International Journal of Multidisciplinary Research and Growth Evaluation.

Treatment of Degenerative Ankle Arthropathy with Autologous Bone Marrow-Derived Stem Cell Infiltration: Mid-Term Clinical Outcomes

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Article Info

ISSN (online): 2582-7138
Volume: 06
Issue: 04
July - August 2025
Received: 15-06-2025
Accepted: 16-07-2025
Published: 25-07-2025
Page No: 758-763

Abstract
Degenerative arthropathies of the talus are quite common following ankle sprains in young and active patients. Once the tissue is damaged, it has poor healing capacity, and therefore the injury may even become irreversible and chronic. The treatment has been widely discussed, and there are various surgical proposals aimed at restoring the cartilage on the talus; however, among these, only osteochondral grafting and the administration of autologous chondrocytes have demonstrated the ability to regenerate and repair the injured site. Ankle osteoarthritis is a chronic condition with a progressive course; therefore, conservative treatment only has a delaying effect on degeneration and remains secondary to the definitive option of surgery. Although regenerative techniques have limitations, unlike conservative treatment, they are able to delay the need for surgical intervention. Therefore, with the goal of reaching surgical treatment for degenerative ankle arthropathies as late as possible, the transplantation of autologous bone marrow-derived stem cell infiltrates has been proposed, maximizing the benefits of their self-renewal and replication capabilities.

Keywords: Arthropathies, Arthropathies, Intervention

1. Introduction

In this study, we will examine the ankle joint which, together with the bones of the foot, is responsible for maintaining balance and enabling body movement during both dynamic and static activities, such as maintaining an upright posture, jumping, walking, and running. It bears the entire weight of the body. From an anatomical perspective, the ankle joint is formed by the distal ends (malleoli) of the tibia and fibula articulating with the tarsal bones, specifically the superior portion of the talus. For this reason, it is also referred to as the talocrural or tibiotarsal joint.

It is a hinge joint with a single degree of freedom, allowing dorsiflexion and plantarflexion of the foot. It governs the movements of the leg relative to the foot in the sagittal plane and is subjected to significant mechanical stresses, as it supports the entire body weight both in static positions and during movement. Although essential for normal biomechanical function, it is not absolutely necessary for ambulation.

The tibiotarsal joint is an anatomically complex structure, and it will be extensively described in this work. Furthermore, we will address modern approaches to the management of degenerative ankle arthropathy, which may be secondary to trauma (particularly sprains and fractures) and affect the subchondral bone and articular cartilage, compromising their biochemical and biomechanical properties. This leads to progressive joint degeneration, resulting in pain, deformity, and loss of function.

Managing the treatment of degenerative ankle arthropathy is a significant and current clinical challenge, as there are no universally accepted guidelines. Conservative treatments are considered to alleviate symptoms when diagnosed in the early stages, while surgical intervention remains the final option to restore joint morphology. The ankle cartilage has unique properties due to the substantial load it bears. Unless compromised by severe trauma or specific pathological conditions, the ankle is less prone to degeneration compared to the knee or hip, where osteoarthritis is a common age-related condition.

In recent years, the emergence of Regenerative Medicine, supported by international research, has aimed to "repair" cells, tissues, and organs not through replacement but via advanced cell regeneration technologies, including the use of stem cells.

Stem cells represent a group of undifferentiated cells with no predefined function within the body. They possess the ability to self-renew and proliferate over an extended period. Under specific conditions, they can be induced to differentiate into specialized cells with distinct functions. The capacity of stem cells to transform into a variety of other cell types is referred to as "totipotency." Ongoing research continues to demonstrate the rapid and functional efficacy of stem cells in repairing and reconstructing damaged tissues.

Orthopedic laboratories primarily utilize two types of stem cells:

Embryonic Stem Cells (ESCs): Derived from human embryos fertilized in vitro or through laboratory procedures.

Autologous Mesenchymal Stem Cells (MSCs): Adult, undifferentiated, and immature stem cells extracted and isolated from the patient's own living tissues. These cells are tissue-specific, making them of greater interest in orthopedic research and widely used by surgeons aiming to repair specific tissues. Upon injection, these cells differentiate through a process of biological intelligence into cells matching the characteristics of the target tissue, stimulating the surrounding cells to self-regenerate. Mesenchymal stem cells (MSCs) are named after their tissue origin.

The most common sources for mesenchymal stem cells are bone marrow (typically from the iliac crest or tibia) and adipose tissue, where they can be easily isolated and utilized. MSCs are a readily available and clinically applicable resource for enhancing biological repair processes.

Our experimental approach involves the direct transplantation of bone marrow aspirate harvested from the tibia, mixed with hyaluronic acid, and subsequently injected into the ankle joint. This procedure is simple and rapid, minimizing surgical risks, operative time, and trauma while reducing recovery times and treatment-associated costs. The primary objective of this intervention is not to achieve complete joint regeneration but to delay the need for surgical solutions as much as possible.

One of the primary criticisms regarding the treatment of degenerative ankle arthropathy is the lack of robust and controlled scientific studies, making it difficult to establish the superiority of this method compared to other treatments, such as joint prostheses or surgery. Therefore, our aim is to evaluate the clinical outcomes of autologous bone marrow-derived stem cell transplantation for ankle osteoarthritis. Clinical results are assessed through subjective and objective evaluation tools, including the Visual Analog Scale (VAS), the Short Form-36 (SF-36), the American Orthopaedic Foot & Ankle Society (AOFAS) score, and the European Foot and Ankle Society (EFAS) score. These data are compared with existing literature to assess their accuracy and positive impact.

The applications of stem cell therapy are diverse and continuously evolving. Stem cells can significantly enhance tissue healing, reduce postoperative pain, and accelerate tissue consolidation, thereby improving recovery and rehabilitation for daily activities and, in specific cases, sports activities.

Materials and Methods

In this study, 26 patients who underwent surgery for ankle osteoarthritis between September 2020 and November 2022 were considered. All patients were treated with autologous bone marrow-derived stem cell injections. Patients younger than 16 years and older than 60 years were excluded. Additionally, patients with ankle injuries related to osteoarthritis or trauma, axial malalignment, or ligamentous instability (if present, these conditions must have been corrected previously), septic arthritis, rheumatic diseases, and metabolic disorders were excluded.

The patient cohort included 17 men and 9 women, ranging in age from 30 to 72 years. The mean age was 51 years, and the most represented age group was between 40 and 60 years. In 13 cases, the affected ankle was the right one, in 9 cases the left, and in 4 cases the condition was bilateral. In 19 out of 26 selected patients, a previous trauma such as fractures of the tibio-tarsal joint and sprains was detected. The remaining patients reported no history of traumatic events in the affected area.

For treatment, bone marrow was aspirated from the tibia, and hyaluronic acid was used. Hyaluronic acid is a sterile, transparent, and viscoelastic hydrogel composed of cross-linked hyaluronate, a derivative of highly purified sodium hyaluronate (hyaluronic acid) extracted from rooster combs.

In Hylink®, hyaluronic acid filaments are cross-linked through cinnamic acid dimers, resulting in increased viscoelasticity. Hylink® is supplied in single-use, pre-filled glass syringes. Each syringe is pre-filled with 3 ml of Hylink®, containing 30.0 mg of cross-linked hyaluronate, 23.3 mg of sodium chloride, 0.89 mg of disodium phosphate dodecahydrate, 1.93 mg of sodium dihydrogen phosphate dihydrate, and water for injection.

Postoperative follow-up was conducted through objective and subjective questionnaires, including VAS, EFAS, SF- 36, and AOFAS (specific for ankle/midfoot), with an average follow-up period of 24 months after the infiltration.

Patients undergoing surgery were assessed through clinical evaluation using both objective and subjective questionnaires on the day of the operation and approximately 24 months postoperatively. The evaluation was conducted using the VAS, EFAS, SF-36, and AOFAS scores.

Surgical Procedure for Tibial Bone Marrow Aspiration and Infiltration

Autologous chondrocyte transplantation involves two phases. During the first phase, a fragment of healthy cartilage is harvested arthroscopically from a non-weight-bearing area of the knee or from the lesion site itself in the ankle. Approximately 30 days after cartilage collection, the second phase is performed, involving the implantation of cultured chondrocyte cells. This procedure is carried out arthroscopically by removing the damaged cartilage to prepare the area for cell reception. A chondrocyte-loaded membrane is then placed on the prepared and debrided area, allowing the cells to colonize the lesion site.

The patient is positioned in the supine position under local anesthesia, and after preparing a sterile surgical field, mesenchymal cells are implanted arthroscopically into the previously debrided area. An 11 G bone marrow needle is inserted approximately 5 cm deep into the tibial cancellous bone (Fig. 1). For each joint to be infiltrated, 3 ml of bone marrow aspirate is collected and mixed with a calcium heparin anticoagulant solution preloaded in a 20 ml syringe.

The aspirate is then combined with the contents of a pre-filled syringe containing hyaluronic acid. The material is repeatedly transferred between syringes to ensure homogeneous mixing (Fig. 2).

Fig 1: Bone marrow aspiration from the tibia

Fig 2: Mixing of the aspirated bone marrow and hyaluronic acid.

The collagen-based or hyaluronic acid biomaterial is enriched with autologous growth factors and mesenchymal cells, which will migrate to the lesion site. The growth factors most involved in this process are Transforming Growth Factor-beta (TGF-beta) and Insulin-like Growth Factor (IGF-1); both can be easily obtained from the platelet gel, produced from venous blood collected from the patient at the time of admission. Using a cannula, the biomaterial containing the mesenchymal cells is placed at the lesion site, after which the wounds are sutured, and the treated area is dressed (Fig. 3) (Fig. 4).

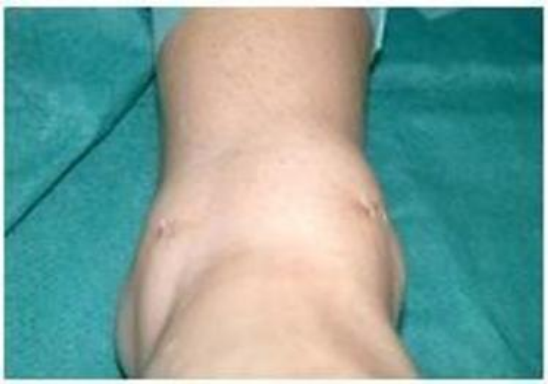


Fig 3: Wound suturing

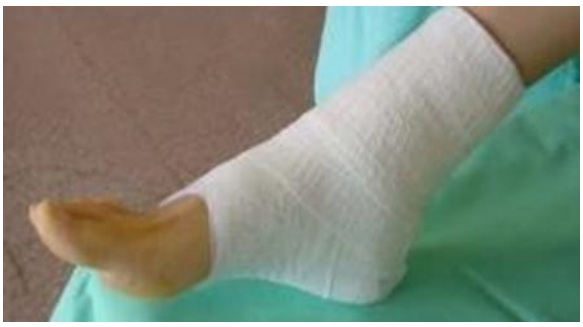


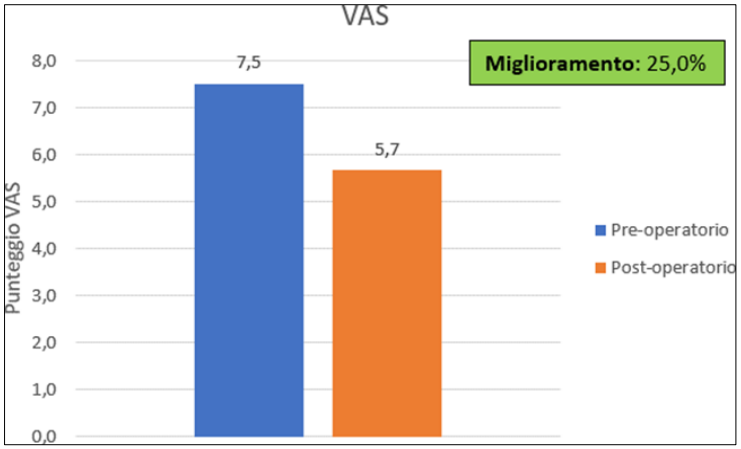
Fig 4: Post-operative dressing.

During recovery and rehabilitation, the goal is to mobilize the ankle. In fact, from the very first day after the surgery, movement is recommended based on tolerance, and the range of motion (ROM) is gradually increased according to pain levels.

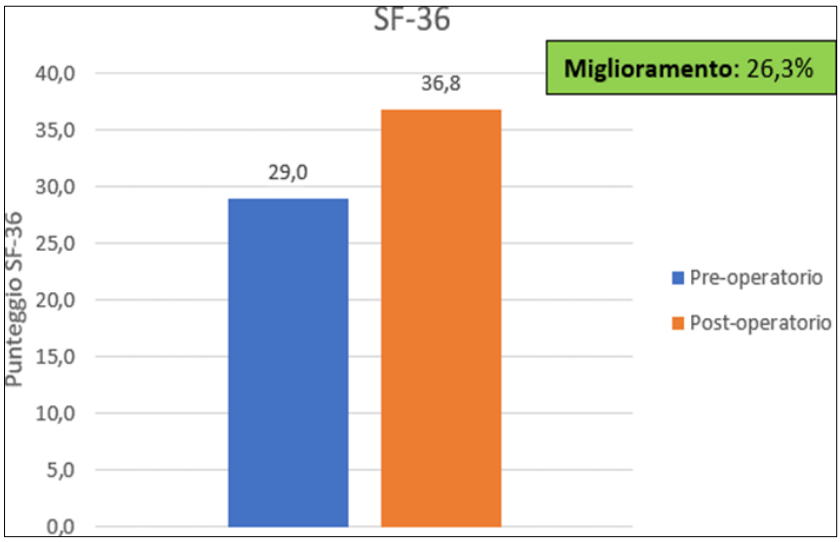
As for the restoration of ambulation, it will clearly be progressive: initially, partial weight-bearing with the use of supports, such as crutches, will be necessary. Starting from 3 weeks, full weight-bearing without support is possible, while low-impact physical activities (such as swimming and cycling) are allowed as early as 2 months post-surgery.

Results

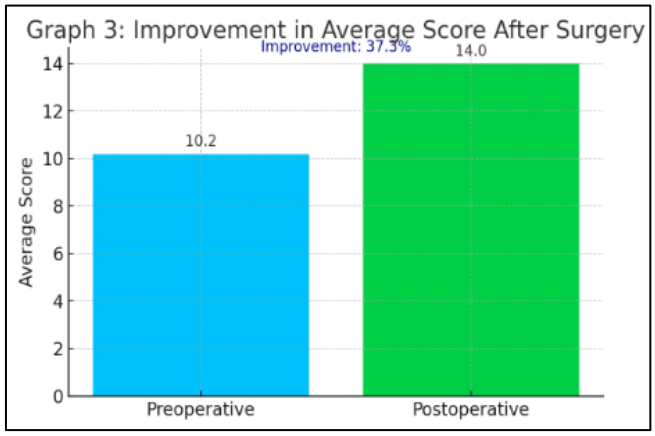
The average clinical score on the preoperative pain scale is quite high, with a value of 7.5 on a scale ranging from 0 to 10, where 10 represents the maximum pain. Following the operation, the average score on the VAS scale improved by 25% (Graph 1).



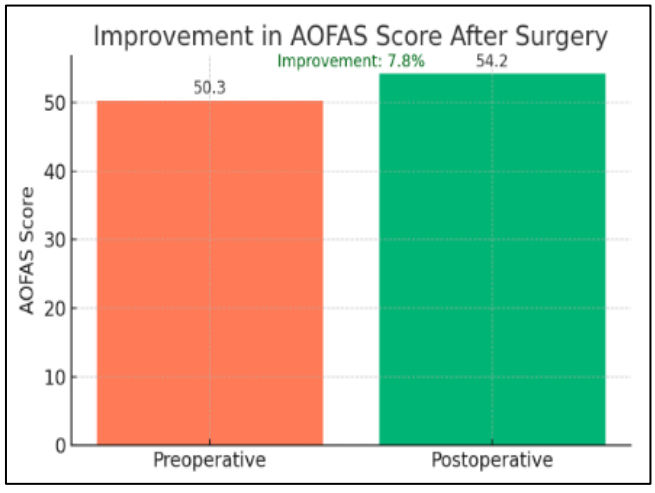
Graph 1: Considering that this study focused solely on the physical functioning section, a significant improvement of 26.3% was observed in the postoperative phase, starting from an average preoperative clinical score of 29.0. On average, patients recovered approximately 8 points



Graph 2: Considering that this study focused solely on the physical functioning section, a significant improvement of 26.3% was observed in the postoperative phase, starting from an average preoperative clinical score of 29.0. On average, patients recovered approximately 8 points



Graph 3: The average preoperative score was 10.2, and after the surgery, the average score increased to 14.0, reflecting an improvement of 47.5%



Graph 4: The average preoperative AOFAS score was 50.3. Following the surgery, there was an improvement of 6.9%, reaching a postoperative score of 54.2.

Discussion

The treatment of degenerative ankle arthropathies is a very delicate topic, subject to various studies and treatments aimed at developing and proposing a valid, rapid, and cost-effective approach for cartilage regeneration. Among these, the most modern is the use of autologous stem cells due to their totipotent ability for self-regeneration.

Research into regenerative treatment is still in development, and there is much yet to be discovered and validated, but so far, the scientific literature reports encouraging results both in terms of the number of interventions and the outcomes. Bone marrow-derived stem cells have the potential to differentiate and regenerate cartilage to repair joint defects caused by osteoarthritis. The results of the study presented in this paper are positive, with improvements in VAS, EFAS, SF-36, and AOFAS scores compared to the pre-operative situation.

Conclusion

The aim of this experimental study was to evaluate the outcomes of treating degenerative arthropathy with an injection of autologous stem cells derived from bone marrow. The final result of this experiment must take into account the limitations inherent in the experimental setup, which, as a whole, partially influence the measured parameters, such as the lack of a significant sample size and the scarcity of scientific studies for a valid comparison. Nevertheless, this study serves as a pilot project to provide important data for future, larger-scale studies. The primary objective of the study was to determine whether this new conservative approach for treating arthritic joints could be suitable for delaying the need for surgical intervention. In conclusion, regenerative medicine adequately responded to our hypothesis.

The improvement rate was consistently more than positive in every score considered (AOFAS, EFAS, SF-36, and VAS), and therefore, in the majority of patients, the final surgical intervention was successfully postponed. Unlike arthrodesis, which limits walking and does not allow a return to sports activities except at a low impact level, the procedure with autologous grafting offers a gradual return to sports activities, even high-impact ones in specific cases, starting almost immediately after the injection, without causing any significant abnormalities in walking, thus ensuring greater joint mobility and flexibility.

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