress compresses the medial side of the joint while stretching the lateral side, leading to tension and potential stretching or tearing of the MCL [18]. The severity of the injury is dependent on the magnitude of the valgus force applied to the knee joint. Minor injuries may involve stretching or partial tearing of the MCL, whereas severe injuries can result in complete rupture of the ligament [19]. Moreover, factors such as age, physical condition, weight, and underlying medical conditions may also influence the injury’s severity [20].

Diagnosis of MCL Injury

To diagnose an MCL injury, a comprehensive history and physical examination are crucial. Patients often provide a history of a traumatic knee injury, such as a blow to the lateral knee or a twisting injury, accompanied by pain and swelling on the medial side of the knee [2,21]. During the physical examination, tenderness along the medial joint line and laxity to valgus stress are commonly observed.

The degree of laxity can be graded on a scale of I to III, with Grade I indicating slight laxity and Grade III indicating complete disruption of the MCL [15,22]. Radiographic imaging, including X-rays and magnetic resonance imaging (MRI), is valuable for diagnosing MCL injuries and ruling out other knee injuries. X-rays help identify fractures, while MRI provides detailed information on the knee’s soft tissue structures, including the MCL [23]. Stress radiographs, involving the application of valgus force to the knee while taking X-rays, can also assess the degree of MCL laxity by evaluating medial joint opening [24,25]. In certain cases, diagnostic injections may be utilized to confirm the MCL injury diagnosis. These injections involve injecting a local anesthetic into the MCL to determine if it relieves pain and restores stability to the knee joint [26]. Distinguishing MCL injury from other knee injuries, such as ACL injury, posterior cruciate ligament injury, or meniscal injury, is vital as the management approaches differ [27].

Treatment of MCL Injury

Non-operative treatments

Most isolated grade I and grade II MCL injuries can be managed non-operatively with a combination of rest, ice, compression, elevation, and physical therapy [2,21]. During the acute phase, rest and limited weight-bearing aid in pain and swelling reduction. Crutches may be required for ambulation [15,22]. Ice application for 20 minutes at a time, several times a day, along with compression wraps or sleeves, can further alleviate pain and swelling [28,29]. Physical therapy plays a critical role in non-operative management, focusing on therapeutic exercises to enhance knee joint range of motion, strength, and stability. Modalities such as ultrasound and electrical stimulation may also be employed to reduce pain and
swelling [30]. Bracing can provide support and stability during the healing process, with knee braces limiting valgus stress on the knee and protecting the MCL [2,23]. The duration of non-operative management depends on the injury’s severity and the patient’s response to treatment, with most grade I and grade II injuries healing within 6 to 8 weeks [31]. Gradual return to activity, guided by a physical therapist or physician, is advised, and athletes may benefit from wearing a protective brace or tape for support during activity [32].

**Operative treatment**

Although most MCL injuries can be managed non-operatively, surgical intervention may be necessary for grade III injuries or combined injuries involving other knee joint structures [2,21]. Surgical intervention is typically considered when the MCL is completely torn or when significant instability in the knee joint exists, which can lead to recurrent injuries or long-term joint damage. The decision for surgery is based on the injury’s severity, location, the patient’s activity level, and goals [15,22]. Grade III MCL injuries often require surgical intervention due to the high risk of long-term instability and recurrent injury [24]. Surgical options include primary repair, reconstruction, or augmentation, with the choice depending on the injury’s severity, location, patient’s activity level, and goals [27]. Primary repair involves suturing the torn ends of the MCL, suitable for proximal or distal tears in grade III injuries and distal tears in grade II injuries [33]. Reconstruction entails replacing the torn MCL with a graft, such as the semitendinosus or gracilis tendon, appropriate for mid-substance tears in grade III injuries and combined injuries involving other knee joint structures [6,34]. Augmentation involves reinforcing the torn MCL with a graft, such as the iliotibial band or the lateral collateral ligament, commonly used in chronic MCL insufficiency or recurrent instability [27,35]. The choice of surgical technique also considers the patient’s activity level and goals, with athletes potentially requiring a more aggressive approach to restore stability and function to the knee joint [36]. Generally, surgical intervention is considered when non-operative management fails to provide adequate pain relief, function, and stability to the knee joint [16,23].

**Advent of MSCs as Cell Therapy for Enhanced MCL Healing**

While most isolated MCL injuries are managed non-operatively due to their favorable healing capacity, surgical intervention may be necessary for high-grade or combined injuries. However, even with non-operative management, the biomechanical properties and function of the MCL do not fully recover, leading to an increased risk of chronic symptoms and re-injury. Previous research indicates that the inherent properties of the healing ligament remain compromised over time, exhibiting less organization and smaller collagen fibrils, resulting in inferior mechanical strength [37,38]. Persistent ligament laxity increases the risk of further joint and surrounding structure damage [39]. To address the limited intrinsic healing potential, alternative approaches utilizing biological augmentation have emerged, including gene therapy, growth factors, biophysical stimulation, and biologics. These methods, whether as standalone or adjunctive therapies to surgery, aim to promote tissue healing and accelerate the healing rate [40–42]. Among these approaches, cell therapy utilizing MSCs is particularly noteworthy due to their ability to differentiate into various tissue cell types and modulate immune and inflammatory responses [47,48].

**Recent Research on MSC Applications for MCL Injury**

In a rat model of MCL injury, Lee et al. [49] observed significant improvements in MCL healing and biomechanical properties following the injection of MSCs, as compared to controls. The MSC-treated group demonstrated enhanced collagen organization and increased mechanical strength. The study involved the direct injection of MSCs into the MCL at the time of injury, highlighting the potential of MSCs in enhancing MCL healing in a rat model.

In a clinical trial conducted by Jo et al. [50], intra-articular injection of autologous MSCs in combination with platelet-rich plasma (PRP) resulted in improved MCL healing and clinical outcomes in patients with grade II and III MCL injuries, compared to PRP alone. The MSC-treated group exhibited significantly higher Lysholm and Tegner scores, as well as lower visual analog scale scores for pain, at 6 months post-treatment. MRI also showed improved MCL healing and reduced signal intensity in the MSC-treated group.

A case series by Pak et al. [51] explored the use of autologous MSCs and PRP in the treatment of chronic MCL injuries. The intra-articular injection of autologous MSCs and PRP resulted in improved pain, function, and radiographic findings in five patients with chronic MCL injuries.

Shen et al. [52] utilized a silk-based scaffold seeded with MSCs in a rat model of MCL injury, which showed enhanced MCL healing and mechanical properties. The MSC-seeded scaffold group exhibited significantly higher ultimate load-to-failure and stiffness, along with enhanced collagen organization and increased collagen density.

Kim et al. [53] evaluated the effect of low-intensity pulsed ultrasound (LIPUS) on MSC-mediated MCL healing in a rat model. LIPUS-treated MSCs demonstrated enhanced MCL healing and biomechanical properties compared to untreated MSCs or controls. Immunohistochemical analysis revealed increased expression of transforming growth factor-beta and vascular endothelial growth factor in LIPUS-treated MSCs, suggesting the potential of LIPUS in enhancing MSC-mediated MCL healing.

Sun et al. [54] investigated the effect of MSCs on MCL healing in a rabbit model of MCL injury. The intra-articular injection of MSCs led to improved MCL healing and biomechanical properties, with enhanced collagen.
organization and increased mechanical strength. The study also suggested that MSCs can differentiate into tenocytes and promote tendon-like tissue formation.

Xu et al. [55] studied the effect of MSCs on MCL healing in a rabbit model of MCL injury using a collagen-platelet scaffold. MSC-seeded scaffolds demonstrated improved MCL healing and biomechanical properties, along with enhanced collagen organization and increased mechanical strength. The study also indicated the potential of MSCs to differentiate into tenocytes and promote tendon-like tissue formation within the scaffold.

Conclusion

In summary, the use of MSCs shows promise in enhancing MCL healing and improving biomechanical properties in both preclinical and clinical settings. However, further research is necessary to elucidate the underlying molecular and cellular mechanisms, optimize cell sources and dosages, and validate the efficacy and safety of MSC-based therapies for enhanced MCL healing in clinical practice.

List of Abbreviations

- ACL: Anterior cruciate ligament
- MCL: Medial collateral ligament
- MRI: Magnetic resonance imaging
- MSCs: Mesenchymal stem cells
- POL: Posterior oblique ligament
- PRP: Platelet-rich plasma

Conflict of interest

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Author details

- Basem Ali Zogei, Hussam Masoud Darraj, Zenat Ahmed Khired, Fahad Yahya AlArishi
- 1. Faculty of Medicine, Jazan University, Jazan, Saudi Arabia
- 2. Department of Surgery, Faculty of Medicine, Jazan University, Jazan, Saudi Arabia
- 3. Department of Orthopedic Surgery, King Faisal Medical City for Southern Region, Ministry of Health, Jazan, Saudi Arabia

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MSCs for enhanced MCL healing in the knee


